# ORAL ABSTRACTS

**5**

## Planned paternity: A healthy child when - and only when - desired

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Men desire fatherhood through natural (not assisted) conception or its prevention through reliable contraception. Men participate widely in fertility treatments and contraceptive practices, yet options to regulate fertility are limited. Decades of animal and human studies provide a good understanding of the hormonal regulation of spermatogenesis and its therapeutic manipulation. Natural fertility can be restored in hypogonadotropic hypogonadism using gonadotrophin therapy. However, most infertility arises from primary spermatogenic failure (1ºSG) for which a cause can be identified in a minority (Klinefelters, Yq microdeletions, testicular damage). For idiopathic 1ºSG new genetic causes are emerging as are environmental and infective impacts. Assisted reproductive treatments (ART), especially intracytoplasmic sperm injection, effectively 'bypass' the male reproductive defect, by using viable sperm retrieved from semen or testis. ART outcomes are now similar to female factor aetiologies. Currently half of ART treatment relate solely, or partly, to male factors. Although reassuring to date, assessment of the heath of ART offspring is a continuing responsibility.

Conversely, a global demand also exists for new safe, effective and reversible male contraceptive options. Male hormonal contraception (MHC) relies on gonadotrophin suppression by exogenous androgens, often combined with progestin, while maintaining virilisation. The loss of FSH action and a 100-fold reduction in intratesticular testosterone (iTT) levels profoundly impairs spermatogenesis, particularly meiotic progression and sperm release. Over 3-6 months sperm densities fall to <1 million/ml with contraceptive efficacy similar to female methods. Inadequate suppression in ~5% of men probably results from residual iTT action. Recovery occurs over 6 -12 months depending on the formulation. Despite decades of encouraging translational studies, including multinational trials under the auspices of the WHO, development has stalled due to industry concerns about the risk: benefit (registration costs, liability, side effect profile, market size). Limited public sector research continues.

**9**

## Year in Obesity

**Priya Sumithran**

This presentation will outline recent developments in the epidemiology, physiology and management of obesity. Over the past year, emerging research has highlighted the health effects of excess weight, uncovered new mechanisms involved in the regulation of body weight, and revealed progress and challenges in obesity pharmacotherapy and bariatric surgery.

**10**

## Year in Cushing's Disease

**David Torpy**[1]

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Cushing's disease (CD) is rare (3/million/year) and due to autonomous pituitary ACTH hypersecretion, generally associated with a pituitary tumour (corticotropinoma). Genetic studies, initially published in 2014, established that ≥40% of corticotropinomas have a causative mutation of the ubiquitin-specific- protease 8 (USP8) gene that plays an important role in regulation of the epidermal growth factor receptor. First line treatment for CD in usually surgical, with success rates of 50-80% depending on tumour size and invasiveness and surgical expertise, but subsequent relapse occurs in 20-30%. Hence long term surgical cure of CD may ensue in only approximately 50% of patients. Adjunctive reoperation and/or pituitary irradiation have varying individualized successes. Final long term cure of CD can be achieved definitively by bilateral adrenalectomy, but with permanent primary adrenal insufficiency which entails risks of chronic reduced well-being and adrenal crises. Accordingly, there is a need for medical therapy for CD. Recently there is a substantial continuing effort to define the extent of effectiveness of traditional CD medical therapies, the adrenal steroidogenesis inhibitors, particularly ketoconazole and metyrapone as assessed by large retrospective databases and the newer pituitary active options, Pasireotide and Cabergoline, as well as the glucocorticoid receptor blocker, Mifepristone. Despite a background of numerous abandoned options in past decades, there are now a range of newer agents in various stages of development which either modify existing options or exploit new targets in pituitary tumours or on ACTH action. These newer agents promise sufficient safety and durable efficacy to allow medical therapy for CD to assume a greater role, with earlier use and reduction in the substantial long term metabolic and neurocognitive morbidity associated with CD.

**11**

## The Year in Osteoporosis and other Bone Diseases

**Emma Duncan**[1]

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The title of this talk really should be “Another extraordinary Year in Bone” - because progress in diagnosis and management of both common and rare bone diseases in the last year has been rapid and exciting. It’s going to be hard in half an hour to cover everything but I will aim to present as least some of the new data – all from the last 12 months! – addressing the following:

1. a) New anabolic agents in osteoporosis (romosozumab, abaloparatide)
2. b) Head-to-head trials in osteoporosis therapeutics
3. c) what is the longterm safety of denosumab?
4. d) what happens after denosumab discontinuation?
5. e) Options after stopping denosumab? (could oral agents be better than IV?)
6. f) Does zoledronate need annual dosing?
7. g) How should we best identify and treat osteoporosis in the community?
8. h) Does HRpQCT add anything useful to BMD?
9. i) Bone protection for women going onto aromatase inhibitors? (our own ESA/ANZBMS publication here!)
10. j) Does exercise do anything useful in osteoporosis?
11. k) What’s the best option for glucocorticoid-induced osteoporosis?

There’s been great progress in rare skeletal diseases:

1. a) The pivotal trial of Burosumab (an FGF23-neutralising antibodies) in children with X-linked hypophosphataemic rickets
2. b) Phase 2 results of palovarotene for fibrodysplasia ossificans progressive data (Phase 3 studies in progress…..)
3. c) Palovarotene for multiple hereditary exostoses
4. d) Romosozumab in skeletal dysplasias (osteogenesis imperfecta and hypophosphatasia)
5. e) Fresolimumab in adults with osteogenesis imperfecta
6. f) The first RCT of zoledronate in bone marrow oedema syndrome

The ongoing saga of calcium and vitamin D has continued, including genetic dissection of calcium in vascular disease. And of course my own personal interest: how many genes contribute to osteoporosis?

Don’t know what some of these agents are, or even some of these diagnoses? Come along and listen. Without doubt bone disease is one area in medicine undergoing significant change!

**12**

## Actions and Interactions of Aldosterone and the Mineralocorticoid Receptor

**Peter Fuller**[1, 2]

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The actions of the mineralocorticoid, aldosterone, are mediated by the mineralocorticoid receptor (MR), a member of the nuclear receptor superfamily of ligand-dependent transcription factors. The MR appears in vertebrate evolution before aldosterone and indeed responds to two physiological ligands, aldosterone and cortisol (and also perhaps a third, progesterone). In epithelial tissues, aldosterone selectivity is determined by 11β-hydroxysteroid dehydrogenase type II. In other tissues cortisol is the primary ligand with multiple roles in cardiovascular function, immune cell signalling, neuronal function and adipocyte differentiation. These actions, beyond simply sodium homeostasis and hypertension, contribute to the disproportionate morbidity associated with hyperaldosteronism and the benefit observed more broadly in cardiovascular disease with the use of MR antagonists. This diversity of responses at the MR, including ligand- and tissue-specificity, is achieved through critical interactions involved in MR-mediated signal transduction. Siganling is initiated by ligand-binding which confers a ligand-specific, agonist or antagonist, conformation upon the receptor. This conformation then determines subsequent interactions within the receptor, with other transcription factors independent of DNA-binding, and with coregulatory molecules. Relatively few coregulators have however been described for the MR although our recent studies have demonstrated both ligand and/or tissue-selectivity for MR-coregulator interactions. The successful identification of the structural basis of antagonism at the MR, and of ligand-specific interactions of the MR, may provide the basis for the development of novel ligands with the ability to modulate the MR response and provide tissue specificity.

**13**

## Premenopausal women with early breast cancer treated with estradiol suppression have severely deteriorated bone microstructure.

**Sabashini Ramchand**[1]

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**Background**: In premenopausal women with early estrogen-receptor-positive breast cancer, combined ovarian suppression and aromatase inhibition reduce estradiol production precipitously. The resulting unbalanced and rapid bone remodelling

replaces older bone with less bone that is less fully mineralized. We hypothesized that these changes result in severe microstructural deterioration and reduced matrix mineralization density.

**Methods:** Images of the distal radius and distal tibia were acquired using high-resolution peripheral quantitative computed tomography in a cross-sectional study of 27 premenopausal women, mean age 43.3 years (range 30.4 to 53.7) with early breast cancer made estradiol deficient for 17 months (range 6–120) using ovarian suppression and aromatase inhibition, 42 healthy age-matched premenopausal and 35 postmenopausal controls, mean age 62.6 years (range 60.2 to 65.5). Cortical and trabecular microstructure were quantified using Strax software.

**Results:** Compared with premenopausal controls, the women with breast cancer had 0.75 SD (95% CI 0.21 to 1.29) lower distal radial trabecular bone volume due to 1.29 SD (0.71 to 1.87) fewer trabeculae. Cortical porosity was 1.25 SD (0.59 to 1.91) higher but cortical thickness was not reduced. Compared with postmenopausal controls 20 years older, cases had comparable or lower trabecular bone volume and comparable cortical porosity and thickness. Matrix mineral density was 1.56 SD (0.90 to 2.22) lower than in premenopausal controls and 2.17 SD (1.50 to 2.84) lower than in postmenopausal controls. Results at the tibia were similar.

**Conclusion:** The severe cortical porosity and trabecular deterioration associated with estradiol depletion and the longevity of premenopausal women with early breast cancer treated with endocrine therapy provide a compelling rationale to investigate the efficacy of antiresorptive therapy initiated at the time of breast cancer treatment.

**17**

## The GH, IGF-I Insulin axis

**Aart Jan van der Lely**[1]

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In many instances, the GH and IGF-I levels in patients with pituitary diseases is a well-known combination of hormones that are tightly intertwined. In diabetes patients the insulin – glucose relation is the driver of treatment in which HbA1c is used as the outcome parameter. However, both in pituitary diseases in which the GH-IGF-I axis is disturbed as well in diabetes, all three hormones (GH and IGF-I and insulin) are equally important factors. To understand how they influence each other is important for proper patient care.

The physiological effects of GH versus IGF-I remain controversial. Historically, it has been difficult to isolate the individual effects of GH and IGF-I at the tissue level during physiological conditions. But the fact that GH possesses a diabetogenic or 'anti-insulin' activity while IGF-I (as the name implies) is similar to insulin in its actions, clearly demonstrates that physiological differences exist between the actions of the two peptide hormones. Human and other mammals are capable of prolonged fasting because they can recruit and utilize lipid stores when they exhaust readily available carbohydrates. Prolonged fasting is associated with a gradual decline in hepatic IGF-I production which makes teleological sense due to the insulin-like effects of IGF-I. A study by Ho et al. suggests that GH-induced hepatic IGF-I production is regulated by portal insulin levels. They reported that insulin promotes the translocation of the hepatic GH receptor (GHR) to the surface. When portal insulin levels are high, the liver becomes GH sensitive, regardless of the cause of the

elevation in insulin production. In addition, portal insulin also inhibits hepatic IGFBP-1 production, which may increase the bioavailability of circulating IGF-I. In conclusion, high portal insulin levels increase liver GH sensitivity (via up regulation of surface GHRs) and therefore, ultimately increase liver IGF-I production with concomitant increases in serum

IGF- I levels. In contrast, low portal insulin levels reduce the sensitivity of liver for GH and,

therefore, reduce serum IGF-I levels.

**18**

## Integrating pasireotide and pegvisomant into an acromegaly treatment algorithm

**Morton Burt**[1]

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Acromegaly can cause substantial morbidity and is associated with increased mortality. Control of growth hormone and insulin-like growth factor-1 secretion can reduce morbidity and normalize life expectancy. However, biochemical control can be difficult condition to attain in a substantial proportion of patients. Recently two new therapeutic options, pasireotide long-acting release (LAR) and pegvisomant, have become available for use in Australia. This presentation will compare the efficacy and safety of these new medications to other therapeutic options and attempt to integrate them into an acromegaly treatment algorithm.

**19**

## Growth Hormone Deficiency in Adults: Who and How to Treat

**Ken Ho**[1]

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GH continues to be produced after cessation of growth regulating the metabolic process and the functional integrity of many tissues in adult life. Adults who lack GH develop a characteristic clinical picture of metabolic and body compositional abnormalities. The clinical manifestations of increased cardiovascular risk, impaired physical function, psychological well being

and diminished quality of life (QoL) are reversed by GH replacement therapy. There is strong evidence from over 25 years of global experience that GH replacement therapy is safe with no increased risk of pituitary tumour recurrence or of de novo malignancies.

Patients with organic pituitary disease should be investigated for GH deficiency with an intention to treat using validated diagnostic tests for GH deficiency(1). A blood IGF-I measurement is not a sensitive diagnostic test but is valuable for guiding the dose of GH replacement which is higher in women. The benefits on physical and psychological function occur over several months in parallel with an improvement in QoL.

PBAC twice rejected (in 2001 and 2011) the subsidizing of GH for adults with GH deficiency on the basis of uncertain cost-effectiveness of treatment. Following a joint application by the ESA and APEG supported by GH Pharmas, the PBAC has recommended the listing of GH as a pharmaceutical benefit for patients with severe GH deficiency and a poor QoL(2). QoL is quantified by an Assessment of Growth Hormone Deficiency in Adults (AGHDA) Questionaire. The scores determines eligibility for initiation and continuation of GH replacement therapy. The impending Section 100 listing is expected to benefit about 1000 patients in Australia.


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2. Lipworth W, Ambler GA, Burt MG, Fairchild J, Inder WJ, Werther G, Ho K. A will and a way to fund medicines for rare diseases: the story of human growth hormone replacement for adults with growth hormone deficiency. Int Med J. 2018;in press.


**20**

## The prostate cancer sub-pathology intraductal carcinoma of the prostate is a high-risk feature of localised prostate cancer


**Laura H Porter[1, 2], Mitchell G Lawrence[1, 2], Carmel Pezaro[1], Heather Thorne[2], Declan Murphy[2], Mark Frydenberg[1], David Clouston[3], Renea A Taylor[1, 2], Gail P Risbridger[1, 2]**

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Publish consent withheld


1. Porter et al. 2017. European Urology. 72(4): 492-495.
2. Porter et al. 2017. BJU International. In press


**21**

## A role for the long non-coding RNA *GHRLOS* in cancer


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Long non-coding RNA (lncRNA) genes are abundant in the human genome and many are recognised to have oncogenic or tumour suppressor properties. We previously characterised the structure of *GHRLOS*, a gene situated on the opposite strand of the multifunctional peptide hormone ghrelin gene (*GHRL*), however, its expression and function in disease haven't been described. Here, interrogating The Cancer Genome Atlas (TCGA), we first revealed that *GHRLOS* is differentially expressed in a number of cancers and in particular, expression was elevated in endometrial and prostate cancer compared to normal tissues. Using qRT-PCR (and commercial cDNA panels) we confirmed that *GHRLOS* expression is upregulated in endometrial and prostate cancer. Forced *GHRLOS* overexpression did not significantly regulate the expression of the overlapping *GHRL* gene. *GHRLOS* overexpression significantly increased *in vitro* migration and proliferation of the PC3 metastatic prostate cancer cell line. In agreement, there was an increase in tumour volume (1.43-fold, unpaired *t*-test $P < 0.0001$) and expression of the cell proliferation marker Ki67 (1.25-fold, unpaired *t*-test $P < 0.0001$) in *GHRLOS*-overexpressing PC3 xenografts ($n$=12) grown subcutaneously in NOD/SCID mice. Associated genome-wide gene expression profiling revealed differential expression of 223 genes, including repression of *ATM* (-3.3-fold, moderated t-test $Q=8.2\times10^{-3}$), a master regulator of DNA repair and tumour suppressor frequently mutated in metastatic prostate cancer. The long non-coding RNAs *MALAT1* (-8.0-fold, $Q=6.0\times10^{-3}$) and *NEAT1* (-9.0-fold, $Q=7.8\times10^{-3}$) were also regulated by *GHRLOS*. Taken together, we show that the lncRNA *GHRLOS* is overexpressed in prostate cancer and may facilitate PC3 prostate cancer cell growth and migration *in vitro*, PC3 xenograft

growth *in vivo*, and inhibit invasion by downregulating key associated non-coding RNAs. Ongoing studies aim to identify mechanisms used by this lncRNA to facilitate the functional effects observed.

**22**

## Ovarian hormones modulate the expression of genes involved in breast cancer diagnosis

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Tests that use gene expression-profiling to help guide treatment decision-making in breast cancer, such as OncotypeDx, were largely validated in postmenopausal women. It remains unclear whether they are suitable for use in premenopausal women, where hormones estrogen and progesterone fluctuate dramatically during the menstrual cycle. To address this, we have used two mouse models of breast cancer to define how ovarian hormones affect breast cancer gene expression and subsequent OncotypeDx diagnosis.

The effect of ovarian hormones on estrogen receptor-positive breast cancer cell line T47D, was examined in mammary fat pad-xenografted BalbC/NUDE mice, treated with exogenous estrogen±progesterone (n=12, n=11 respectively). Our second model investigated the effect of fluctuations in ovarian hormones on mammary tumours collected from naturally cycling MMTV-PyMT mice, at either the estrus or diestrus phase of the ovarian cycle (n=30/group). For both mouse models, gene expression was assessed using quantitative RT-PCR.

Significant changes in the expression of 6/16 OncotypeDx signature genes were observed in xenografted tumours dissected from progesterone and estrogen treated mice, compared to estrogen only treated mice ($p \leq 0.05$). Through immunohistochemical analysis these tumours also showed reduced progesterone receptor ($p=0.02$) and Ki67 ($p=0.02$) protein expression. No changes were observed in estrogen receptor protein expression ($p=0.20$). Furthermore, tumours collected from naturally cycling MMTV-PyMT mice at diestrus, when circulating concentrations of progesterone are highest, showed significant differences in 8/16 OncotypeDx signature genes ($p \leq 0.05$), and a significant increase in their OncotypeDx recurrence score (15.9±1.9; mean±SEM), compared to tumours dissected at estrus (11.7±1.7; $p \leq 0.05$).

Together our studies suggest ovarian hormones significantly alter breast cancer biomarker expression and OncotypeDx recurrence scores in mouse models. If used in premenopausal women, OncotypeDx may give a different diagnosis depending on the woman's menstrual cycle stage at the time of tissue collection. We are currently investigating this in a prospective study in premenopausal women with breast cancer.

**23**

## Periconceptional ethanol exposure results in altered behaviour and HPA activity in a rodent model.

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Alcohol (ethanol [EtOH]) consumption during pregnancy is associated with altered offspring neurobehaviour and hypothalamus-pituitary-adrenal axis (HPA) function[1]. Although many cease alcohol upon pregnancy detection, 30% of women admit to drinking during the periconceptional period (PC)[2]. However, the impacts of EtOH exposure during PC on HPA outcomes is unknown. This study aimed to investigate the impacts of PC:EtOH exposure on rodent behavioural and HPA activity outcomes.

Sprague Dawley dams were treated with 12.5% ethanol or control liquid diet from 4 days before conception to embryonic day 4. Offspring were delivered naturally and at 3 months of age offspring underwent forced swim (FST) and social interaction (SI) tests followed by a dexamethasone suppression (DST), corticotropin hormone stimulation (CST) and restraint tests at 6 months of age. Further subsets of animals were culled for tissue collection for analysis of basal corticosterone and mRNA expression of HPA pathways at 6 and 15 months of age.

PC:EtOH resulted in increased immobility within the FST in offspring ($p < 0.05$). There was an increase in social interaction ($p < 0.05$) and elevated plasma corticosterone responses to the DST and CST in female offspring only ($p < 0.05$). Interestingly, there was no significant PC:EtOH effect on corticosterone response during restraint test in either male or female offspring. Relative gene expression of the adrenal steroidogenic pathway (*Mc2r*, *StAr*, *Cyp11a1*, *Hsd3ab*, *11bhsd2*, *Cyp11a1*, *Nr3c1* and *Hsp90*) was not significantly different at 6 months of age, however hippocampal genes (*Nr3c1* and *Hsp90*) were significantly elevated within female PC:EtOH offspring only at 15 months of age.

These results suggest that PC:EtOH alters behavioural outcomes and HPA reactivity within rodent offspring, with potential changes in the hippocampal regulation of the HPA axis of female offspring. Our results highlight that exposure to alcohol even before organogenesis and brain development can have significant adverse outcomes for offspring.

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2. Muggli E, O'Leary C, Donath S, Orsini F, Forster D, Anderson P, Lewis S, Nagle C, Craig J, Elliott E, Halliday J (2016). Did you ever drink more? A detailed description of pregnant women's drinking patterns. BMC Public Health, 16(1):683-696.

**24**

## IRX4, a novel mediator of androgen receptor transcriptome in prostate cancer

**Janaththani Panchadsaram[1], Gregor Tevz[1], Anja Rockstroh[1], Atefeh Taherian Fard[1], Melanie Lehman[1, 2], Colleen Nelson[1], The Australian Prostate Cancer BioResource[1], Judith Clements[1], Jyotsna Batra[1]**

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Iroquois-Homeobox 4 (*IRX4*) is recently implicated to be associated with prostate cancer (PCa) risk through Genome-Wide Association Studies and follow-up functional studies (1-3). However, the mechanism of IRX4 action in PCa aetiology and regulation of its expression is poorly understood.

Expression of *IRX4* was upregulated in prostate tumour samples compared to adjacent non-malignant tissues. *IRX4* knockdown reduced LNCaP cell proliferation and migration. Pathway analysis of the transcriptome from *IRX4* knockdown samples in LNCaP cells revealed that the Androgen Receptor (AR) pathway was inhibited, suggesting that IRX4 may mediate effective androgen signaling. This was further strengthened by our observation that IRX4 directly interact with an important AR co-factor, FOXA1, in IRX4 immunoprecipitation assays.

Interestingly, *IRX4* expression was up-regulated in VCaP cells with androgen treatment, while down-regulated in LNCaP cells. *In-silico* analysis identified binding of ERG and AR , upstream of *IRX4* only in VCaP cells. Knockdown of ERG in VCaP cells up-regulated the androgen mediated expression of *IRX4*, while ERG overexpression in LNCaP cells down-regulated *IRX4* expression, suggesting ERG and AR coordinate the expression of *IRX4*. Sequencing of AR/ERG binding region identified a Multiple-Nucleotide Length polymorphism (MNLP-rs386684493) where a stretch of 47bp sequence is replaced by a novel 21bp sequence. VCaP cells have an intact AR binding site (47bp/47bp) whereas LNCaP cells have disrupted AR binding site (21bp/21bp), thus showing opposite directionality during androgen stimulation. The androgen responsiveness of the 47bp allele of MNLP was further confirmed by reporter vector assay. Moreover, 21bp/21bp genotype was correlated with poor overall survival in the PCa patients who underwent androgen deprivation therapy.

Herein, we have demonstrated that *IRX4* is regulated by androgens in an MNLP allele-specific manner and IRX4 may mediate effective androgen signaling. Further studies on IRX4 structure and its interaction with AR-cofactors may provide insights for developing novel drugs for PCa treatment.

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**25**

## Effect of sex and stage of menstrual cycle on cold- and meal-induced brown adipose tissue thermogenesis in humans

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Adaptive thermogenesis is the dissipation of energy as heat. Earlier studies, on retrospective data, indicate that brown adipose tissue (BAT) activity is greater in women than in men. We aimed to characterize BAT thermogenesis using infrared thermography (IRT) in healthy men (n=14; age 23.07 ± 0.7 years, BMI 23.22 ± 0.7 kg/m$^2$) and in women during 2 stages of the menstrual cycle (luteal, n=9; age 25.22 ± 1.7 years, BMI 21.56 ± 0.4 kg/m$^2$ and follicular, n=11; age 24.64 ± 1.2 years, BMI 22.12 ± 0.9 kg/m$^2$). IRT measured cutaneous temperature at the supraclavicular region (BAT positive) and the manubrium as control (BAT negative). Temperature recordings were at 1 min intervals, at an ambient temperature of 18.5-20°C. To activate cold-induced thermogenesis, one hand was immersed into water at 15°C for 5 min. Post-prandial thermogenesis was stimulated by the consumption of a liquid meal (Ensure, 10 kcal/ kg body weight). Females had greater ($P<0.05$) thermogenic responses to cold and dietary stimuli than males; this effect was greater ($P<0.05$) during the luteal phase of the menstrual cycle. With cold-exposure, the increase in BAT temperature was lower ($P<0.05$) in females during the follicular phase than the luteal phase. Similarly, there was a trend towards reduced meal-induced thermogenesis in women during the follicular phase. Regression analyses demonstrated correlations between the degree of temperature change after a meal and serum progesterone levels ($P<0.01$, $R^2=0.12$), and temperature response to cold and estrogen levels ($P<0.05$, $R^2=0.13$). There was an inverse relationship between BAT temperature response and serum cortisol ($P<0.01$, $R^2=0.17$) and testosterone ($P<0.05$, $R^2=0.13$) concentration. In summary, females typically display greater thermogenic responses than males, but there are different responses in females in the luteal and follicular phases of the menstrual cycle. Differences in thermogenic responses are associated with variations in circulating sex and stress steroid concentrations.

**39**

## The Muscle-Bone relationship in Cerebral Palsy

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**Context:** Cerebral palsy (CP) is the most common motor disorder in children, with impaired mobility, increased falls and fracture risk. With increasing life expectancy, a greater understanding of bone fragility in CP is paramount as fractures further limit mobility.

**Objective:** The influence of clinical factors and body composition on bone microarchitecture, as defined by trabecular bone score (TBS), bone mineral density (BMD) and fractures in adults with CP was determined.

**Design:** Retrospective cross-sectional study.

**Setting and Participants:** 43 adults (25 male) with CP of median age 25 years (interquartile range 21.4 - 33.9) who had dual-energy x-ray absorptiometry (DXA) imaging of the lumbar spine from a single tertiary hospital between 2005-March 2018. TBS was calculated retrospectively using TBS iNsight Software (version 3.0.2.0, Medimaps).

**Results:** 29/43 (67.4%) of adults were non-ambulatory and 15/43 (34.9%) had a prevalent fragility fracture. Low BMD (Z-score ≤-2) at the lumbar spine (LS) and femoral neck (FN) was seen in 51.2% and 40% respectively. 8/43 (18.6%) had partially degraded and 16/43 (37.2%) had degraded TBS. TBS correlated with BMD at the LS, FN and total body. TBS was significantly associated with arm and leg lean mass, with adjustment for age, gender and height (adjusted $R^2$ =0.18, p=0.042 for arm lean mass; adjusted $R^2$ = 0.19, p=0.036 for leg lean mass). There was no association between fat mass and TBS. There was no difference in TBS when patients were grouped by fracture status, anticonvulsant use, gonadal status or PEG feeding. TBS was lower in non-ambulatory patients compared with ambulatory patients (1.28 vs 1.37, p=0.019).

**Conclusions:** Abnormal bone microarchitecture, measured by TBS, was seen in more than 50% of young adults with CP. TBS correlated with both areal BMD and appendicular lean mass confirming the importance of maintaining muscle function for bone health in young adults with CP.

**40**

## Bone microarchitecture in transgender individuals on established cross-sex hormone therapy: A controlled cross-sectional study.

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**Background:** While sex steroids have complex effects on bone structure, experimental studies suggest that testosterone predominantly regulates trabecular, and estradiol, cortical bone[1]. The impact of cross-sex hormone therapy on bone in transgender individuals is based on insensitive technology and consequently, existing studies report conflicting effects[2]. A better understanding of bone effects is paramount given hormone therapy is typically started at a young age and continued lifelong. We hypothesized that estradiol therapy will increase cortical volumetric bone mineral density (vBMD) in male-to-female transgender individuals relative to male controls, while testosterone therapy will increase trabecular vBMD in female-to-male transgender individuals relative to female controls.

**Aims:** To assess cortical and trabecular vBMD in transgender individuals receiving cross-sex hormone therapy compared with controls.

**Methods:** High-resolution peripheral quantitative computed tomography (XtremeCT; Scanco Medical, Switzerland) of the radius and tibia was performed in a cross-sectional study of 39 male-to-female and 45 female-to-male transgender individuals on established hormone therapy (at least 12 months). Unpaired students t-test was used to compare transgender individuals with healthy age and birth-assigned sex matched controls.

**Results:** Distal tibial trabecular vBMD (p=0.011) was decreased in male-to-females compared to control males and cortical vBMD was also decreased (Table). Conversely, compared to female controls, female-to-male transgender individuals receiving testosterone therapy had increased distal tibial trabecular vBMD (p<0.001), with increased trabecular number (p<0.001) and decreased trabecular separation (p=0.008) but no significant difference in cortical vBMD. Similar findings were seen at the radius.

**Table:** Distal tibial bone microarchitectural parameters

| Distal tibia | MTF (n = 39) Mean ± SD | Control male (n = 57) Mean ± SD | *p* | FTM (n = 45) Mean ± SD | Control female (n = 79) Mean ± SD | *p* |
|---|---|---|---|---|---|---|
| *Cortical bone* | | | | | | |
| **Cortical vBMD (mg HA/cm³)** | **841.7 ± 39.4** | **861.5 ± 40.3** | **0.019** | 898.6 ± 34.4 | 892.5 ± 41.3 | 0.398 |
| *Trabecular bone* | | | | | | |
| **vBMD (mg HA/cm³)** | **189.7 ± 29.6** | **206.5 ± 32.2** | **0.011** | **202.3 ± 29.6** | **180.5 ± 35.2** | **<0.001** |
| Thickness (mm) | 0.088 ± 0.011 | 0.089 ± 0.015 | 0.615 | **0.093 ± 0.014** | **0.086 ± 0.017** | **0.038** |
| **Number (1/mm)** | **1.82 ± 0.29** | **1.96 ± 0.32** | **0.029** | 1.84 ± 0.25 | 1.78 ± 0.37 | 0.369 |
| **Separation (mm)** | **0.477 ± 0.088** | **0.436 ± 0.081** | **0.019** | **0.462 ± 0.068** | **0.500 ± 0.114** | **0.044** |
| *Total* | | | | | | |
| **Average vBMD (mg HA/cm³)** | **297.9 ± 49.0** | **326.3 ± 42.0** | **0.003** | **343.4 ± 50.6** | **308.7 ± 48.5** | **<0.001** |

vBMD = volumetric bone mineral density, SD = standard deviation, MTF = male-to-female, FTM = female-to-male, HA=hydroxyapatite

**Conclusion**: The findings in female-to-male (increased trabecular vBMD) and male-to-female individuals (decreased vBMD) support a role for testosterone in building trabecular bone. However, in contrast to our hypothesis, this study of transgender individuals did not confirm a role for estradiol in building cortical bone. Further well-designed prospective studies using sensitive methodology are required to assess long-term bone microarchitecture and fracture risk in transgender individuals.


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2. Singh-Ospina, N., et al., Effect of Sex Steroids on the Bone Health of Transgender Individuals: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab, 2017. 102(11): p. 3904-3913.


**41**

## The evolution of primary hyperparathyroidism in MEN 1


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**Background**

Multiple Endocrine Neoplasia type 1 (MEN 1) is an autosomal dominant neoplastic disorder resulting from inactivating mutations of the MEN1 gene. There is significant variability in phenotypic presentation, however the majority of patients with MEN 1 will ultimately develop primary hyperparathyroidism.

**Aim**

To determine the age-related progression and natural history of untreated primary hyperparathyroidism in MEN 1 patients.

**Methods**

A retrospective cohort study of 144 MEN 1 patients with a confirmed MEN 1 genotype undergoing biochemical screening for parathyroid function prior to parathyroidectomy. Data for serum calcium, parathyroid hormone (PTH), phosphate, magnesium and alkaline phosphatase (ALP) were analysed in 5-year age categories spanning birth to 50 years of age. The peak serum calcium in conjunction with the paired serum PTH concentration and the serum phosphate, magnesium and ALP concentrations were determined for each patient within each age category.

**Results**

Serum calcium was elevated in 81% of cases by 20-25 years. The mean serum calcium in this cohort reached a peak in the fourth decade of life. The corresponding serum PTH progressively increased over time, with the calcium:PTH homeostatic ratio showing a declining trend with advancing age, suggestive of progressively increasing parathyroid hormone resistance. Serum phosphate and ALP exhibited a decline from childhood levels to the normal adult range during the second decade of life in the majority of patients, though ALP showed a late rise from 40-44.9 years. Serum magnesium remained within normal limits in all age groups, and was stable over time.

**Conclusions**

The prevalence of MEN 1-related primary hyperparathyroidism increases during adolescence and early adulthood, with maximal serum calcium levels achieved by the fourth decade of life in the majority of patients. Advancing age was associated with evidence of increasing PTH resistance.

## 42

### Adjuvant endocrine therapy in non-metastatic breast cancer: an opportunity to ascertain bone health

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**Introduction:**

Due to superior efficacy and tolerability, aromatase inhibitors (AI) have replaced tamoxifen as the endocrine therapy of choice in post-menopausal women with breast cancer. However, its long-term use is associated with decreased bone mineral density and increased fracture risk. We aimed to assess if serum parathyroid hormone (PTH) may predict those at increased risk of aromatase inhibitor-associated bone loss.

**Methods:**

A retrospective analysis of all women diagnosed with non-metastatic breast cancer and commenced on endocrine therapy (anastrazole, letrozole or tamoxifen) at our tertiary referral breast service between August 2007 and June 2012 was conducted. Inclusion criteria included having a baseline dual-energy x-ray absorptiometry (DEXA) scan and blood test within 6 months of commencing endocrine therapy, and at least one follow-up DEXA scan prior to ceasing or switching endocrine treatment.

**Results:**

Of 232 patients started on endocrine therapy for non-metastatic breast cancer, 139 patients (113 AI; 26 tamoxifen) fulfilled the inclusion criteria. Median age was 65 (IQR 56, 68). After a median time of 3.5 years (IQR 3.0, 4.4) between baseline and final DEXA, tamoxifen use resulted in a significant increase in femoral neck T-score per year compared with AI use (0.078 versus -0.110, p=0.001). Baseline PTH was negatively associated with increased baseline femoral neck T-score on linear regression analysis (p=0.043), while no significant association was identified with vitamin D or calcium. A non-significant trend towards an improvement in the percentage change in lumbar spine BMD per year (0.964% versus -1.043%, p=0.087) and femoral neck T-score per year (-0.867 versus -0.111, p=0.740) was observed in women taking AI with a baseline PTH >5.90pmol/L compared with a PTH ≤5.90pmol/L.

**Conclusion:**

Parathyroid hormone measurement provides information regarding baseline bone health in women with non-metastatic breast cancer, but is of no predictive value in determining future bone loss following initiation of endocrine therapy.

## 43

### Mechanism of hypercalcaemia in patients with primary hyperparathyroidism: role of $1,25(OH)_2D$

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**Background** Hypercalcaemia in primary hyperparathyroidism (PHPT) is thought to be due to increased bone resorption, renal calcium conservation, and increased 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) production, which in turn increases gastrointestinal calcium absorption. Data regarding serum $1,25(OH)_2D$ concentrations in PHPT is, however, very limited.

**Aim** To examine mechanisms of hypercalcaemia in patients with PHPT.

**Methods** We studied 88 consecutive patients with PHPT diagnosed on fasting metabolic bone studies (based on venous blood and spot urine samples after overnight fast) at PathWest, QEII Medical Centre. Bone resorption was assessed using urine N-telopeptide/creatinine ratio (NTx) and urine calcium excretion calculated in umol/L of glomerular filtrate (GF). Serum $1,25(OH)_2D$ was measured using Liason chemiluminescent immunoassay, using the manfuacturer's reference range (48-190 pmol/L). Patients with eGFR <60 ml/min or on anti-resorptive treatment were excluded, leaving 73 patients for analysis.

**Results** Patients were predominantly female (79%), with median age 68.5 y. Median values for analytes (with IQR) were: ionised calcium 1.35 mmol/L (1.33-1.41), PTH 9.5 pmol/L (7.5-12), 25(OH)D 67 nmol/L (53-88nmol/L), $1,25(OH)_2D$ 132 pmol/L (107-164), NTx 40 nmol BCE/mmol creatinine (29-69) and urine calcium excretion 18 umol/L GF (IQR 13-37). Of 73 patients, 40 (55%) had reduced urine calcium excretion, 30 (41%) had increased NTx, and 12 (16%) had elevated serum $1,25(OH)_2D$. By regression analysis, PTH was positively correlated with $1,25(OH)_2D$ (r=0.306, p=0.008) and negatively correlated with 25(OH)D (r=-0.391, p=<0.001); $1,25(OH)_2D$ was positively associated with NTx (p=0.027) but not significantly correlated with ionized calcium.

**Conclusions** In this cohort of patients with PHPT, higher PTH was associated with lower 25(OH)D and higher $1,25(OH)_2D$. Higher serum $1,25(OH)_2D$ was associated with increased bone resorption but not with ionized calcium and was frankly elevated in only a minority of patients. Hypercalcaemia was predominantly attributable due to renal calcium conservation and increased bone resorption.

## 44

### Degraded Trabecular Bone Score is common in Young Adults with Premature Ovarian Insufficiency

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**Background:** Premature ovarian insufficiency(POI), gonadal failure ≤40 years, occurs secondary to medical(M-POI) or surgical(S-POI) therapies or is spontaneous(SP-POI). Bone loss and fractures are increased in POI. However, trabecular bone score(TBS), an indirect measure of spinal bone microarchitecture, has not been investigated in POI.

**Aim:** Prevalence of low BMD, degraded TBS and fractures in women with POI.

**Method:** Cross-sectional and longitudinal study of 70 POI women aged 20-50 years at a tertiary centre from 2005-2018. Medical history, including fracture and oestrogen replacement therapy(ERT) were obtained. Dual-energy X-ray absorptiometry(DXA) spine and femoral neck(FN) BMD and TBS(TBSiNsight v3.0.2.0) were measured. Low bone mass defined as Z-score<-2.0. Partially degraded and degraded TBS defined as TBS=1.20-1.35, and TBS<1.20, respectively. Analysis included logistic regression and linear mixed models.

**Results:** Women with SP-POI (n=25), M-POI (n=16) and S-POI (n=29) were identified. Median(range) age of POI diagnosis was 33(11-40)years with baseline DXA performed median 1(0-13)year after diagnosis. ERT was used by 68.8%[lower rates in M-POI women secondary to breast cancer(p=0.001)]. Prevalence of low bone mass at the spine and FN was 8.6%: SP-POI women had lower spine BMD, FN BMD and FN Z-score than S-POI women(p<0.05). Normal, partially degraded, and degraded TBS occurred in 51.4%, 41.4%, and 7.1%, respectively, and were similar across POI groups. Longitudinal analysis of 28 POI women[median follow-up 5(1-12) years], where 15/28 had continued ERT, revealed a decline in FN BMD[-0.006g/cm$^2$/year (95%CI -0.010, -0.002), p<0.05] but no significant change in spine BMD or TBS. Fractures occurred in 5/70(7.1%) women following POI onset, of which 4/5(80%) fractures occurred in bone with high trabecular component. No significant difference in BMD or TBS between fracture and non-fracture groups was observed.

**Conclusion:** Higher prevalence of abnormal TBS was observed in women with POI versus abnormal BMD Z-score. Further research is required to elucidate the role of TBS.

**45**

## Androgen receptor signalling promotes luminal differentiation in mammary epithelial cells

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**Introduction:** Androgens have long been used in advanced breast cancer therapy, though the basis for androgen receptor (AR) action in normal mammary epithelial cells (MECs) is poorly understood. Mammary epithelium is composed of three principal lineages: one basal lineage and two luminal sub-lineages: milk-producing alveolar MECs, and oestrogen receptor (ER)- and progesterone receptor (PR)-positive hormone-sensing MECs (HS-MECs). The prevailing view is that androgens act in breast cancer to inhibit the function of ER and PR, particularly in HS-MECs.

**Hypothesis/Aims:** With the hypothesis that androgens act beyond ER- and PR-expressing HS-MECs, this study aimed to assess the effect of AR activation using a non-steroid agonist, GTx-024, and inactivation through transgenic knockout on the differentiation of MEC sub-populations. Mouse MEC sub-populations were assessed by flow cytometry and immunohistochemistry for markers of MEC lineage specification (P63 - basal, ER – HS-MEC, ELF5 – alveolar). Differentiation potential of basal and luminal progenitors was assessed using *in vitro* Matrigel colony assays. Finally, association of AR with markers of MEC lineage specification was assessed in normal pre-menopausal breast tissue.

**Results/Conclusion:** AR was expressed in basal and luminal MECs. AR activation *in vivo* increased the proportion of luminal MECs and decreased the proportion of basal MECs. Conversely, inhibition of AR *in vivo* decreased the proportion of luminal MECs and increased the proportion of basal MECs. Concordantly, *in vitro* inhibition of AR increased basal but not luminal progenitor activity. A small population of AR-positive cells in a basal-to-luminal transition were evident in human breast lobules. Collectively, this data support a role for AR to promote luminal differentiation in basal MECs. This data provides a novel potential basis for the benefit of androgen therapy in breast cancer through the promotion of a luminal phenotype.

**46**

## Pathological analyses for the early detection of treatment-related neuroendocrine prostate cancer.

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Publish consent withheld

## 47

### The forkhead transcription factor FOXA1 directs an oncogenic androgen receptor cistrome in estrogen receptor negative breast cancer cells

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The estrogen receptor (ER) drives the majority (>70%) of breast cancers, a feature that requires the forkhead transcription factor FoxA1 to open chromatin for ER to bind DNA. In breast cancers that lack ER, the androgen receptor (AR) has been implicated as an oncogenic driver. In support of this concept, we have previously shown that AR genomically phenocopied ER in associating with FOXA1 and inducing a luminal gene expression profile in ER-negative breast cancer cells (1). Herein, we investigated the consequences of FoxA1 loss on AR signalling in this context. Transient knock-down of FoxA1 in the MDA-MB-453 cell line model inhibited cell proliferation but did not prevent AR from binding to DNA. Rather, the AR cistrome was substantially reprogrammed, with gain of AR binding at a large number of genomic loci. Genome-wide analysis of histone marks associated with active transcription (H3K4me1, H3K27Ac) demonstrated that the “AR reprogrammed” sites were pre-marked before the loss of FoxA1. Quantitative proteomic comparison of the chromatin-bound AR transcriptional complex in the absence of FoxA1 revealed an increased interaction with AP2α, a transcription factor associated with the AR cistrome in mouse epididymis. Stimulation of AR/AP2α interactions by FoxA1 knockdown was validated using proximity ligation assays in the MDA-MB-453 and MFM-223 cell line models. Transient knockdown of AP2α revealed this factor was required for AR to bind to loci associated with FOXA1 loss. Importantly, these AP2α-dependent/FoxA1-independent AR binding sites were associated with genes up-regulated in ER-positive (luminal) compared to more aggressive ER-negative (basal/mesenchymal) breast cancers. Overall, our findings suggest that loss of FoxA1 can result in a switch to AP2α-directed AR signalling, which is associated with reduced proliferative capacity and a more luminal phenotype in ER-negative breast cancers. These findings suggest the oncogenic activity of AR in this disease context may be dependent upon interaction with FOXA1.

1. Robinson et al, EMBO J, 2011

## 48

### Novel nuclear receptor targeted treatments for triple negative breast cancer

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Triple negative breast cancers (TNBCs), lacking estrogen (ER), progesterone (PR) or Her2 receptors, are a heterogeneous group, which have an overall poor outcome, being generally higher grade and often occurring in younger women. In contrast to ER positive cancers, there are currently no good biomarkers to predict outcome and no targeted treatments for TNBC. Hormone receptors play a pivotal role in breast cancer: ER and PR are favourable outcome markers, and ER-targeted treatments are standard of care. They are members of the nuclear receptor superfamily (NRs) of transcription factors, which mediates the signals of endogenous and exogenous ligands, including hormones, metabolic factors and xenobiotics. NRs have high therapeutic potential because their ligands are often lipophilic, passing easily into cells. Moreover, numerous synthetic analogues already exist targeting specific NRs, many of which are therapeutically approved in other clinical settings. We investigated NR gene expression in a large meta-dataset of TNBC and discovered that many of the NR family members are expressed in subsets of TNBC and that NR expression classified TNBCs into good and poor outcome groups. We screened a panel of drugs targeting the NRs that were most strongly associated with outcome in TNBC, to ask whether any could act as novel treatments combined with existing therapies. We showed that the fibrate class of lipid lowering drugs dramatically halted the growth of TNBC cells in our culture model, suggesting that these clinically approved drugs may have some benefit in treating TNBC. We also developed a precision medicine NR gene signature-based test, which predicts a patient’s risk of relapse when treated with existing therapies. This new test will assist clinicians when deciding the best treatment plan for their patients with TNBC and may allow some patients with low risk TNBC to be spared damaging cytotoxic chemotherapies.

## 49

### The *Rag1*$^{-/-}$ mouse: establishing links between obesity and prostate cancer

**Michelle Maugham, Patrick Thomas, Gabrielle Crisp, Esha Shah, Adrian Herington, Chen Chen, Laura Gregory, Colleen Nelson, Inge Seim, Penny Jeffery, Lisa Chopin**

Publish consent withheld

## 50

### Inherent prostate contractility is significantly increased in men with benign prostatic hyperplasia and is regulated by the peptide hormone oxytocin

**Sophie N Lee[1], Jenna Kraska[1], Melissa Papagiris[1], Ralf Middendorff[2], Stuart J Ellem[1], Michael Whittaker[3], Gail P Risbridger[1], Betty Exintaris[3]**

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Androgens are essential for prostate growth and development of the prostate gland but aberrant signalling significantly contributes to both malignant (prostate cancer) and benign (Benign Prostatic Hyperplasia (BPH)) disease in adult men. BPH affects 80% of men by the age of 80 and its aetiology beyond the involvement of androgens is poorly understood. There are two components; a static component (driven by androgens increasing stromal proliferation) and a dynamic component (changing contractility of the prostate). Based on previous literature, the objective of this study was to define the role and action of locally synthesised Oxytocin on endogenous (myogenic) contractility.

Tension recordings of myogenic tone were obtained from primary human prostate tissue collected from a clinically diverse cohort of men. Preparations were incubated with increasing concentrations of Oxytocin in the presence or absence of Atosiban (300nM; Oxytocin Receptor (OXTR) antagonist). Unstimulated preparations were incubated with Atosiban (300nM) alone.

The frequency of myogenic contractions was significantly ($p < 0.05$) greater in specimens from men with clinically diagnosed BPH compared to age- or volume-matched controls. Application of exogenous Oxytocin significantly ($p < 0.05$) increased the frequency of myogenic contractions in a dose dependent manner and was attenuated in the presence of Atosiban. Application of Atosiban on unstimulated sections significantly ($p < 0.05$) reduced the frequency of myogenic contractions by 34.9 ± 7.8%.

Utilizing our unique model of human prostate contractility, we have established that myogenic tone is significantly upregulated in men with clinically diagnosed BPH. Exogenous Oxytocin, acting through the OXTR, amplified the frequency of myogenic contractions. Antagonism of the OXTR in unstimulated tissue attenuated the frequency of contractions, suggesting endogenous production of Oxytocin contributes to myogenic tone. Collectively, our data indicates that Oxytocin is a regulator of myogenic tone and should be investigated further as a potential pharmacotherapy for BPH.

**51**

## Complications of Obesity in Men

**Gary Wittert[1]**

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The prevalence of overweight and obesity is similar in males and females aged 2 to 17 years but is higher in adult men (70%) than adult women (56%) (ABS 2011-2012). The proportion of men with severe and very severe obesity is increasing rapidly and obesity is now the second highest contributor to burden of disease in Australian men ahead of smoking (AIHW). The risk of obesity-associated comorbidities is higher in men who are socially disadvantaged, live in a rural or remote location, have limited functional health literacy or are migrants.

Most descriptions of the complications of obesity tend to focus on a 'generic human' with little attention to differences between men and women. Obesity has specific deleterious effects on sexual, reproductive and lower urinary tract function in men.

This presentation will focus on the effect of overall obesity, distribution of fat and presence of metabolic abnormalities associated with insulin resistance, and interaction with other obesity related co-morbidities, health related behaviours, occupational, and psychosocial factors on: (i) the hypothalamo-pituitary testicular axis and sex steroid physiology, sexual desire, erectile function, sperm quality and function and intergenerational transmission of chronic disease risk; (ii) lower urinary tract symptoms; (iii) diagnosis and progression of prostate cancer.

The implications for management at an individual and public health level will be discussed in the context of data relating to masculinity and health service utilisation.

**52**

## Androgen deprivation therapy for prostate cancer: mitigating adverse-effects.

**Ada s Cheung[1, 2]**

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Androgen deprivation therapy (ADT) is an effective treatment used in approximately 30% of men with prostate cancer, however is associated with multiple adverse endocrine effects due to profound hypogonadism. In addition to sexual dysfunction, fatigue and hot flushes, sarcopaenic obesity also significantly contributes to increased cardiovascular risk, and importantly, poor quality of life. Accelerated bone loss also occurs in association with an increase in fracture risk, hence optimization of musculoskeletal health in addition to preventing fat gain in men undergoing ADT is crucial. Adverse-effects can persist for many years after cessation of ADT. The role of exercise, and current and emerging anabolic therapies for muscle as well as various new strategies to prevent loss of bone mass in men undergoing ADT will be discussed. Given excellent cancer-specific survival in men with prostate cancer, additional strategies to improve quality of life including treatments for hot flushes, depression and sexual dysfunction must also be considered. Men undergoing ADT for prostate cancer require a multidisciplinary co-ordinated approach to care.

**53**

## Infertile update: male evaluation, management and outcome

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Male infertility is the sole or contributory cause of infertility in half of all couples. Good clinical practice demands evaluation of the male partner, as it may identify reversible or treatable conditions (e.g. gonadotrophin deficiency) and prevalent co-morbidities (e.g. testosterone deficiency, testis cancer).

Primary spermatogenic failure is the most common diagnosis, encompassing diverse pathogenic processes resulting in reduced sperm number, motility, morphology and/or function. A cause is evident in a minority, such as genetic defects (karyotypic anomalies, Y chromosomal microdeletions) or testicular damage from vascular, chemo/radiotherapy or infective agents. However, most are unexplained (idiopathic). Medical interventions for idiopathic infertility often lack an evidence base. Obstruction is the second most common of azoospermia, notably post-vasectomy or due to bilateral congenital absence of the vas that is associated with cystic fibrosis gene defects

Assisted reproductive treatments (ART), particularly intracytoplasmic sperm injection (ICSI), allow fertility in many otherwise untreatable male factor couples. ICSI is widely used and offers excellent fertility prospects with poor quality ejaculated or testicular/epididymal sperm. In azoospermic men with severe spermatogenic failure, sperm isolation is possible in 30-60% of cases, including post-chemotherapy or in Klinefelter's syndrome (wherein most sperm are euploid). Microsurgical dissection as opposed to random biopsy improve recovery rates.

A modestly increased rate of congenital malformations and karyotypic anomalies in IVF/ICSI offspring is recognised. Overall data on the health and development of IVF-conceived adult offspring is reassuring. However, data on the health outcomes of ICSI offspring for specific types of male infertility is extremely limited. Aside from Y microdeletions, the risk of vertical transmission of the male infertility phenotype via ICSI is unclear, however but subnormal semen quality appears more frequent in offspring. Follow up studies are ongoing and in future databases must include more data on male etiology.

**62**

## The effect of acute and chronic glucocorticoid exposure on the Thrombospondin-1:Osteocalcin ratio in humans

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**Background:** There is currently no readily measurable biomarker of glucocorticoid activity in clinical use. We have investigated a ratio between Thrombospondin-1 (TSP1), a matricellular protein and Osteocalcin (OCN), a non-collagenous protein secreted by osteoblasts, known to be up-regulated and down-regulated by glucocorticoids, respectively. The aim was to determine if the TSP1:OCN ratio was useful for the diagnosis of Cushing's syndrome (CS) and/or as a tool for therapeutic drug monitoring in patients on exogenous glucocorticoids.

**Material and Methods:** Patients with CS (n=19), asthma or giant cell arteritis on chronic prednisolone treatment (PRED, n=13), primary or secondary adrenal insufficiency (AI, n=16) and healthy controls (HC, n=20) were included in this prospective observational study. We measured plasma TSP1 and serum total OCN (by ELISA) across the day at 8am, 12pm and 4pm in patients with CS, in patients with AI taking their usual substitution therapy, in HC before and after a single 4 mg dexamethasone dose and in patients on PRED measured pre-dose at 8am and 4-hours post-dose at 12pm.

**Results:** Circulating concentrations of TSP1 in CS were higher ($P<0.0001$) and OCN were lower ($P<0.001$) compared to HC. A TSP1:OCN ratio of >73 diagnosed CS with a sensitivity of 95% and a specificity of 100%. The TSP1:OCN ratio in HC increased significantly after 4 mg dexamethasone at all time points ($P<0.001$) and increased during the day in AI patients after taking their hydrocortisone replacement therapy ($P<0.001$). Patients on PRED had a higher TSP1:OCN ratio as compared to HC at both 8am and 12pm ($P=0.002$ and $P=0.003$), but no significant change was found from pre- to post-dose.

**Conclusion:** The TSP1:OCN ratio in plasma/serum is a sensitive marker of total body glucocorticoid activity. It is high in patients on PRED and in CS, allowing the identification of patients with CS with high sensitivity and specificity.

**63**

## Human and mouse *FGF9* mutations affect male sex determination

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Disorders of Sex Development (DSDs) encompass a wide spectrum of conditions and often manifest with atypical gonads or genitalia. The majority of 46,XY DSD patients cannot be given an accurate diagnosis, which severely compromises their clinical management.

In the mouse, FGF9 is a key testis-determining gene which functions by repressing pro-ovarian signalling pathways such as WNT4/RSPO1 and FOXL2. This maintains sufficient SOX9 expression in the somatic cells of the embryonic gonad to drive Sertoli cell differentiation and ultimately, male testicular development. Loss of Fgf9 results in complete male to female sex reversal. Yet *FGF9* mutants that impair FGF9 homodimerization and FGF receptor binding have only been examined in skeletal defects.

Here we investigate the requirement of FGF9 dimer formation and receptor binding in testicular development, using two homodimer-defective FGF9 mutants from an established mouse model and a human 46,XY DSD patient.

In humans we have identified a 46,XY Gonadal Dysgenesis DSD patient with an amino acid substitution (D195N), previous studies indicated that the D195 residue is critical for the homodimerization of FGF9. The purified recombinant FGF9D195N protein showed reduced affinity for heparin, a property required for homodimerization. *In vitro* analysis showed reduced ability to induce Sertoli cell proliferation, which is required for normal testis development.

In mice, we examined the spontaneous mouse Elbow knee synostosis (Eks) which harbours a missense mutation in Fgf9 (N143T), that impairs FGF9 homodimerization. Examination of XY *Fgf9*$^{N143T/N143T}$ gonads showed delayed testes cord development and ectopic expression of the female Granulosa cell marker FOXL2 at the gonadal poles, indicative of XY sex reversal.

Our results suggest that FGF9 homodimerization and heparin binding are required for FGF9 function during testis development. As a disruption in one or both of these pathways causes sex reversal.

**64**

## Patients on dialysis have markedly abnormal cortical hip parameters by dual-energy X-ray absorptiometry

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Background: Patients with chronic kidney disease (CKD) have fracture rates above the general population and higher post-fracture mortality, yet bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) is less predictive of fractures in this population. HR-pQCT scans indicate a reduction in cortical thickness and increased cortical porosity in patients on dialysis, but it has limited accessibility and high expense. Cortical assessment of the hip using DXA has not been performed in this population.

Aim: To assess cortical parameters using BMD and advanced hip analysis (Lunar iDXA) in dialysis patients awaiting transplantation.

Methods: Normal ranges were first determined from 4,298 femur scans of women (mean age 72±7 years) and men (mean age 73±7 years) enrolled in the Dubbo Osteoporosis Epidemiology Study (DOES), and then compared with 65 women (age 46±13 years) and 90 men (age 49±13 years) receiving dialysis.

Results: Compared with older patients from DOES, women receiving dialysis had T-scores of -1.52±1.33 vs. -1.27±1.11 (non-significant), but significantly lower mean cortical thickness at the femoral neck (FN) of 2.53 ± 1.52 mm vs. 5.13±1.79 ($p<0.001$), and calcar of 3.26±1.20 mm vs. 3.82±1.2 ($p<0.001$). Buckling ratios (higher values indicate FN instability) were 8.01±4.57 vs. 3.97±1.68 ($p<0.001$). Men receiving dialysis had lower T-scores (-1.38±1.3 vs. -0.49±1.17, $p<0.001$), FN cortical width 2.91±1.98 mm vs. 5.84±2.32 ($p<0.001$) and calcar: 3.67±1.0 mm vs. 4.43±1.92 ($p<0.001$) compared with DOES men. Buckling ratios were 8.43±6.32 vs. 3.94±1.67 ($p<0.001$). Differences at the femoral shaft were non-significant in both men and women.

Conclusion: Stage 5D CKD has a profoundly adverse effect on cortical bone structure and strength. Cortical parameters measured non-invasively by DXA are markedly reduced in patients with CKD, even when compared to significantly older men and women, and should be assessed prospectively for utility in fracture prediction in this population.

**65**

## Polymorphisms in the 5α-reductase gene (*SRD5A2*) modulate serum testosterone, dihydrotestosterone and sex hormone-binding globulin, and polymorphisms in the aromatase gene (*CYP19A1*) modulate serum estradiol and luteinising hormone in men

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*Context*

Secretion of luteinising hormone (LH) by the pituitary stimulates testicular production of testosterone (T) and is under negative feedback control. T is metabolised to dihydrotestosterone (DHT) by 5α-reductase and to estradiol (E2) by aromatase. How activity of population variants in these enzymes impact on the male gonadal axis is unclear.

*Objectives*

We examined whether polymorphisms in 5α-reductase (*SRD5A2*) and aromatase (*CYP19A1*) genes predict circulating sex hormone concentrations.

*Participants and methods*

1,865 community-dwelling men aged 50.4±16.8 years. Early morning sera assayed for T, DHT and E2 using mass spectrometry, and sex hormone-binding globulin (SHBG) and LH using immunoassay. Two *SRD5A2* and eleven *CYP19A1* polymorphisms were analysed by PCR with genotyping successful in >98% of samples. Regression models were adjusted for age and cardiometabolic risk factors.

*Results*

*SRD5A2* polymorphism rs9282858 GA vs GG was associated with higher serum T (+1.5 nmol/L, P<0.001), lower DHT (-0.14 nmol/L, P=0.029) and higher SHBG (+3.3 nmol/L, P=0.001). Four *CYP19A1* polymorphisms were associated with higher serum E2 and lower LH: rs2470152 CC/CT vs TT (E2 +3.4 pmol/L, P=0.048; LH -0.47 IU/L, P=0.003), rs17703883 TT/TC vs CC (E2 +7.1 pmol/L, P=0.014; LH -1.62 IU/L, P<0.001), rs2899470 GG/GT vs TT (E2 +3.8 pmol/L, P=0.039; LH -0.54 IU/L, P=0.006) and rs11575899 II/ID vs DD (E2 +7.2 pmol/L, P=0.001; LH -0.78 IU/L, P<0.001). *CYP19A1* polymorphisms were associated with larger differences in circulating LH in men aged ≥65 years compared with <60 years. The two-copy haplotype rs10046=T, rs2899470=G, rs11575899=I, rs700518=G and rs17703883=T (prevalence 27.5%) was associated with higher E2 (+6.8 pmol/L, P=0.001) and lower LH (-0.61 IU/L, P=0.001).

*Conclusions*

A 5α-reductase polymorphism predicts circulating androgens and SHBG, while aromatase polymorphisms predict circulating E2 and LH. Further studies are needed to determine how these functional 5α-reductase and aromatase gene polymorphisms impact on male gonadal axis activity in reproductive and general health outcomes.

**67**

## High-dose pre-thyroidectomy cholecalciferol reduces postoperative hypocalceamia when stratified by PTH status a randomized double blinded placebo-controlled trial

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Introduction

Hypocalcemia remains the most frequent complication following thyroidectomy. We hypothesized that pre-operative supplementation with cholecalciferol may mitigate this risk.

Methods

This was a randomised, double-blind, placebo-controlled trial comparing cholecalciferol (300000 units) with matched placebo administered orally seven days prior to thyroidectomy. Primary outcome was incidence of post-operative hypocalcaemia (corrected calcium <2.1mmol/L). Secondary outcomes were supplementation requirements and length of hospital stay (LOS). Outcomes were further analysed with in a Cox regression model based on first postoperative day parathyroid hormone (PTH) levels.

Results

Out of 160 patients who were randomised, 150 underwent thyroidectomy and were analysed. The incidence of post-operative hypocalcaemia in the cholecalciferol group was 29%, compared to 38% in the placebo group (p=0.23). When stratified by post-operative PTH level, the hazard ratio for hypocalcemia was 0.56 (95% CI 0.32-0.98; p=0.04) in the cholecalciferol group. In 115 patients with normal PTH (≥10pg/mL), a lower rate of hypocalcaemia (10% vs 24%; p=0.05) and reduced requirement for calcium or calcitriol supplementation (8% vs 24%; p=0.02) was observed in the cholecalciferol group. In 35 patients with low-PTH <10pg/mL), rate of hypocalcaemia was lower (60% vs 93%; p=0.03) and LOS was shorter (2 vs 3 days; p=0.04) in the cholecalciferol group when compared to placebo. Cholecalciferol was well tolerated, and the rate of hypercalcaemia was not increased compared to placebo.

Conclusion

Pre-treatment with high dose cholecalciferol improves clinical outcomes following thyroidectomy. The low and normal post-operative PTH groups had different rates of hypocalcaemia, which blunted the magnitude of treatment effect when considered as a whole cohort, but significant reduction in morbidity was observed in both groups.

**68**

## A liver mediated mechanism for loss of muscle mass during androgen deprivation therapy

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**Introduction:** Androgen deprivation therapy (ADT) is a common prostate cancer (PCa) treatment but results in muscular atrophy. Progressive resistance training (PRT) can mitigate changes in body composition. Testosterone regulates protein metabolism through inhibiting the hepatic urea cycle, limiting amino acid nitrogen elimination. We hypothesize that ADT enhances protein oxidative losses by increasing hepatic urea production, resulting in loss of muscle mass. The effect of ADT and PRT on hepatic urea production has not been studied.

**Aim:** To investigate the effect of ADT on whole body protein metabolism and hepatic urea production with and without a home-based PRT program.

**Patients and Methods:** Hepatic urea production and whole-body protein metabolism were studied in 24 PCa patients before and after 6 weeks of ADT. Patients were randomised into either usual care (UC) (n = 11) or PRT (n = 13) starting immediately after their first ADT injection. The rate of hepatic urea production was measured by the urea turnover technique using $^{15}N_2$-Urea as a stable tracer. Whole-body leucine turnover was measured, and leucine rate of appearance (LRa), and index of protein breakdown and leucine oxidation (Lox), a measure of irreversible protein loss, was calculated.

**Results:** ADT resulted in a significant increase in hepatic urea production (from 427.6±18.8 to 486.5±21.3; $p < 0.01$). Net protein loss, as measured by Lox/LRa increased by 12.6±4.9% (p=0.02). Lox/LRa significantly increased in the UC ($p = 0.03$), but not in the PRT group (p=0.23). There were no significant differences between the UC and PRT arms in terms of hepatic urea production or protein turnover.

**Conclusion:** The suppression of testosterone to castrate levels during ADT increases protein loss and hepatic urea production. Thus, the loss of muscle mass during ADT may be due to greater nitrogen losses through the urea cycle.

**69**

## Saline suppression test parameters may predict bilateral subtypes of primary aldosteronism.

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**Background:** The saline suppression test (SST) serves to confirm the diagnosis of primary aldosteronism (PA) while adrenal vein sampling (AVS) is used to determine whether the aldosterone hypersecretion is unilateral or bilateral. An accurate prediction of bilateral PA based on SST results could reduce the need for AVS.

**Aim:** We sought to identify SST parameters that reliably predict bilateral PA.

**Methods:** The results from 121 patients undergoing SSTs at Monash Health from January 2010 to January 2018 including screening blood tests, imaging, AVS and histopathology results were evaluated. Patients were subtyped into unilateral or bilateral PA based on AVS and surgical outcomes.

**Results:** Of 113 patients with confirmed PA, 33 had unilateral disease while 42 had bilateral disease. In those with bilateral disease, plasma aldosterone concentration (PAC) was significantly lower post-SST, together with a significant fall in the aldosterone-renin ratio (ARR). The combination of PAC <300 pmol/L and a reduction in ARR post-SST provided 96.8% specificity in predicting bilateral disease. Eighteen out of 39 patients (49%) with bilateral PA could have avoided AVS using these criteria.

**Conclusion:** A combination of PAC <300 pmol/L and a fall in ARR post-saline infusion predicts bilateral PA with high specificity in patients undergoing the recumbent SST and may spare a significant number of patients from undergoing AVS. This will simplify the PA diagnostic process and reduce the demand for a costly and invasive procedure. This finding may be centre-specific, and therefore should be validated in an independent cohort.

**78**

## KEEP CALM and CRISPR: joining the genome editing revolution

**Paul Thomas[1]**

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CRISPR genome editing technology enables targeted genetic modification of virtually any species with unprecedented efficiency. For biomedical research, CRISPR technology offers unparalleled opportunities to develop accurate and sophisticated cell and animal disease models using virtually any species or cell type. Importantly, CRISPR can also be used to modify the human genome in vivo, enabling functional correction of disease-causing mutations for precision medicine applications.

Prof Paul Thomas is Director of the SA Genome Editing (SAGE) facility and the Genome Editing Laboratory (GEL) at SAHMRI. He was an early adopter of CRISPR technology and his lab has generated over 60 mutant mouse lines using CRISPR editing. Prof Thomas will provide an overview CRISPR editing and describe novel applications and unexpected outcomes of this relatively new technology.

**79**

## Transgenerational impacts of paternal stress on offspring behavioural phenotypes and stress-response

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Parental preconception exposures to non-genetic and environmental challenges including stress, imbalanced nutritional intake, and drugs of abuse, can impact offspring behaviour, health and risk for disease. There is growing evidence of these transgenerational influences evidenced from retrospective human studies and multiple animal models. While the maternal influence and the mode of transmission is well-studied, the extent of paternal inheritance remains poorly understood. Our lab has developed a mouse model of physical stress in which male breeders are provided corticosterone supplementation in drinking water (Short et. al., 2016). The resulting adult male F1 offspring display heightened levels of anxiety, with abnormal anxiety behaviours also observed in F2 generation. Interestingly, only juvenile female F1 offspring display abnormal patterns of fear extinction. More recent work has also revealed alterations in the drug-response and stress-responsivity of the F1 generation (Rawat et. al., *in press*). To begin to elucidate the origin of these shifts in offspring phenotypes, small RNA sequencing analysis of male breeders revealed significant changes in the expression levels of sperm-borne microRNAs. Consistent with transmission via the male germ line, expression of the paternally-imprinted gene *igf2* was down-regulated in the hippocampus of F1 and F2 male offspring despite being unaltered in F0 breeders. Finally, I will speculate on the potential mechanisms linking stress exposure to the changed molecular profile of sperm.

**80**

## Maternal glucose tolerance and pregnancy outcomes in sheep exposed to a simulated shift work protocol

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Epidemiological studies have suggested a small but significantly increased risk of miscarriage, preterm birth and fetal growth restriction when working night or rotating shift schedules during pregnancy. Shift workers are also at increased risk of developing type 2 diabetes and obesity, however the impact during pregnancy on maternal metabolic homeostasis is unknown. This study assessed the impact of simulated shift work exposure during pregnancy on maternal glucose tolerance and pregnancy outcomes in sheep. Following estrus synchronisation, 65 merino ewes were naturally mated then group housed in light controlled sheds. Ewes were randomly allocated to a control photoperiod (12h light: 12h dark), or to simulated shift work conditions whereby the timing of light exposure and food presentation was reversed twice each week throughout pregnancy. At week 7 and 19 of gestation, ewes were subjected to intravenous glucose tolerance test (0.25 g/kg). Simulated shift work exposure during pregnancy impaired glucose tolerance and increased glucose stimulated insulin secretion at week 7 but not week 19 of gestation. Gestation length was greater in simulated shift work exposed ewes with twin fetuses (+2.4 days, P=0.024). There was a treatment x litter size interaction effect on birth weight, with evidence of fetal growth restriction in singleton fetuses exposed to simulated shift work (-478g, P=0.016). These results have implications for the large number of Australian women currently engaged in shift work, and further studies are underway to determine the impact upon progeny health.

**81**

## A vegetarian diet is associated with different gut microbiota composition in early pregnancy

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The gut microbiota is influenced by multiple factors, including diet. In studies of non-pregnant groups, the composition of the gut microbiota in vegetarians has higher abundance of bacteria that are associated with anti-inflammatory properties and lower levels of pro-atherogeneic metabolites in the host. The impact of a vegetarian diet on gut microbiota in pregnancy has not been examined. This study evaluated the gut microbiota composition at 16 weeks gestation in all (N=9) vegetarian women and 18 omnivores matched for BMI, future gestational diabetes status and energy intake from faecal samples at 16 weeks gestation from the SPRING (Study of PRobiotics IN Gestational diabetes) RCT by 16S rRNA sequencing. Sequencing data was analysed with the QIIME and Calypso software tools. Vegetarian women reported significantly lower protein, sugar and saturated fat intake but higher polyunsaturated fat intake than matched omnivorous women. The beta diversity of the gut microbiota diversity was higher in vegetarian women but alpha diversity was not affected. The gut microbiota of vegetarian women showed higher abundance of the carbohydrate-fermenter *Bacteroides,* the butyrate producers *Roseburia* and *Clostridium* but lower abundance of the lactose-user *Collinsella* and of *Odoribacter*. Protein intake was negatively correlated with *Bacteroides* and *Roseburia* abundance whereas polyunsaturated fat intake was negatively correlated with *Collinsella* abundance but positively with *Bacteroides.* Saturated fat and sugar intake were negatively correlated with *Roseburia* abundance. Sugar intake was also negatively correlated with *Bacteroides* abundance but positively with *Odoribacter* abundance. In summary, this analysis describes differences in macronutrient intake between vegetarians and omnivores which are associated with changes to the abundance of specific genera in their gut microbiota. These changes are consistent with studies outside pregnancy suggesting that vegetarian compared to omnivorous diets result in increased *Bacteroidetes, Prevotella* and *Clostridium* species – bacteria which can engage in polysaccharide degradation and fermentation.

**82**

## Sex-specific placental androgen receptor isoform expression varies with maternal asthma and growth

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Androgen concentrations rise as gestation progresses in both the maternal and fetal circulations and may drive sex-specific differences in fetal growth, especially in the presence of an adverse environment. Males have increased birthweight compared to females in pregnancies complicated by asthma and we have proposed that males continue to grow under adverse conditions while females reduce growth due to a difference in androgen sensitivity. There are at least 20 different androgen receptor (AR) isoforms that may confer differences in androgen sensitivity. We have questioned whether the expression of these AR isoforms are detectable in the human placenta, whether they vary by cellular localisation, between the sexes, by birthweight, or in the presence or absence of maternal asthma. Placental protein (n=34 male, n=30 female) and mRNA (n=51 male, n=49 female) was used to identify AR protein isoform levels and downstream target gene expression. Protein and mRNA levels were analysed against multiple neonatal measurements to assess any relationships. Four known AR isoforms (AR-FL, AR-V1, AR-V7, and AR-45) were identified in the human placenta. Male placentae from asthmatic pregnancies had decreased nuclear AR-FL, 90 kDa, AR-V1, and AR-V7 protein expression, but increased AR-45 mRNA and protein. Nuclear AR-45 protein positively correlated with IGF1, IGF1R, and IGFBP5 mRNA expression. IGF1R, IGFBP3, IGFBP5, and VEGF mRNA was significantly higher in male placentae from asthmatic pregnancies. These differences in AR protein expression and downstream signalling targets may contribute to sex-specific differences in fetal growth in response to an adverse environment.

**83**

## Taft Lecture

**Susan Mandel[1]**

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Thyroid nodules are a common medical diagnosis, and are detected increasingly as incidental findings on imaging studies performed for other indications, rather than by physical examination. Associated with increased diagnostic imaging and fine-needle aspiration biopsy rates (FNA), the incidence of thyroid cancer has risen over recent years, mostly attributable to the diagnosis of small (<2cm) papillary thyroid cancers. Hence, this supports the contention that thyroid cancer may now be overdiagnosed, a patient dies with and not from the cancer, which drives the motivation for developing a rational approach to the management of thyroid nodules. Thyroid ultrasound (US) is fundamental for nodule evaluation. Sonographic pattern systems have been developed by several organizations and are used to assign nodules into several categories, each associated with a defined cancer risk. Based upon the assigned risk, nodule size cutoffs for FNA are recommended. Importantly, FNA is not required for a common pattern called spongiform which has a cancer risk of <2-3%. Once FNA is performed, cytology results are reported using the Bethesda system and ~20% of specimens are diagnosed as indeterminate (Bethesda 3 or 4) with an associated 15-30% cancer risk. The likelihood of cancer in a nodule with an indeterminate cytology diagnosis can be refined by both its sonographic appearance as well as by subsequent molecular testing of the specimen. Lacking a known single driver mutation, the different malignant histologies are associated with various mutations, translocations and gene expression changes. Hence, commercial tests reflect varied methodologies and testing targets. In addition, the validation of a molecular test as a predictor of malignancy or benignity relies on the nodule's baseline probability of cancer determined by the sonographic pattern and cytology diagnosis. Therefore, real world application of molecular testing may demonstrate different predictive values than validation studies. The clinician is confronted with multiple diagnostic options that are rapidly evolving.

**87**

## International Evidence Based Guideline for the Assessment and Management of PCOS

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**Objective:** To develop and translate rigorous, comprehensive evidence-based diagnosis, assessment and treatment guidelines, to improve the lives of women with polycystic ovary syndrome (PCOS) worldwide.

**Participants:** Extensive health professional and patient engagement informed guideline priority areas. International Society-nominated panels included consumers, paediatrics, endocrinology, gynaecology, primary care, reproductive endocrinology, psychiatry, psychology, dietetics, exercise physiology, public health, project management, evidence synthesis and translation experts.

**Evidence:** Best practice evidence-based guideline development involved extensive evidence synthesis and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework covered evidence quality, feasibility, acceptability, cost, implementation and ultimately recommendation strength.

**Process:** Governance included an international advisory board from six continents, a project board, five guideline development groups with 63 members, consumer and translation committees. The Australian Centre for Research Excellence in PCOS, funded by the National Health and Medical Research Council (NHMRC), partnered with European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine. Thirty seven organisations across 71 countries collaborated with 23 face to face international meetings over 15 months. Sixty prioritised clinical questions involved 40 systematic and 20 narrative reviews, generating 170 recommendations. Convened Committees from partner and collaborating organisations provided peer review and the guideline was approved by the NHMRC.

**Conclusions:** We endorse the Rotterdam PCOS diagnostic criteria in adults (two of clinical or biochemical hyperandrogenism, ovulatory dysfunction, or polycystic ovaries on ultrasound) excluding other causes. Where irregular menstrual cycles and hyperandrogenism are present, we highlight that ultrasound is not necessary in diagnosis. Within eight years of menarche, both hyperandrogenism and ovulatory dysfunction are required, with ultrasound not recommended. Ultrasound criteria are tightened with advancing technology. Anti-Müllerian hormone levels are not yet adequate for diagnosis. Once diagnosed, assessment and management includes reproductive, metabolic and psychological features. Education, self-empowerment, multidisciplinary care and lifestyle intervention for prevention or management of excess weight are important. Depressive and anxiety symptoms should be screened, assessed and managed with the need for awareness of other impacts on emotional wellbeing. Combined oral contraceptive pills are first-line pharmacological management for menstrual irregularity and hyperandrogenism, with no specific recommended preparations and general preference for lower dose preparations. Metformin is recommended in addition or alone, primarily for metabolic features. Letrozole is first-line pharmacological infertility therapy; with clomiphene and metformin having a role alone and in combination. Gonadotrophins and laparoscopic surgery are second line and in-vitro fertilisation third line in isolated PCOS. Overall evidence is low to moderate quality, requiring significant research expansion in this neglected, yet common condition. Guideline translation will be extensive including a multilingual patient mobile application and health professional training.

**91**

## Activation and suppression of microglia during early development similarly disrupt neuroendocrine function in the female rat.

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Microglia, the major brain immune cells, play an important role in brain development. Early-life immune challenges that lead to long-term increases in microglial numbers and activity, induce a wide range of neuroendocrine abnormalities. Microglia are also activated in response to early-life and adult diet high and fat, with overfeeding and obesity having chronic neuroinflammatory effects. We have shown that rodents suckled in small litters, where they have greater access to their mother's milk, maintain overweight throughout their life. These overweight rats have increased microglial proliferation and activation throughout the brain as early as postnatal day (P) 7, and these changes are maintained into adulthood. In females, these metabolic and neuroinflammatory changes are associated with a reduction in circulating gonadotropins, changes in ovarian follicle reserve, as well as changes in hypothalamic-pituitary-adrenal (HPA) axis activity, with reduced anxiety under non-stressed conditions, but increased central responsiveness to stress. Here, we investigated whether a suppression of microglia during early development, rather than its activation, can similarly induce neuroendocrine alterations in female rats. We used the *Cx3cr1-Dtr* rat model to investigate the long-term effects of acute microglial ablation on neuroendocrine end-points in females. Rat pups were administered with diphtheria toxin during critical time-points within the development of hypothalamic connectivity (P7) and immediately after its completion (P14). Our findings show microglial ablation on P7, but not P14, leads to a significant increase in adult body weight, reduction in circulating luteinising hormone (LH), reduction in basal release of adrenocorticotropic hormone (ACTH) and impacts on the ovarian follicle reserve. These findings suggest that both activation and suppression of microglia in early-life lead to long-term changes in neuroendocrine function impacting both the stress and reproductive axes. These data also indicate a critical time-window that occurs during hypothalamic development and when this region is more vulnerable to neuroinflammatory challenges.

**92**

## Metabolic Regulation of Stress Response Pathways and Chemoresistance in Colon Cancer is Mediated via B-Raf Dependent Inhibition of PPARγ

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Colon cancer is the third most common form of cancer and is the second most deadly. Initiator mutations are well characterised with over 70% of colorectal tumours containing APC truncation leading to dysregulated β-catenin signalling. Other mutations including B-Raf and K-Ras are common with more advanced stage tumours and further associated with chemo-resistance via unregulated pro-survival signalling. Other important regulators of proliferation and differentiation in the colon is mediated through PPARG, a master regulator of lipid metabolism. Interestingly, inhibition of PPARG in many cancer models suggest that it plays a role in inhibition of proliferation, while high levels of PPARG transactivation is associated with a well-defined cellular identity. Through use of the TCGA-COAD cancer dataset we have shown dysregulation of crucial PPARG regulated pathways associated with poor cancer prognosis. Furthermore, we have shown that B-Raf is an important negative regulator of PPARG with B-Raf mutants showing resistance to Rosiglitazone mediated cellular cytotoxicity and lipid accumulation. Inhibited lipid partitioning observed in B-raf mutant cells was shown to be normalised through PPARG agonism through an autophagy dependant pathway. Phosphatidylcholine metabolism was shown to be a PPARG regulated pathway and one key enzyme that was shown to be negatively regulated by PPARG was DHRS7B. DHRS7B has been shown to be important in the terminal steps of phosphatidylcholine synthesis while high expression is associated with poor cancer prognosis. DHRS7B overexpression resulted in up-regulation of pro-survival pathways including PI3K/Akt and MAPK, while important stress response genes including cJun and cFos were also shown to be up-regulated. Finally, DHRS7B knockout cells were shown to have decreased cellular growth and were significantly more susceptible to chemotherapy. These results further identify PPARG as a potent tumour suppressor in the colon. Co-treatment of PPARG agonists with commonly used chemotherapy agents promote a significant increase in cell cytotoxicity.

**93**

## SGLT2 inhibitor prevents hyperinsulinemia and restores pulsatile growth hormone secretion in obese pre-diabetic mice

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The sodium/glucose cotransporter 2 inhibitor (SGLT2i), which promotes urinary glucose excretion, is a novel drug for overt type 2 diabetes (T2D) patients. It has not been used for obese pre-diabetic individuals. Insulin and growth hormone (GH) are both important hormones in regulating glucose and lipid metabolisms but in opposite ways. Insulin promotes fat storage, while GH promotes lipolysis and fat oxidation. Hyperinsulinemia inhibits GH secretion, and physiological GH secretion in pulsatile pattern does not cause insulin resistance. In obese pre-diabetic individuals, hyperinsulinemia and reduced pulsatile GH secretion co-exist. The imbalance of two hormones contributes to fat accumulation and insulin resistance, leading to more severe hyperinsulinemia and hypo-GH, forming a vicious cycle. Whether SGLT2i treatment ameliorates hyperinsulinemia and hypo-GH in obese pre-diabetic individuals remains unknown. In this experiment, 8-week SGLT2i (dapagliflozin, 1mg/kg/d) treatment reduced hyperinsulinemia and partially restored pulsatile GH secretion in hyperphagia obese pre-diabetic melanocortin 4 receptor knockout (MC4RKO) mice (both sex, but GH measurement performed only in male mice, 18 weeks of age at the end of treatment). Lipolysis and lipid oxidation gene expression were increased in treated mice, whereas lipogenesis and inflammation gene expression were reduced, leading to decreased whole body fat mass. Along the amelioration in lipid metabolism, triglyceride content in liver and muscle was decreased and the insulin sensitivity was significantly improved. In addition, the glucose tolerance was improved in treated mice, with the increase in first phase glucose-stimulated insulin secretion from pancreatic beta cells. The treatment did not change food intake, daily activity or energy expenditure, but promoted lipid usage under a negative energy balance through increasing urinary glucose excretion. Therefore, by preventing hyperinsulinemia and restoring pulsatile GH secretion, SGLT2i improved glucose and lipid metabolisms in hyperphagia obese pre-diabetic mice. Our work highlights the potential application of SGLT2i in obese pre-diabetic individuals.

**94**

## Systemic administration of propeptides attenuates activin A-induced cachetic wasting

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Activin abundance in cancers promotes lethal 'cachetic' wasting of muscle, irrespective of tumour progression. In excess, activins A and B can hijack the myostatin signalling pathway, triggering a protein degradative pathway bias, ultimately resulting in muscle atrophy. In a recent study, we demonstrated that the co-inhibition of activin- and myostatin-induced signalling using virally (AAV) delivered propeptides (natural polypeptide inhibitors) could induce profound muscle hypertrophy in healthy mice. Additionally, the propeptides effectively attenuated localised muscle wasting in models of dystrophy and cancer cachexia. In this follow-up study, we sought to examine the ability of systemically administered propeptides to rescue activin A-induced cachetic wasting in mice. To address this, we first transplanted stable CHO cells expressing activin A (CHO:ActA) into the quadriceps of immunogenic mice. Establishment of CHO:ActA tumours elevated circulating activin A concentrations by 85-fold, and caused a 16% loss of starting body mass, and a 10% reduction in lean mass at 12 days post-implantation. In alignment with our previous findings, we found that CHO:ActA-induced muscle wasting could be attenuated using AAV delivered activin A propeptides. Significantly, here we show that systemic delivery of the activin A propetides can rescue CHO:ActA induced loss of body mass by 50%, lean mass by 70%, and protect from CHO:ActA mediated fat loss. It was also found that systemically delivered propeptides could protect the heart, liver, kidney and brown fat from activin A insult. This is the first study to demonstrate that systemic propeptide therapy can effectively attenuate chronic activin A insult in multiple tissues.

## 95

### Efficacy and safety of a fixed combination of insulin degludec/insulin aspart in children and adolescents with type 1 diabetes

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**Background:**

Insulin degludec/insulin aspart (IDegAsp) is the first soluble co-formulation that combines two insulin analogues.

**Aims and Objectives:**

To assess the efficacy and safety of IDegAsp administered once-daily (OD) plus meal-time IAsp for remaining meals in controlling glycaemia as assessed by change in $HbA_{1c}$ from baseline in a paediatric population.

**Methods:**

A 16-week, 1:1, open-label, parallel group, randomised, treat-to-target trial.

**Results:**

Children aged 1–5 years (n=82), 6–11 years (n=122), 12–17 years (n=158) with a diabetes duration of 1.6–6.0 years, $HbA_{1c}$ of 7.9–8.3% and fasting plasma glucose (FPG) of 8.1–8.6 mmol/L (all range of means at baseline) were randomised to receive either IDegAsp OD+meal-time IAsp for remaining meals (n=182) or insulin detemir (IDet)+meal-time IAsp (n=180). IDegAsp was non-inferior (limit 0.4%) to IDet for change in $HbA_{1c}$ (estimated treatment difference [ETD] –0.04 $[–0.23; 0.15]_{95\%CI}$), which was accomplished with a numerically lower basal insulin dose: IDegAsp+IAsp: 0.36 vs IDet+IAsp; 0.5 U/kg. ETD for FPG at Week 16 was 0.31 $(–0.70; 1.33)_{95\%CI}$. Rates of confirmed hypoglycaemia were 46.2 (IDegAsp+IAsp) vs 49.6 (IDet+IAsp) events/patient-years of exposure (PYE) (estimated ratio [ER] 0.95 $[0.76; 1.17]_{95\%CI}$). Rates of nocturnal hypoglycaemia were 5.77 (IDegAsp+IAsp) vs 5.40 (IDet+IAsp) events/PYE (ER 1.09 $[0.81; 1.48]_{95\%CI}$). Rates of severe hypoglycaemia were 0.26 (IDegAsp+IAsp) vs 0.07 (IDet+IAsp) events/PYE (ER 3.20 $[0.88; 11.66]_{95\%CI}$; p=ns). Rates of hyperglycaemic episodes with ketosis were 0.11 (IDegAsp+IAsp) vs 0.22 events/PYE (IDegAsp+IAsp) (ER 0.44 $[0.11; 1.74]_{95\%CI}$) and ETD for body weight SD scores was 0.07 $(0.02; 0.12)_{95\%CI}$. Adverse event profiles were similar.

**Conclusions:**

IDegAsp+IAsp was non-inferior to IDet+IAsp for change in $HbA_{1c}$, at a numerically lower basal insulin dose. There were no significant differences in rates of confirmed or severe hypoglycaemia between IDegAsp+IAsp and IDet+IAsp. IDegAsp+IAsp offers an alternative to basal–bolus treatment with one injection of combination insulin per day.

## 96

### Contemporary risk of menstrual and reproductive dysfunction in women with Type 1 diabetes: a population-based study

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**Background**: Type 1 diabetes mellitus (T1DM) is historically associated with perturbations of the hypothalamic-pituitary ovarian axis, leading to hypogonadism, amenorrhea and infertility. Given modern therapies and aims for tighter glycaemic control, few studies have re-evaluated reproductive abnormalities in T1DM.

**Aims**: To evaluate menstrual disturbance, contraceptive use and reproductive outcomes in women of reproductive age with T1DM, compared to age-matched women without T1DM.

**Methods**: A cross-sectional analysis was performed using data from the Australian Longitudinal Study in Women's Health, a large community-based study. Women from two different age cohorts were included in this study: women aged 18-23 years old who participated in Survey 1 (2013) born between 1989-1995, and those aged 34-39 years old who responded to Survey 6 (2012) born between 1973-1978. Univariable analyses were performed, followed by multivariable logistic regression analyses adjusting for significant and clinically relevant covariates.

**Results**: A total of 23,752 women were included, comprising 162 women with self-reported T1DM and 23,590 non-diabetic, age-matched controls. There were no differences between mean age (25.3 vs. 25.8 years, p=0.37), body mass index (25.9 vs. 25.0 kg/m$^2$, p=0.06) or age at menarche (12.8 vs. 12.8 years, p=0.59) between groups. Self-reported polycystic ovary syndrome was significantly higher in T1DM (14.2% vs 5.1%, p<0.001). Irregular menses (54.3% vs. 39.2%, p=0.008), menorrhagia (54.9% vs. 39.5%, p=0.006) and dysmenorrhea (58.0% vs. 40.7%, p=0.002) were more common in T1DM in univariable analyses. The increased risk of menstrual dysfunction persisted after adjustment for clinical and sociodemographic factors. No differences between modes of contraceptive use or pregnancy rates were observed between groups; however the adjusted risk of stillbirth was significantly higher in T1DM (OR 4.31, 95%CI 1.40-12.55, p<0.01).

**Conclusions**: Young women with T1DM are at increased risk of menstrual disturbance and adverse pregnancy outcomes. Screening for menstrual irregularities and pre-conception counselling in this cohort remains vital.

**97**

## Examination of stress hyperglycaemia and stroke outcomes using the stress hyperglycaemia ratio

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**Background**

Stress hyperglycaemia in non-diabetic patients admitted with stroke is associated with increased morbidity and mortality[1,2]. The stress hyperglycaemia ratio (SHR), defined as admission glucose divided by estimated average glucose derived from HbA1c, measures relative hyperglycaemia[3]. Using SHR as a marker of relative hyperglycaemia is a superior biomarker for critical illness outcomes compared to glucose[3].

**Hypothesis**

In patients admitted with acute stroke SHR may predict mortality and morbidity.

**Methods**

HbA1c and serum glucose was measured at time of hospital admission in patients with an acute stroke (n=443, 30.7% known diabetes). Endpoints were stroke severity at admission (either modified Rankin 5 at admission (mRS), GCS ≤10, or need for critical care) and poor outcome at discharge (either higher level of care, increased mRS, decreased GCS, stroke extension, haemorrhagic transformation or death). Outcomes were determined for quintiles (Q) classified for SHR and glucose.

**Results**

Odds ratios for Q5 (highest quintile) vs Q1 (lowest) were 2.94 (p<0.001) and 1.94 (p=0.039) for severity at admission for SHR and glucose respectively, and 2.16 (p=0.004) and 1.94 (p=0.039) for poor outcomes at discharge. Of those admitted with stroke severity (n=22), 25% of Q5 SHR had a poor outcome at discharge compared to 18% (n=18) for Q5 glucose. Identification of stress hyperglycaemia using SHR was independent of HbA1c (6.5+1.6 v 6.3+1.6, p=0.13 for Q1 and Q5 respectively), but not serum glucose (5.6+0.5 v 8.1+2.2, p<0.001).

**Conclusions**

While both SHR and glucose were associated with stroke severity and poorer outcomes at discharge, SHR was independent of HbA1c. Multivariable analysis enabling direct comparison of SHR and glucose is pending and will be presented. In acute stroke SHR may be a useful prognostic marker and guide individualised glucose lowering therapy targets which may improve stroke outcomes.

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**98**

## Comparison of triceps and suprailiac skin fold thickness versus body mass index and waist circumference in predicting body fat percentage and metabolic syndrome in young adults with diabetes

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Introduction:

Increased body fat percentage (BFP) and metabolic syndrome (MS) are major risk factors for cardiovascular disease. Triceps skinfold thickness (SFT) and suprailiac SFT are easier to measure than waist circumference (WC) or calculating body mass index (BMI) and if found to be predictive of MS and BFP, can be used to identify patients with high cardiovascular risk.

Aims:

To compare triceps and suprailiac SFT against WC and BMI in predicting BFP and/or MS in young adults with diabetes.

Methodology:

A sample of 1007 Sri Lankan adults with diabetes (age 20- 45 years) were randomly selected and their anthropometric measurements including SFT in triceps, biceps, subscapular and suprailiac areas were obtained. BFP was measured using bio impedance analysis. Correlation of BFP and components of MS with anthropometric measurements were tested using linear regression analysis.

Results:

Overall 42.3% were males. Mean age was 36.6 (±5.8) years. MS was present in 59.5% of patients. Mean BFP was 28.6% (±8.3%). Mean WC, BMI, triceps and suprailiac SFT were 87.2 cm, 24.6 kg/m$^2$, 15.6mm and 21.5mm respectively. BFP showed highest correlation with SFT at triceps (R=0.67, p<0.01) followed by BMI (R=0.4, p<0.01) and WC (R=0.22, p<0.01). Out of the SFTs triceps (R=0.67, p<0.01) and biceps (R=0.61, p<0.01) regions showed the strongest correlation followed by SFT of suprailliac (R=0.42, p<0.01) and subscapular (R=0.4, p<0.01) regions. All anthropometric measurements showed less correlation with MS than with BFP. Out of the SFTs, suprailiac SFT correlated most with MS (R=0.259, p<0.01) while WC (R=0.263, p<0.01) and BMI (R=0.256, p<0.01) showed similar correlation.

Conclusion:

Triceps SFT is a better indicator of BFP than BMI or WC. Suprailiac SFT is equally good as BMI and WC in predicting metabolic syndrome. Triceps and suprailiac SFT can be used as a quick screening tool to identify high risk young adults with diabetes.

**99**

## Plasma estradiol concentration is independently associated with longer leucocyte telomere length in older men

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*Context*

Telomeres protect chromosomes from damage, and shorter leucocyte telomere length (LTL) is a marker of advancing biological age. Men have shorter LTL compared with women, and experience a decline in circulating testosterone (T) with age. However the association between T and its bioactive metabolites, dihydrotestosterone (DHT) and estradiol (E2) with telomere length, particularly in older men, is uncertain.

*Objectives*

To determine associations of sex hormones with leucocyte telomere length (LTL) in older men.

*Participants and methods*

2,913 community-dwelling men aged 70-84, mean (±SD) 76.7±3.2 years. Early morning blood samples were assayed for T, DHT, E2 using mass spectrometry, and luteinising hormone (LH) and sex hormone-binding globulin (SHBG) using immunoassay. LTL was measured using PCR in triplicate with median values used for analysis, expressed as the T/S ratio. Cross-sectional analyses utilised multivariable linear regression with adjustment for age, cardiometabolic risk factors and prevalent cardiovascular disease (CVD).

*Results*

Average difference per decade of age was T -0.46 nmol/L, DHT -0.11 nmol/L, E2 -7.5 pmol/L, SHBG +10.2 nmol/L, LH +2.9 IU/L and LTL (T/S ratio) -0.065. E2 correlated with T/S ratio (r=0.038, p=0.039) and SHBG was inversely correlated (r=-0.053, p=0.004). After adjusting for age, cardiometabolic risk factors and prevalent CVD, E2 remained associated with T/S ratio (per 1SD increase in E2: coefficient 0.011, p=0.043). T, DHT and LH were not associated. When E2 and SHBG were simultaneously included in the model, E2 remained positively (coefficient 0.014, p=0.014) and SHBG inversely (coefficient -0.013, p=0.037) associated with T/S ratio.

*Conclusions*

In older men, neither T nor DHT are associated with LTL. E2 is independently associated with LTL and SHBG is inversely associated, implicating gonadal axis activity with biological age in this demographic group. Further research is needed to explore causality and the feasibility of interventions to slow biological ageing.

**100**

## Selective loss of levator ani and leg muscle volumes in men undergoing androgen deprivation therapy

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**Background:** Androgen deprivation therapy (ADT) for prostate cancer leads to adverse endocrine effects including a global loss of lean mass and sexual dysfunction. ADT leads to a selective loss of leg muscle function[1], however individual muscle volumes have not been evaluated. We aimed to assess in men undergoing ADT, the muscle volumes of levator ani, a highly androgen-responsive muscle in mice[2], and of lower-limb muscles.

**Methods:** We conducted a prospective case-control study involving 34 men newly commencing ADT and 29 age-matched prostate cancer controls. Levator ani and leg muscle volumes (litres) of primary muscles involved in walking (iliopsoas, quadriceps, gluteus maximus, gluteus medius, calf) were measured using MRI and quantitated using Slice-O-Matic software at 0, 6 and 12 months. Generalised linear models determined the mean adjusted difference (MAD) [95% confidence interval] between groups over time.

**Results:** Compared with controls over 12 months, men receiving ADT had a mean reduction in total testosterone level from 14.1 to 0.4nmol/L and demonstrated greater decreases in levator ani (MAD -0.005 litres [-0.007, -0.002], p=0.002, -16% of initial median value), gluteus maximus (MAD -0.032 litres [-0.063, -0.002], p=0.017, -5%), iliopsoas (MAD -0.005 litres [-0.001, 0.000], p=0.013, -5%) and quadriceps (MAD -0.050 litres [-0.088, -0.012], p=0.031, -3%). No significant differences were observed in gluteus medius and calf muscles.

**Conclusion:** Testosterone deprivation causes marked decreases in levator ani muscle, demonstrating that it's androgen responsiveness is evolutionarily conserved across men and mice. Further studies are required to investigate whether loss of levator ani muscle mass contributes to the profound sexual dysfunction seen in men on ADT. Consistent with previously reported functional deficits[1], ADT selectively decreases volume of muscles that support body weight. Future interventional studies aimed at reducing ADT-related sarcopenia and sexual dysfunction should evaluate the role of targeting these muscle groups, including the pelvic floor.


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## 101

## Gender-affirming hormonal therapies and surgical interventions among non-binary transgender individuals


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**Introduction:**

There is paucity in the literature regarding gender-affirming hormone use and surgical interventions in individuals identifying as gender non-binary. Currently, provision of such interventions is predominantly guided by our knowledge of the treatment of trans men and women. The objective of this retrospective study was to characterise the hormonal regimens, surgical interventions, and the medical comorbidities that may be exacerbated by hormone depletion and treatment in a cohort of gender non-binary individuals.

**Methods:**

All new referrals for gender dysphoria to an Australian primary care and a specialist endocrine clinic between 2013 and 2017 were analysed. 99 patients identifying as gender non-binary were included in the analysis. Baseline characteristics, medical comorbidities, gender-affirming hormonal and surgical therapies, and history of fertility counselling were recorded.

**Results:**

The median age was 25 years (IQR: 23, 29). Low rates of medical comorbidities were observed, with asthma (19.2%) and hypertension (11.6%) most frequently reported. 51.5% reported hormonal therapy use, which was greater in endocrine specialist clinics compared to in primary care (81.0% versus 43.7%, p = 0.003). A wide variety of hormonal regimens were observed, with 58.8% of patients taking testosterone-based therapies, 37.3% taking estradiol-based therapies, and 3.9% taking an anti-androgen alone. 68.6% of estradiol-based therapies involved the use of estradiol with an anti-androgen (either cyproterone acetate or spironolactone). 86.4% of patients on hormonal therapy had previously received fertility counselling. 14.1% of patients had previously undergone gender affirmation surgery, which included breast mammoplasty or augmentation, orchiectomy, and laryngeal surgery.

**Conclusion:**

Half of all gender non-binary patients reported hormonal therapy use, with most previously receiving fertility counselling. A variety of testosterone-based and estradiol-based therapies were observed, with a large proportion of estradiol-based regimens involving the use of estradiol with an anti-androgen. More prospective studies are required to better guide the prescription of gender-affirming treatments.

## 102

## Lifestyle changes in women with polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 4 to 18 % of reproductive-aged women with reproductive, metabolic and psychological co-morbidities. Lifestyle management (diet, physical activity and behavioural advice) is the first-line treatment for PCOS according to NHMRC-approved guidelines. This study aimed to update a previous Cochrane review which assessed the effectiveness of lifestyle treatment in improving reproductive, anthropometric, metabolic and quality of life factors in PCOS. Electronic databases (e.g. MEDLINE, EMBASE, PsycINFO etc), clinical trial registries and grey literature databases were searched. Fourteen studies were included with n=682 participants. Four studies compared combined dietary, exercise and behavioural interventions to minimal intervention while ten studies involved exercise only. Risk of bias varied with 7/14 having adequate sequence generation and clinician or outcome assessor blinding and 6/14 having adequate allocation concealment, complete outcome data and being free of selective reporting. There were no studies assessing the fertility primary outcomes of pregnancy, live birth and miscarriage. Lifestyle intervention provided benefits when compared to minimal treatment for secondary reproductive, anthropometric and reproductive outcomes. These included endpoint values for total testosterone (mean difference (MD) -0.17 nmol/L, 95% confidence interval (CI) -0.31 to -0.02), hirsutism or excess hair growth by the Ferriman-Gallwey score (MD -1.19, 95% CI -2.35 to -0.03), weight (MD -2.91 kg, 95% CI -4.20 to -1.63), waist circumference (MD -1.88 cm, 95% CI -3.23 to -0.53), fasting insulin (MD -1.96 µU/mL, 95% CI -2.78 to -1.14), total cholesterol (MD -0.21 mmol/L, 95% CI -0.33 to -0.09), low-density lipoprotein cholesterol (MD -0.35 mmol/L, 95% CI -0.48 to -0.22), high density lipoprotein cholesterol (MD 0.09, 95% CI 0.06 to 0.13) and quality of life (MD 0.39, 95%CI 0.16 to 0.61). Lifestyle intervention improves body weight, hyperandrogenism (high male hormones and clinical effects), cholesterol levels and insulin resistance in women with PCOS.

**111**

## Animal sex determination by genes, chromosomes and the environment

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Humans and other mammals have an XX female: XY male system of sex determination, in which a gene *SRY* on the Y chromosome kick-starts testis-differentiation in the embryo. The testis makes male hormones, which induce male development of the fetus. Birds have a different system of ZZ male: ZW female, in which dosage of a gene *DMRT1* on the Z controls sex; the ZW pair is not homologous to the mammal XY. Other reptiles, frogs and fish have different sex chromosome systems and we now know of many distinct sex determining genes which act at different points of the conserved sex determining pathway. This astonishing variety of sex determining genes and chromosomes is the result of the rapid birth and death of sex chromosomes.

Many reptiles and some fish have no sex chromosomes. Sex is determined by environmental factors such as temperature (TSD), through epigenetic changes whose nature has been a longstanding mystery. We work with an Australian dragon lizard, which has a ZW system driven by yet another sex determining gene. However, when it's hot, all the eggs hatch as females. We have used this system to investigate how TSD works. We found that the transcriptome of ZZ females contains upregulated stress markers and unique transcripts of two epigenetic markers. This suggests that temperature acts, via the stress pathway, to activate epgenetic modifications involved in male determination. Have we discovered the mechanism of TSD at last?

1. Quinn et al (2010) Science 316: 411
2. Holleley et al (2015) Nature 523:79
3. Deveson, Holleley et al (2017) Science Advances 3:e1700731

**116**

## Endocrine Therapy for Triple Negative Breast Cancer: Targeting the Androgen Receptor - When and How?

**Jennifer Richer[1]**

*1. University of Colorado, Aurora, CO, United States*

Androgen receptor (AR) protein is expressed in up to half of triple negative breast cancers (TNBC) and is often retained or even increased during progression to metastatic disease. AR+ TNBC are slow growing and respond relatively poorly to chemotherapy, yet AR is positively associated with node positive disease. In preclinical models, increased AR facilitates anchorage independent survival and activated AR increased mammosphere formation, tumor initiation, and other stem-cell like properties. Human AR+ TNBC xenografts in mice treated with anti-androgen and chemotherapy do not recur in vivo and AR+ TNBC patient derived xenografts (PDX) show significantly increased growth in response to AR agonist and decreased growth and tumor volume with treatment with antagonist. AR activity under anchorage independent conditions was studied in the presence or absence of AR agonist and antagonists by chromatin immunoprecipitation (ChIP)-seq and RNA-seq. Genes regulated by AR were identified and many confirmed at the protein level. AR chromatin binding and gene regulation increased in TNBC under anchorage independent conditions, and pathway analysis showed enhanced mTOR signaling, aryl hydrocarbon receptor activity, altered metabolism and production of immune-suppressive factors. Nuclear AR and classical AR-regulated genes such as KLK3 and FKBP5 were increased in TNBC PDX in vivo by activation of AR, as were specific tumor-derived immune-suppressive factors. We continue to identify markers of AR dependence and responsiveness to AR-targeted therapy in human TNBC and syngeneic mouse mammary carcinoma models in order to study the effects of endocrine therapy in immune-competent systems.

## 117

### Targeting the androgen receptor in estrogen receptor-α (ER) positive breast cancer

**Wayne Tilley**[1]

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Therapies that modulate estrogen receptor-α (ER) action have improved the survival of patients with ER-positive breast cancer, but resistance to treatment is a major clinical problem. Targeting alternative or parallel signalling pathways has potential to improve the efficacy and benefit of currently available treatments. For example, emerging data have shown that other sex hormone receptors may regulate the sites at which ER binds to DNA to suppress the oncogenic activity of ER in breast cancer. The ER, progesterone receptor (PR) and androgen receptor (AR) are ligand-activated transcription factors that bind DNA and interact with a host of other nuclear proteins to regulate gene expression. The cognate hormones and their receptors are structurally and functionally related. ERα is the prototype from which AR and then PR evolved. Our recent findings indicate that cross-talk between PR or AR with ER in breast cancer can influence response to ER-target therapies and disease outcomes. We recently showed that the PR can reprogram the ER DNA binding landscape towards genes associated with a favourable outcome. Similarly, the AR, which is expressed in the majority of breast cancers, can reprogram ER DNA binding to inhibit the growth of ER-positive tumours. Despite the potential benefit of targeting AR in ER-positive breast cancer, uncertainties remain. For example, AR antagonists as well as selective androgen receptor modulators (SARMs) that activate AR in breast cancer cells are currently being evaluated as potential therapeutic strategies. It is therefore critical that the mechanisms of crosstalk between ER and AR be fully elucidated and the effect on reprogramming of ER is tested in optimal preclinical models to better inform the design of clinical trials.

## 118

### New patient-derived models for rapid preclinical testing of castration-resistant prostate cancer

**Mitchell Lawrence**[1, 2], **Daisuke Obinata**[1], **Shahneen Sandhu**[2, 3], **Stephen Wong**[2], **Luke Selth**[4], **Laura Porter**[1], **Natalie Lister**[1], **David Pook**[1], **Carmel Pezaro**[1], **David Goode**[2], **Richard Rebello**[1], **Ashlee Clark**[1], **Melissa Papargiris**[1, 5], **Jenna Van Gramberg**[1, 2], **Hong Wang**[1], **Shivakumar Keerthikumar**[2], **Adrienne Hanson**[4], **Roxanne Toivanen**[2], **Heather Thorne**[2, 6], **Scott Dehm**[7], **Wayne Tilley**[4], **Richard Pearson**[2], **Ross Hannan**[2, 8], **Declan Murphy**[2], **Mark Frydenberg**[1], **Luc Furic**[1, 2], **Renea Taylor**[1, 2], **Gail Risbridger**[1, 2]

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*7. University of Minnesota, Minneapolis, USA*

*8. Australian National University, Canberra, ACT, Australia*

Over the last decade, new systemic treatments for advanced prostate cancer have extended patient survival, but raised new clinical challenges. Castration-resistant prostate cancer (CRPC) can be treated with second generation AR-directed inhibitors, such as abiraterone or enzalutamide; however, tumors inevitably develop diverse molecular and phenotypic mechanisms of resistance. To identify novel treatments, new models that accurately represent the changing clinico-pathologic features of CRPC are required. Unfortunately, there is a shortage of such models, due in part to the difficulty in propagating prostate tumours *in vitro* and *in vivo* compared to other cancers. To address these issues, we established the Melbourne Urological Research Alliance (MURAL) as part of the international effort to develop new patient-derived models of prostate cancer. We successfully established a new collection of PDXs from abiraterone and enzalutamide-resistant prostate cancer, which closely represent the features of the original patient tumours. These PDXs exemplify the heterogeneity of CRPC, exhibiting differing genomic features and distinct mechanisms of AR-driven resistance, including genomic structural rearrangements of the *AR* gene driving AR variant expression, known and novel *AR* mutations, and transformation to an AR-null phenotype. We used these PDXs, as well as explants and organoids derived from them, to test candidate treatments. This revealed the effectiveness of dual inhibition of ribosome biogenesis and function, downstream of c-MYC signaling. Together, this work provides both a new collection of contemporary patient-derived models and a promising therapeutic strategy to target a diverse range of CRPC.

1. Lawrence, et al., 2018, European Urology

## 119

### Towards improved treatment of prostate cancer: novel strategies to target the androgen receptor

**Luke Selth**[1]

*1. University of Adelaide, Adelaide, SA, Australia*

The androgen receptor (AR) is a major driver of prostate cancer and the primary therapeutic target. Recent approvals of potent second-generation AR-targeted therapies – including the AR antagonist Enzalutamide and androgen synthesis inhibitor Abiraterone – have improved outcomes for men with advanced prostate cancer, but are never curative. All AR-targeted therapies in clinical use aim to disrupt AR's ligand-binding activity, but we believe that this strategy is approaching a ceiling of

benefit for patients. In this presentation, I will describe our group's efforts to develop novel therapeutic approaches to target the AR, including strategies aimed at: i) inhibiting the AR amino-terminal domain; and ii) "reprogramming" AR activity such that it promotes a differentiative, rather than oncogenic, transcriptional program.

**120**

## Identification of immunogenic thyroid-specific self-peptides in Graves' disease

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Graves' disease is an autoimmune disorder characterised by pathogenic thyroid stimulating receptor (TSHR) antibodies. With a global prevalence of 0.5-2% and an annual incidence of 1 in 4000/year, it has significant physiological, emotional and financial burden [1,2]. Current treatment options do not target the underlying immune mechanism and are suboptimal with issues of inadequate remission, side effects and chronic pill burden [3]. Previous studies have examined T cell responses to autoantigens in the peripheral blood of Graves' disease patients, but results have been inconclusive as to the most immunogenic self-peptides[4-6]. To better understand the local autoimmune response, this study aims to identify the most immunogenic TSH receptor epitopes from thyroid tissue itself.

Human thyroid tissue was obtained from three Graves' disease patients undergoing elective thyroidectomy. In a novel technique, CD4+ T cells were isolated, expanded and cloned from thyroid tissue over 3-4 weeks. Reactivity of each clone towards 31 overlapping peptides of the TSHR extracellular domain was tested in the presence of matched antigen presenting cells using IFN-g ELISA.

Preliminary results in a HLA-DR DRB1*1301+ 1501+ patient with treatment-resistant Graves' disease shows that individual clones produce IFN-g in response to several TSHR peptide groups. Reactivity of identified epitopes will be confirmed in this patient's peripheral blood mononuclear cells, and peptide reactivity of clones derived from the other 2 patients will be tested. This study will provide important information regarding the thyroid-specific T cell immune responses in Graves' disease. Through delineation of the immunogenic peptides, we will develop a precise understanding of the immunogenic region of the TSHR autoantigen in Graves' disease. This will provide a foundation for further research into new diagnostic tests and treatment options.

**121**

## Teriparatide improves healing of medication-related osteonecrosis of the jaw: a placebo-controlled, randomized trial

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*5. Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia*

Medication-related osteonecrosis of the jaw (MRONJ) is an infrequent, but potentially debilitating, condition associated with antiresorptive therapy. Whereas MRONJ incidence can be reduced by optimising oral health, management of established cases remains challenging.

We conducted a prospective double-blind, placebo-controlled, randomised trial investigating the efficacy of 8 weeks teriparatide (20µg/day) treatment in 34 participants, with a total of 47 MRONJ lesions. Ten participants had multiple lesions. Most participants had at least moderate severity MRONJ, with 61.8% being stage 2 or 3, ie exposed bone associated with infection and/or complications such as fistulae or fracture. Participants were followed up for 12 months, with primary outcomes including the clinical and radiological resolution of MRONJ lesions. The Oral Health Impact Profile-14 (OHIP-14) questionnaire was used to assess quality of life. Baseline characteristics were similar between groups, with the mean time from MRONJ diagnosis being 12 months. Antiresorptive therapy was indicated for treatment of skeletal-related events in the setting of malignancy in the majority of participants (79.4%).

In the teriparatide arm, P1NP increased by 47% ($p < 0.001$) and fluoride-PET tracer uptake increased by 24% ($p = 0.008$). 10 of 22 (45.4%) MRONJ lesions in the teriparatide group resolved by 52 weeks compared with 8 of 24 (33.3%) lesions in the placebo group, with a greater rate of resolution of MRONJ sites with teriparatide (OR = 0.15 vs OR 0.40, $p = 0.013$). Bone mineral density and OHIP-14 scores were similar between groups. The incidence of adverse events was low and balanced between groups. Adverse events were mild in severity, including nausea, anorexia and musculoskeletal pain.

Therefore, teriparatide improves the rate of resolution of established MRONJ lesions, and represents an efficacious and safe treatment for MRONJ.

**122**

## Brown adipose tissue thermogenesis in polycystic ovary syndrome

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**Context.** Polycystic ovary syndrome (PCOS) is associated with increased obesity with a greater propensity to weight gain and a lack of sustainable lifestyle interventions. Altered brown adipose tissue (BAT) thermogenesis is a potential contributor to obesity in PCOS. BAT activity and modulation has not been studied in PCOS.

**Objective.** This observational study explored BAT thermogenesis and its associations in women with and without PCOS.

**Design.** A cross sectional sub-study nested within a randomized control trial

**Setting.** Community recruitment

**Patients or other participants.** Pre-menopausal women with (n=47, Rotterdam diagnostic criteria) and without (n=11) PCOS

**Intervention(s).** None

**Main outcome measure(s).** Cutaneous temperature recorded from supraclavicular (indicator of BAT activity) and upper arm regions using Dataloggers (SubCue, Calgary, Canada)

**Results.** Complete temperature data were available in 44 PCOS (mean age: 30.0±6.2, mean BMI: 29.3±5.5) and 11 non-PCOS (mean age: 33.0±7.0, mean BMI: 25±3) women. Women with PCOS had lower supraclavicular skin temperature compared to controls overall (33.9±0.7 vs 34.5±1, $p < 0.05$) and during sleep (34.5±0.6 vs 35.2±0.9, $p < 0.001$). In the PCOS group, supraclavicular skin temperature overall and over sleep and waking hours correlated inversely with testosterone ($r = -0.41$ $p < 0.05$, $r = -0.485$ $p < 0.01$ and $r = -0.450$ $p < 0.01$ respectively). Testosterone levels explained approximately 15%, 30% and 20% of the variability in supraclavicular skin temperature overall and over sleep and waking hours in women with PCOS, respectively.

**Conclusion.** Women with PCOS have lower BAT activity compared to controls. BAT thermogenesis is negatively associated with androgen levels in PCOS.

**123**

## The impact of Multiple Endocrine Neoplasia Type 1 on fertility in a multigenerational cohort

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Background

Literature concerning the impact of Multiple Endocrine Neoplasia Type 1 (MEN 1) on fertility is limited to case reports. We examined the intrinsic impact of MEN 1 on fertility in a multigenerational MEN 1 cohort.

Methods

All *MEN 1* positive (*MEN 1*$^+$, $n$=63) and *MEN 1* negative (*MEN 1*$^-$, $n$=75) descendants of a common founder born between 1825 and 1951 were included. Review of birth, death, marriage and medical records provided data on date of birth and death, gender, MEN 1 status and the number of pregnancies and children per parent.

Results

Compared to *MEN 1*$^-$ parents, *MEN 1*$^+$ parents had more children (RR 1.32, 1.04-1.66) and live births (RR 1.36, 1.15-1.61) with no excess of stillbirths (RR 1.19, 0.23-6.08). Compared to the era-matched Tasmanian fertility rate, *MEN 1*$^+$ parents had more children (4.87±4.11 *vs* 3.40±0.61, $p$=0.006), whereas *MEN 1*$^-$ parents had similar numbers of children (3.67±3.27 *vs* 3.36±0.62, $p$=0.55). *MEN 1*$^+$ parents had a similar number of *MEN 1*$^+$ and *MEN 1*$^-$ offspring (2.1±1.9 *vs* 2.5±2.3, $p$=0.31) with observed *MEN 1*$^+$ offspring frequency consistent with that expected for autosomal dominant MEN 1 ($p$=0.23). Indirectly assessed miscarriage rate was similar between *MEN 1*$^+$ and *MEN 1*$^-$ mothers ($p$=0.77). Clinically overt pituitary disease reduced *MEN 1*$^+$ kindred member likelihood of parenthood (33% *vs* 97%, $p$<0.001).

Conclusion

MEN 1-related pathology directly impaired the reproductive potential of a subset of individuals, but there was no adverse impact of MEN 1 on cohort fertility overall.

**124**

## Optimizing care for patients with primary aldosteronism: putting research into practice

**Jun Yang[2, 3, 1], Jimmy Shen[3, 1], Nicholas YN Chee[3], James CG Doery[4], Kay Weng Choy[4], Winston Chong[5], Peter J Fuller[3, 1]**

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*4. Pathology, Monash Health, Clayton, Victoria, Australia*

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**Background:**

Primary aldosteronism (PA) is the most common endocrine cause of hypertension, affecting 5 – 10 % of hypertensive patients and up to 30% of those with resistant hypertension. Early diagnosis is crucial as it is potentially curable. Unfortunately very few centres have established protocols or expertise in its diagnosis and management.

**Objectives:**

Building on our expertise in aldosterone research, our aim was to develop centre-specific guidelines for the diagnosis and management of PA with an evidence-based pathway of care.

**Methods:**

An extensive literature review of PA was performed. The information was collated into a centre-specific protocol after consultation with all stakeholders involved in the pathway of care, including endocrinologists, radiologists, chemical pathologists and endocrine surgeons. The PA protocol was introduced in January 2010 and education sessions were delivered to both tertiary and primary care sectors. Outcomes were audited in 2018 to evaluate the impact of the protocol on clinical practice.

**Results:**

The number of cases of PA diagnosed at Monash Health, Victoria's largest health service, increased from 2 per year in 2011-12 to 31 in 2016. The increased demand led to the establishment of the Endocrine Hypertension Service which reviewed 87 patients in its first year of operation from May 2016 and diagnosed 62 cases of PA. Of these, 14 were surgically cured and 37 experienced clinical improvement on targeted PA therapy. The engagement of a dedicated interventional radiologist to perform all of the adrenal vein sampling led to an increase in procedural success from 30 – 40% pre-2011 to almost 100% in 2018.

**Conclusion:**

An evidence-based center-specific protocol developed from PA research has been successfully implemented in clinical practice, leading to increased diagnoses and improved patient care. Further research to evaluate local PA community prevalence and improvements in diagnosis can now be embedded into the Endocrine Hypertension Service.

**125**

## Androgen actions in ovarian health and pathogenesis

**Kirsty Walters**[1]

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Androgen actions mediated via the androgen receptor (AR) are well established as playing a vital role in male reproductive development and function, but the biological role of androgen actions in female reproduction has only recently started to be unravelled. Deciphering the specific mechanisms by which AR-mediated actions impact on ovarian function has been hindered by ambiguity of pharmacological investigations relying on aromatizable androgens that also act via estrogen receptors. Using novel global and cell-specific female AR knockout mouse models (ARKO) we confirmed a role for AR-mediated androgen actions in regulating ovarian function and maintaining optimal female fertility. Furthermore, observational human studies and animal experiments provide substantial evidence of a role for AR-mediated androgen actions in the origins of the most frequent endocrine condition in women, polycystic ovarian syndrome (PCOS). Hyperandrogenism is the most consistent PCOS characteristic, however it is unclear if androgen excess, is a cause or a consequence of PCOS. We combined a hyperandrogenised PCOS mouse model with global and cell-specific AR ARKO mice to uncover the sites of androgen action that mediate the development of the PCOS phenotype. These studies proved that global loss of AR actions (ARKO) protects females from the induction of PCOS features. Furthermore our findings highlighted the importance of non-ovarian (neuroendocrine) AR-mediated androgen actions in the origins of PCOS, as a neuron-specific loss of AR signaling protected against the development of most PCOS traits. In concert, these findings illuminate the key roles of AR-mediated androgen actions in optimizing ovarian function and female fertility, as well as providing evidence to support excess androgen receptor (AR)-mediated actions in the brain, as major drivers of the mechanisms underpinning the development of PCOS.

**138**

## Androgen Receptor in Breast Cancer: potential utility as a prognostic indicator or therapeutic target in breast cancer

**Jennifer Richer**[1]

*1. University of Colorado, Aurora, CO, United States*

Androgen receptor (AR) has long served as a therapeutic target for treatment of prostate cancer and drugs exist that either bind to AR directly and serve as agonists or antagonists, or work by inhibiting enzymes involved in androgen synthesis. In breast cancer (BC), AR is even more widely expressed across subtypes than estrogen or progesterone receptors (ER and PR) as it is expressed in a portion of triple negative BC (TNBC) (~20-50%), HER2+ disease (~60%) and ~91% of ER+ tumors. The role of AR in the various subtypes of BC is controversial and context dependent, varying with hormonal milieu (menopausal status) of the patient, levels of the other steroid receptors in tumors, treatment, and disease progression. While preclinical models demonstrate that optimal ER activity is dependent on nuclear AR, ligand activated AR can also inhibit ER activity since in the presence of their cognate ligands, the two receptors compete to regulate some of the same genes. Tamoxifen has partial agonist activity that increases AR, and the selective pressure of tamoxifen or estrogen deprivation (aromatase inhibitors) in post-menopausal women with BC can lead to increased dependence on AR. AR upregulates the growth factor receptors HER2 and HER3 and also upregulates amphiregulin, a ligand for EGFR. In TNBC, AR can substitute for ER, drive the "luminal AR/ LAR" phenotype and support the survival of such tumors. AR regulates genes involved in tumor metabolism as well as anti-stress, pro survival genes/proteins. AR+ TNBC are slower growing, but consequently respond relatively poorly to chemotherapy

and AR is positively associated with node positive disease. This lecture will summarize recent clinical trials with various AR modulating drugs as well as agents that inhibit androgen synthesis.

**139**

## Bone Health During Endocrine Therapy for Breast Cancer

**Mathis Grossmann**[1]

*1. University of Melbourne Austin Health, Heidelberg, VIC, Australia*

This presentation will focus on the assessment and management of bone health in women with oestrogen receptor-positive breast cancer receiving endocrine therapy, and is based on a 2018 position statement of the Endocrine Society of Australia, the Australian and New Zealand Bone & Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia.

**140**

## A renaissance in therapies for hormone receptor positive breast cancers

**Elgene Lim**[1]

*1. Garvan Institute of Medical Research and The Kinghorn Cancer Centre, Darlinghurst, NSW, Australia*

Hormone receptor positive (HR+) breast cancer constitute the largest subtype of breast cancers. With the advent of new high throughput research technologies, there has been a profound acceleration in the identification and understanding of resistance mechanisms to endocrine therapies. The landscape of treatment options for HR+ breast cancers have changed dramatically in the last 5 years with the introduction of molecular targeted therapies such as CDK4/6 inhibitors, and as a result, changing the natural history of this breast cancer subtype. New treatment algorithms of combination therapies that are more complex than ever before have emerged, and so has the emergence of new patterns of treatment resistance.The strategies to combat these cancers resistant to combination therapies are not yet defined, and represent the next major clinical challenge in HR+ breast cancer. I will discuss new treatment strategies, how the molecular landscape of endocrine therapy resistance may affect the response to CDK4/6 inhibitors, and novel strategies that are required to overcome the next wave of treatment resistance in HR+ breast cancer.

**141**

## Fertility considerations for breast cancer patients

**Kate Stern**[1]

*1. Melbourne IVF, East Melbourne, Vic, Australia*

For young women, a diagnosis of breast cancer brings additional trauma regarding the risk of infertility and implications for having a family.

Provided the diagnosis is associated with a good prognosis, these young women should expect to be able to safely have children after completion of their treatment, without an adverse impact on prognosis

Therefore all patients in the reproductive age should be counselled about:

1. The risk to fertility from the cancer treatment and associated delay before being able to conceive
2. The implications of having a genetic risk for, or a genetic diagnosis of, breast cancer, where relevant, and the options available
3. The options available for both fertility preservation and ovarian protection prior to treatment
4. The options available for having a baby safely after treatment

Close collaboration between oncology and reproductive medicine teams allows optimal and timely referral and opportunities for discussion, treatment and follow up.

**142**

## The interplay between insulin resistance and β-cell dysfunction

**Rohit Kulkarni**[1]

*1. Joslin Diabetes Center, Boston, MA, United States*

Insulin resistant states such as obesity are generally characterized by an increase in beta cell mass as a form of compensation to maintain normoglycemia in mammals. The factors that promote the growth of beta cells and the mechanisms and signaling pathways that mediate these effects have been a focus of investigation for several decades. This presentation will include a discussion on inter-organ cross talk and the role of circulating factors, such as Serpinb1, that are able to enhance beta cell proliferation and mass in insulin resistant states. The discussion will include the role of growth factor signaling (e.g. insulin and insulin-like growth factor 1) proteins and the emerging importance of *epitranscriptomics* (RNA methylation) in the regulation of islet cell biology and metabolism with therapeutic significance.

## 152

### Glucocorticoid receptor isoform regulation: Unfolding the mechanisms behind glucocorticoid induced anti- inflammatory actions

**Zarqa Saif[1], Vicki L Clifton[1]**

*1. Mater Medical Research Institute, Woolloon Gabba, Brisbane, QUEENSLAND, Australia*

***Introduction:***

Glucocorticoids mediate anti-inflammatory effects through the ubiquitously expressed glucocorticoid receptor (GR). The tissue-specific inhibition of proinflammatory pathways by glucocorticoids may be conferred by the expression of different GR isoforms regulated by GR gene exon 1 promoter variants. In the human placenta we have shown sexually dimorphic differences in expression and localization of several GR isoforms with increased expression of GRα-A, GRα-C3 and GRα-D3 in female placentae which was associated with anti-inflammatory glucocorticoid effects. Conversely male placentae had high GRβ, GR-A and GR-P expression with increased pro-inflammatory gene expression in vivo. We hypothesised that selective regulation of GR isoforms was through differential upregulation of GR Exon 1 regions which induces a shift from anti-inflammatory actions of glucocorticoids to upregulation of proinflammatory pathways.

***Methods:*** BeWo cells were treated with hydrocortisone, dexamethasone or budesonide (1µM) or LPS (1ug/ml) alone or in combination for 4 and 24 hours. Protein lysates were analysed using western blot while the GR exon 1 variants mRNA was measured using QRT-PCR.

***Results:*** Glucocorticoid treatment resulted in an increased expression of GRα-A, GRα-C3, GRα-D1 and D3. A significant increase in GRαD1 protein was observed at 4 hours with LPS treatment. However, LPS and glucocorticoids combination resulted into increased GRαD3 expression. Changes in GR isoform expression were associated with upregulation of selective GR promoters. LPS stimulation resulted in a 15-fold induction of GR promoter 1E region compared to control treatment. Budesonide treatment selectively upregulated exon 1J and 1I promoter regions.

***Conclusion:*** Selective switching between GR isoforms following an inflammatory challenge suggests a specific role for GRα-D1 in promoting a proinflammatory response. The observed change in GRα-D1 expression may be associated with increased Exon1 E expression. The increased expression of Exon 1E and GRα-D1 may be responsible for the shift from glucocorticoid induced anti-inflammatory effects to the activation of proinflammatory pathways.

## 153

### Genome Wide Association Study Identifies 5 Novel Loci Associated with Polycystic Ovary Syndrome (PCOS) in Caucasian Women

**Kharis Burns[2, 1, 3], Benjamin H Mullin[2, 4], Purdey Campbell[2], Suzanne J Brown [2], Ee Mun Lim[2, 3, 5], Narelle Hadlow[3, 5], John Joseph[5], Timothy Spector[6], Gerald F Watts[3, 7], Scott G Wilson[2, 4, 6], Bronwyn GA Stuckey[2, 1, 3]**

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PCOS is the most common reproductive endocrinopathy, affecting 5-10% of women. Familial inheritance patterns suggest a genetic basis, however polymorphisms identified through GWAS do not explain the entirety of PCOS aetiology. Additionally these investigations have been conducted in ethnically diverse women and do not differentiate between lean and obese phenotypes.

PCOS-affected Caucasian subjects, defined using NIH criteria, were recruited through clinics and study advertisement. Relative to local population phenotypes, a higher proportion of lean subjects was included. Blood was collected for DNA extraction, genetic analysis and hormonal profiling, including gonadotrophins, androgens, fasting glucose and insulin.

Genotyping was performed using the Illumina HumanOmniExpress array. Imputation was performed using the Haplotype Reference Consortium panel. Control subjects were sourced from the TwinsUK cohort. A case-control GWAS was performed in 305 PCOS-affected women and 4986 controls. Analysis was performed using GEMMA software (MAF threshold 0.05).

Approximately one third (30.2%) of the affected population was of lean/normal BMI (<25kg/m$^2$). An elevated LH:FSH ratio was seen in 30.4% and 68.5% were insulin resistant (HOMA-IR>1.8). Five novel loci were identified for association with PCOS at genome-wide significance level ($p<5x10^{-8}$). These loci have not previously been linked with PCOS, though some have been implicated in gonadotrophin release, infertility, insulin and glucagon metabolism, features which may be abnormal in PCOS. All SNPs are intronic, hence may be involved in the regulation of genes implicated in PCOS. Directionally consistent significant ($p<0.05$) associations were noted for two signals previously identified in Caucasian women, rs7563201 within the gene *THADA*, and rs1351592, within *ERBB4/HER4*.

Identification of these novel SNPs provides further evidence for a genetic aetiology in PCOS. The function of these newly elucidated loci may be complex, varying from direct effects on the aetiology of PCOS-associated traits, including metabolic derangement and infertility, to the involvement in regulation of other potential contributory genes.

## 154

## Dihydrotestosterone (DHT) enhances wound healing from severe burn injury through regulating inflammatory response

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Rationale: In treatment of childhood burns, synthetic androgens are reported to better maintain lean body mass, with reduced hypermetabolic responses characteristic of severe burns injury and shortened healing time for severe burns injury. These findings are contrary to experimental evidence in rodents that androgens inhibit skin wound healing. The aim of this study therefore is to identify the role of androgens in complex severe burn injury, in particularly to determine the impact of androgens on local healing process and on systemic burns-induced hypermetabolic state.

Methods: A severe burn injury mouse model (40% TBSA, full thickness) was established featuring increased circulating corticosteroid, energy expenditure and lean body mass loss. Using this experimental model, mice underwent subdermal insertion of silastic implants containing the pure DHT or placebo and wound healing rate was observed over 21 days. Body weight, energy expenditure and circulating cytokines (Multiplex Immunoassay System) were measured. Spleen histology was analysed and immune cells enumerated by flow cytometry. Local wound healing process including inflammation, re-epithelialization, cell proliferation and collagen deposition were assessed using histology, immunohistochemistry and RT-PCR.

Results: DHT treatment significantly enhanced wound healing over 14 days with better maintained body weight, whereas DHT treatment had no effect on burn-induced hypermetabolism. In the control group, injured mice showed chronic inflammatory response with significantly increased number of splenic monocytes and wound macrophages at day 14. In comparison, DHT treatment accelerated inflammatory responses with early increase of circulating inflammatory cytokines and number of splenic monocytes as well as wound macrophages. Furthermore, DHT promoted cell proliferation and collagen deposition over wound healing process.

Conclusion: DHT accelerate wound healing by regulating inflammatory response but not through the hypermetabolism.

**155**

## Increased nerve density around papillary thyroid cancers and primary thyroid cancers with nodal metastases

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Introduction: Nerve-dependent growth and metastatic spread is established in several cancers including prostate, gastric and skin cancers.[1] The relationship between nerves and thyroid cancer is unknown.

Methods: 4 micron sections of formalin-fixed paraffin-embedded blocks of primary papillary (n=75) or follicular (n=14) thyroid cancers or benign thyroid (n=27) were labelled for the pan-neuronal marker PGP9.5 using the Ventana Discovery immunohistochemistry platform, then counterstained with hematoxylin and scanned at 20x magnification using the Aperio AT2 scanner. Analysis was performed within QuPath.[2] Nerve trunks were counted if they demonstrated (1) immunoreactivity; (2) typical morphology; (3) contained 3 or more axons and (4) were within 1mm of thyroid tissue. Correlation was made with clinical parameters. Results are presented as median [IQR], with significance assessed by Mann-Whitney with alpha of 0.05.

Results: Nerve trunks were frequently identified adjacent to and within thyroid tissue, typically near the anatomical edge. Tissue blocks containing cancer had a significantly higher total nerve-trunk density than tissue blocks containing benign thyroid only (11 [6-24] vs 7 [3-10] trunks/cm$^2$, p=0.001). Significantly higher whole-slide nerve-trunk density was detected around papillary (14 [9-27] trunks/cm$^2$) compared to follicular (4 [3-12] trunks/cm$^2$) cancers (p=0.01); and around cancers with nodal metastases (17 [7-26] trunks/cm$^2$ vs 10 [4-18] trunks/cm$^2$ for cancers without nodal metastases, p=0.03). Because nerve-trunks grew in from the gland edge, we also divided lesional nerve density by the length of associated anatomical border. Assessed in this way, nerve-trunk density within 1mm of thyroid cancer was 7 [3-13] trunks/cm of anatomical edge, compared to 3 [1-6] trunks/cm of benign anatomical edge (p<0.0001).

Conclusion: Nerve density is increased around papillary thyroid cancers compared to benign thyroid tissue; and also around cancers with nodal metastases compared to cancers without nodal metastases. These data warrant further investigation to determine the role of innervation in thyroid cancer growth and progression.

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## 156

### Detection frequency of BRAF mutation in benign thyroid nodules

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**Background** Papillary thyroid cancer (PTC) is the most common type of thyroid follicular epithelial-derived malignancy. It is usually slow-growing and most patients do not die of their disease, however a V600E mutation of the BRAF gene worsens its prognosis. This mutation is present in 40-60% of PTCs. Currently, thyroid nodules are deemed benign or malignant after cytopathological assessment; a benign cytological finding has high reliability for a benign histopathology and behaviour. As such, the incidence of BRAF V600E should be very low in such specimens.

**Hypothesis** That BRAF V600E mutation is not present in thyroid nodules classified benign by cytopathology.

**Methods** Fine needle aspirate (FNA) samples of thyroid nodules that were determined to be benign by cytopathology were used. Samples were snap frozen immediately after excision. Genomic DNA was extracted using the QIAamp DNA Micro Kit and quantified using ultraviolet spectroscopy. The presence of wild type or V600E mutant BRAF was detected using a commercial validated droplet digital polymerase chain reaction (ddPCR) with relevant negative and positive controls.

**Results** 63 patient samples were tested, of which only 26 could be analysed due to insufficient DNA yield. None of the 26 samples were positive for BRAF V600E. Thus, cytopathological assessment of these nodules aligned with the ddPCR analysis.

**Discussion** Data from this experiment suggests that BRAF V600E mutation is not present in thyroid nodules classified to be benign by cytopathology. We have therefore confirmed the reliability of a benign cytology in excluding BRAF positive PTC. This experiment was limited by the small number of samples that could be analysed; it would be worthwhile revising the biopsy technique, perhaps taking a FNA sample for ddPCR separate to one for cytopathology to increase the concentration of the extractions. Moreover, the sensitivity of the ddPCR in detecting BRAF V600E could be further explored.

## 157

### The islet ß-cell and type 2 diabetes –victim or perpetrator of the crime?

**Christopher Nolan[2, 1]**

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It is a generally held view that obesity-related type 2 diabetes develops as a consequence of failure of islet b-cell compensation for insulin resistance. This is more likely to develop if the islets have an underlying genetic and/or acquired susceptibility to failure. Implicit in this view is that insulin resistance comes first, as a consequence of poor lifestyle, overweight and obesity, and b-cell compensation and failure follows. If this is correct, the islet b-cell is a victim to insulin resistance.

An alternative view places the islet b-cell more in a primary role or as the perpetrator. The hyper-responsiveness of genetically predisposed islet b-cells to nutrient-induced stress results in hyperinsulinaemia that favours weight gain and insulin resistance. A hyperinsulinaemia/insulin resistance viscious cycle results, which is followed by the development of metabolic syndrome and its related conditions of non-alcoholic fatty liver disease, polycystic ovarian syndrome, type 2 diabetes and cardiovascular disease.

Focus of this symposium talk will be on reviewing the evidence from the literature and our laboratory for this alternative view that places the islet b-cell as the perpetrator. If this alternative view is substantiated, a paradigm shift in prevention and treatment strategies for obesity-related type 2 diabetes and the conditions of metabolic syndrome may be warranted. The the key objective would then be to develop therapies that attenuate the islet b-cell's hyper-responsiveness to stress such as that caused by an adverse nutrient supply.

## 158

### Human pancreatic ducts as a source of beta cells.

**Rohit Kulkarni[1]**

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A major focus of research in the diabetes field has been the identification of a 'source' of insulin-secreting beta cells to enable the development of therapeutic approaches to enhance the mass of functional beta cells to cure and/or prevent the development of all forms of diabetes. While reduplication of adult beta cells is considered a major source in rodents the potential long half-life of beta cells in humans suggests alternative mechanism(s) likely play a role to maintain optimum beta cell mass to insure the blood glucose remains with the normal physiological range. This presentation will include the discussion of a series of studies that support a role for the pancreatic duct as an important source of beta cells in humans.

## 159

### Local integrin activation in pancreatic beta cells targets insulin secretion to the vasculature

**Peter Thorn[1], Wan Jun Gan, Oanh Hoang Do, Louise Cottle, Elena Kosobrodova, Marcela Bilek**

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We have previously shown that insulin secretion from beta cells within an islet is selectively targeted to the area where each beta cell makes contact with the vasculature[1, 2]. Focal adhesions are known to affect insulin secretion[3] and one of the factors that might underlie a mechanism of targeting secretion is an integrin-extracellular matrix interaction. Here we test the hypothesis that extracellular matrix proteins, secreted by endothelial cells of the vasculature, induce integrin responses in the beta cells which through focal adhesions provide a cue for beta cell orientation and targeted insulin secretion.

Immunostaining *in situ,* within islets of Langerhans, show active focal adhesions are formed in b cells exclusively at the point where they contact the capillary basement membrane. *In vitro*, we demonstrate b cells respond to the basement membrane substrates, collagen IV, laminin 511 and fibronectin, with an increase in proliferation and insulin secretion. Using function blocking antibodies we show the enhanced secretion is dependent on $b_1$ integrin activation. To determine any spatial consequences of local integrin activation we use 3D mapping of insulin granule fusion to show exocytosis is targeted to where the b cells contact the basement membrane. This targeting is not seen with cells cultured on poly-l-lysine and is disrupted either by blocking the $b_1$ integrin receptor or by inhibition of focal adhesion kinase. Micro-pattern printing of stripes of E-cadherin and fibronectin shows individual b cells grow across both stripes but selectively respond to the fibronectin stripe with focal adhesion activation, targeting of the exocytic machinery and regional targeting of insulin granule fusion.

We conclude that integrin activation occurs exclusively at the vascular face of pancreatic b cells and is a mechanism that targets insulin granule fusion to this region.


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**160**

## Human beta-cell function and islet transplantation: can we improve?


**Jenny Gunton**


Diabetes develops when the pancreatic beta-cells are no longer able to compensate for the prevailing insulin resistance. Factors which aid in this compensation are important for avoiding diabetes and for optimal islet transplant outcome. Because the pancreas is difficult to access in humans, there is relatively little human data. Regulation of human beta-cell function and proliferation will be discussed.

**161**

## Mechanisms controlling hormone secretion in human gut and its relevance to metabolism


**Damien Keating**[1]

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Gut endocrine cells (called enteroendocrine cells) are scattered amongst the gastrointestinal epithelium and collectively constitute the largest endocrine tissue in our body. They consist of an array of different cell types, each synthesising different peptide hormones. Many of these hormones have significant effects on metabolism, food intake and body weight. Our studies have focused on cells that release GLP-1, PYY and serotonin (5-HT). We have combined secretion studies using ex vivo tissue from human colon, ileum and duodenum with in vivo studies in lean, obese and type 2 diabetes individuals. Gut-derived 5-HT suppresses thermogenesis in mice and causes obesity. We have identified that gut-derived 5-HT increases in obese humans, and that gut 5-HT acts as a link between the gut microbiome and host obesity. GLP-1 is an incretin hormone and, along with PYY, can regulate central pathways associated with food intake. We have elucidated the pathway by which glucose triggers GLP-1 secretion in human small intestine and identified that the melanocortin pathway, typically associated with central pathways controlling food intake, also exists within the gut epithelium and activates GLP-1 and PYY secretion in human gut via the MC4 receptor. Identifying novel mechanisms controlling peripheral gut hormone secretion may have direct relevance to developing new approaches to regulating metabolism and obesity in humans.

**162**

## Contributions of gut functions to the regulation of food intake in humans


**Christine Feinle-Bisset**[1]

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As the first point of contact for ingested nutrients, the upper gastrointestinal (GI) tract plays a key role in sensing the characteristics of the ingested meal content and in signaling this information to the brain. The interaction of nutrients with small intestinal nutrient-sensing receptors also triggers the release of gut hormones and initiates feedback loops that lead to adjustments in the rate of gastric emptying, both of which are involved in the regulation of energy intake. Lipid has potent effects on these GI functions, requiring fat digestion and fatty acids with a chain length of ≥12 carbon atoms. Dietary modifications can influence these effects of fat, so that overconsumption of a high-energy, high-fat diet reduces, while energy restriction enhances, sensitivity to the GI and appetite-suppressant effects of fat. Obesity is associated with compromised GI responses to dietary fat, particularly the release of gut hormones, with recent research indicating that this is due, at least in part, to a reduced number of enteroendocrine cells, changes that can be reversed by obesity surgery. Dietary protein, particularly whey, is also a highly satiating macronutrient, in part, mediated by changes in GI functions, although the GI effects

of protein appear to be less potent than those of lipid. In contrast to lipid, the appetite-suppressant effects of protein appear to remain intact in obesity, consistent with the efficacy of high-protein diets to achieve significant weight loss. Interestingly, our recent research, investigating the potential role of amino acids in mediating the effects of protein on GI functions and energy intake, has established that certain amino acids, e.g. L-tryptophan or L-leucine, suppress subsequent energy intake, in excess of their own energy content, despite diverse effects on GI functions, with the effect on energy intake more closely related to their respective plasma concentrations, suggesting that the energy intake-suppressant effects of these amino acids, and protein, may be mediated not primarily by GI effects, but through effects of circulating amino acids. Taken together, the role of the gut in mediating the energy intake-suppressant effects of dietary nutrients appears to vary according to macronutrient class. Moreover, the adaptive changes in GI function that occur in response to a high fat intake may, at least in part, underlie the obesogenic properties of fat. Much more research is required to establish whether, and how, specific dietary nutrients can be utilized in the management of obesity and associated comorbidities.

**163**

## Mechanisms linking artificial sweeteners to impaired glycaemic control in healthy subjects

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**Background and aims:** Epidemiological studies indicate that regular high intake of beverages sweetened with low-calorie sweeteners (LCS) increase the risk of developing type 2 diabetes mellitus (T2DM), but the underlying mechanisms are unknown. We recently showed that LCS supplementation in healthy non-diabetic subjects over 2 weeks led to clinically relevant increases in glycaemic response to enteral glucose. Increased glucose absorption (serum 3-O-methyl glucose, 3-OMG) and attenuated release of glucagon-like peptide-1 (GLP-1) contribute to this dysglycaemia, however it is unclear whether gut dysbiosis due to LCS also contributes to dysglycaemia, as occurs in rodents.

**Materials and methods:** 29 non-diabetic subjects (age 30 ± 2 years, body mass index 24 ± 3 kg/m$^2$, HbA1c 32 ± 1 mmol/mol (5.2%), 16 male) were randomised, in double-blind fashion, to diet supplementation with LCS containing capsules (92 mg sucralose + 52 mg acesulfame-K, N=14) or placebo capsules (N=15); capsules were taken three times daily over 2 weeks (equivalent to ~1.5L of diet beverage consumption/day). The gut microbiome was assessed by shotgun metagenomic sequencing in stool collected before and after treatment. Differences in taxonomic and functional microbiome characteristics were determined using MetaPhlAn2 and HUMAnN2 abundance, respectively.

**Results:** LCS-treated subjects exhibited a greater variation in faecal microbiota composition, along with a significant reduction in the health-associated bacterium *Eubacterium cylindroides* (-11 $\log_2$ fold change, FC) and an increased abundance of 11 opportunistic gut pathogens, including *Klebsiella* (17 FC)*, Porphyromonas* (15 FC) and *Finegoldia* (12 FC; all $P \leq 0.001$). A decrease in beneficial and fermentative *Bifidobacterium*, *Lactobacillus* and *Bacteroides* populations correlated with augmented glucose absorption (3-OMG), while a decrease in *Butyrivibrio* populations correlated with attenuated GLP-1 release (Spearman correlation: $\rho \geq \pm 0.37$; $P \leq 0.05$). Finally, shifts in the abundance of microbial genes involved in sucrose degradation and pyruvate metabolism correlated with a deterioration in glucose regulation in LCS-treated subjects.

**Conclusion:** In healthy non-diabetic subjects 2 weeks of LCS supplementation (i) causes gut dysbiosis and (ii) increases the abundance of gut pathogens normally absent in health. Moreover, a decrease in fermentative microbial populations and shifts in bacterial energy harvesting pathways due to LCS predict a deterioration in glucose regulation. Our findings support the concept that LCS disrupt glycaemic responses in healthy humans via dysregulation of glucose uptake and disposal, and secondary to dysbiosis of gut commensal bacteria. This highlights the clinical relevance of dietary LCS patterns in overall glycaemic control.

**164**

## Glucagon-like peptide-1 (GLP-1) - incretin or enterogastrone?

**Michael Horowitz**[1]

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The rate of gastric emptying, which exhibits a wide inter-, but low intra-individual, variation is a critical determinant of postprandial glycaemic excursions. Because nutrients empty from the stomach at 1-4 kcal/min, humans are predominantly in the 'postprandial', rather than 'fasting', state. In type 2 diabetes 'fasting' glucose has the greatest impact on glycated haemoglobin (HbA1c) in patients with poor glycaemic control (HbA1c >8.0%), while in better-controlled patients (HbA1c ≤8.0%) postprandial glucose predominates. Agonists of glucagon-like-peptide (GLP-1 RAs) which may be 'short' or 'long-acting' based on their plasma half-lives, are prescribed widely for the management of type 2 diabetes. Their use is empirical despite the recognition that the lowering of HbA1c is highly variable. GLP-1 RAs have been 'sold' on the basis of their 'pancreatic' actions (ie glucose-dependent insulin stimulation and glucagon suppression). This is despite the recognition that the GLP-1 antagonist, exendin 9-39, accelerates gastric emptying and when pharmacological doses of GLP-1 are given intravenously with a meal the reduction in glycaemia is associated with a decrease, rather than an increase, in plasma insulin. The effect of exogenous GLP-1 to slow gastric emptying is, however, attenuated markedly with continuous, rather than acute, or intermittent, exposure. This 'tachyphylaxis' suggests that sustained stimulation of the GLP-1 receptor by 'long-acting' GLP-1 RAs will diminish, and potentially abolish, their effect to slow gastric emptying, which would account for them being less effective than 'short-acting' GLP-1 RAs for targeting postprandial glucose. There is clearly a differential effect of 'short'- and 'long-acting' GLP-1RAs on

gastric emptying - 'short-acting' GLP-1 RAs , exenatide BID and lixisenatide, delay gastric emptying in type 2 diabetes and the reduction in postprandial glucose can be predicted by the magnitude of this slowing, which is greater in patients with normal, or rapid, gastric emptying . These insights provide a rationale for the personalised use of 'short'- or 'long-acting' GLP-1 RAs in type 2 diabetes.

**169**

## Predictors of long-term outcome following parathyroidectomy in MEN 1

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**Introduction:** The optimal approach to parathyroidectomy (PTx) for primary hyperparathyroidism (PHPT) in Multiple Endocrine Neoplasia Type 1 (MEN 1) remains unclear. Reliable predictors of short and long-term outcomes could improve decision making regarding surgical approach and prognosis.

**Methods:** We conducted a retrospective cohort study involving 62 MEN 1 patients who underwent PTx with follow-up at the Royal Hobart Hospital. Preoperative and postoperative serum calcium and parathyroid hormone concentrations were extracted from medical records and analysed in relation to PTx extent: Total PTx (TPTx) = all glands removed; Near Total PTx (NPTx) = 0.5 glands retained; Subtotal PTx (SPTx) = 0.5-1 gland retained, Less Than Subtotal PTx (<SPTx) = more than 1 gland retained.

**Outcomes:** Rates of hypercalcaemia (HC), long-term remission (LR) (minimum follow-up 1 year), permanent hypocalcaemia (PH) or indeterminate (ID) were: TPTx (PH 100%), NPTx (HC 43%, LR 30%, PH 24%, ID 3%), SPTx (HC 86%, LR 0%, PH 14%), <SPTx (HC 67%, LR 27%, PH 0%, ID 6%). NPTx with parathyroid tissue autografting prevented PH 0% compared to 23% without autografting. NPTx (n=37) had significantly less hypercalcaemic events than SPTx (n=7) (p=0.01). Median duration to hypercalcaemia was: NPTx 203 months, SPTx 33 months. NPTx preoperative Calcium Homeostatic Ratio (CHR) ($Ca^{2+}$/PTH-ratio) was associated with PH 50% (CHR <1.0) compared to PH 13% (CHR ≥1.0). NPTx week-1 postoperative $Ca^{2+}$ was associated with HC 38%, LR 25%, PH 33%, ID 4% ($Ca^{2+}$<1.10 mmol/L) compared to HC 64%, LR 36%, PH 0% ($Ca^{2+}$≥1.10 mmol/L).

**Conclusion:** Parathyroidectomy in MEN 1 is associated with high rates of recurrence and permanent hypocalcaemia. NPTx with parathyroid tissue autografting provides an optimal balance between PHPT persistence, PHPT recurrence, long-term remission and risk of permanent hypocalcaemia. Preoperative CHR and week-1 postoperative $Ca^{2+}$ levels were useful predictors of long-term PTx outcome and may enable prediction of individual patient prognosis.

**170**

## Combination of Captopril Challenge Test and Saline Infusion Test Does Not Improve the Diagnostic Accuracy of Primary Aldosteronism

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**Context:** Both saline infusion test (SIT) and the captopril challenge test (CCT) are accurate alternatives to the fludrocortisone suppression test (FST), which is generally accepted as a reliable but cumbersome confirmatory test in primary aldosteronism (PA). The combination of two independent diagnostic tests gets a higher accuracy in some diseases. However, whether a combination of CCT and SIT could improve the diagnostic accuracy of PA is still unknown.

**Objective:** To evaluate the diagnostic accuracy for a combination of CCT and SIT in PA diagnosis.

**Methods:** This study is an extension of Chongqing Primary Aldosteronism Study (CONPASS), which is a prospective study with some published results. We retrospectively recruited 164 patients with PA and 116 patients with essential hypertension (EH) who had completed FST, CCT and SIT. The post-test plasma aldosterone concentration (PAC) was used for the three confirmatory tests. The reference standard was FST, and the cut-off was set at 8 ng/dL. The index tests were CCT, SIT and a combination of CCT and SIT. Area under receiver operator characteristics curve (AUC), sensitivity and specificity were calculated.

**Results:** AUCs for CCT, SIT and a combination of CCT and SIT were 0.94(95% CI 0.91, 0.97), 0.95(0.91, 0.98) and 0.96(0.92, 0.98) respectively (*P* =0.204 for CCT vs. combination; *P*= 0.512 for SIT vs. combination). When the optimal cutoff of PAC post-CCT was set at 8 ng/dL and PAC post-SIT at 11 ng/dL, the sensitivity for CCT and SIT was 0.87 and 0.86 respectively, and the specificity for CCT and SIT was 0.91 and 0.92 respectively. A combination of CCT and SIT generated a sensitivity of 0.86 and a specificity of 0.92. Neither sensitivity nor specificity of the combination was significantly different from CCT or SIT.

**Conclusion:**. A combination of CCT and SIT does not improve the diagnostic accuracy of primary aldosteronism.

**171**

## Prevalence of hereditary pheochromocytoma and paraganglioma and associated genotypes within a paediatric and adolescent population: a review of patients presenting to familial cancer services within NSW between 1994-2017.

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Phaeochromocytoma and paraganglioma (PPGL) syndromes associated with germline mutations are highly morbid. Published data has consistently demonstrated a high occurrence of tumours due to hereditary PPGL in childhood with a predominance of cluster 1 mutations (*VHL* and genes relating to the SDH complex). This cluster is associated with more aggressive features including bilateral, multiple and extra-adrenal tumours.[1,2,3]

As knowledge of these rare syndromes continues to develop and new implicated genes have only recently been discovered, data relating to hereditary PPGL has not been captured in the Australian Paediatric Cancer Registry. The findings of this study will therefore establish for the first time accurate prevalence of PPGL within this demographic within Australia. The outcomes will also give further insight into genotype-phenotype correlations and contribute to the body of evidence used to develop genotype-specific surveillance guidelines.

**Objective:** The retrospective element of this study established the prevalence of hereditary PPGL, including underlying genotype. Genotypes included *VHL*, *SDHB, SDHD, SDHC, SDHA*, *RET*, *NF1*, *TMEM127* and *MAX***.** In those patients who had not been exhaustively investigated to exclude a germline mutation, multi-gene panel testing was performed.

**Methods:** Information was collected through 'TrakGene'. Patient characteristics included age at diagnosis, gender, clinical features. Tumours were classified by hormone secretion profile, tumour number, anatomical location, histological features and benign/malignant. Stored DNA was accessed for further testing, if appropriate.

**Results(prelim):** Results from a single centre identified 13 paediatric patients. 9 (69%) carried a germline pathogenic variant: 6 *SDHB* (of which 5 were extra-adrenal, 5 were multi-focal and 2 were metastatic) and 3 *VHL*.

**Conclusions:** PPGLs diagnosed in children and adolescents in Australia are likely to be associated with germline pathogenic variants in *VHL* or *SDHB*. These patients should be referred to specialist services for comprehensive perioperative work-up, detection of bilateral, multifocal or metastatic disease, and family counselling.

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**172**

## Clinically significant inter-assay discordance in serum prolactin in Australia

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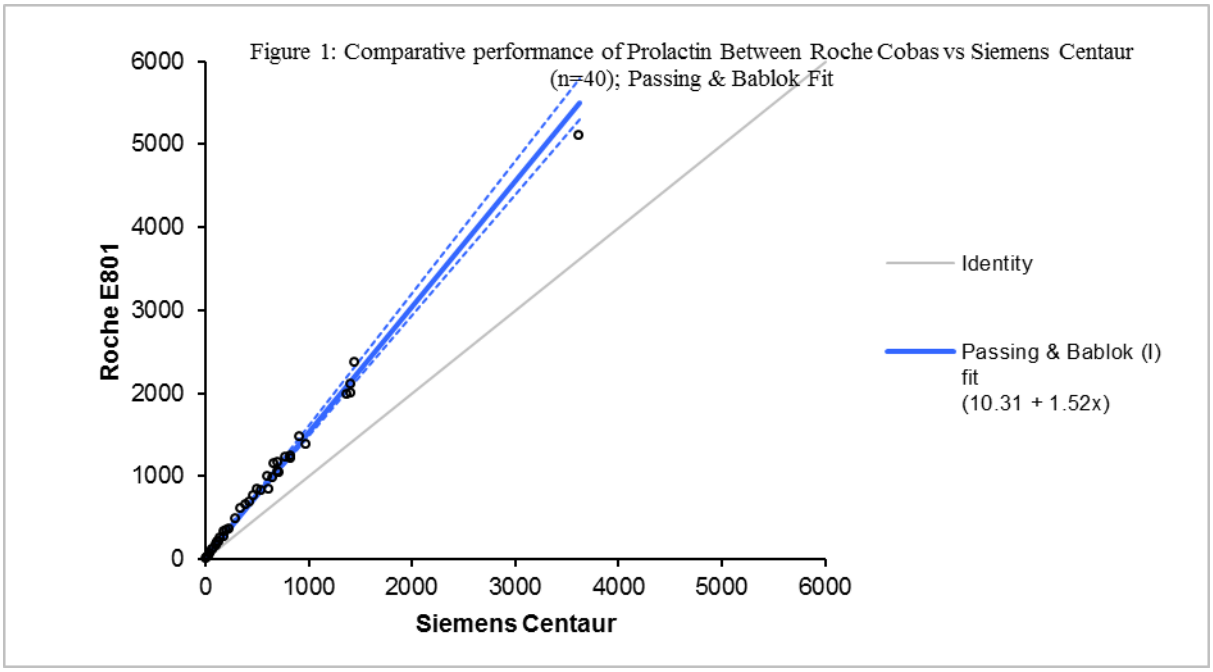
The magnitude of prolactin elevation guides the differential diagnosis of hyperprolactinaemia and parallels prolactinoma diameter. Severe hyperprolactinaemia (>10-fold ULN) is generally due to macroprolactinoma or pregnancy.[1] Causes of mild hyperprolactinaemia (<4-fold ULN) include microprolactinomas, dopamine interference, primary hypothyroidism, polycystic ovary syndrome, prolactin co-secretion in acromegaly or Cushing's disease, and physiological changes (e.g. stress).[2-5]

We observed eight patients with 28-166% higher prolactin by the Roche versus Siemens platform during routine clinical practice. Some patients had cause for true hyperprolactinaemia but there were no clinical changes in any case to explain the higher Roche levels. For example, a woman with schizophrenia had hyperprolactinaemia at 7-fold ULN by Roche, prompting investigation for prolactinoma. Pituitary MRI was normal and repeat prolactin by Siemens was only 2.5-fold ULN, consistent with her longstanding antipsychotic use.

Hence, we measured serum prolactin in both assays using split clinical samples (n=40) across a range of serum prolactin (5-5051 mIU/L). This revealed that serum prolactin was approximately 50% higher by Roche compared to Siemens (Fig 1), despite similar reference ranges. Review of the original Roche data showed no technical error in reference interval calculation; the reason for discordance thus remains unexplained. We speculate that the recent divergence in measurements may relate to either progressive positive bias with successive reagent lot numbers, or antibody deterioration.

Our findings of prolactin inter-assay discordance emphasise the importance of verifying reference intervals and performing bias checks over time. Endocrinologists should be aware of the potential for prolactin overestimation and the utility of repeat testing on different platforms. In mild hyperprolactinaemia by the Roche platform with normoprolactinaemia by other platforms, patients may be spared from unnecessary endocrine reviews and MRI studies. In true hyperprolactinaemia, separating patients with mild versus severe hyperprolactinaemia will narrow the diagnostic possibilities.





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**173**

## Aldosterone-producing adenoma associated with non-suppressed renin: a case series


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The aldosterone-to-renin ratio (ARR) is widely accepted as the preferred screening test for primary aldosteronism (PA). Although a suppressed renin is considered a hallmark of PA, patients with non-suppressed renin and a falsely negative ARR have been reported that would have been missed if the recommended diagnostic pathway was followed. This report describes eight patients (2 women and 6 men, median age 48 [range 35-63]) with a proven aldosterone-producing adenoma (APA) but a non-suppressed renin (PRC > 8.4 mU/L). Their systolic and diastolic blood pressures on referral were 157 (114-195) and 103 (74-119) mmHg on 2.5 (1-6) antihypertensives. Five were on potassium-sparing diuretics and/or potassium replacement. After medication adjustment to agents known to have minimal effect on renin and aldosterone levels, PRC, PAC and ARR were 18.5 (9-43) mU/L, 780 (270-1940), and 47 (8-78, normal <75), respectively. Seven patients had two consecutive ARR measurements and five of them had two negative tests. Renal artery stenosis (RAS) was carefully ruled out in all patients. Further evaluation for PA was pursued because of high clinical suspicion (hypokalaemia and/or an adrenal mass lesion on imaging). Five patients underwent a suppression test and although aldosterone did not suppress, renin also failed to suppress. All underwent adrenal vein sampling confirming unilateral PA. Seven were managed with unilateral adrenalectomy and one is awaiting surgery. Postsurgical follow-up data were available for seven patients. Three had a postoperative suppression test confirming biochemical cure; the other four displayed an excellent clinical or biochemical response.

Many known and unknown factors influence the ARR. Strict control of these factors is crucial to avoid false-negative results. Other causes that could explain a non-suppressed renin should be ruled out. In patients with a consistently non-suppressed renin further diagnostic workup for PA should be considered if clinical suspicion remains high.

**174**

## Use of a semiquantitative point-of-care cortisol assay in adrenal vein sampling: experience from a local centre


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**Background:** Adrenal vein sampling (AVS) is the gold standard to identify surgically curable causes of primary aldosteronism. AVS is recognised as technically challenging, with reported success rates of 42-98%[1] depending on local expertise. We have 2 new radiologists performing AVS. A semiquantitative point-of-care (POC) cortisol assay was recently reported which increased successful cannulation from 63% to 93%, even in inexperienced hands[2].

**Aims:** Review effectiveness of the POC cortisol assay for successful cannulation

**Methods:** AVS was performed using ACTH stimulation protocol (50ug/hr continuous cosyntropin). Approximate thresholds were established for each POC cortisol batch (courtesy of Trust Medical, Japan) using stored serum samples. Cortisol levels of 480 nmol/L, 830nmol/L, and 1060 nmol/L resulted in a clear, faint, and absent band respectively. POC assays were evaluated during AVS on 6 consecutive patients between January-May 2018. For this initial phase the intraprocedural decision was made by radiologists using standard radiological criteria.

Successful cannulation was defined biochemically as adrenal/paired peripheral cortisol levels (Selectivity index= SI ) ≥ 3.0

Assessment of cannulation success using the POC assay was evaluated on site and retrospectively by 3 independent reviewers blinded to the lab results.

**Results:** Mean cortisol levels were 14375.1nmol/l (right adrenal); 605.9nmol/l (paired right peripheral); 12048.3nmol/l (Left adrenal vein) and 526.0nmol/l (paired left peripheral).

In all 6 cases, the radiologist assessed both adrenal veins as successfully cannulated. 4 were successfully cannulated bilaterally using biochemical criteria of SI > 3.0, one borderline (SI 2.7) and one clear failure (SI 1.1). The POC cortisol assay consistently and correctly identified cannulation failure, and in one case, further exploration resulting in successful cannulation. The assay range limited confirmation of cannulation where cortisol levels > 500nmol/l, so may be more useful in protocols without ACTH stimulation.

**Conclusion**

POC cortisol assays may assist in improving AVS cannulation success, even in less experienced hands.

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# POSTER ABSTRACTS

## 176

### Calbindin-$D_{9k}$ ablation induces diabetes mellitus like symptom

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Publish consent withheld

## 177

### Bisphenol A and Octylphenol induced insulin resistance by endoplasmic reticulum stress in Type 1 diabetes mellitus model

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In pancreatic β cells, which produce and secrete insulin, calcium ($Ca^{2+}$) signals are contribute to insulin production and secretion. Bisphenol A (BPA) and octylphenol (OP) were known to increase plasma insulin levels and insulin transcription factors, but regulation of plasma glucose levels did not decrease proportionally to the insulin increase. We hypothesized that BPA and OP disrupt calcium homeostasis results in insulin resistance, by inducing ER stress. BPA and OP treatment leads to survival of pancreatic β cells against streptozotocin, but despite of increased insulin level, serum glucose regulation does not properly regulated. The expression of genes involved in transporting calcium ions to the cytosol and ER were decreased while the expression of those affecting the removal of calcium from the cytosol and ER were increased. Depletion of calcium from the ER leads to ER stress and can induce insulin resistance. Insulin resistance is also confirmed with insulin responsive gene such as glucose transporter 4 (*glut4*) and *Irs2* expression. Taken together, these results imply that the disruption of calcium homeostasis by BPA and OP induces ER-stress and leads to insulin resistance especially in streptozotocin (STZ) -induced type 1 diabetes mellitus model.

## 178

### Manifestation of polycystic ovary syndrome (PCOS) in women in the peri and post-menopausal years

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**Introduction:** PCOS is a common endocrine disorder with a diverse range of metabolic, reproductive and psychological features. Although considered a dynamic condition, little is understood about how this condition progresses across the life course. In particular, it is unclear whether the endocrine and metabolic abnormalities associated with PCOS worsen in women as they age, particularly after menopause. We undertook a systematic review of observational studies of women with PCOS aged 45 years or more, to examine the range and severity of symptoms in women in the peri and post-menopausal period.

**Methods:** We searched the following databases until 31st May 2018: Pubmed, Psychinfo, Embase, and CiNAHL. Studies that examined any aspect of PCOS (variously diagnosed) in women aged 45 years or more were eligible for inclusion. Two review authors are currently independently extracting data and assessing study quality using the Newcastle-Ottawa Scale. Results will be synthesized by study type and broad category of endocrine, metabolic and psychosocial parameters will be examined. Where possible, meta-analyses will be undertaken to estimate pooled effects for outcomes of interest.

**Results:** We identified 3156 articles from the searches, and of these 1593 were excluded based on title alone. The remaining 1563 studies are currently being assessed for eligibility; data extraction and quality assessment are ongoing. Results will be presented with a focus on synthesising the evidence about age at menopause and severity of menopausal symptoms; degree of ovarian dysfunction, hyperandrogenism and psychosocial complications; and the extent of co-morbidities (e.g. cardiovascular disease, diabetes, cancer, depression etc.) as women age.

**Conclusion:** This review will present the current state of evidence regarding the expression of PCOS as women age. This will help to clarify the postmenopausal phenotype of PCOS, and provide directions for strategies to improve diagnosis and management of this condition in later life.

## 179

### Structural mechanism of antagonists and partial agonists of PPARgamma for use as antidiabetics

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Synthetic full agonists of PPARγ have been prescribed for the treatment of diabetes due to their ability to regulate glucose homeostasis and insulin sensitization. While the use of full agonists of PPARγ has been hampered due to severe side effects, partial agonists and antagonists have shown promise due to their decreased incidence of such side effects in preclinical models. No kinetic information has been forthcoming in regard to the mechanism of full versus partial agonism of PPARγ to date and little structural and dynamic information is available which can shed light on the mechanistic difference between full and partial agonists as well as antagonists. We have used X-ray crystallography, cellular assays, Hydrogen Deuterium Exchange (HDX), and Surface Plasmon Resonance (SPR) to probe the mechanism of several PPARγ partial agonists and antagonists. Our findings demonstrate that not only do partial agonists and antagonists act through distinct transcriptional mechanisms, they also demonstrate differences in structure, dynamics, and kinetics as compared to full agonists.

**180**

## Functional analysis of novel Kir6.2 mutations causing neonatal diabetes

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In pancreatic beta-cells, ATP-sensitive potassium channels link changes in blood glucose concentration to insulin secretion. The β-cell $K_{ATP}$ channel is characterised by pronounced channel inhibition in response to increased intracellular ATP concentration.

A lack of insulin secretion causes diabetes mellitus. Neonatal diabetes mellitus (NDM), however, is a rare disease which presents within the first six to nine months of life, and approximately half of these patients have $K_{ATP}$ channel mutations.

In high glucose concentrations, ATP generated from glucose metabolism binds to $K_{ATP}$ channels causing them to close, which leads to membrane depolarisation and insulin secretion. Mutant $K_{ATP}$ channels found in neonatal diabetes patients are less sensitive to ATP inhibition and thus remain open when blood glucose rises, preventing their beta-cells from secreting insulin. In the past, patients with neonatal diabetes were dependent on lifelong insulin treatment for survival, but in recent years the preferred treatment has been oral sulphonylureas. In addition to improving their quality of life, this provides them with better glycaemic control and a lower risk of subsequent complications.

We investigate the effect of heterozygous activating mutations at residues G334 and C166 in Kir6.2 (*KCNJ11*), the pore-forming subunit of the channel, as well as the first known homozygous activating mutation: G324R. We confirm that these mutations lead to neonatal diabetes mellitus, and the data of these novel mutations and the mutations occurring at the same residues provide more evidence to support the strong correlation between greater loss of ATP sensitivity and more severe phenotype; that is, neonatal diabetes accompanied by neurological symptoms. Additionally, the success of sulphonylurea therapy in patients with Kir6.2 mutations reflects the *in vitro* response of the KATP channel with the same mutation to tolbutamide, and there is a threshold of 65-75% block required in order to cause insulin secretion.

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**182**

## Knowledge assessment of type 2 Diabetes Mellitus in Pakistan

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Objective:

We aim to assess the knowledge, behavioral and environmental risk factors and complications of type 2 Diabetes Mellitus among non diabetics in Pakistan.

Methodology:

A cross sectional study was conducted in peripheral areas of Lahore, Pakistan during the month of January 2015. A structured questionnaire was established that targeted 350 population >18 years. The questionnaire was designed to access knowledge, associated risk factors and complications of Diabetes Mellitus.

Knowledge was assessed and risk assessment scoring was performed according to the guidelines of American Diabetic Association. Using SPSS, data was analyzed, frequencies were calculated and p-values were determined to find associations between the variables.

Results:

Out of 350 people subjected to the survey, only 130 adults(37%) had any awareness of Diabetes Mellitus. Knowledge regarding cause, signs, symptoms, risk factors and complications was found inadequate. Practices regarding diet and life style were also found unsatisfactory. Awareness of risk factors was present in 110 (31%) of targeted population. About 41% individuals were found obese and 28% were overweight and on risk assessment score 62% were found at high risk, 48% at low risk of developing diabetes mellitus. Awareness of complications was present only in 16%. Gender male, education and urban

residence showed significantly better knowledge regarding diabetes but scored more on risk assessment scale due to poor dietary habits and lack of physical activity.

Conclusion:

We concluded that a significant number of people have little or no awareness of Diabetes Mellitus. A formal, structured approach should be designed to deliver the necessary educational information especially in the peripheral areas of Pakistan. The individuals found high risk and low risk needs further screening for diabetes. It should be our goal to prevent the morbidity and mortality of Diabetes Mellitus among non diabetics by raising public awareness through outreach programs and mass med

**183**

## Identifying the association of depression and diabetic distress in Pakistani patients diagnosed with type 1 diabetes

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**Background and aims:**

Depression plays an important role among patients diagnosed with Type 1 Diabetes. It is believed that diabetes distress is recognised as major psychological issue in Pakistan. Our study aims to identify diabetes distress among Pakistani children patients diagnosed with type1 Diabetes. We also aim to find out the relationship among depression, distress caused by Diabetes and glycemic control

**Materials and methods:**

A cross sectional study was conducted in Sir GangaRam Hospital Lahore during June 2016 to October 2017. Total 80 patients diagnosed with Type1 Diabetes Mellitus were included in the study. Hb A1C levels were collected via venous puncture. A personalized health questionnaire was used to classify depression among patients. Diabetes distress scale was used to identify diabetes distress and other factors such as social distress, interpersonal distress, physician related distress, emotional distress and regimen related distress.

**Results:**

The rate of depression was 39% among patients diagnosed with type 1 Diabetes. 8% were categorised as mild depression, 14% moderate depression and 17% with severe depression. Diabetes depression was found in 71% of the selected population. Rates of social distress, interpersonal distress, physician related distress, emotional distress, regimen related distress were 23%, 33.5%, 17.8%, 73.4% and 42.6 respectively. There was no association between depression and glycemic index.

**Conclusion:**

Our study concludes that Diabetes distress is very common among patients with type 1 Diabetes and this is an alarming condition for Pakistani population. We need to develop and modify our management plans in order to combat this deadly distress. Mass media should be involved in order to raise awareness about diabetes distress and depression.

**184**

## Ablation of glucocorticoid receptor in the hindbrain of the mouse provides a novel model to investigate stress disorders

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According to the World Health Organization, mood disorders will be the second leading cause of disability by the year 2020(1), so the need for appropriate models to understand these disorders is ever pressing. The hypothalamic-pituitary-adrenal (HPA) axis is part of the body's neuroendocrine system which regulates responses to internal and external stressors. Hyper-stimulation of the HPA axis results in sustained elevated levels of glucocorticoids which has been shown to impair neuronal function and can ultimately result in mental, neurological and substance use conditions (2, 3). Studies investigating the role of GR in the brain has primarily focused on the forebrain, however, glucocorticoid receptor (GR) is also expressed in the hindbrain (4) and has recently become a region of interest for the development of anxiety and HPA-axis dysregulation, yet, its exact role has not been clearly defined.

To determine the role of glucocorticoid signalling in the hindbrain we have developed a novel mouse model that specifically ablates hindbrain GR to ascertain its role in behaviour, HPA-axis regulation and adrenal function. Our study highlights that ablation of GR in the hindbrain results in a stressed phenotype in mice, characterised by excessive barbering and obsessive compulsive digging with lack of cage exploration. These mice also develop kyphosis, elevated circulating corticosterone and severe adrenal cortex disruption, highlighting that functional hindbrain GR is required for normal HPA-axis regulation, adrenal cortex function and behaviour.

Together, this data demonstrates a role for hindbrain GR signalling in regulating stress-related behavior and identifies a novel mouse model that recapitulates what is observed in patients, allowing further investigation into the pathways impacting stress

and anxiety. Furthermore, it builds on previous literature that describes a relationship between stress and the dysregulation of the HPA axis leading to adrenal cortex damage.


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**185**

## Role of Hepatocyte Vitamin D Signalling in Liver Fibrosis


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**Objective:** To investigate whether Vitamin D signalling in hepatocytes ameliorates liver fibrosis.

**Methods & Results:** Hepatocyte vitamin D receptor (h-VDR) knockout (KO) mice and their floxed controls (FC) were created. Mice were subjected to twice weekly intraperitoneal injections of thioacetamide (TAA) or saline for 10 weeks and subsequently sacrificed. The liver sections of mice from the h-VDR KO group demonstrated increased fibrosis staining and collagen compared to those of the FC group. qPCR results show an increase in mRNA levels of TNFa, and TIMP1, markers of hepatic inflammation, in the KO group when compared to the FC group, as well as increased mRNA levels of the macrophage marker F480, indicating that liver macrophage infiltration was increased by loss of h-VDR.

**Conclusions:** h-VDR may play a role in modulating chronic liver injury. These hepato-protective effects may be of therapeutic use in human liver disease.

**Lay description:** Liver Vitamin D Receptor (VDR) may play a role in modulating chronic liver injury, as indicated by our TAA model. Mice lacking hepatocyte VDR, the receptor through which Vitamin D functions, had increased markers for liver fibrosis compared to those with a functioning VDR.


**186**

## Accuracy of pre-operative parathyroid localisation with parathyroid 4D-computer tomography in patients with negative, discordant or bilateral disease on ultrasound and sestamibi scintigraphy – review of single centre experience.


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Introduction: Parathyroid 4D computer tomography (4D-CT) has emerged as a complimentary technique to ultrasound and sestamibi scintigraphy particularly in the localisation of ectopic or multigland disease.

Methods: A retrospective review of patients with primary hyperparathyroidism who underwent 4D-CT (performed at a single practice) over the period 2017-2018 because of suspected bilateral disease or discordant or negative imaging on prior localisation ultrasound (performed by a single operator) and sestamibi scintigraphy (majority performed with 99mTcpertechnetate subtraction). Adenoma localisation was confirmed at parathyroidectomy with subsequent cure.

Results: 28 patients were identified, 13 had undergone parathyroidectomy at time of abstract submission: average age was 70 years, 77% had mild (corrected calcium<2.75mmol/L) and 23% had moderate (corrected calcium 2.75-3.0mmol/L) primary hyperparathyroidism. Detection of findings 'probably consistent' with parathyroid adenoma at a specific location with ultrasound had sensitivity of 29% and positive predictive value (PPV) of 71%, scintigraphy had sensitivity of 53% and PPV of 82% and 4D-CT had sensitivity of 59% with PPV of 63%. Ten glands had concordant abnormality on two modalities with sensitivity 59% and PPV for adenoma at that site of 83%. Detection of findings 'possibly consistent' with parathyroid adenoma at a specific location with ultrasound had sensitivity of 41% with PPV of 70%, scintigraphy had sensitivity of 65% and PPV of 73% and 4D-CT had sensitivity of 71% with PPV of 55%. 13 glands had concordant abnormality on two modalities with sensitivity 76% and PPV for adenoma at that site of 76%. In this group all patients were cured with surgery.

Conclusions: Parathyroid 4D-CT is a complimentary imaging technique to localise parathyroid adenomas where other imaging is inconclusive. Concordant abnormalities in two of the three modalities improves localisation of parathyroid adenomas.


**187**

## Validation study of developmental toxicity test using mouse embryonic stem cells derived embryoid bodies

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Embryonic stem cell test (EST) from the European Centre for the Validation of Alternative Methods (ECVAM) evaluates the embryotoxic potential of substances and measures the half inhibition in viability of mouse embryonic stem cells (ESCs), fibroblasts (3T3 cells) and in cardiac differentiation of ESC. Previously, we established the developmental toxicity test method (termed EBT) applying area of embryoid bodies (EBs) instead of cardiac differentiation of EST. In the assessment of 15 substances for intralaboratory test and 6 substances for interlaboratory test. EB area was logarithmically decreased only in the toxic chemical with dose-dependent manner. In classification by the EBT-based prediction model reflecting decline in cell viability and EB area, toxicity for 20 chemicals showed similarity with the result of in vivo embryotoxic test. Conclusively, EBT is advanced and is a useful tool to assess and classify various embryotoxicants in a short time with less effort with accuracy.

**188**

## The effect of Octylphenol and Bisphenol A on calcium signaling in differentiated cardiomyocyte from mouse embryonic stem cell

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Endocrine-disrupting chemicals (EDCs) are structures similar to steroids hormones which can interfere with hormone synthesis and normal physiological functions of male and female reproductive organs. EDCs tend to bind to steroid hormone receptors. Sex steroid hormones influence calcium signaling of the cardiac muscle in early embryo-development. Progesterone (P4) has been reported to affect both blood pressure and other aspects of the cardiovascular system. To confirm the effect of progesterone (P4), octyl-phenol (OP) and bisphenol A (BPA) on early differentiation of mouse embryonic stem (mES) cells into cardiomyocytes, the hanging-drop method was performed to form embryoid bodies. The mouse embryoid bodies (mEB) were suspended, attached onto 6 well plates and cultured in differentiation medium containing steroid-free FBS without LIF. P4, OP and BPA were treated at two days after attachment and media were replaced every two days. To investigate the calcium signaling, the mRNA level of calcium channel genes such as *Trpv2* and contraction-related genes such as *Ryr2*, *Cam2* and *Mlck3* was analyzed. In addition, mifepristone (RU486), which is a synthetic steroid that has an affinity for progesterone receptor (PR), was used to confirm the impact of P4 through PR. To determine if RU486 is capable of attenuating the inhibition effect, RU486 was applied for one day starting on day 11. The *Pgr* mRNA level was significantly increased in P4, OP and BPA-treated group. However, the calcium channel genes such as *Trpv2* mRNA level was significantly decreased in the P4, OP and BPA-treated group. In addition, expression of contraction-related genes such as *Ryr2*, *Cam2* and *Mlck3* were significantly decreased in the P4, OP and BPA-treated group. Interestingly, treatment of RU486 rescues altered calcium channel genes and contraction-related genes. Taken together, these results suggest that OP and BPA may impact on differentiation of mESCs into cardiomyocytes, and disrupts differentiation of cardiomyocytes.

**189**

## Transthyretin uptake by the high-density lipoprotein receptor, scavenger receptor class B type 1.

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Transfer of thyroid hormone into cells is critical for normal physiology. Free thyroid hormone is known to enter cells through specific cell surface transport proteins, and for many years this uptake of unbound thyroid hormones was assumed to be the only relevant mechanism. In the last few years, substantial evidence has emerged of alternate pathways for hormone entry into cells that are dependent on hormone binding proteins. We have recently identified and demonstrated that the high-density lipoprotein receptor Scavenger Receptor class B type 1 (SR-B1) plays a role in the uptake and transport of the thyroid hormone binding protein transthyretin and transthyretin-thyroxine by placental trophoblast cells (1). High-density lipoprotein increases expression of SR-B1 in placental cells but also reduces uptake of transthyretin-thyroxine through the SR-B1 transporter. SR-B1 is expressed in many cells and this study suggests that it may be universally important in transthyretin and thyroid hormone uptake. Transthyretin is expressed and secreted into the serum by liver. Transthyretin and transthyretin-thyroxine have previously been shown to be taken up by primary hepatocytes via a previously unidentified receptor (2). Cholesterol is carried from peripheral tissues by HDL and taken up by hepatocytes through SR-B1. Our preliminary data suggest that SR-B1 plays a role in hepatic uptake of transthyretin (± thyroxine) and that HDL competes with transthyretin for uptake through hepatocyte SR-B1. Further investigation of SR-B1-transthyretin interactions may fundamentally change our understanding of hormone transport and biology.

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**190**

## Reference interval for Total Bile Acids on Abbott Architect c8000 analyser

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**Introduction**

Bile acids are synthesised in the liver from cholesterol and secreted into bile. The latter is stored in the gall bladder, which discharges bile acids into the small intestine usually after a meal to facilitate digestion and absorption of lipids. Bile acids can also bind to nuclear receptors to modulate expression of proteins involved in cholesterol homeostasis.

The concentration of total bile acids in blood can serve as a biomarker of liver function. Serum levels of bile acids are increased in many liver diseases including cholestasis, hepatitis and cirrhosis.

One main clinical indication for performing this test is in pregnant women presenting with generalised or localised skin itching (pruritus). Obstetric cholestasis is a cause of pruritus. In such patients, serum levels of bile acids can be elevated and a serum liver function panel should be requested.

In this study, we aimed to establish the reference interval for total bile acids assay on an Abbott Architect c8000 analyzer.

**Methods**

A total of 148 residual serum samples from women between 10 to 12 weeks of gestation were used. In order to exclude underlying liver disorders, all samples were screened for alkaline phosphatase, alanine aminotransferase, gamma-glutamyl transferase and total bilirubin prior to testing for total bile acids. The results were analysed using the Microsoft Excel and Analyse-It softwares.

**Results**

Serum total bile acids levels in these women were found to be normally distributed. The mean total bile acids level was 5.9 umol/L with 95% confidence interval of 5.3 to 6.4 umol/L. The 5$^{th}$ percentile and 95$^{th}$ percentile were determined to be 2.0 and 11.9 umol/L respectively.

**Conclusion**

We have established the 95$^{th}$ percentile from the data analysis as the upper limit of the reference interval for total bile acids i.e. < 12 umol/L for female patients in the first-trimester.

**191**

## SDHB mutation presenting with spermatic cord and neck paraganglioma

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Paragangliomas (PGL) are rare neuroendocrine tumours often associated with hypersecretion of catecholamines, and are found along the sympathetic chains or parasympathetic paraganglia. PGL can occur in the context of hereditary syndromes and commonly with succinate dehydrogenase (*SDH*) complex mutations. PGL of the spermatic cord or testes are extremely rare and reports of synchronous spermatic cord and neck PGL have not been reported before. In previous cases of spermatic cord PGL screening for an underlying genetic cause was not performed apart from one case where the patient was positive for a succinate dehydrogenase subunit D mutation.

We report the case of a 55 year old man with a one year history of dysphonia resulting in radiological diagnosis of a right vagal PGL treated with radiation. Laboratory investigations excluded a secretory PGL. Simultaneously he was diagnosed with a positron emission tomography avid testicular mass. An orchidectomy histologically confirmed a spermatic cord PGL. Genetic testing was positive for a heterozygous germline variant c.380T>G, p.(Ile127Ser) within exon 4 of the succinate dehydrogenase subunit B (*SDHB*) gene which has not been reported with spermatic cord PGL before.

This case reports the synchronous occurrence of a spermatic cord and neck PGL with *SDHB* mutation. It highlights the necessity for clinicians to screen patients with PGL for an underlying genetic aetiology, even if found in unusual locations, as this has significant implications for future treatment, screening and family planning.

**192**

## Should all patients with hyperparathyroidism be screened for a CDC73 mutation?

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Primary hyperparathyroidism (PH) is a common endocrine abnormality and may occur as part of a genetic syndrome. Inactivating mutations of the tumour suppressor gene *CDC73* have been identifed as accounting for a large percentage of hyperparathyroidsm-jaw tumour syndrome (HPT-JT) cases and to a lesser degree account for familial isolated hyperparathyroidism (FIHP) cases. Reports of *CDC73* whole gene deletions are exceedingly rare.

We report the case of a 39 year old woman with PH secondary to a parathyroid adenoma associated with a large chromosomal deletion (2.5Mb) encompassing the entire *CDC73* gene detected years after parathyroidectomy.

This case highlights the necessity to screen young patients with hyperparathyroidism for an underlying genetic aetiology. It also demonstrates that molecular testing for this disorder should contain techniques that can detect large deletions.

## 193

### A rare case of Meningococcal sepsis induced testicular failure, primary hypothyroidism and hypoadrenalism – is there a link?

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Severe illness can lead to multiple transient endocrinopathies. In adult patients neuroendocrine alterations include sick euthyroid syndrome, an increase in corticosteroid levels, increase in prolactin levels, decreased IGF-1 levels and hypogonadism.

We report the case of a 24 year old man with meningococcal sepsis with multiple end-organ complications who developed severe transient hypoparathyroidism, persistent non-autoimmune hypothyroidism, adrenal insufficiency, and primary hypogonadism all requiring hormone replacement. While adrenal insufficiency as part of the Waterhouse-Friderichsen syndrome is well described, reports of primary hypothyroidism and persistent primary hypogonadism in severe illness are exceedingly rare. Multiple combined endocrinopathies as in this case have not been reported previously.

This case highlights the necessity of screening for endocrine abnormalities in severe illness and the need for treatment if persistent. It also raises a novel concept of meningococcal sepsis causing multiple endocrinopathies possibly via disseminated intravascular coagulopathy related ischaemic damage.

## 194

### Prodigious hepatic paraganglioma - a long road to diagnosis

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Paragangliomas (PGLs) are uncommon neuroendocrine tumours usually arising from sympathetic chains or parasympathetic paraganglia. Hepatic PGLs are rare, with only 12 cases described in the literature.[1]

We present the case of a 69-year old woman found to have a liver lesion measuring 8.2 x 5.6 cm in 1994. Originally thought to represent focal nodular hyperplasia the lesion showed progressive growth prompting concerns of hepatocellular carcinoma. Alpha-fetoprotein (AFP) was 1.3 ug/L (normal <12). 24 years after initial imaging, she underwent a liver biopsy of the 13.2 x 6.6 x 12.7 cm lesion infiltrating the right lobe of the liver demonstrated on computer tomogram (CT) and magnetic resonance imaging (MRI). The biopsy was complicated by haemorrhage leading to a large hepatic subcapsular haematoma with extensive haemoperitoneumrequiring laparotomy. Histology revealed a paraganglioma (PGL). $^{18}$F-FDG-PET-CT and $^{68}$Ga-DOTATATE-PET-CT showed intensely increased activity associated with the liver lesion and multiple lymph nodes. The patient had no clinical or biochemical evidence of catecholamine excess. A primary hepatic origin is possible as metastases were not seen on earlier CT scans. The patient is being considered for peptide receptor radionuclide therapy with $^{177}$Lutetium.

Of the 12 hepatic PGLs reported, the primary diagnosis was HCC in 6 cases. It is difficult to differentiate PGL from HCC radiologically. Similar appearances are seen on CT, MRI and PET scans, 60% of HCC showed focal tracer uptake on octreotide scans.[2] One case of late uptake (> 24 hours) of metaiodobenzylguanidine has been reported in HCC.[3] AFP is elevated in 70% of cases of HCC, and in 80-90% of HCC where the tumour in greater than 5cm in diameter.[4] AFP has not been reported to be elevated in hepatic PGL.

Hepatic PGL should be considered with large liver tumours where AFP is normal or when there are symptoms of catecholamine excess.

## 195

### Immunotherapy-induced diabetes mellitus: better recognised and better understood

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Introduction:

With a rise in use and indications for immunotherapy in malignancy, immune-related adverse effects and immune-mediated endocrinopathies are becoming more commonly seen in clinical practise. Autoimmune diabetes is a more recently recognised manifestation and the mechanisms by which it occurs is an evolving area.

Case Description:

We describe a case of a 60-year-old woman who prior to her third cycle of immunotherapy for metastatic melanoma was found to have hyperthyroidism reflecting autoimmune thyroiditis. She then presented again 3 weeks later with diabetic ketoacidosis requiring an intravenous insulin infusion, before transitioning to subcutaneous insulin. HbA1c was 7.2%, C-peptide 0.17 pmol/ml (0.33-1.47 pmol/ml) and GAD Ab > 2000 units/ml (< 5 units/ml) indicating a rapidly progressive autoimmune diabetes. Repeat thyroid function testing demonstrated progression to overt hypothyroidism necessitating treatment with levothyroxine.

Discussion:

Autoimmune diabetes is now a more recognised adverse effect of immunotherapy. Incidence is reported at 0.2% and most cases are related to nivolumab.

Pathophysiology is believed to include aberrant T-cell activity, increased inflammatory cytokine production and antibody seroconversion. There is evidence implicating the PD1-PDL1 pathways with PD-1 deficiency in NOD (non-obese diabetic) mice being shown to accelerate the development of T1DM and polymorphisms in PD-1 conferring a greater risk of T1DM.

Early diagnosis is difficult to make as patients typically present with rapidly progressive diabetes mellitus, often with DKA. Management is more straightforward with subcutaneous insulin therapy. There is no evidence of deterioration of glycaemic control with ongoing immunotherapy.

Autoimmune thyroiditis, in contrast, is thought to be a destructive thyroiditis mediated by cytotoxic T cells. Symptomatic control with beta-blockade is typically sufficient for hyperthyroidism with thionamide therapy reserved when suspecting Graves' Disease.

Majority of cases of hyperthyroidism will progress to hypothyroidism requiring long-term thyroxine replacement, however both hypo- and hyperthyroidism may be the presenting feature of autoimmune thyroiditis.


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**196**

## Recurrent non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS): what else can we do?


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A 38 year-old mother of three, presented in 2015 with recurrent, predominantly meal-related hypoglycaemia, 6 months after Roux-en-Y gastric bypass surgery.

Roux-en-Y surgery had been performed for persistent abdominal pain, bloating and weight loss occurring on a background of a vertical banded gastroplasty for obesity in 1993, and gastrostomy in 2013 for symptomatic gastric stomal stenosis.

Mixed meal testing elicited a pronounced insulin surge 30 minutes post meal ingestion resulting in hypoglycaemia at 120 minutes. A 72 hour fast excluded a fasting hyperinsulinaemic state.

GLP-1 Ga-68 PET imaging was consistent with diffuse islet cell hyperplasia/nesidioblastosis.

Trials of Diazoxide, Verapamil SR, Octreotide, Acarbose, Exenatide and Prednisolone were eventually inefficacious or not tolerated, and the patient continued to experience debilitating severe hypoglycaemia with declining awareness.

A subtotal 80% pancreatectomy initially resulted in symptomatic improvement and reduction in hypoglycaemia frequency, however after 6 months recurrent hypoglycaemia was again encountered. Repeat mixed meal testing was consistent with recurrent nesidioblastosis, albeit with a milder insulin surge.

Refractory to Octreotide, care proceeded to a trial of Pasireotide 600 micrograms twice daily. This was up-titrated to 900 micrograms twice daily after 1 week. This was then changed to 600 micrograms three times a day, which eventually proved ineffective.

A completion total pancreatectomy was then performed with a reduction in hypoglycaemia events and improvement in hypoglycaemia awareness. She has however, developed brittle diabetes requiring subcutaneous insulin, with wide swings in blood sugar readings as well as complications of pancreatic exocrine insufficiency.

NIPHS, a rare disease entity in its own right, is being increasingly recognised as a complication of gastric bypass procedures. There are limited effective non-operative management strategies. Although the novel somatostatin analogue Pasireotide has had some recent success with sustained control in some cases, in our patient it proved ineffective, ultimately necessitating a completion total pancreatectomy.


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**197**

## Spindle cell oncocytoma: a rare but important cause for the sellar mass


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A 75-year-old woman was found to have a pituitary macroadenoma on MRI after presenting to her GP with visual disturbance, fatigue and a serum Na 129 mmol/L.

Examination revealed bitemporal hemianopia, and no features of pituitary hormone excess or deficiency. Laboratory findings were consistent with panhypopituitarism and a mildly elevated prolactin 1924 mIU/L likely related to stalk compression.

MRI revealed a 20x17x18mm lobulated enhancing soft tissue lesion in the pituitary fossa suggestive of pituitary macroadenoma, extending into the suprasellar cistern and impinging on the optic chiasm, with compression of the pituitary stalk.

She underwent uncomplicated transphenoidal secretion of her pituitary tumour 5 weeks later, that resulted in rapid complete resolution of visual field defect.

Histopathology surprisingly revealed a diagnosis of pituitary spindle cell oncocytoma (SCO). There were sheets and nodules of cells with ovoid to spindle nuclei and a moderate to large amount of brightly eosinophilic coarsely granular cytoplasm. Ki-67 index was 2%. Tumour cells stained positively for S100 and TTF-1 and negative for pituitary hormones.

Discussion:

SCO arises from the folliculostellate cells of the pituitary and is a benign non-endocrine neoplasm that accounts for only 0.1-0.4% of all sellar tumours.

These tumours are often indistinguishable clinically and macroscopically from non-functioning pituitary adenomas (NFA). However, there are two important points to note about SCO. First, these tumours are highly vascular and are associated with an increased risk of haemorrhage, at surgery. Second, preoperative diagnosis is therefore desirable. T1- and T2-weighted MRI may show hypointense foci and linear signal void areas in these tumours. Additionally, intense contrast enhancement can be seen during early stages of dynamic contrast enhanced MRI.

As with NFA, surgery is the cornerstone of management of SCO especially with visual field compromise. With complete surgical resection of the tumour, recurrence rates are low; however longer-term surveillance is required.


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**198**

## Hypo-aged hypovolaemic hyponatraemia


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This case describes the diagnosis and management of an infant with clinically diagnosed aldosterone synthase deficiency (genetics pending). She is now being managed with medical therapy and is growing well.

A 5 month-old female infant was born at 40+4/40 weeks gestation to a 24yo primiparous woman, following an uneventful pregnancy. The infant's birth weight was 3640g, length 51.0cm, head circumference of 34.5cm. She was formula-fed from birth with no issues initially over the first week or so of life. Subsequently she fed progressively more poorly tolerating only 30-40mL at a time and failed to gain weight and lost 4% of her birth weight.

Four days later she re-presented with no improvement in symptoms or weight gain and persistent marked hypotonia. Further investigations including MRI brain, serum ammonia, urine metabolic screen, and karyotype (46XX) were normal. Hyponatraemia was noted. Urine sodium excretion was inappropriately high (59 mmol/L). Cortisol (410 nmol/L, adult ref: 145-619), ACTH (1.6 pmol/L, ref: <20), and 17-hydroxyprogesterone (1.5 nmol/L, ref: 0.0-6.0) were all unremarkable. Aldosterone/renin showed renin above the upper detectable limit and aldosterone in the lower half of the adult reference range. The biochemical diagnosis of aldosterone synthase deficiency was made. Fludrocortisone 300microg PO daily and sodium chloride supplements 5mL PO TDS were commenced with good clinical effect and improvement in the plasma sodium and renin concentrations.

The likely aetiology of hyponatraemia differs with age at presentation ranging from excess total body water, most commonly due to the syndrome of inappropriate antidiuretic hormone secretion, in the first 5 days of life to low total body sodium of various aetiologies during the late newborn period from 6-28 days. A rare cause of infant hyponatraemia is congenital isolated hypoaldosteronism, an autosomal recessively inherited disorder of the CYP11B2 (aldosterone synthase) enzyme that catalyses the production of aldosterone from corticosterone.


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**199**

## ST-elevation myocardial infarction: an unusual presentation of Klinefelter Syndrome


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A 22-year-old male presented with central heavy chest pain, associated with radiation to the upper arm and jaw, dyspnoea and anxiety. Medical history was significant only for one-year cigarette smoking. Family history included ischaemic heart disease affecting his grandfather in old age. He had been unsuccessful conceiving with his partner for twelve months. Cardiovascular examination was unremarkable. Further clinical examination revealed normal secondary sexual characteristics, bilateral gynaecomastia and 10mL testicular volumes bilaterally. Electrocardiogram suggested ischaemia with 1mm ST-elevation in leads II,III and aVF and ST-depression in leads V2-V4 and aVL. Cardiac enzymes were significantly elevated (Table 1). Transthoracic echocardiogram showed inferior wall motion abnormalities and patent foramen ovale (PFO). Cardiac CT did not suggest coronary artery atheroma. Cardiac MRI demonstrated acute mid-inferior transmural left ventricular myocardial infarction and preserved left ventricular ejection fraction. Transoesophageal echocardiogram confirmed a PFO but two agitated saline contrast studies demonstrated no evidence of right-to-left shunting. There was no evidence of deep vein thrombosis on lower limb Doppler ultrasonography. Lipid profile, vasculitis, autoimmune and thrombophilia screening were unremarkable. A reproductive hormone profile showed primary hypogonadism with 47XXY karyotype, confirming Klinefelter's syndrome (KS) (Table 2). The diagnosis of thromboembolic ST-elevation myocardial infarction in the setting of PFO and KS was made and the patient commenced low-dose aspirin. Fertility was discussed and the patient will be followed-up in outpatient clinics to further discuss testosterone therapy.

KS is characterised by hypergonadotropic hypogonadism, small testes, gynaecomastia and infertility. There is also significant increased risk of arterial and venous thromboembolism (VTE), the pathophysiology of which is likely multifactorial. The role of testosterone replacement therapy in thromboembolic risk in KS remains unclear. This case demonstrates the hypercoagulable state associated with KS and highlights management issues including anticoagulation and antiplatelet agents. KS warrants consideration in unusual presentations of thromboembolism in young males.

**Table 1. Relevant baseline laboratory values**

| Test | Result | Reference range |
|---|---|---|
| Serial cTni (ug/L) | 0.51 to 32 | <0.01 |
| Creatine kinase (U/L) | 1290 | 46-171 |
| cTnI (i-stat) (ug/L) | 10.19 | <0.04 |
| LDL(mmol/L) | 2.2 | |
| HDL (mmol/L) | 1.2 | |
| Triglyceride (mmol/L) | 1.0 | <1.5 |
| Total cholesterol (mmol/L) | 3.8 | |
| TSH (mU/L) | 1.9 | 0.3-4.5 |
| FT4 (pmol/L) | 10 | 7.0-17 |
| Anti-cardiolipin Abs (CU) | 6 | <20 |
| Anti-beta 2 glycoprotein (G units) | 0 | <20 |
| Lupus anticoagulant | Negative | |
| APC resistance | 6.36 | |
| Antithrombin III | 1.01 | |
| Prothrombin 20210G>A | Absent | |
| Factor V Leiden | Absent | |
| Protein C (U/mL) | 1.17 | |
| Protein S (U/mL) | 0.92 | |
| C-ANCA | Negative | |
| P-ANCA | Negative | |
| ANA | Negative | |
| ENA | Negative | |
| APTT | 29 | |
| Platelets | 217 | |
| Fibrinogen | 2.3 | |
| INR | 1.1 | |

**Table 2. Reproductive profile**

| Test | Result | Reference range |
|---|---|---|
| Testosterone (nmol/L) | 3.7 | 9.0-35 |
| FSH (U/L) | 13 | 1.0-15 |
| LH (U/L) | 13 | 1.9-9.0 |
| SHBG (nmol/L) | 57 | 10-50 |
| Free testosterone (pmol/L) | 48 | >110 |
| Karyotype | 47XXY | |


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**200**

## The prevalence and risk factors for renal calcific disease in Multiple Endocrine Neoplasia Type 1-related primary hyperparathyroidism


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**Background**

Renal calcific disease (calculi and nephrocalcinosis) and renal impairment are potential sequelae of primary hyperparathyroidism (PHPT). Patients with Multiple Endocrine Neoplasia Type 1 (MEN 1) typically develop PHPT in the second decade of life. Management strategies for MEN 1 aim to treat PHPT at an early age to prevent complications including renal calcific disease (RCD) however, the prevalence and calcaemic thresholds for RCD development are unclear.

**Objective**

To determine the age-related prevalence and calcaemic thresholds RCD in MEN 1.

**Methods**

Patients with an MEN 1 genotype evaluated by the RHH were assessed in a retrospective longitudinal cohort study. The relationship between serum calcium [ionised (ICa); albumin corrected (CCa)] and RCD (on abdominal CT and ultrasound) was examined.

**Results**

Of 94 patients studied 28.7% manifest RCD, with renal calcification in up-to one quarter by age 30 (Table).

**RCD Prevalence (All Patients)** **RCD Prevalence (Patients stratified by serum calcium)**

| Age Range(yr) | Total n= | Sex(M:F) n= | RCD n=(%) | ICA<1.30;CCa<2.60 Total Pts n= (%RCD) | ICa1.30-1.40;CCa2.60-2.80 Total Pts n= (%RCD) | ICa>2.80;CCa>2.80 Total Pts n= (%RCD) |
|---|---|---|---|---|---|---|
| 0 -9.99 | 0 | 0:0 | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| 10 -19.99 | 16 | 7:9 | 0(0) | 2(0.0) | 5(0.0) | 9(0.0) |
| 20 -29.99 | 43 | 14:29 | 7(16.3) | 1(0.0) | 19(5.3) | 23(26.1) |
| 30 -39.99 | 50 | 21:29 | 7(17.0) | 1(0.0) | 18(5.6) | 31(19.4) |
| 40 -49.99 | 53 | 19:34 | 6(11.3) | 0(0.0) | 17(0.0) | 36(16.7) |
| 50 -59.99 | 38 | 12:26 | 10(26.3) | 1(0.0) | 9(33.3) | 28(25.0) |
| 60 -69.99 | 22 | 6:16 | 2(9.1) | 1(0.0) | 2(0.0) | 19(10.5) |
| >=70 | 10 | 2:8 | 0(0.0) | 1(0.0) | 0(0.0) | 9(0.0) |
| **Total** | **94** | **38:56** | **27(28.7)** | **4(0.0)** | **27(14.8)** | **63(36.5)** |

**Discussion/Conclusions**

Hypoparathyroidism is recognized as an important complication of the subtotal total parathyroidectomy used for treating PHPT in MEN 1. Concern regarding hypoparathyroidism is particularly important when contemplating parathyroidectomy in adolescents with MEN 1. Our findings suggest patient age and degree of hypercalcaemia do influence RCD risk and this information could be used to inform parathyroidectomy timing.

**201**

## Insulin Autoimmune Syndrome: a case of clopidogrel-induced autoimmune hypoglycaemia

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Insulin Autoimmune Syndrome (IAS) is characterized by hyperinsulinaemic hypoglycaemia with elevated anti-insulin antibodies. The syndrome is commonly reported in the Japanese population without known precipitants, but in other populations there are reports of IAS occurring with other autoimmune diseases, plasma cell dyscrasias and sulfhydryl group medication use. The active metabolite of clopidogrel has a sulfhydryl group and here we report a case of clopidogrel-induced IAS.

A 67 year-old Caucasian male presented with progressive, intermittent confusion and conscious collapses in the setting of spontaneous hypoglycaemia (plasma glucose ~1.5mmol/l). The patient's symptoms commenced nine months previously when he was started on clopidogrel therapy following an acute myocardial infarction.

The patient's hypoglycaemia was persistent, independent of meals or fasting, and was associated with elevated levels of insulin (>600 mU/L,Reference Range [RR]<10), C-peptide (9.9 pmol/mL,RR<0.7), pro-insulin (>100 pmol/L,RR<13) and anti-insulin antibody (76,RR<0.7). Other endocrine axes were within normal limits and sulfonylurea screen was negative. Insulinoma was excluded on multiple localising studies including Dotate and GLP-1 PET scans. Given the above, a diagnosis of IAS was made. The patient had no evidence of a plasma cell dyscrasia or other autoimmune diseases. HLA typing revealed the HLA-DRB1*04 haplotype which has been associated with IAS. Furthermore, clopidogrel was the only new medication that the patient was taking that contained a sulfhydryl group.

During a prolonged hospital stay, intravenous administration of 10% dextrose, oral dexamethasone and diazoxide therapy and cessation of clopidogrel failed to alleviate the persistent hypoglycaemia. Plasmapharesis was started which quickly normalised the patient's glucose, insulin, anti-insulin antibody levels. At four months follow-up the patient has remained normoglycaemic without any further interventions.

We believe that this is only the second reported case of clopidogrel induced IAS. Given the ubiquity of clopidogrel use, IAS should be considered as a rare adverse effect of this medication.

**202**

## Lessons from beyond the Graves'

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**Introduction:** We report 2 patients with Graves' disease (GD) who had 'silent' thyroid cancers.

**Case 1:** A 20yo female was diagnosed with GD (clinical signs of Graves' ophthalmopathy, goitre, sinus tachycardia, unintentional weight loss; TSH <0.005mIU/L [0.40-3.50mIU/L]; FT4 40.9pmol/L [9.0-19.0pmol/L]; FT3 >46.1pmol/L [2.6-6.0pmol/L]; TRAb 27.5IU/L [<1.0IU/L]). She commenced on carbimazole.

Her initial thyroid ultrasound (January 2017) demonstrated a heterogenous, hypervascular goitre, , which had on her repeat ultrasound (April 2017) increased in size. A thyroid technetium scan revealed diffuse radiotracer uptake (82.51%).

Due to refractory GD, a total thyroidectomy was performed (February 2018), revealing a 60mm papillary thyroid carcinoma in the right lobe and a 36mm papillary thyroid carcinoma in the left lobe, with lymphovascular and adipose tissue invasion. The tumours were negative for BRAF V600E.

Six weeks post-thyroidectomy, she had a thyroglobulin level at 16.3µg/L [0-28µg/L], undetectable anti-thyroglobulin antibody and TRAb 4.4IU/L. Radioactive iodine remnant ablation is planned.

**Case 2**: A 44yo female had severe thyrotoxicosis from GD (clinical signs of sinus tachycardia, unintentional weight loss, lid-lag and goitre; TSH <0.005mIU/L; FT4 43.1pmol/L; FT3 >46.1pmol/L; TRAb 176IU/L) requiring propanolol and carbimazole. A thyroid technetium scan revealed diffuse radiotracer uptake consistent with GD.

She was refractory to treatment, developing Grave's ophthalmopathy. A total thyroidectomy was performed (July 2015). Histopathology revealed a 12mm follicular thyroid cancer in her left lobe, surrounded by Graves' thyroiditis. Lymphovascular and right lobe invasion were not present. Radioactive iodine ablation was performed in Sept 2015, with a whole-body I-123 scan indicating absent residual iodine-avid tissue. She has not had recurrence of her follicular thyroid carcinoma.

**Conclusions:**

Patients with GD have an increased risk of thyroid carcinomas, possibly related to TRAbs. It is usually either clinically apparent or occult micro-carcinomas. Large papillary thyroid carcinomas in GD not detected by thyroid scan or ultrasound is rare.

## 203

### Graves' disease, but not as we know it!

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**Introduction:** Although uncommon, unilateral Graves' disease (GD) can occur in a bilobar thyroid gland. We report an unusual case of not only unilateral GD, but also a concurrent aggressive form (tall cell variant) of papillary thyroid carcinoma (PTC).

**Case**: A 54yo male was referred with dysphonia, nervousness, unintentional weight loss of 7kg and diarrhoea for the last 3 months. He was cachexic and had a fine tremor. He had 2 non-tender nodules in his left thyroid gland.

He had suppressed TSH (<0.04mIU/L [0.20-3.5mIU/L]), elevated FT4 (51.7pmol/L [10.0-22.0pmol/L]) and FT3 levels (22.2pmol/L [3.2-6.3pmol/L]). Thyroid auto-antibodies (TRAb not measured) were normal and thyroglobulin level was 7IU/mL [0-60IU/mL]. Thyroid ultrasound identified an irregular, highly vascular, isoechoic nodule involving the superior and mid poles of the left lobe only [16x10x18mm]. His thyroid technetium scan demonstrated diffuse, avid radiotracer uptake, particularly in the superior and mid poles of the left lobe, whilst the right lobe remained suppressed. At the time, these investigations were reported as being consistent with toxic adenomata. He was commenced on carbimazole.

On the assumption that he had toxic adenomata of the left lobe, a left hemithyroidectomy was performed. Histopathology revealed an 11mm multifocal PTC, with features of a tall cell variant, in the left lobe. There were also diffuse, mild hyperplastic changes, consistent with treated GD. He had completion thyroidectomy 14 days later. Histopathology demonstrated a microscopic (0.5cm) PTC in the inferior pole of the right lobe.

Post-operatively he received radioiodine remnant ablation. He remains euthyroid, with no further recurrence of his PTC 12 years after initial presentation.

**Conclusions:**

GD can occur unilaterally and imaging of the thyroid may be misleading. The exact aetiology for unilateral GD is unknown. Aggressive variants of PTC, such as the tall cell variant, are more frequent in patients with GD.

## 204

### A difficult case of Cushing's disease

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A 61-year-old legal assistant presented to the Endocrinology Clinic with symptoms and signs of cortisol excess. She was found to have extremely aggressive Cushing's disease with recurrence and regrowth within the left cavernous sinus despite two trans-sphenoidal debulking surgeries, three treatments with radiotherapy, two cycles of Temozolomide in conjunction with Ketaconazole and Metyrapone and finally bilateral adrenalectomies. Dosage of medical treatment was limited by adverse side-effects. Pituitary histology was concerning with a high mitotic-count and an elevated Ki67 of 12%. It stained weakly for ACTH, but not for prolactin or Programmed-Cell-Death-1 ligand (PDL-1). She progressed to develop left sided ptosis, a below knee deep venous thrombosis and new fragility vertebral fractures. Retrospective immunohistochemistry staining of her pituitary tumour revealed mismatch repair gene (MMR) mutations, and negative staining for Epithelial Growth Factor Receptor (EGFR). With limited treatment options remaining, she is being considered for PD1-inhibitor and possibly tyrosine-kinase inhibitor therapies.

PD-L1 expression has been measured in pituitary tumours with reports that functional tumours are more likely to express PD-L1, and therefore respond to PD1-inhibitors than non-functional tumours(1). PD1-inhibitors have also been reported to be effective in PD-L1 negative tumours staining for MMR mutations(2). Finally, a large proportion of ACTH-secreting adenomas express EGFR. Tyrosine-kinase inhibitors bind to the tyrosine-kinase domain of EGFR and deactivates EGFR activity(3).

This case highlights firstly the significant morbidity in Cushing's disease. Secondly, in persistent/recurrent Cushing's disease, treatment has largely involved the use of steroidogenic inhibitors, whose therapeutic efficacy has often been limited by adverse effects. Therefore, there remains the need for more effective systemic medical therapies that can target the residual pituitary tissue. PD1- and tyrosine-kinase inhibitors are novel classes of therapy that may be considered in functioning pituitary tumours. However, the role of immunohistochemistry in predicting treatment response in pituitary tumours requires further study.

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**205**

## Symmetrical Changes on Bone Scan in a Patient with Breast Cancer

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Introduction: In the absence of renal osteodystrophy, symmetrical uptake on $^{99m}$Tc-bone scans is an exceedingly rare finding and not the typical pattern seen in metabolic bone disease or skeletal metastases. We report a rare case of Erdheim-Chester disease in a patient with breast cancer.

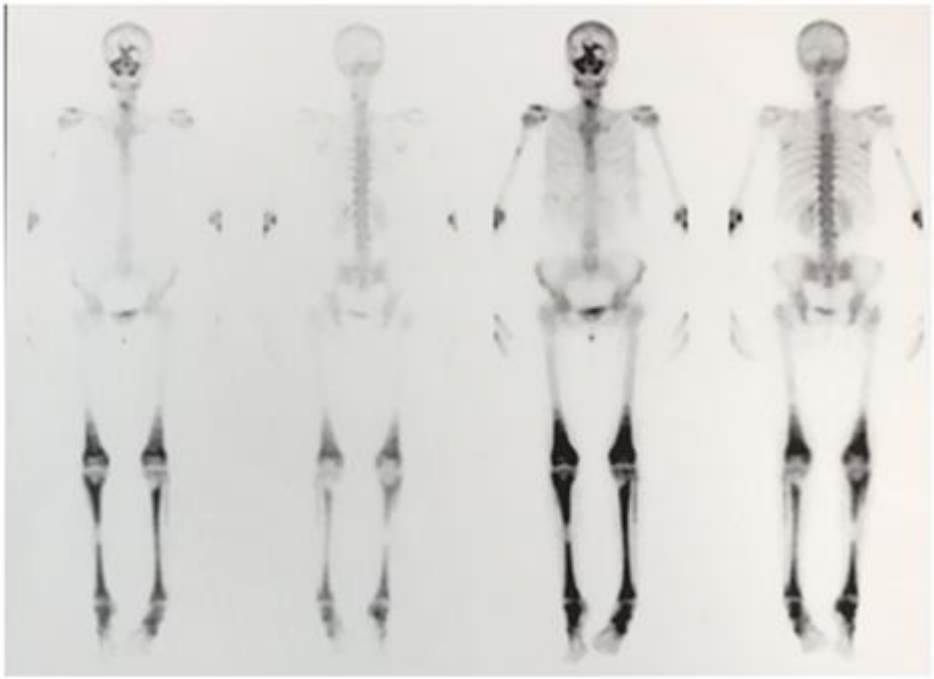
Case: A 63-year old female with hormone-receptor-positive breast cancer was referred for evaluation of an abnormal bone scan, which had been performed for staging. This displayed increased $^{99m}$Tc activity bilaterally in the long bones of the upper and lower limbs (Figure 1). She was asymptomatic. There was no history of metabolic bone disease, osteosclerosis or sickle cell anaemia. A regional bone scan performed 5 years prior showed increased uptake, but to a lesser extent, in the distal long bones.

Myeloma, hyperparathyroidism and vitamin D deficiency were excluded and a maker of bone turnover, specifically urine deoxypyridinoline, was mildly elevated.. Plain radiograpphy demonstrated sclerotic changes of the long bones and MRI demonstrated symmetrical abnormalities within the trabecular compartment and marrow signal . Bone biopsy of the proximal tibia demonstrated foamy histiocytes with weak BRAF positivity, associated fibrosis and sclerosis, supporting a diagnosis of Erdheim-Chester Disease. There was no evidence of associated endocrinopathy or typical changes seen in Erdheim-Chester such as hairy kidney or cerebral involvement.

Discussion: Erdheim-Chester disease is a rare histiocytic disorder that classically results in symmetrical bone scan uptake with sclerosis of the long bones. Our patient was asymptomatic and may display an indolent course. Other cases may result in endocroniopathy such as diabetes insipidus, and potentially fatal multi-organ involvement. BRAF inhibitors, interferon or glucocorticoids may modify the disease course,

Conclusion: Symmetrical long bone sclerotic changes are classical of Erdheim Chester disease. Due to potential multi-system involvement, recognition of this disorders and regular monitoring even in an asymptomatic patients is necessary.

Figure 1: Bone scan



## 206

## Lactation ketoacidosis: a rare cause of metabolic acidosis

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**Background:** Lactation ketoacidosis is an infrequent but clinically significant cause of high anion gap metabolic acidosis.[1,2] We describe a case of severe ketoacidosis in a non-diabetic lactating woman.

**Case:** A 20-year-old 12 weeks postpartum woman who was breastfeeding her child presented with 2 days of nausea, vomiting and was unable to tolerate any oral intake. Since delivery, she had been having irregular small meals with an overall low daily calorie intake. Her pregnancy and medical history were unremarkable, and she was not on any regular medications. She had mild epigastric tenderness with a soft abdomen. Investigations revealed severe non-diabetic ketoacidosis: pH, 7.13; pCO2, 25mmHg; bicarbonate, 8mmol/L; point-of-care ketone, 5.7mmol/L; glucose, 4.4mmol/L; and with an elevated anion gap of 25mmol/L. Lactate was normal and history did not reveal alcohol or toxin ingestion. Full blood count, lipase, liver enzymes and electrolytes were unremarkable. Acidosis, ketosis and symptoms rapidly resolved with the administration of intravenous dextrose. A diagnosis of lactation ketoacidosis was made. The patient was discharged with dietary advice to ensure sufficient energy intake while breastfeeding.

**Discussion:** While fasting under ordinary circumstances produces mild acidosis at maximum, it can be dangerous during lactation. The increased energy requirements of lactation cause enhanced gluconeogenesis, decreased insulin secretion, lipolysis and can subsequently induce ketogenesis. The metabolic demands of breastfeeding coupled with carbohydrate deficiency put lactating women at risk of ketoacidosis.[3,4] There have been only a few reported cases of lactation ketoacidosis.[2,4] Most commonly reported precipitating factors include fasting in the context of an acute illness and low-carbohydrate diets. Energy replacement and rehydration resulted in complete symptomatic and biochemical resolution in all cases.[1,2]

**Conclusion:** Awareness of this potential cause of ketoacidosis is vital for early recognition and appropriate management. Glucose administration is the mainstay of treatment. Education regarding the nutrition requirements during breastfeeding is essential.[1,2]

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## 207

## Proton pump inhibitor-induced hypomagnesaemia and hypocalcaemia

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We present the case of a 75-year-old man who was admitted with symptomatic severe hypomagnesaemia of 0.17mmol/L (range:0.70-1.05) and concomitant severe hypocalcaemia 1.73mmol/L (corrected calcium, range:2.15-2.55), with perioral and distal extremity paraesthesias. He had been taking Omeprazole 40mg daily for Barrett’s oesophagus for several years. He had also had many years of mild intermittent diarrhoea following partial colectomy for colorectal cancer. Review of past pathology results revealed previous persistent hypomagnesaemia since he was commenced on Omeprazole. Magnesium supplementation was started, and magnesium levels had remained normal whilst on regular magnesium supplements. However, these were self-ceased by patient in the preceding week. Examination was unremarkable. Other investigations showed parathyroid hormone (PTH) level of 5.7pmol/L (range:1.0-7.0), phosphate of 1.22mmol/L (range:0.8-1.5), potassium of 3.2mmol/L (range:3.5-5.5), 25-hydroxyvitaminD of 112nmol/L (range:50-200) and normal kidney function. Electrocardiogram revealed mild prolonged QT interval.

Omeprazole was considered to be the primary cause of his hypomagnesaemia, although his diarrhoea could have also contributed. He was not malnourished and was not on diuretics. His symptoms, biochemistry and electrocardiogram normalised following intravenous electrolytes replacement. Ranitidine was substituted for Omeprazole. Oral magnesium supplements were restarted. Repeat serum magnesium and calcium 2 weeks after hospital discharge remained normal.

Hypomagnesaemia is a rare, potentially life-threatening, adverse class effect of proton pump inhibitors (PPIs).[1,2] The hypomagnesaemia often coexists with hypocalcaemia, hypokalaemia and functional hypoparathyroidism, with low or low-normal PTH.[1,3] Hypomagnesaemia is typically seen in patients over age 50 on prolonged PPI treatment (>1 year). The proposed mechanism is impaired active and passive absorption of magnesium.[1] Hypomagnesaemia may lead to secondary hypocalcaemia due its inhibitory effects on PTH secretion and action, increased breakdown of PTH into inactive metabolites and interference with calcium sensing receptor transduction.[2,3] Hypomagnesaemia-induced kaliuresis can lead to hypokalaemia.[1]

Our case highlights the potential association of severe hypomagnesaemia with the long-term use of PPIs.

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**208**

## Extremely low high-density lipoprotein cholesterol

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We report the case of a 58-year-old woman who was referred to the Endocrine clinic in November 2017 with longstanding dyslipidaemia. Past lipid panel since 2006 (table) had revealed intermittent hypertriglyceridaemia, a mild elevation in her total cholesterol and low-density lipoprotein (LDL) levels and notably, extremely low high-density lipoprotein cholesterol (HDL-C) levels, with a nadir of 0.21mmol/L. Cardiovascular risk factors included overweight (body mass index 26.3kg/m2) and a 10-pack-year smoking history. She had no diabetes, hypertension or symptoms of cardiovascular disease (CVD). There was no known family history of dyslipidaemia or premature CVD. She took no regular medications. Her Australian Absolute CVD risk score indicated moderate to high risk.[1] Advice on lifestyle modification was provided. Treatment with low dose Pravastatin was started in August 2017. Repeat lipid analysis whilst on Pravastatin revealed improved lipid levels however with persistently low HDL-C levels of 0.20-0.34mmol/L. Pravastatin dose was gradually uptitrated with a goal to reduce her LDL-C level to improve her LDL-C/HDL-C ratio.

**Table: Lipid panel from 2006 to 2018**

| | June 2006 | Aug 2007 | Feb 2011 | Feb 2016 | June 2017 | Aug 2017 | Sept 2017 | Jan 2018 | April 2018 |
|---|---|---|---|---|---|---|---|---|---|
| Cholesterol (2.30-5.50 mmol/L) | 4.69 | 4.06 | 3.92 | 4.18 | 5.02 | **5.62↑** | 3.88 | 4.12 | 4.14 |
| Triglyceride (0.00-2.00 mmol/L) | **2.09↑** | **2.26↑** | 1.57 | 1.64 | 1.68 | **3.24↑** | 1.39 | 1.77 | 1.65 |
| HDL (1.00-3.00 mmol/L) | - | **0.29↓** | **0.24↓** | - | **0.35↓** | **0.21↓** | **0.34↓** | **0.24↓** | **0.20↓** |
| LDL (0.00-3.50 mmol/L) | - | 2.7 | 3.0 | - | **3.9↑** | **3.9↑** | 2.9 | 3.1 | 3.2 |

Low HDL-C correlates with an increased risk of CVD [2,3] and extremely low HDL-C is defined as level <0.52mmol/L.[3,4] Causes of low HDL-C, either familial or acquired, must be ascertained. Management of acquired low HDL-C involves correction of secondary factors including insulin resistance, hypertriglyceridaemia, overweight and obesity, very high carbohydrate intake, dysglobulinaemia, cigarette smoking and use of progestational agents and anabolic steroids.[2,4] Reduction of the risk of atherosclerosis is the primary goal in the management of low HDL-C, with lifestyle intervention as the first line management.[2,4] Currently available drugs do not robustly raise HDL-C. Statins generally increase HDL-C by 5-10%, however most risk reduction is achieved by lowering LDL-C.[5] No clear recommendations are available thus far for targeting HDL-C due to lack of convincing outcomes data for HDL-C specific therapies. Several HDL-C-raising novel therapies are currently undergoing trials.[4,5]

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**209**

## Patients receiving teriparatide in a tertiary referral centre have multiple co-morbidities and fractures but a similar bone mineral density response to published literature

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**BACKGROUND:** Teriparatide is subsidised for patients with severe osteoporosis who fracture despite anti-resorptive therapy. Clinical trials with teriparatide demonstrate improvements in bone mineral density (BMD) and fracture risk reduction but the application of these findings to real-world practice is uncertain.

**OBJECTIVE:** To characterise patients prescribed teriparatide in a tertiary hospital and evaluate teriparatide completion and consolidation with anti-resorptive therapy.

**METHODS:** Retrospective audit of patients commencing teriparatide between January 2014-April 2018. Clinical information was extracted from medical records. Analysis included calculation of co-morbidity score (Silverman SL. *et al. Osteoporosis International*, 2016) and descriptive statistics.

**RESULTS:** Of 49 patients commencing teriparatide, most were female (82%), post-menopausal (97%), had a median (IQR) age of 70 (58,76) years and received bisphosphonates prior to teriparatide (83%). All patients had multiple fragility fractures, with ≥5 and ≥10 fragility fractures observed in 46% and 10% respectively. Median (IQR) pre-treatment spine and femoral neck T-scores were -2.6 (-3.3,-1.1) and -2.8 (-3.5,-1.9) respectively. Median co-morbidity score was 4 (2,5). In 2018, 22/49 patients were currently taking, 14/49 completed and 4/49 patients discontinued teriparatide (inadequate information for 9/49). Reasons for teriparatide discontinuation were: death (n=2), side-effects (n=1) and non-compliance (n=1). Anti-resorptive therapy post-teriparatide was not received within 3 months in 2/14 patients due to missed appointment (n=1) and loss to follow-up (n=1). After a median (IQR) teriparatide duration of 16 months (13,18), the median change in lumbar spine and femoral neck BMD was: +0.055g/cm$^2$ (+0.020,+0.114) and +6.8% (+2.2,+12.6) at the lumbar spine and +0.027 g/cm$^2$ (+0.004,+0.038) and +4.1% (+0.5, +4.8) at the femoral neck.

**CONCLUSIONS:** Patients receiving teriparatide in a tertiary hospital have multiple fractures, low BMD and a high co-morbidity index. The BMD increase is consistent with clinical trials of teriparatide in patients with prior bisphosphonate exposure. Care should be taken to ensure timely antiresorptive therapy following teriparatide completion.

**210**

## A novel paraganglioma syndrome driven by both germline and somatic mutation

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**Introduction:** Following the well-established association between succinate dehydrogenase (SDH) deficiency and PGL, *SDHA/B/C/D* mutations have been associated with paraganglioma (PGL), renal cell carcinoma (RCC), gastrointestinal stromal tumour (GIST) and pituitary adenoma (PA).[1,2] Some individuals/families have developed more than one tumour;[3,4] however, no family has been reported with all tumours. A subset of phaeochromocytoma/PGL associated with germline *SDHB* mutations harbour somatic *ATRX* variants, suggesting digenic models of SDH-deficient tumorigenesis.[5]

**Methods:** A kindred presented with head and neck PGL in two siblings, GIST in a third sibling and macroprolactinoma in the fourth sibling. Their mother died from RCC. Despite loss of normal SDHB immunostaining in the PGL specimens, routine genetic testing of *SDHB/C/D/AF2*, as well as *RET*, *VHL* and *TMEM127* failed to identify causative mutations. We performed in-house whole exome sequencing (WES) using germline DNA from the four siblings and tumour DNA from PGL and GIST formalin-fixed, paraffin-embedded specimens.

**Results:** WES yielded 199 germline variants that were: rare (<1% population); heterozygous in each sibling (consistent with autosomal dominant inheritance); likely damaging (by *in silico* analysis); and of high quality and depth of coverage (>30x). These included a novel deep intronic *SDHC* variant predicted to generate an alternate splice donor site with downstream frameshift, and a novel missense variant in *PTCH2*, a gene implicated in nevoid basal cell carcinoma syndrome ('Gorlin's syndrome'). Transcriptome analysis of whole blood by RNA-Seq is underway to confirm altered *SDHC* expression and to evaluate other candidate variants. Using similar filtration, we identified 437 somatic variants with involvement of known PGL- and GIST-predisposing genes, raising the possibility of multigenic tumorigenesis pathways.

**Conclusions:** The highly penetrant coexistence of PGL, RCC, GIST, PA and a novel segregating *SDHC* mutation describes a new paraganglioma syndrome, with possible contributions from germline and somatic variants in other genes.

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## 211

### Case reports of SIADH in lung-transplant patients on tacrolimus

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Two retrospective studies (see references) presented a small case series of tacrolimus induced hyponatraemia in lung transplant recipients, which has not been reported in lung transplant patients previously. We present two cases of Syndrome of Inappropriate Anti-Diuretic Hormone Secretion in post bilateral lung transplant cystic fibrosis patients on tacrolimus.

First case is a 34 year old gentleman who underwent bilateral sequential lung transplantation via bilateral anterior thoracotomies. He was commenced on prednisolone and tacrolimus. His immediate post-operative course was complicated by Clostridium difficile, subcutaneous emphysema and a hyponatraemic seizure 2 weeks post-transplant which required an ICU admission for hypertonic saline and close monitoring. His sodium decreased from 133 mmol/L pre-lung transplant to 117 mmol/L on day of seizure. Concurrent plasma osmolality was 261 mmol/kg [275-295 mmol/kg], urinary osmolality was 636mmol/kg and urinary sodium 36mmol/L. Post-acute management of hyponatraemia, tacrolimus was changed to cyclosporine. Patient's medical history includes CF related diabetes and pancreatic exocrine insufficiency, and he was normoglycaemic during the seizure. Hyponatraemia screening bloods included HbA1c of 5.6%, TSH 1.80 mu/L [0.4 – 4.0], fT4 11 pmol/L [9-19] and a cortisol 770 nmol/L (on prednisolone).

Second case is a 54 year old gentleman, 5 months post bilateral lung transplant also on tacrolimus, who presented to hospital with 2 week history of abdominal crampy pain and watery non-bloody diarrhoea. Tests for pancreatitis, inflammatory bowel disease, carcinoid and amyloidosis were unremarkable. His sodium decreased from 140 to 117 mmol/L, plasma osmolality was 248 mmol/kG with a urine sodium 162 mmol. Patient's hyponatraemia resolved with aggressive fluid restriction (600ml). Hyponatraemia screening tests included TSH 1.10 mU/L [0.4 – 4.0], fT4 15 pmol/L [9-19 pmol/l] and a HbA1c 6.4%.

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## 212

### Optimising adrenal vein sampling: assessing the influence of ACTH stimulation

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**Objective:** Adrenal vein sampling (AVS) is the gold standard investigation for primary hyperaldosteronism. By differentiating unilateral versus bilateral hyperaldosteronism, AVS can influence the decision for surgical or medical treatment. However, AVS yield depends upon successful cannulation of both adrenal veins, which is technically challenging (1). Adrenocorticotropic hormone (ACTH) stimulation has been reported to improve bilateral adrenal vein cannulation rates (2). The aim of this study was to investigate the influence of ACTH stimulation on AVS studies performed at a single tertiary metropolitan hospital.

**Method:** AVS studies were performed in 43 individuals between 1999 and 2018 by 11 proceduralists. 17 procedures were performed with ACTH stimulation. Successful cannulation was defined as a selectivity index (SI) (adrenal vein:peripheral vein cortisol) greater than 2 pre-ACTH and greater than 3 post-ACTH. Lateralisation was defined as a lateralisation index (LI) (ipsilateral aldosterone/cortisol:contralateral aldosterone/cortisol) greater than 4. An experienced proceduralist was defined as having performed more than the median number of AVS procedures.

**Results:** 43 procedures were conducted and the median number performed per proceduralist was 1. 15 procedures achieved bilateral adrenal vein cannulation. Unsuccessful right adrenal vein cannulation occurred in 23 patients. 17 of the total and 12 of the successful procedures were performed with ACTH stimulation; the rate of bilateral adrenal vein cannulation improved from 3 of 26 without stimulation to 12 of 17 with stimulation. Post-stimulation cannulation was significantly more successful than pre-stimulation ($p = 0.001$). 9 of 15 successful procedures were performed by the most experienced proceduralist, 7 of which were performed with stimulation; however, there was no association between above median experience and successful cannulation ($p = 0.40$).

**Conclusion:** Successful bilateral adrenal vein cannulation improved with ACTH stimulation. In future, point-of-care cortisol and Cone Beam CT to image the adrenal veins may further assist bilateral cannulation rates (3).

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## 213

## Maternal metyrapone use during breastfeeding: safe for the breastfed infant

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***Abstract:***

*Context:* Metyrapone is an inhibitor of endogenous adrenal corticosteroid synthesis which has been proven to be a viable and safe option in controlling maternal serum cortisol concentrations during pregnancy. The infant exposure to maternally ingested metyrapone through breast milk is, however, largely unknown.

*Case Description:* We report the excretion of metyrapone into breast milk and subsequent infant exposure from a lactating woman on 250mg of metyrapone three times daily. At steady state, the average concentrations in milk and absolute and relative infant doses (AID and RID) were 176 ug/L, 26.45 ug/kg/d, and 0.7% respectively for metyrapone, and 310 ug/L, 46.52 ug/kg/d, and 1.21% for its active metabolite rac-metyrapol. The breastfed infant was found to have a plasma metyrapone concentration of 0.05 ug/L, with no evidence of disruption to his adrenocortical axis biochemically.

*Conclusion:* These findings indicate that maternal metyrapone use during breastfeeding did not pose a significant risk to the breastfed infant.

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**214**

## The pathogenesis of hypergastrinaemia in MEN 1 and its relationship to Helicobacter Pylori infection

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**Background**

*Helicobacter pylori* (*H. Pylori*) infection is typically acquired in the early decades of life and, if not cleared, is associated with gastritis and hypergastrinaemia [1]. Similarly, Multiple Endocrine Neoplasia Type 1 (MEN 1) predisposes gene carriers to a 30-40% risk of developing either hypergastrinaemia or overt Zollinger-Ellison Syndrome (ZES). Gastrinomas in MEN 1 are typically multifocal submucosal duodenal lesions. Further, *H. Pylori* incidence is augmented by the acid environment which prevails in MEN 1 and ZES.

**Objective**

To determine if a relationship exists between *H. Pylori* IgG seropositivity and hypergastrinaemia /ZES in MEN 1.

**Methods**

A retrospective longitudinal cohort study involving 99 individuals with MEN 1 who underwent fasting serum gastrin and *H pylori* serum IgG immunoassay assessment (mean age 43.9±17.9 years, 66.0% female). All patients were confirmed to have the Tasman 1 *MEN1* gene mutation. ZES-range hypergastrinaemia was defined as gastrin >10-fold normal elevated.

**Results**

Of the 99 patients tested for *H pylori*, 36 (36.4%) of cases were IgG seropositive. Serum gastrin was elevated greater than one-fold normal in 29 (80.6%), five-fold normal in 17 (47.2%) and ten-fold normal in 11 (30.6%) of the *H pylori* IgG positive patients. Of the 63 patients with negative *H pylori* serology, serum gastrin was elevated greater than one-fold normal in 30 (47.6%), five-fold normal in 6 (9.5%) and ten-fold normal in 2 (3.2%) patients. Of those patients with ZES-range serum gastrin elevation, 11 of 13 (85%) were *H pylori* IgG seropositive.

**Conclusion**

Severe hypergastrinaemia and ZES was strongly associated with *H. Pylori* seropositivity in this study. Chronic mild-moderate *H. Pylori*-related hypergastrinaemia may have the potential to stimulate pathogenesis of gastrinoma in MEN 1 by promoting neuroendocrine cell hyperplasia. This warrants further investigation.

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## 215

### The natural history of borderline TSH elevation and suppression: a longitudinal population study

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**Background**

Current guidelines recommend TSH testing for initial evaluation of thyroid function. Borderline TSH abnormalities (0.1-0.4mIU/L and 4.0-10mIU/L) are seen in this context. However, unlike subclinical hypothyroidism and hyperthyroidism, the natural history of borderline TSH abnormalities, including frequency of progression to overtly abnormal TSH, is poorly characterised.

**Objective**

To determine the likelihood of progression to overt TSH abnormality for patients with borderline TSH abnormalities.

**Methods**

We performed a population-based retrospective longitudinal data-linkage study for TSH tests performed in Tasmania from 1996-2013. TSH results were linked to identifier numbers to permit patient-specific follow-up. Kaplan-Meier methodology was used to summarise time to conversion to overtly elevated (>10mIU/L) and suppressed (<0.1mIU/L) TSH for patients with borderline elevated and suppressed TSH, respectively.

**Results**

367,917 patients had 1,296,060 TSH tests analysed. Of the 21,426 patients with borderline-elevated TSH, those in the >80yo age group at the time of incident testing were most likely to progress to full elevation (conversion rate 9.0% at 2.5yrs, 11.3% at 5yrs, 12.6% at 10yrs), with those in the <20yo age group least likely to progress (3.8% at 2.5yrs, 5.1% at 5yrs, 6.5% at 10yrs).

Of the 20,366 patients found to have borderline-suppressed TSH, those in the 60-79yo age group at the time of incident testing were most likely to progress to full suppression (12.1% at 2.5yrs, 16.0% at 5yrs, and 19.4% at 10yrs), with those in the <20yo group again least likely to progress (5.3% at 2.5yrs, 6.7% at 5yrs, 9.0% at 10yrs).

**Conclusions**

Periodic TSH re-testing is appropriate for patients with borderline TSH abnormalities, but the re-testing interval should be determined by the likely rate of progression. Progression from borderline to overt TSH abnormality increases with the patient's age at the time of initial testing. Borderline TSH suppression is also more likely to progress than borderline TSH elevation.

## 216

### Headaches from the heart

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Ms PI, a 38 year old female living in a rural town, presented with a 12 month history of paroxysmal severe headaches, flushing, tachycardia and unintentional weight loss of eight kilograms. She had seen multiple different GP's over this time, and had been diagnosed with migraines and psychological issues. Endocrine was consulted upon review with a new GP. Upon Endocrine review, Ms PI was not hypertensive, and examination was unremarkable. She had no personal or family medical history. Work-up revealed significantly elevated urine fractionated metanephrines and catecholamines, including noradrenaline, dopamine, vanillylmandelic acid, normetanephrine, and 3 methoxytyramine. This correlated with raised plasma metanephrines, and so work-up proceeded to localise the source of her excess catecholamines. Initial MRI abdomen was unremarkable, thus she went on to have a Gallium-68 DOTATE PET, which revealed an intensely DOTATATE avid left atrial/inter-atrial septum lesion consistent with neuroendocrine tumour/paraganglioma. Further imaging included a cardiac MRI and echocardiogram. Ms PI underwent pre-operative assessment with a coronary angiogram, which showed 3 coronary artery tributaries feeding the tumour. She was pre-operatively treated with phenoxybenzamine, followed by metoprolol. She had a surgical resection which revealed a highly vascular 70mm tumour in the inter-atrial groove. Histopathology was consistent with paraganglioma and her genetic studies are pending. Cardiac paraganglioma's are exceptionally rare, and this case was the second case in our centre over the past decade. Her case highlights the importance of considering a pathological cause for all systemic symptoms, and that excellent and prompt specialist care can still be delivered despite living in a rural location. Her case also demonstrates the utility of DOTATATE PET in localising paragangliomas.

## 217

### Diabetic Nephropathy and its early marker

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**Objective:**

Diabetic nephropathy is a non-communicable progressive disease which is the reason of high mortality rates in Pakistan. The study aims to detect early markers in diabetic nephropathy.

**Methods:**

An observational study was conducted Sir Ganga Ram Hospital, Lahore. The duration of study was one year. A total of 100 patients were selected in the study. The selection was done by distributing a questionnaire containing particulars age, gender, history of blood pressure, weight and socio economic status. Blood films were prepared after collecting blood samples for the determination of plasma glucose, serum creatinine and blood urea. Urine sample was also obtained for the screening of microalbuminuria which was supposed to be the first marker of diabetic nephropathy.

**Results:**

A total of 100 patients were selected with 60% male and 40 % female. The mean age of the patients were 50 years. 75% were the patients of diabetes and hypertension while 25% were only diabetic. The prevalence of microalbuminuria was present in 42% males and 58 % females. It was analyzed that duration of diabetes, serum glucose level and blood pressure correlates with microalbuminuria. Serum urea and creatinine was also raised in 27% patients.

**Conclusion:**

Microalbuminuria is an early marker of diabetic nephropathy. Hence in order to prevent this communicable disease, all diabetic patients should be screened routinely.

**219**

## Issues of hypoglycaemia unawareness in a 55 year old man with a proinsulinoma

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Clinically significant hypoglycaemia, in the absence of glucose lowering agents, is uncommon. Current guidelines recommend investigating hypoglycaemia only when Whipple's triad is documented, i.e. symptoms and/or signs of hypoglycaemia, low measured plasma glucose and resolution of symptoms/signs after increasing the glucose concentration. (1)

We describe an unusual case of hypoglycaemia in a healthy asymptomatic 55-year-old man, who often drove 3h at a time for work and did not meet the requirements of the Whipple's triad. An incidental low fasting plasma glucose concentration of 2.4 mmol/L led to further assessment in which morning plasma glucose measured twice was low (2.9-3.3 mmol/L) with insulin, proinsulin and c-peptide levels suggestive of a possible (pro)-insulinoma. Sulphonylurea screen was negative. As Whipple's triad had not been documented, a 72 hour fast was undertaken which was terminated after only 12 hours due to hypoglycaemia (laboratory plasma glucose 2.4mmol/L), albeit asymptomatic. The corresponding plasma insulin (4.7 mU/ml), proinsulin (>99 pmol/L) and C-peptide (1.1 nmol/L) concentrations indicated a likely diagnosis of proinsulinoma. Endoscopic ultrasound (EUS) revealed a well circumscribed mass in the body of the pancreas and cytological analysis of a needle aspirate was in keeping with a neuroendocrine tumour. A subsequent Gallium-68 dotatate positron emission tomography demonstrated intense uptake in the region corresponding to the EUS lesion and a hypodense lesion, retrospectively seen, on a computed tomography scan (previously reported normal). The patient has been referred for surgical resection of this suspected proinsulinoma.

This interesting case highlights the challenges faced in diagnosis, when Whipple's triad cannot be documented, and in management, when hypoglycaemia occurs in a completely asymptomatic person who drives for work. This case suggests a very insidious course in the development of hypoglycaemia that may be a feature of proinsulinomas. The case also underlines the utility of proinsulin levels when investigating for suspected insulinoma.

**220**

## Ethical medico-legal and practical considerations for management of hyperthyroidism in the uncooperative patient two case reports

**Kathy Fu[1]**

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Background: Treatment of hyperthyroidism in an unwilling patient is challenging. For those who lack capacity to make medical decisions, urgent and life-saving treatment can be provided under the principle of duty-of-care. For ongoing or major treatment, consent can be sought from next-of-kin or the Guardianship Tribunal. Carbimazole and propylthiouracil are available only in enteral formulations but can be given rectally. Definitive treatments usually result in hypothyroidism requiring lifelong levothyroxine supplementation; there are case reports of successful weekly intramuscular administration[1,2]. Treatments aiming for euthyroidism, including partial thyroidectomy or low dose radioactive iodine have unpredictable outcomes[3].

Cases:

An 80 year-old lady with chronic schizophrenia was admitted with rapid atrial fibrillation and thyrotoxicosis due to Grave's disease. She had long-term refusal of antipsychotics and rigid delusions of poisoning. She was scheduled as mentally ill under the Mental Health Act and assessed as lacking capacity to refuse medical treatment. A Guardian was appointed for substitute decision-making, with specific provision for covert and coercive treatment. A combination of oral propylthiouracil hidden in foodstuffs, and per-rectal propylthiouracil under restraint was administered to achieve euthyroidism. Subsequently, a subtotal thyroidectomy resulted in permanent mild-to-moderate hypothyroidism. The patient continues to refuse levothyroxine replacement, but is living independently in the community.

A 32 year-old prison inmate presented with thyroid storm. Due to extreme aggression he was sedated, with prophylthiouracil and other supportive medications administered via nasogastric tube. Corroborative history revealed a background of Grave's disease, antisocial personality, traumatic brain injury, and longstanding refusal of all oral medications. He required prolonged

intubation and sedation, with attendant complication of ventilator-associated pneumonia. Definitive treatment options were explored including radioactive iodine and surgery; finally consent for a hemi-thyroidectomy was obtained through an emergency hearing of the Guardianship Tribunal. Post-operatively, he continues on oral carbimazole voluntarily with marked improvement in aggressive behaviour.


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**221**

## Histiocytic diseases affecting the hypothalamic pituitary axis two case reports


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Background:

The histiocytic disorders are a group of inflammatory myeloid neoplasias. Abnormal proliferation of histiocytes accumulate in many tissues, including the pituitary, and are a rare cause of pituitary dysfunction (particularly diabetes inspidus). Langerhan's cell histiocytosis has an incidence of 1-2 per million adults; Erdheim Chester disease has about 500 case reports in the literature. There are broad systemic manifestations including bony infiltration, cutaneous, lung, cardiac, or retroperitoneal involvement. Therapies may include cytotoxic chemotherapy, radiotherapy and interferon. There is increasing evidence that MAPK pathway mutations (including BRAF and MEK) are the driver of these neoplastic conditions; these are currently being explored as therapeutic targets.

Cases:
A 36 year-old female presented with confusion, thirst, polyuria, amenorrhoea and headaches. She was found to have pan-hypopituitarism with diabetes insipidus, in association with an isolated suprasellar mass. She underwent a craniotomy with partial resection. Histopathology revealed a histiocytic infiltrate with immunohistochemistry consistent with Langerhan's cell histiocytosis. Further staging investigations did not reveal any systemic involvement. Treatment with chemo- and radiotherapy was hampered by worsening hypothalamic dysfunction. She developed adipsia with extreme hypernatremia, hyperphagia and subsequent diabetes mellitus, and marked behavioural disturbance. The patient ultimately passed away within 9 months due to hyperosmolar state.

A 47 year-old female presented with thirst and polyuria. A water deprivation test confirmed complete cranial diabetes insipidus. No other pituitary hormone abnormalities were identified and initial MRI pituitary was normal. Approximately 15 months later a repeat MRI found new nodular thickening of the pituitary stalk, suspicious for an infiltrative process. Bone scan was performed due to an incidental complaint of knee pain, and the pathognomonic appearance of Erdheim Chester disease (a non-Langerhan's histiocytosis) was seen. Bone biopsy revealed histiocytic infiltrate with confirmatory immunohistochemistry. BRAF mutational status was negative. Treatment with interferon-based therapy is now being contemplated.

**222**

## Neoadjuvant Lenvatinib: A promising pathway for anaplastic thyroid cancer?


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Introduction: Anaplastic thyroid cancers (ATC) are aggressive malignancies and have a disease specific mortality approaching 100%. There are few therapies for ATC in clinical use and all have limited efficacy. Lenvatinib is a tyrosine kinase inhibitor targeting VEGF, which has shown substantial improvements in progression free survival in radioiodine refractory differentiated thyroid cancer. Phase II trials have shown some promise in utilising lenvatinib following surgery in ATC, but Phase III trials were abandoned due to disappointing results.

Case Report: We report a 67 year old male with a 70x45x48mm right sided thyroid calcified cyst which on core biopsy was confirmed as anaplastic thyroid carcinoma of spindle cell type. The lesion marginated the medial 180 degrees of the right common coronary artery and was thought to be surgically precarious. Baseline imaging confirmed pulmonary metastases at diagnosis. The patient was commenced on 24mg lenvatinib daily. He received one fraction (3Gy) of radiotherapy at diagnosis. Side effects including hypertension, fatigue and foot ulcers necessitated a single dose reduction after 2 months to 20mg. He continued lenvatinib until he progressed with a new liver lesion. At 6 weeks the lesion had dramatically reduced to 33x33mm. Following 18 weeks of treatment the primary lesion reduced to 23x17mm (>70% reduction) which facilitated surgery, and he had a successful hemithyroidectomy with central neck dissection three months after completion of lenvatinib. Pathology confirmed extensive necrosis in the specimen with morphological features and immunoprofile consistent with ATC.

Discussion: This case highlights the effectiveness of lenvatinib in ATC in a neoadjuvent setting, which has not been previously reported. The lenvatinib facilitated surgery in an otherwise inoperable lesion.

**223**

## Recurrent metastatic phaeochromocytoma

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PL was first diagnosed with phaeochromocytoma at age 23. He sustained a football injury, resulting in a right adrenal hemorrhage leading to a right adrenalectomy. Histopathology revealed the incidental finding of a phaeochromocytoma.

Over the next twenty years, PL experienced multiple recurrences of phaeochromocytomas. These were discovered on surveillance 24-hour urinary catecholamines and imaging studies. In 2000, he had elevated 24-hour urine adrenaline level of 174 nmol (0-80) associated with three Iodine-123 MIBG avid foci around the right kidney and base of the liver. He underwent a right nephrectomy and partial hepatectomy, followed by external beam radiotherapy to the right adrenal bed. Histopathology confirmed multiple foci of phaeochromocytoma.

In 2004 and 2008, he underwent two further surgical resections of the liver and on Morrison's pouch respectively. These were detected based on recurrent palpitations and follow-up surveillance imaging. 24 urinary catecholamines were negative on both occasions and plasma metanephrines were not performed. PL remained well in between events and was never hypertensive.

In 2017, he represented with palpitations and diarrhoea. 24-hour urinary catecholamines were normal, however a Gallium 68 DOTATATE PET scan identified two focal areas of intense tracer uptake in the right bowel wall. Repeat 24-hour urinary catecholamines became positive five months later with normetanephrine 2.5umol (0.3-2.0), noradrenaline 1.07 umol (0.00-0.70), and dopamine 4.3 umol (0.0-3.5). Three sets of plasma metanephrines were normal.

PL was referred to the oncologists for consideration of peptide receptor radionuclide therapy (PRRT) however it was deemed unsuitable given the small volume disease. He underwent a right hemicolectomy, which confirmed two foci of phaeochromocytoma. Interestingly, PL did not receive alpha blockade pre or intra-operatively. In spite of this, there was no hypertensive crisis. Genetic assessment found no pathological mutation on the phaeochromocytoma and paraganglioma panel. PL recovered well post operatively and his symptoms have completely resolved.

**224**

## Difficulties interpreting serum cortisol measurement by Immunoassay in a patient with ectopic ACTH syndrome receiving metyrapone therapy

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**Background**: Ectopic adrenocorticotropic hormone (ACTH) is an uncommon, but not rare presentation of Cushing's syndrome. Distinguishing the cause of Cushing's syndrome, once established, can be difficult. Clinicians should be suspicious of Ectopic ACTH syndrome as underlying Cushing's syndrome in patients who have a history of malignancy.

**Case:** We present the case of a 73-year-old male who presented with several months of nausea, weight loss, and abdominal discomfort. Imaging demonstrated multiple hepatic lesion, left apical lung lesion and lymphadenopathy. Biopsy of liver lesion demonstrated immunohistochemistry staining consistent with neuroendocrine tumour. He underwent systemic chemotherapy for metastatic atypical carcinoid tumour of the lung. Following chemotherapy he developed rapid weight gain, despite stability of metastatic carcinoid disease on serial imaging. Examination findings were consistent with Cushing's syndrome. Biochemistry demonstrated new onset of hypokalaemia, 1mg and 8mg dexamethasone suppression test demonstrated lack of suppression of early morning cortisol. He was commenced on metyropone for treatment of Cushing's syndrome, likely ectopic ACTH. Ongoing concerns of lack of normalization in serum cortisol resulted in up-titration of metyrapone, as well as the addition of ketoconazole. Subsequent serum cortisol levels performed using a more specific immunoassay, at a different laboratory, demonstrated a decline in serum cortisol levels. More specific liquid chromatography-tandem mass spectrometry is being undertaken.

**Discussion:** Dose titration of adrenal enzyme blockade therapy continues to be largely based on serum cortisol levels. Metyropone inhibits 11ß-hydroxylation in the adrenal cortex, leading to reductions in cortisol and aldosterone, with associated increased levels of circulating precursor steroids. Several cortisol immunoassays are susceptible to positive interference, with cross-reactivity of circulating cortisol precursors. Clinical vigilance, knowledge of the specificity of cortisol assay utilized, as well as an awareness of possible cross-reactivity with steroid precursors is essential to guide treatment decisions in ectopic ACTH syndrome, to avoid erroneous clinical decisions being performed.

**225**

## Common metabolic disorders among patients with neck of femur fracture reveals underdiagnoses and undertreatment of osteoporosis in the community

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Acute orthogeriatrics unit of John Hunter Hospital was involved in management of 1206 neck of femur fracture (NOFF) admissions sustained by minimum trauma (fall from standing height) in between February 2015 to February 2018. Retrospective audit was performed analysing admissions data of ICD 10 codes and data from Australia and New Zealand Hip Fracture Registry. Of these patients, average age 83.7 years, 68.7% (829) were female, 1.1% were aboriginal, 30.4% were from residential aged care facility, 42.5% were not requiring any walking aids, and 58.1% were with normal cognition. Overall, 27.6% patients had at least one common metabolic condition (19.3% Type 2 diabetes, 5.8% either hypo or hypernatremia, 1.1% hypo or hypercalcemia, 0.7% thyroid disorders, 0.7% obesity) which is significantly underestimated as dyslipidaemia is not captured despite substantial number of patients were on at least one antidyslipidemic medication (combined data extraction from hospital pharmacy registry and community records are in progress) either for primary or secondary prevention, only 2.7% patients were weighed during the admission. On presentation, 55.5% patients were not on any bone protective agents, 31.6% were on calcium and or vitamin D supplementation and 12.6% on bisphosphonate or another potent bone modifying agent. During discharge, these figures changed to 13.7%, 51.7% and 30% respectively (4.6% not recorded). Overall there is a rise of 37.5% in receiving bone protective agents as a result of admission. More recently during first quarter of 2018, direct questioning collected data from another 52 patients with NOFF revealed 88.5% patients or their relatives (19.2% with established dementia) did not have any discussion regarding fracture risks. Assessments of risk factors are incorporated in RACGP osteoporosis algorithm, however recognition of these risk factors (especially common metabolic disorders as risks) and addressing risks with bone protection agent remains significantly underachieved, potentially contributing to increased number of NOFF.

## 226

## The paediatric and young adult manifestations and outcomes of Multiple Endocrine Neoplasia Type 1

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Publish consent withheld

## 227

## The central australian experience in thyroid cancer

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*3. Department of Endocrinology, Royal Darwin Hospital, Darwin*

Publish consent withheld

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## 228

## Shrinking Giant

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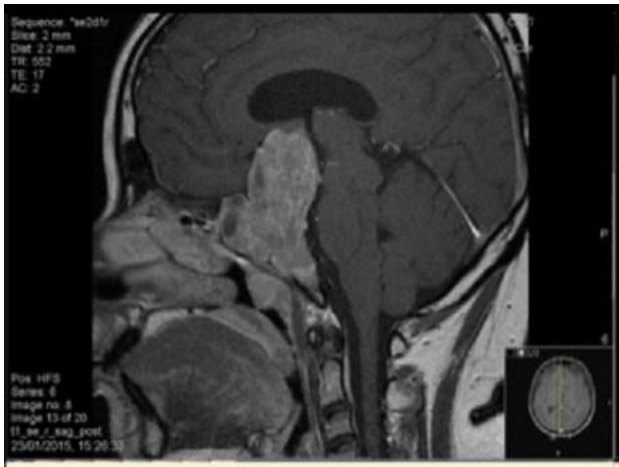

Figure 1A. Sagittal view T1 weighted MRI pituitary demonstrating a large pituitary macroadenoma (56 x 40 x 28mm) with hydrocephalus

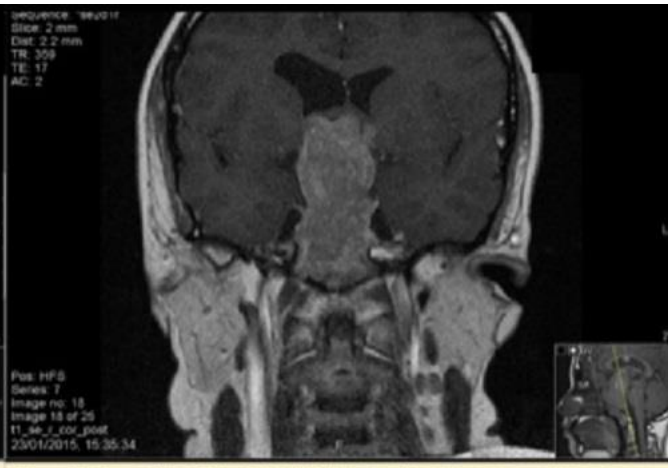

Figure 1B. Coronal view T1 weighted MRI showing the sellar mass exerting pressure on optic chiasm and prechiasmatic optic nerves, which are stretched. There was no involvement of the cavernous sinuses.

We present the case of a 19-year old male who presented with a generalized tonic-clonic seizure associated with visual loss. Examination revealed severe visual field defects and arrested pubertal development. Laboratory evaluation revealed a very elevated prolactin of 298 410 mU/L, hypogonadotropic hypogonadism, secondary adrenal insufficiency, and secondary hypothyroidism. He was also found to have JAK 2 essential thrombocythaemia. Pituitary MRI revealed a large pituitary macroadenoma (58 x 40 x 28mm) exerting significant pressure on the optic chiasm, associated with acute hydrocephalus. X-rays of the hands and wrist revealed delayed bone age of 16 years. The patient was diagnosed with a giant prolactinoma. Treatment was initiated with cabergoline 0.5mg daily, hydrocortisone 5mg BD, thyroxine 75mcg daily and testosterone 100mg IM injection every four weeks. Despite an impressive and rapid reduction in tumour size and prolactin levels, the visual defects and hypogonadal axis have not recovered after 24 months of therapy. Given his age; he will undergo testing for AIP and MEN mutations.

Giant prolactinomas represent 0.5% of all pituitary adenomas(1). They are characterised by their size (>40mm) and extremely high prolactin levels. The most common presentations include visual field defect, headache and sexual dysfunction, often accompanied by hypopituitarism. The goals of treatment are to relieve acute compressive symptoms, reduce tumour mass, normalise prolactin levels, and to preserve pituitary function(2). Dopamine agonists are first-line therapy for giant prolactinomas and can rapidly decrease tumour size and prolactin levels. Prolactin belongs to a cytokine family using the JAK-STAT signal transduction pathway, which regulates cellular proliferation and apoptosis(3). Constitutional activation of JAK2/STAT 5 pathway has been implicated in a variety of tumours; however, there has been no previous account of lactotroph proliferation. To our knowledge, this is the first case report of a JAK2 mutation occurring in a patient with giant prolactinoma.


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**229**

## Maternal resistance to thyroid hormone with foetal genotype unknown


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A 34-year-old G2P1 female with known RTH-beta, currently at 34 weeks gestation who has declined prenatal testing. Her mother, a maternal aunt and grandmother, are also affected. She initially presented with hair loss at age 13 years, and later developed a small goitre, intermittent palpitations and tremors. Investigations revealed elevated free T4 of 26-33 pmol/L (11-21), free T3 of 0.6-8 pmol/L (3.5-6.5) and nonsuppressed TSH of 0.66-8.1mIU/L (0.5-4.0). Genetic testing confirmed a heterozygous mutation R429Q in the THRB gene. Her first pregnancy was complicated by intrauterine growth restriction in the third trimester, with genetic testing later confirmed her daughter did not harbour the THRB mutation. During this pregnancy, her free T4 levels range from 22-26.4 pmol/L (10-19 pmol/L) and TSH 0.96-1.26 mU/L (0.5-4.0). To date, foetal monitoring has not demonstrated tachycardia, fetal goitre or growth restriction. This case raises the question of how we should best manage women with RTH-β during pregnancy?

RTH-beta is characterised by elevated thyroid hormones, nonsuppressed TSH, and variable clinical phenotype encompassing both hyperthyroid and hypothyroid features(1). High levels of thyroid hormones in pregnant mothers with RTH adversely affects normal foetuses, suppressing their TSH and producing infants with low for gestational age(2). Due to autosomal dominant inheritance, there is a 50% the foetus will have the mutation and therefore protected from the toxic effect of maternal thyroid hormone excess. Currently, there are no established guidelines for management of RTH in pregnancy. However, a suggested approach is first to determine the genotype of the foetus. For mothers carrying an affected foetus, no intervention is necessary. For mothers carrying an unaffected fetus, the aim is to maintain free T4 levels 20-50% of the upper limit of normal. Judicious use of antithyroid medication has been shown to prevent low birth weight and postnatal TSH suppression (3,4).

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**230**

## Hyperthyroidsim: To treat or not to Treat?

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*4. Genetic Medicine, Westmead Medical School, University of Sydney, Sydney*

Ms TM is a 21 years old Eurasian female presenting with goitre and TSH of 1.99 mIU/L (0.4-3.8), free T4(FT4) of 23.9 pmol/L (10-22) and free T3(FT3) of 6.6 pmol/L. She has one year' history of fatigue, muscle weakness and decline in her academic performance. She has history of appendicetomy and family history of leukemia. Her height was 153 cm, weight 54.5 kg and BMI of 23.3 kg/m$^2$. She has a non-tender, firm right thyroid nodule. Thyroid ultrasound revealed a normal sized thyroid gland with a mixed solid and cystic nodule measuring 29x21x15mm in the interpolar region. Repeated TFTs at different laboratories demonstrated persistent elevation of FT4 and FT3 and non-suppressed TSH (Table 1). Several assays confirmed the absence of heterophil antibodies. Her pituitary profile was normal. She has elevated an alpha subunit of 0.82 IU/L (0-0.6) and a normal sex hormone binding globulin (SHBG) of 48 nmol/L (20-118). Magnetic Resonance Imaging (MRI) of the pituitary revealed multiple small cystic lesions in the posterior aspect. Thyotropin (TRH) stimulation test showed exaggerated TSH response. She is currently awaiting thyroid hormone receptor beta (THRB) mutation testing.

Table 1: Thyroid function tests done at different laboratories

| | Sydpath Beckman Coulture assay | Douglas Hanley Moir Abbott assay | Laverty Roche assay | Units |
|---|---|---|---|---|
| TSH (normal range) | 2.67 (0.4-4.2) | 2.75 (0.4-3.5) | 3.5 (0.5-4.0) | mIU/L |
| T4 (normal range) | 36.7 (11.0-22.0) | 23.3 (9.0-19.0) | 32 (10.0-20.0) | pmol/L |
| T3 (normal range) | 9.7 (3.0-6.2) | 7.7 (2.6-6.0) | 12 (3.5-6.0) | pmol/L |

Table 2: TRH stimulation test

| Time(minutes) | -15 | 0 | +15 | +20 | +30 | +45 | +60 | +90 | +120 |
|---|---|---|---|---|---|---|---|---|---|
| TSH (mIU/L) | 1.37 | 1.29 | 14.7 | 15.9 | 16.1 | 12.7 | 10.5 | 6.59 | 4.91 |

Resistance to thyroid hormone (RTH) is characterised by reduced sensitivity of target organs to thyroid hormone[1,2,3]. Eight five percent of cases are caused by mutation in THRB which is inherited in autosomal dominant pattern while 28% occurred denovo.[1] Incidence of RTH is reported to be one case per 40,000 live birth[4]. Gotire is present in 65-95% of the cases[5]. An important differential diagnosis is TSH-secreting pituitary adenoma[2,5]. In TSH-producing tumour, the ratio of alpha subunit-to-TSH will be raised. Management of RTH is aimed at managing the patient's clinical symptoms[2,6]. Normalising of thyroid hormone levels is not required[2,6]. Management of RTH in pregnancy is challenging[2,6]. Family counselling and genetic testing are a crucial part of RTH management[2,6].

**231**

## The effect of glucocorticoid therapy on adrenal reserve in patients with multiple myeloma.

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**Context**

The intermittent nature of high-dose glucocorticoid(GC) therapy in patients with multiple-myeloma could result in secondary adrenal-insufficiency (AI) and reduced quality of life.

**Objective**

We investigated the likelihood of secondary AI in patients with multiple-myeloma receiving intermittent GC therapy using the LDSST, measuring both serum and salivary cortisol levels. We investigated differences in AddiQoL scores during periods with and without GC therapy.

**Design**

Cross-sectional, prospective-cohort study.

**Setting**

This study was conducted from February 2017 to December 2017 at Toowoomba Hospital.

**Participants**

We included five patients with multiple-myeloma who received GC therapy as part of their chemotherapy protocol.

**Intervention**

All 5 patients underwent a LDSST and salivary cortisol tests at the nadir of GC effect. AddiQoL surveys were completed pre- and post-GC therapy.

**Main Outcome Measures**

Primary outcome measure was the presence of biochemical AI and the correlation between results of the validated AddiQoL questionnaires in the period pre- and post-GC therapy. Our secondary outcome measure was assessing the utility of salivary cortisol in a LDSST.

**Results**

One participant had more than 83% likelihood of secondary AI with a baseline serum cortisol level of 93nmol/L and 30minute serum cortisol of 389nmol/L after LDSST. Three participants had baseline serum cortisol levels 147nmol/L, 242nmol/L and 279nmol/L with elevations to 473nmol/L, 580nmol/L and 574nmol/L respectively after LDSST indicating 33% likelihood of AI. The remaining participant had a baseline serum cortisol of 380nmol/L increasing to 614nmol/L at 30minutes post LDSST indicating 5% likelihood of AI. Low pre-GC therapy AddiQoL scores is associated with low serum 30minute cortisol results. In all 5 patients, 30minute salivary cortisol incremented 3 to 8 times compared to baseline levels.

**Conclusions**

This pilot study demonstrates that current GC regimes used in patients with multiple-myeloma are likely to affect adrenal reserve. Repeat assessment in a larger sample size would be of value.

**232**

## Outcomes of pituitary surgery at the Gold Coast University Hospital; the rates of cure for pituitary adenomas, need for subsequent therapy and post-operative hypopituitarism

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Background:

Surgery has a major role in the treatment of pituitary adenomas, however risks damage to the optic chiasm and loss of normal pituitary function, the very outcomes treatment aims to prevent.

Aims:

To determine the outcomes of pituitary surgery at the Gold Coast University Hospital (GCUH) and compare it to other health services both nationally and internationally.

Methods:

HBCIS coding was used to identify patients discharged from the GCUH between January 2000 and May 2016 who had a "pituitary procedure". A retrospective chart review was then conducted to gather information regarding patient demographics, type of tumour, pre-operative and post-operative anterior pituitary function and other surgical outcomes.

Results:

Results are available for 94 patients; 86 patients who had their first operation at the GCUH and 8 patients who had initial treatment elsewhere. The majority (76.6%) of patients had a non-secretory adenoma. After 1 surgery, 76.6% of patients with a non-secretory adenoma were in remission with 21.9% of patients requiring a subsequent operation and 6.3% radiation. For patients with secreting pituitary tumours 27.3% were cured after one operation. New pituitary dysfunction developed in 20.9%. Post operative diabetes inspidus occurred in 13.0%, but it was permanent in only 1.7%. CSF leak (19.1%) was the most common surgical complication.

Conclusions:

Patients in this study experienced similar rates of tumour control to other studies. The rates of anterior pituitary dysfunction in this population group were comparable to other Australian studies but higher than international findings.

**233**

## Systematic review and appraisal of clinical practice guidelines using AGREE II instrument to develop an algorithm for assessment and management of bone health in women with premature ovarian insufficiency

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**Background:** Osteoporosis is a key concern of women with premature ovarian insufficiency (POI)[1] and bone health knowledge gaps are reported by clinicians[2].

**Objectives:** 1) To systematically evaluate the quality of clinical practice guidelines (CPGs) related to POI and bone health, 2) to formulate a management algorithm.

**Methods:** Systematic search for English language CPGs from August 2012 to August 2017. Four reviewers independently evaluated the methodological quality of included CPGs with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (comprising 23 items across 6 domains) using the My AGREE PLUS platform[3]. Inter-rater reliability was assessed using the intraclass correlation coefficient (ICC) (SPSS v23.0). Appraisers discussed scoring where ICC<0.70 to achieve consensus. Individual domain and total percentage scores were calculated for each CPG[4]. Data from high-scoring CPGs was extracted and summarised to develop the algorithm, with subsequent refinement via expert and end-user clinician feedback.

**Results:** Systematic search yielded 16 CPGs for appraisal. ICC values were 0.71(good) to 0.95(very good). Appraisal yielded 4 “high”, 8 “average” and 4 “low” quality CPGs. High quality CPGs had mean total scores of 82-96%. Recommendations from high quality CPGs were summarised into 6 categories: Screening; Risk factors; Initial assessment; Diagnosis; Subsequent assessment; and Management. Only “Management” had recommendations (moderate to low quality evidence) from all four CPGs. Limitations are reflected in the algorithm.

**Conclusions:** Most CPGs regarding bone health and POI are average to poor quality. High quality CPGs have evidence limitations and recommendation gaps indicating the need for further research.

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**234**

## Disproportionate Hypertriglyceridaemia in a patient with Familial Lipodystrophy

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A 35 year old lady with a heart transplant in 2015 for dilated cardiomyopathy cardiomyopathy secondary to familial partial lipodystrophy (Dunnigan type- confirmed LMNA gene mutation) was admitted to hospital with features of congestive cardiac failure.

Complications include post transplant diabetes, fatty liver disease, hypertension, paroxysmal atrial flutter and steroid-related osteopenia. Medications include prednisone 9mg/day, tacrolimus, everolimus, mycophenolate, gemfibrozil, insulin Isophane 40units BD, irbesartan, metoprolol, calcitriol, esomeprazole, magnesium supplements.

On examination, with a BMI of 23kg/$m^2$ , she had ‘moon-like’ facies with minimal adipose tissue in her trunk and extremities consistent with familial partial lipodystrophy. Elevated jugular venous pressure (JVP) with peripheral oedema and bilateral lung crackles confirmed congestive cardiac failure.

A visibly lipaemic serum sample showed very severe hypertriglyceridaemia, hypercholesterolaemia, mild hyperglycaemia and equivocal troponin. Lipase was normal.

Current cholesterol and triglyceride level were out of proportion to usual levels. Prednisone dose was being reduced and Everolimus started over the past 5 months.

The patient was treated with insulin infusion, heparin infusion, fenofibrate, pravastatin, fish oil and withdrawal of everolimus.

| Test | Result | Normal range | Units |
|---|---|---|---|
| $Na^+$ | 131 | 137-146 | mmol/L |
| Creatinine | 83 | 40-90 | umol/L |
| Troponin T | 31 → 33 | 0-14 | ng/L |
| Triglycerides | 57.5 | 0-2.0 | mmol/L |
| Cholesterol | 21.7 | 0-6.0 | mmol/L |
| Lipase | 47 | 0-60 | U/L |
| Amylase | 39 | 0-100 | U/L |
| Glucose | 14.0 | 3-7.8 | mmol/L |
| pH | 7.43 | 7.35-7.45 | - |
| $HCO_3^-$ | 23 | 22-32 | mmol/L |
| Ketones (capillary) | 0.1 | - | |

*Table 1: Blood tests showing mixed hyperlipidaemia.*

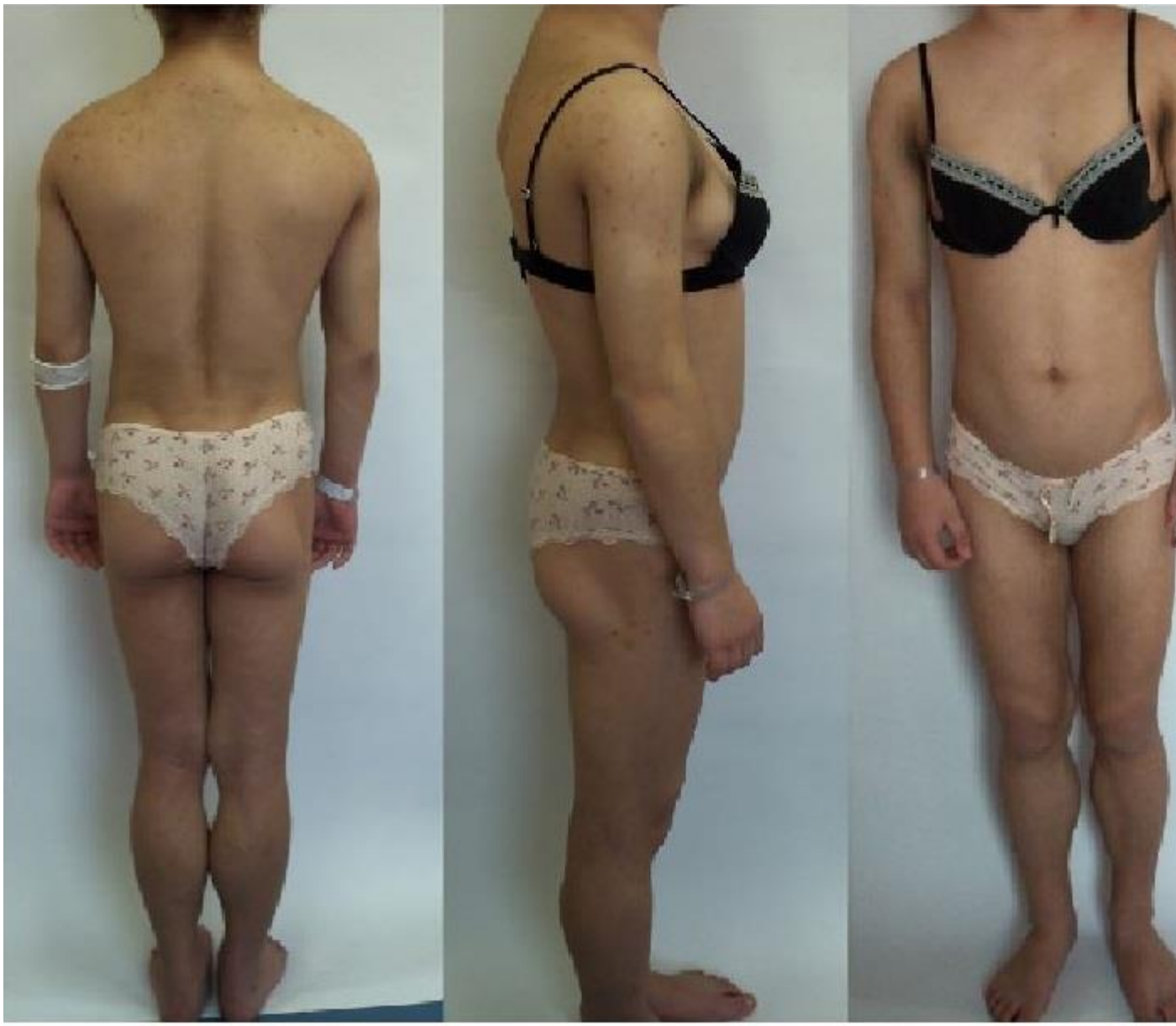

*Figure 1. Features of Dunnigan type familial partial lipodystrophy. Reproduced from Krawiec e*
*2016.*

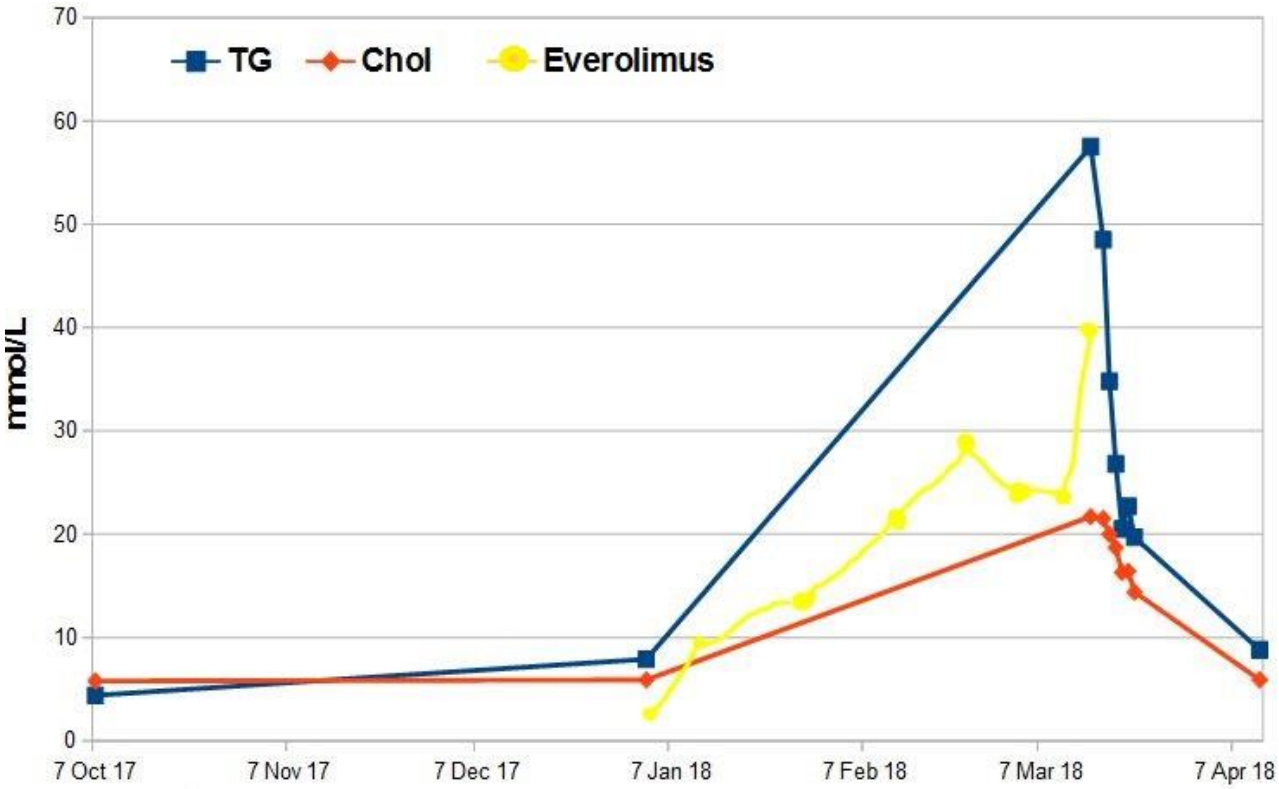


**Figure 3. Trend of serum Triglycerides (TG), Cholesterol (Chol) and Everolimus (ug/L-scale not shown)**

**Discussion:**

Dunnigan type familial partial lipodystrophy is an autosomal dominant mutation of the LMNA gene leading to varying degrees of lipodystrophy and cardiomyopathy. Secondary causes of hypertriglyceridaemia should be considered if extent of hypertriglyceridaemia is above patient's usual baseline.

Our patient had severe hypertrygliceridemia secondary to Everolimus similar to some previous reported cases. Treatment insulin infusion, fibrate therapy, statin, fish oil and nicotinic acid. Plasmapharesis has been used in some cases.

Learning Points:

1. Severe hyperlipidaemia can present with congestive cardiac failure.
2. Facial features of Dunningan type familial partial lipidystrophy can be Cushingoid.
3. In familial hyperlipidaemia, further elevations of lipid levels suggest secondary causes.
4. Prompt treatment of hypertriglyceridaemia is required to avoid pancreatitis.

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**235**

## Follow-up of incidental thyroid nodules detected on computed tomography angiography of the head and neck

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Background: The detection of an incidental thyroid nodule is a common clinical scenario. Due to their potential for malignancy, the follow-up of thyroid nodules is important.

Aims: This study aimed to determine the prevalence of thyroid nodules identified on computed tomography angiography (CTA) of the head and neck performed at a single centre and the extent of follow-up organised by treating clinicians as well as the factors that influenced this.

Methods: The radiological reports for inpatient CTA head and neck scans performed in 2016 at a single high-volume metropolitan tertiary stroke centre at which endovascular clot retrieval is performed were screened for mention of thyroid nodules. The medical records of patients in whom thyroid nodules were detected were reviewed to collect demographic data and determine what thyroid nodule follow-up, if any, was organised. Exclusion criteria were a previously established diagnosis of thyroid nodular disease or other thyroid pathology, death, or the absence of a discharge summary.

Results: Of 1,240 CTA head and neck scans performed during the study period, 95 patients with thyroid nodules were identified (7.7% prevalence). After applying the exclusion criteria, 69 patients were included in the analysis. Of these, 13 (18.8%) had some form of thyroid nodule follow-up organised. Factors significantly associated with follow-up included lower comorbidity status, specification of the size of the nodule in the radiological report, and mention of the thyroid nodule in the conclusion of the radiological report.

Conclusions: Follow-up of incidental thyroid nodules in this population was suboptimal. However, it appears that the way in which these findings are communicated in radiological reports can influence the likelihood of follow-up, which represents an opportune target for improvement.

**236**

## Management of an intrathyroidal cystic parathyroid gland with posttraumatic haemorrhagic transformation causing acute airway compromise

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Case Report:

A 68-year old male presented to a peripheral hospital following a motor accident, sustaining manubrium and rib fractures. A large neck mass was identified causing tracheal compression, requiring semi-elective intubation for airway compromise. Relevant background included atrial fibrillation on rivaroxaban, obstructive sleep apnoea and renal calculi awaiting lithotripsy. Computed tomography confirmed a hypopharyngeal mass 90x52x57mm, thought to be large goitre resulting in trachea compression. Serum biochemistry revealed marked PTH-dependent hypercalcemia ((calcium 3.35mmol/L (RR 2.1-2.6), PTH 342pg/ml (15-68)) and hypophosphatemia. TSH was normal.

Persistent tracheal compression from the hypopharyngeal mass precluded extubation, necessitating transfer to a tertiary centre. In the absence of dedicated parathyroid imaging, and to minimize surgical insult in the setting of critical illness, a unilateral para/thyroid resection was proposed (proceeding contralaterally only if pathologic parathyroid was not identified). He underwent right hemithyroidectomy, isthmusectomy and right superior parathyroidectomy. Histopathology showed a 30mm (5.04g) right superior parathyroid, while the right thyroid lobe was substituted by a 62mm (124g) hyperplasic intrathyroidal parathyroid, both showed extensive central haemorrhage. Following unilateral parathyroidectomy, extubation was achieved, but hypercalcaemia persisted. An elective contralateral exploration cured multigland parathyroid hyperplasia; evaluation for familial disease was arranged.

Discussion:

Parathyroid tissue causing airway obstruction is rare, with few cases reported [1-5]. In this case, neck trauma and systemic anticoagulation may have precipitated intra-parathyroidal haemorrhage within already hyperplastic tissue, resulting in rapid parathyroid enlargement, airway compromise, and rise in serum PTH and calcium. This case of a hyperfunctioning haemorrhagic parathyroid masquerading as thyroid goitre highlights the paradigm of “damage control neck surgery”. We believe that in the presence of life-threatening airway obstruction, and in the absence of preoperative parathyroid localization a unilateral approach should be favoured to release tracheal compression whilst minimizing the risks associated with bilateral neck exploration such as recurrent laryngeal nerve palsy or hypoparathyroidism [6-8].

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**237**

## Spermatic cord paraganglioma

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A 62-year-old man presented with a 15-year history of paroxysms typical of pheochromocytoma. Previous cardiac and neurological investigations were unremarkable. There had been no intraoperative haemodynamic instability during surgery two years prior.

On examination blood pressure was 141/93mmHg with normal general physical examination and no signs of hormonal excess.

Further testing elucidated elevated plasma normetanephrine 1.45nmol/L (<1.05) and urine noradrenaline 980nmol/24hr (45-680). A CT adrenals did not identify a pheochromocytoma. $^{68}$Ga-DOTATATE PET/CT demonstrated avid uptake (SUVmax 23.75g/mL) in the left inguinal region corresponding with a 24x21x24mm nodule in the left inguinal canal with no abnormal uptake elsewhere.

The provisional diagnosis of left inguinal paraganglioma was made. Commencement of pre-operative alpha-blockade with prazosin 2mg three times daily resulted in symptomatic improvement. Beta-blockade with atenolol 25mg daily was commenced pre-operatively after adequate alpha-blockade.

During left inguinal exploration a 25x50cm lesion was identified within the inguinal canal adherent to the spermatic cord, a rare site of genitourinary paraganglioma (1). During manipulation of the lesion the patient became transiently hypertensive to 216/126mmHg with an otherwise unremarkable operative and post-operative course.

Histopathology demonstrated a 30x40x20mm encapsulated nodular lobulated tumour weighing 9g with a solid, hetrogenous yellow and brown surface. Microscopically there was mixed nesting (zellballen) with occasional capsular invasion without tumour extension beyond the fibrous capsule. No vascular invasion was seen and mitotic activity was scant (Ki-67 index <1%). Immunohistochemistry demonstrated positive staining for SDHA and negative staining for SDHB. Negative immunohistochemistry staining for SDHB is strongly associated with a mitochondrial complex II abnormality and can therefore be used to triage formal genetic testing for SDHB, SDHC, or SDHD mutations (2).

Post-operatively his progress has been stable with no further paroxysms and normalisation of his blood pressure off antihypertensives. Both the 24 hour urine noradrenaline level (346nmol/24hr) and plasma normetanephrine (0.37nmol/L) normalised post-operatively.

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**238**

## Streptococcus anginosus suppurative thyroiditis: a case report

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38-year-old Malaysian builder, previously well, presented with a 2-week history of worsening right neck pain associated with odynophagia, high fevers, weight loss of 6kg and palpitations. His right thyroid lobe was enlarged, firm and tender to palpation.

Investigations showed marked thyrotoxicosis and elevated inflammatory makers. Thyroid ultrasound was consistent with a large nodule or coalescent nodules with features suggestive of recent haemorrhage without evidence of infection. A 99mTc-Thyroid scan showed generalised reduced uptake of 0.7%.

He was treated for suspected subacute thyroiditis (SAT) but failed to improve. A fine needle aspirate (FNA) performed on day-3 drained pus. The diagnosis of acute suppurative thyroiditis (AST) was made and piperacillin/tazobactam was administered for a total of 19days. Cultures grew Streptococcus anginosus and mixed anaerobes with normal histology. Despite initial improvement, he required surgical exploration revealing a multiloculated abscess in the right thyroid lobe and a separate abscess in the right sternomastoid. He became afebrile on day-1 post surgical washout. Extensive investigations into the source of AST revealed no cause.

**Discussion**

AST is very rare but overlapping clinical features can make it difficult to distinguish from the more common SAT. Moreover, both conditions show reduced 99mTc-Thyroid scan uptake. SAT is a self-limiting condition but AST has a mortality of up to 12% and therefore it is crucial to make a timely diagnosis.

Although ultrasound and CT thyroid may identify a thyroid abscess, findings in the early stages are indistinct. Helpful findings may include fluid around the affected thyroid lobe, heterogenous low-density areas within the thyroid gland and unifocal hypoechoic lesions. Thyroid FNA is diagnostic.

Treatment comprises broad-spectrum antibiotics and drainage by ultrasound-guided FNA or by surgical washout.

Pyriform sinus is a common cause of left recurrent AST. Other causes include lymphatic or haematogenous spread, neck trauma and ruptured oesophagus among others.

## 239

## A retrospective audit of $^{99m}$Tc-sestamibi parathyroid scans with SPECT reconstruction at Maroondah Hospital

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**Background –** $^{99m}$Tc-sestamibi parathyroid scans with SPECT reconstruction are used to localise parathyroid adenomas pre-operatively in primary hyperparathyroidism to facilitate minimally invasive surgery. In clinical practice we noticed that a significant number of $^{99m}$Tc-sestamibi parathyroid scans were negative. The aim of this study was to determine the rates of positive $^{99m}$Tc-sestamibi parathyroid scans and the outcomes of patients with both negative and positive scans.

**Methods** – We performed a retrospective analysis of all patients who underwent a $^{99m}$Tc-sestamibi parathyroid scan with SPECT reconstruction between August 2011 and July 2012 at Maroondah Hospital. Files were reviewed and all patients with primary hyperparathyroidism were included. Investigations including biochemistry, imaging, histology and type of surgery were analysed.

**Results –** Of the 61 patients who underwent $^{99m}$Tc-sestamibi parathyroid scans, 17 did not meet criteria for primary hyperparathyroidism. Of the 44 patients with primary hyperparathyroidism, 24 (54%) scans localised an adenoma. Of these, 17 (70%) proceeded to surgery and in 13 (76%) the scan was concordant with surgical findings. 10 (59%) underwent minimally invasive surgery, 2 (12%) underwent 4 gland exploration, 3 (17%) underwent unilateral exploration and 2 (12%)had total thyroidectomies with parathyroidectomy.

Of the patients with a negative scan, 17 (80%) had a thyroid US and 1(5%) localised a parathyroid adenoma. Only 9 (43%) of the patients with negative scans underwent surgery, 3 (33%) underwent minimally invasive surgery, 4 (44%) had 4 gland exploration, 1(11%) had a total thyroidectomy and the last patient did not have surgical records available.

**Conclusion -** Almost half of all $^{99m}$Tc-sestamibi parathyroid scans did not identify an adenoma. This study suggests that patients with a negative $^{99m}$Tc-sestamibi parathyroid scan were less likely to proceed to surgery despite similar age and disease severity. This raises concern that patients with negative imaging may miss out on surgery that is otherwise indicated.

## 240

## Comparison of LCMSMS, HPLC and two automated immunoassay methods in a cohort of patients with clinically confirmed Cushing's syndrome

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**Background**

Measurement of 24 hour urine free cortisol (UFC) is one of the initial investigations for the diagnosis of Cushing's syndrome (CS). Automated immunoassay (AIA) methods are prone to interferences from exogenous glucocorticoids and cortisol metabolites leading to overestimation of urinary cortisol and reduced specificity. Other methods with greater specificity including high performance liquid chromatography (HPLC) and liquid chromatography tandem mass spectrometry (LCMSMS) are not subject to this interference and are being used with increasing frequency.

**Aims**

To compare different methods of UFC measurement in patients investigated for CS.

**Methods**

PathWest QEII routinely measures UFC on automated immunoassay platform Siemens Immulite 2000 XPi with reference interval (RI) <900 nmol/day. Since June 2016, aliquots of UFC were collected and stored at -20°C for LCMSMS method evaluation. The LCMSMS uses a Xevo TQ-S (Waters Corporation, Milford, MA) with prior solid phase extraction and measures cortisol, cortisone, deoxycorticosterone, 11-deoxycortisol, prednisolone and dexamethasone (provisional RI <170 nmol/day). Analysis of urine cortisol was also performed on another immunoassay platform, Abbott Architect (RI <330 nmol/day), as well as our in-house HPLC method (RI <170 nmol/day).

**Results**

9 patients had clinically confirmed CS: Cushing's disease (5), ectopic ACTH secretion (2), metastatic adrenocortical carcinoma (ACC) (1) and adrenal CS (1). 7 of 9 patients had concordant increase in UFC by all methods. Two patients failed overnight dexamethasone suppression test but had normal UFC by all methods. Cortisol/cortisone ratio was elevated in 3 cases, including ectopic CS (2) and ACC (1). One additional patient had 11-deoxycorticosterone and 11-deoxycortisol secreting metastatic ACC.

**Conclusion**

Results are concordant on the specific LCMSMS and HPLC methods compared to the unextracted automated immunoassay platforms as long as appropriate diagnostic cut-offs are applied. LCMSMS has the additional benefit of looking at other corticosteroid metabolites.

## 241

## Evolution of an unexpected lump

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Mr. S.J, 39 year old male, first presented to his general practitioner with 18 months history of globus sensation in his throat in conjunction with dysphagia for both solids and liquids. Physical examination was unremarkable apart from a large soft, well circumscribed subcutaneous painless mass on posterior upper left chest wall. Non-contrast CT chest demonstrated a fat containing lesion measuring 95 x 80 x 30mm suggestive of intramuscular lipoma. Incidentally, there was a 48 x 55 x 25mm well circumscribed nonenhancing soft tissue density in the superior anterior mediastinum without associated lymphadenopathy. PET-CT scan done 3 months after the initial CT scan showed stable size of the mediastinal mass with no FDG avidity. The patient underwent mini median sternotomy with excision of mediastinal mass and thymus. Histology revealed a normal thymus without evidence of lymphoma or thymoma. The entire mediastinal mass consisted of a 45 mm stage 1 T3N0M0 cystic papillary thyroid carcinoma with clear margins. In light of the histological findings, Mr. S.J underwent total thyroidectomy of orthotopic thyroid. Histology showed a benign thyroid tissue with one normal parathyroid gland within the left hemithyroid.

Majority of ectopic thyroids are discovered incidentally on imaging. Hounsfield units of ectopic thyroid tend to be lower than that of orthotopic thyroid. Most common anatomical location for an ectopic thyroid is within the Wölfler region. Lingual ectopic thyroid comprises 50-90% of the all ectopic thyroids. So far, fewer than 10 cases of mediastinal ectopic thyroid have been reported, with majority in the anterior mediastinum. Other intrathoracic locations of ectopic thyroid have been described in the right ventricle and lung parenchyma. Thyroid carcinoma in ectopic thyroids are rare, comprising of less than 1% of all lingual thyroids.

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## 242

## REDCap is a secure web-based application and provides a useful tool for establishing a national audit of pituitary surgery

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Recently there has been a call for a national registry of pituitary surgery to monitor safety and efficacy[1]. To date, the resources have not been available to initiate and coordinate this. REDCap[2] is a user-friendly, web-based tool for building databases and is supported by many local health networks around Australia. Using REDCap, we conducted a 10-year (2008-2018) retrospective audit of pituitary surgery at Concord Repatriation General Hospital. There were 29 cases during this period. Most cases (59%) were performed by one surgeon. All cases were elective, except for one emergency. The majority were for the first pituitary surgery; 10% were for tumour recurrence. The median age of patients was 56 years. All were pituitary adenomas except two (one meningioma, one craniopharyngioma) and were predominantly non-functioning (78%). Median tumour size was 24 mm (range 5-59 mm). Suprasellar extension was observed in 76%, optic chiasm compression in 59%, cavernous sinus extension in 52%, and sella floor erosion in 24%. Nine patients (33%) had documented visual field defects prior to surgery. Transsphenoidal surgery was undertaken in the majority (90%); three patients underwent craniotomy. The median length of stay was 7 days. Postoperatively, CSF leak developed in 24%; one patient required endoscopic repair. Three patients had serious surgical complications (temporal lobe haemorrhage with mass effect; intraoperative right internal carotid artery injury; tension pneumocephalus requiring extraventricular drain insertion). There were no deaths. Transient and permanent diabetes insipidus was seen postoperatively in 45% and 10%, respectively. At discharge, 59% of patients were on glucocorticoids. Many factors influence pituitary surgery outcome including tumour size and invasiveness, surgical approach, reoperation, endocrinopathy, and patient co-morbidities. The measurement of outcomes requires assessing a combination of imaging, endocrine and clinical parameters. REDCap provides a suitable database for this. Our data adds support to the establishment of a national pituitary surgery database.

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## 243

## Adrenal Venous Sampling (AVS): Practical Implementation and Outcomes

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**Background**

Adrenal venous sampling (AVS) is the gold standard for distinguishing between unilateral aldosterone-producing adrenal adenomas and bilateral adrenal hyperplasia, and decision-making between unilateral adrenalectomy versus lifelong medical therapy. The difficulties in successful AVS, and the need for experienced personnel are generally acknowledged[1]. We audited the outcomes of AVS at our institution, and subsequent outcomes after modifying our AVS protocol. This aims to provide a real world review as to practical factors affecting success of AVS.

**Methods**

We reviewed the results of AVS from 15 consecutive patients between January 2013 to Nov 2016. Subsequent revisions in the protocol included ACTH stimulation (50ug/hr cosyntropin)[1], simultaneous paired peripheral/adrenal sampling, CT mapping, greater rigour in protocol implementation, and testing of point-of-care cortisol assays. Results from a further 17 patients between Dec 2016 to Apr 2018 were subsequently analysed. Successful cannulation was defined as a selectivity index (adrenal cortisol/paired peripheral vein cortisol) of ≥ 2 (unstimulated) or ≥ 3 (ACTH stimulated). Lateralisation was defined as a Right:left (or vice versa) Aldosterone to cortisol ratio of ≥ 3 (without ACTH) or ≥ 4 (with ACTH).

**Results**

Between 2013- Nov 2016, 7/15 (46%) AVS were successfully cannulated. Of these, 4 patients clearly lateralised (3.9 ±1.2, 16.1, 23.0, 43.6) but interpretation was not clear cut in the other cases due to high sample variability. Of 17 consecutive AVSs performed after Nov 2016, bilateral cannulation has been successful in 10 cases (59 %), even with the commencement of less experienced radiology personnel in transition plan. All cases which has been successfully cannulated have clearly distinguished between a unilateral vs bilateral source of hyperaldosteronism. The practicalities of the protocol will be discussed.

**Conclusion**

Ongoing local audit and rigorous implementation of AVS protocols are essential to improving the success in real world AVS for use in diagnosis and care.

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**244**

## Masquerade or mystery?

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A 51-year-old gentleman was admitted for routine cystoscopy. Intra-operatively, he developed hypertensive emergency requiring admission to Intensive Care Unit. Background consisted of hypertension, type 2 diabetes mellitus, stage 3 chronic kidney disease, anxiety/depression and cannabis use. Prescribed medications were Irbesartan and metformin, albeit with poor compliance. Upon admission, plasma and urinary normetanephrines were elevated at 2347pmol/L (<820, 2.9x upper limit of normal [ULN]) and 11.6umol/day (<3.5, 3.3x ULN) respectively. Plasma metanephrines were normal, 261pmol/L (<447), urinary metanephrines elevated at 2.8umol/day (<1.5). Primary hyperaldosteronism and Cushing's syndrome were excluded. Angiogram revealed renal artery stenosis (right 70%, left 30%).

CT/MRI head were performed for visual blurring, demonstrating 18mm pituitary tumour, with optic chiasm displacement and right internal carotid encasement. Visual field testing was normal. Anterior pituitary function testing revealed hypogonadotrophic hypogonadism (FSH 4.0IU/L [1.5-13.0], LH 4.2IU/L [1.7-8.6], testosterone 6.6pmol/L [8.0-32.0]), secondary hypothyroidism (TSH 2.66mIU/L [0.4-4.2], fT4 9.3pmol/L [11.0-22.0], fT3 2.8pmol/L [3.0-6.2]), hyperprolactinaemia consistent with stalk effect (680mIU/L [<350]) and likely growth hormone deficiency (GH <0.4mU/L and IGF-1 3.4nmol/L [10-30]). Hypothalamic-pituitary-adrenal axis was sufficient (ACTH 4.1pmol/L [0-12], cortisol 518nmol/L). The patient was discharged on irbesartan and amlodipine pending further work-up for phaeochromocytoma/ paraganglioma (PC/PGL). Plasma and urinary normetanephrines remained persistently elevated (1.5-2x ULN). $^{68}$Ga-DOTATATE-PET/CT demonstrated pituitary tumour avidity and no evidence of PC/PGL. Ultrasound neck and MRI pelvis did not detect PC/PGL.

One month later, the patient represented with pituitary apoplexy. Persistent malignant hypertension precluded immediate operative management, with alpha-blockade prior to uneventful transsphenoidal resection. Histopathology demonstrated largely ischaemic tissue; architecture was consistent with pituitary tumour. Subsequent ongoing resistant hypertension prompted performance of a plasma clonidine suppression test.

Evaluation of possible PC/PGL is challenging, requiring careful consideration and interpretation of evolving biochemical and imaging diagnostic modalities (1,2). A plasma clonidine suppression test may assist in identification of false positive elevations in catecholamines (3).

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**245**

## A novel *CASR* variant (c.2540G>A;p.Gly847Asp) in an Fijian Indian man with familial hypocalciuric hypercalcaemia

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Familial hypocalciuric hypercalcaemia (FHH) is a rare autosomal dominant disorder due to a loss-of-function mutation in the *CASR* gene encoding the calcium-sensing receptor. It can be challenging to differentiate FHH from primary hyperparathyroidism as both are characterised by PTH dependent hypercalcaemia and can be asymptomatic.

In this case report, we present a 64 year old gentleman referred to our clinic with persistent hypercalcaemia after originally being diagnosed with primary hyperparathyroidism and treated with parathyroidectomy. We outline our patient's history and investigative findings which were consistent with FHH. We also present the results of his genetic testing where he was found to have a heterozygous unclassified variant (c.2540G>A;p.Gly847Asp) of the Calcium Sensing Receptor gene.

This CASR gene variant has not previously been reported to be associated with FHH. We discuss our suspicion this variant is pathogenic given its position, effect on polar charge and proximity to several known pathogenic CASR gene variants. Finally, we discuss the value of further genetic testing in our patient's relatives to confirm segregation of this variant with the FHH phenotype with respect to guiding future management of our patient and others affected.

**246**

## Not your usual case of Low Testosterone

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Mr WM aged 48 years was seen in the Cairns endocrine clinic for evaluation of his hypogonadotrophic hypogonadism. WM's medical history included new onset hypertension. WM didn't smoke, avoided alcohol excess and was not depressed. WM reported "muscular fatigue" for 12 months with marked wasting of his quadriceps. WM had very low libido and erectile dysfunction.

WM's mother died at age 52 years from metastatic colorectal cancer. MW had regular surveillance colonoscopies which were normal. His father has essential hypertension.

Clinical examination revealed a BP of 179/111mmHg with a BMI of 24.9kg/m$^2$. He had a round plethoric face with skin thinning, central adiposity and wasting of his limbs. There was also prominent supraclavicular fat pads as well as proximal myopathy. Visual field to confrontation was normal. WM had normal testicles of 25mls.

At this point, the working diagnosis was highly suggestive of Cushing's Syndrome and WM's Cushing's Screen showed very elevated late nigh salivary cortisol, no suppression with the 1mg dexamethasone suppression test and a 24 hour urinary cortisol over 13 times above normal. A full pituitary profile showed a measurable ACTH of 11 ng/L and in the presence of WM's marked Cushingoidism, it was thought the cause was due to ACTH dependence. WM's pituitary MRI however, did not show an adenoma.

Within a month, WM had rapid escalation of new complications including diabetes, hypokalaemia, fractures, community acquired pneumonia and spontaneous bruising. The working diagnosis now shifted towards ectopic Cushing's Syndrome with a two day high dose dexamethasone showing a lack of suppression suggestive of this new working diagnosis. Whilst waiting for CRH to become available, a whole body CT was ordered which showed alarmingly a 16.5cm left supra-renal mass in keeping with an adrenal cortical carcinoma which would explain entirely WM's presentation of hypogonadotrophic hypogonadism and Cushing's Syndrome.

Table 1: Initial biochemistry

| | 8am (20/4/17) | 2pm (21/4 |
|---|---|---|
| Testosterone | 3.4 | 1.9 |
| LH | | 1 |
| Potassium<br>GFR<br>Glucose | 3.6<br>>90<br>5.2 | |
| TSH<br>fT4 | 1.1<br>10.3 | |
| Ferritin | 385 | |

Table 2: Cushing's screen

| | Measured levels |
|---|---|
| Late night salivary cortisol<br>1 (10/7/17)<br>2 (11/7/17) | <br>37<br>52 |
| 1mg DST (10/7/17) | 525 (baseline)<br>488 |
| 24 hour urinary free cortisol<br>(22/7/17) | 2.33<br>U creatinine 11.2<br>U cortisol 1748 |

Table 4: 2 day high dose dexamethasone suppression test (4

| | Measured C |
|---|---|
| Baseline collection | |
| 7/8/17 0800 | 529 |
| 7/8/17 0830 | 517 |
| 7/8/17 0900 | 541 |
| 8mg dexamethasone taken at 2300 on 7/8/17 | |
| 8/8/17 0800 | 534 |
| 8/8/17 0830 | 548 |
| 8/8/17 0900 | 553 |

Table 5: Repeat ACTH levels with 2 other different laboratori

| | Laboratory | Measured Leve |
|---|---|---|
| Cortisol | Queensland Pathology | 613 |
| ACTH | (17/8/17 at 11am) | <10 |
| ACTH | South Eastern Area Laboratory (17/8/17 at 11am) | <1 |

## Radiological Investigations

Figure 1: Pituitary MRI

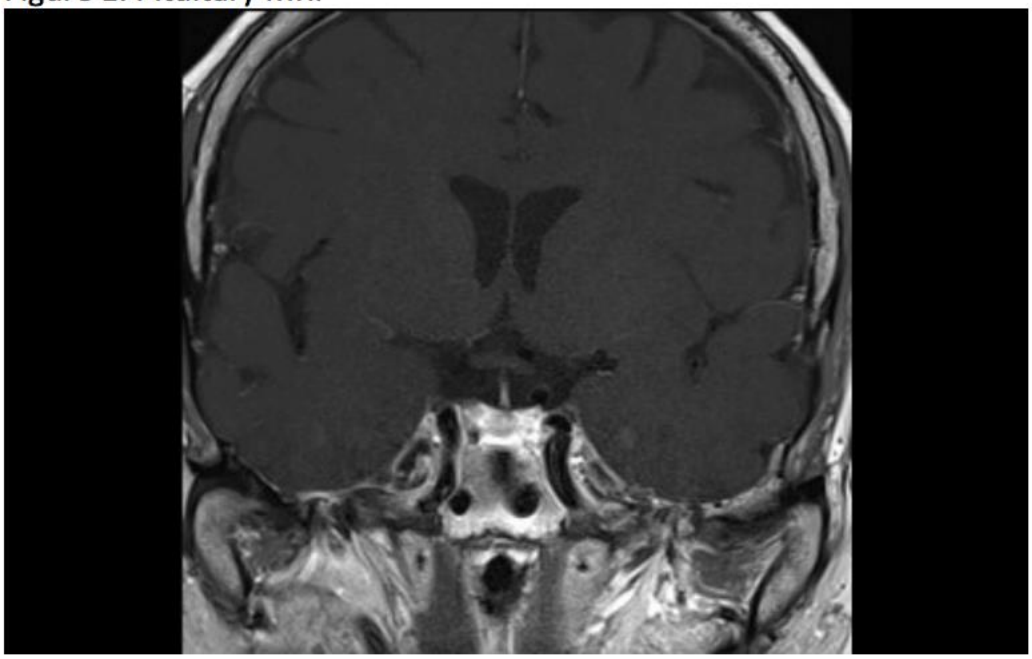
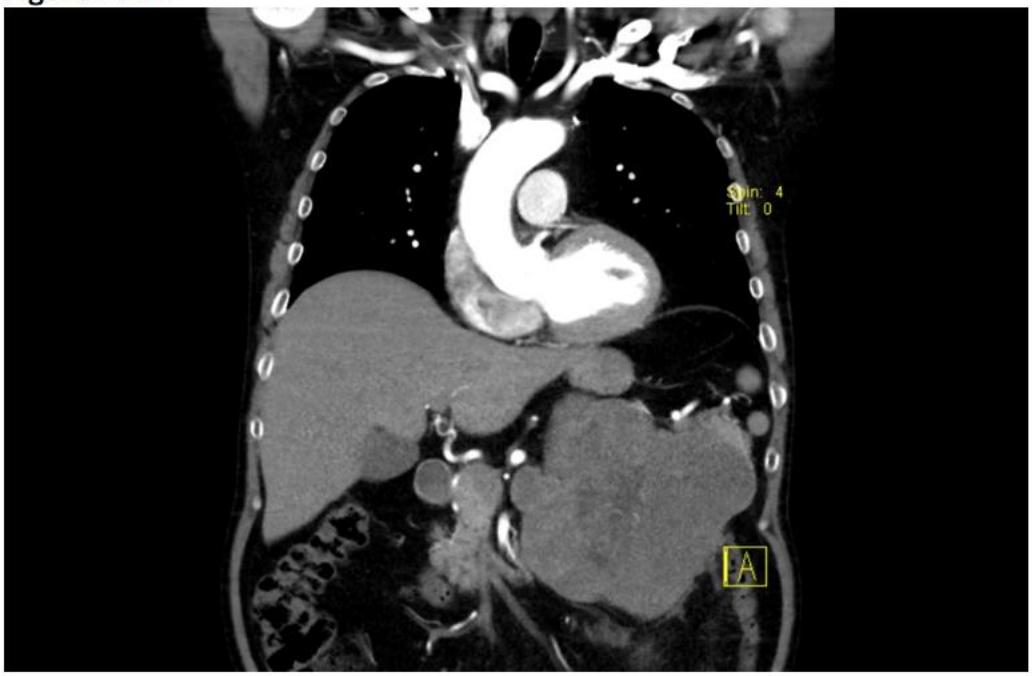


Figure 2: CT

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## Urea improves hyponatraemia in fluid restriction refractory SIADH

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**Background**

Hyponatraemia in hospitalised patients has been associated with increased mortality. The syndrome of inappropriate anti-diuretic hormone (SIADH) is a common cause of hyponatraemia. Recent European and American guidelines gave conflicting advice regarding the role of urea in the treatment of SIADH. We hypothesised that urea would be a more effective treatment of hyponatraemia than fluid restriction in this setting.

**Methods**

Review of urea use for the treatment of hyponatraemia in patients admitted to a tertiary hospital during 2016-17. Primary endpoint: Proportion of patients achieving a serum sodium ≥130mmol/L at 72h.

**Results**

Urea was used on 75 occasions in 66 patients. The median age was 67 (IQR 52-76), 41% were female. Sixty-seven (89.3%) had hyponatraemia due to SIADH of which CNS pathology (62.7%) was the most common underlying cause. The median nadir serum sodium was 122mmol/L (IQR 118-126). Fluid restriction was first line treatment in 62.2%. Urea was first line treatment in 23% and second line in 77%. In fifty three patients who received other treatment prior to commencement of urea, the mean sodium change in the 72h following urea initiation (7.0±4.9mmol/L) was significantly greater than with the preceding treatments (-1.0±4.8mmol/L; p<0.001). Thirty-two (62.7%) achieved serum sodium ≥130mmol/L at 72h post-initiation of urea, and 13 (25.5%) ≥135mmol/L. The initial urea dose range was 15-90g daily (mode 30g, 54.7%), and median treatment duration 6 days (IQR 4-8). Seventeen patients (22.7%) had side effects, distaste the most common (7), followed by nausea (6) and hypokalaemia (4). None were severe. No patients developed hypernatraemia, over-correction (>10mmol/L in 24h or >18mmol/L in 48h), or died.

**Conclusion**

Urea is a safe, effective treatment for moderate-severe hyponatraemia in patients who failed or were unable to have fluid restriction with a tolerable side effect profile.

**248**

## Aetiology of Hyperparathyroidism in Coeliac Disease: Tertiary and Quaternary Hyperparathyroidism?

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Background

Metabolic bone disease in patients with coeliac disease is commonly associated with secondary hyperparathyroidism due to impaired vitamin D and calcium absorption. However, primary, tertiary and quaternary hyperparathyroidism, characterised by hypercalcaemia, have also been reported in coeliac disease. Tertiary or quaternary hyperparathyroidism result from the chronic stimulation of the parathyroid glands secondary to longstanding vitamin D and calcium deficiency. Quaternary hyperparathyroidism suggests parathyroid adenoma emerge from transformation of pre-existing gland hyperplasia.

Case presentation

We present a patient who had re-operative parathyroidectomy on a background of coeliac disease. A 53-year-old Caucasian female was referred to an endocrinologist for severe osteoporosis with multiple fractures. Screening for secondary causes of osteoporosis revealed positive gliadin and tissue transglutaminase antibodies as well as high PTH (8.0pmol/L), calcium levels between 2.45 and 2.63mmol/L and vitamin D of 59nmol/L. The urine ca/cr ratio was 0.014. Coeliac disease was confirmed on duodenal biopsy. No adenoma was localised on ultrasound, sestamibi scan and 4-dimensional CT. She was referred to ENT with provisional diagnosis of primary hyperparathyroidism and underwent a neck exploration where the enlarged left superior parathyroid gland (200mg) was removed. The biopsy was unable to distinguish between parathyroid hyperplasia and adenoma histologically. Her PTH and calcium levels only temporary improved and therefore a second operation was performed. The right superior and a part of the right inferior parathyroid gland were removed, and histology confirmed a superior parathyroid adenoma. Her PTH and corrected calcium levels normalised after the second operation at 5.6pmol/L and 2.33mmol/L, respectively.

Conclusion

Tertiary and quaternary hyperparathyroidism in coeliac patients are important considerations especially with negative localisation studies and a high chance of prolonged undiagnosed coeliac disease. If hyperplasia is present, a different surgical technique may need to be applied, and patients may need to consent to more than one parathyroid resection pre-operatively.

**249**

## Life after denosumab: strategies to mitigate bone density loss in patients discontinuing denosumab

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**Background and aims:**

Denosumab is an antiresorptive agent that acts by the unique mechanism of binding to the receptor activator of nuclear factor-κβ ligand (RANKL) on osteoclast precursors, thereby preventing their maturation into activated osteoclasts. It is a popular alternative to bisphosphonate therapy, administered as a six-monthly subcutaneous injection, which minimises the issue of medication non-compliance.

Mounting evidence suggests that denosumab discontinuation, however, results in rebound increases in bone turnover with subsequent rapid decline in bone mineral density and in some cases, spontaneous vertebral fractures [1-4]. In patients seeking to discontinue denosumab, there is uncertainty surrounding the optimal choice of post-denosumab agent and timing of its administration to mitigate bone density loss and subsequent fractures.

**Methods:**

We report a case series of five patients who discontinued denosumab and were prescribed either an oral or intravenous bisphosphonate. Temporal patterns of BMD in relation to denosumab treatment and post-cessation antiresorptive treatment choices were assessed.

**Results:**

Our series includes 1 male and 4 females, with a mean age of 67 years. All demonstrated improvements in BMD over the period they received denosumab. Two of the three patients given zoledronic acid following denosumab discontinuation demonstrated reductions in BMD down to pre-denosumab levels over the subsequent 12 months, and the third demonstrated increased bone turnover markers suggesting accelerated bone resorption. In all 3 patients zoledronic acid was administered 6 months following the last injection of denosumab. In contrast, two patients who received oral bisphosphonates following denosumab cessation demonstrated gains in BMD in the follow up period. There were no spontaneous vertebral fractures in this group within the period of observation (18 months post denosumab). Further research is necessary to clarify the optimal treatment approach in this context, with this case series providing contrasting treatments and outcomes for consideration.

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**250**

## Not always as easy as 'αβC': A case of phaeochromocytoma with challenging pre-operative preparation

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A 55-yo woman presented with a left incidentaloma detected while being investigated for secondary causes of hypertension. She has 10-year history of hypertension controlled with olmesartan and hydrochlorothiazide with occasional hot flushes since menopause 3 years ago. She did not have any weight loss, night sweats, palpitations or diarrhoea. Examination revealed a BP of 138/79mmHg and HR 53 bpm. Initial investigations did not suggest any hormonal hypersecretion. A CT scan confirmed a 22mm adrenal lesion with pre-contrast Hounsfield measurement of 39 and avid enhancement on the arterial phase. The washout ratios were not consistent with a typical adrenal adenoma. An MRI confirmed a 20x16x16mm circumscribed solid left adrenal mass. Approximately 18 months later, biochemistry became elevated: 24-hour urinary assay for normetanephrines was 3.1 mmol/day (<2.3) and metanephrines was 0.5 mmol/day (<1.7). Plasma normetanephrine was 1400 pmol/L (<920) and plasma metanephrine was 140 pmol/L (<447). She was referred for a laparascopic adrenalectomy and was admitted 10 days pre-operatively. Despite routine alpha and beta blockade, with escalation of phenoxybenzamine doses up to 30mg TDS (1.7mg/kg) and propranolol 20mg BD, her SBP remained elevated at 140-160 mmHg. Surgery was delayed and amlodipine 10mg was added. However, despite initial response, she continued to have SBP elevations up to 150mmHg associated with palpitations. She required the addition of verapamil 40mg, with a reduction in BP to 117/80 mmHg and surgery proceeded. Her left adrenal gland was resected via laparoscopic approach. Histopathology revealed a well circumscribed, round, solid nodule measuring 22x17x18mm. Microscopic examination showed features consistent with phaeochromocytoma, with positive chromogranin and synaptophysin staining and clear margins with no vascular or perineural invasion. She is being followed up with regular screening of plasma metanephrines.

**251**

## Screening for metabolic adverse effects in men with prostate cancer treated with androgen deprivation therapy in a large Melbourne hospital network

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*2. Department of Endocrinology & Diabetes, Western Health, Melbourne, Victoria, Australia*

*3. Department of Urology, Western Health, Melbourne, Victoria, Australia*

*4. Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia*

*5. Department of Medicine, Western Precinct, University of Melbourne, Melbourne, Victoria, Australia*

**Introduction**

Androgen Deprivation Therapy (ADT) has an established role in the management of prostate cancer but is associated with multiple adverse metabolic effects [1]. Despite availability of national guidelines for management [2] the metabolic consequences of ADT may be overlooked in the time-poor public outpatient setting where the focus tends to be on cancer control.

**Aim**

To determine whether metabolic side-effect screening of ADT patients in our health service is in accordance with current practice guidelines.

**Method**

A retrospective audit (January 2016-September 2017) was undertaken of 104 patients treated with ADT at Western Health, Melbourne. Relevant medical records were identified through International Classification of Diseases version 10 Australian Modification coding. Data were collected to assess prevalence of testing for bone mineral density (BMD), blood pressure, BMI, lipids and glycaemic control at any time prior to or after initiating ADT. We reviewed use of pharmacological treatment of bone, metabolic, and cardiac conditions, and referrals made to endocrine specialist clinics after ADT commencement. These data were compared to current guidelines [2].

**Results**

Prior to or during administration of ADT, 71% of patients were receiving pharmacotherapy for bone, cardiovascular or metabolic disease. 39% were receiving bone-related therapy (one or more of calcium, cholecalciferol, anti-resorptives), but only 8% had documentation of BMD screening. Screening for metabolic syndrome was variable; blood pressure was documented in 73% and BMI in 79%. Lipid profiles were documented in 24% and glucose levels in 32%. Referrals for Endocrinology input were infrequently performed, with referrals to the Diabetes Clinic in 2%, Endocrinology Clinic 4%, and Metabolic Bone Clinic 5%.

**Conclusion**

When compared to national guidelines, significant deficiencies were apparent in screening for the metabolic consequences of ADT within our health service. Multi-disciplinary patient-centred care is essential to improve patient outcomes beyond oncological control, and minimise harm from the metabolic consequences of ADT.

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**252**

## Experience with sodium–glucose co-transporter 2 inhibitors initiation in a public hospital diabetes outpatient population

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**Table 1. Side effects during treatment with SGLT2 inhibitors**

| Side effect | Patients affected | Side effect led to discontinuation of treatment |
|---|---|---|
| Genital infection | 11 (22%) | 7 |
| Hypoglycaemia | 7 (14%) | 0 |
| Urinary tract infection | 5 (10%) | 3 |
| Polyuria | 4 (8%) | 1 |
| Diabetic foot ulcer | 2 (4%) | 0 |
| Osteoporotic fracture | 0 | 0 |
| Adverse cardiovascular event | 0 | 0 |
| Ketoacidosis | 0 | 0 |

**Table 2. Paired Samples Test**

| | Initial Mean | Final Mean | Sig. (2-tailed) |
|---|---|---|---|
| Weight | 98.19 | 95.16 | .000 |
| Systolic BP | 135.73 | 128.09 | .045 |
| Diastolic BP | 84.13 | 79.37 | .045 |
| HbA1c % | 8.88 | 8.03 | .000 |
| Total cholesterol (mmol/L) | 4.00 | 4.24 | .189 |
| HDL cholesterol (mmol/L) | 0.98 | 1.07 | .005 |
| LDL cholesterol (mmol/L) | 2.14 | 2.25 | .544 |
| Triglyceride (mmol/L) | 2.04 | 2.05 | .704 |
| Estimated glomerular filtration rate- eGFR (ml/min/1.73m2) | 79.76 | 78.78 | .304 |

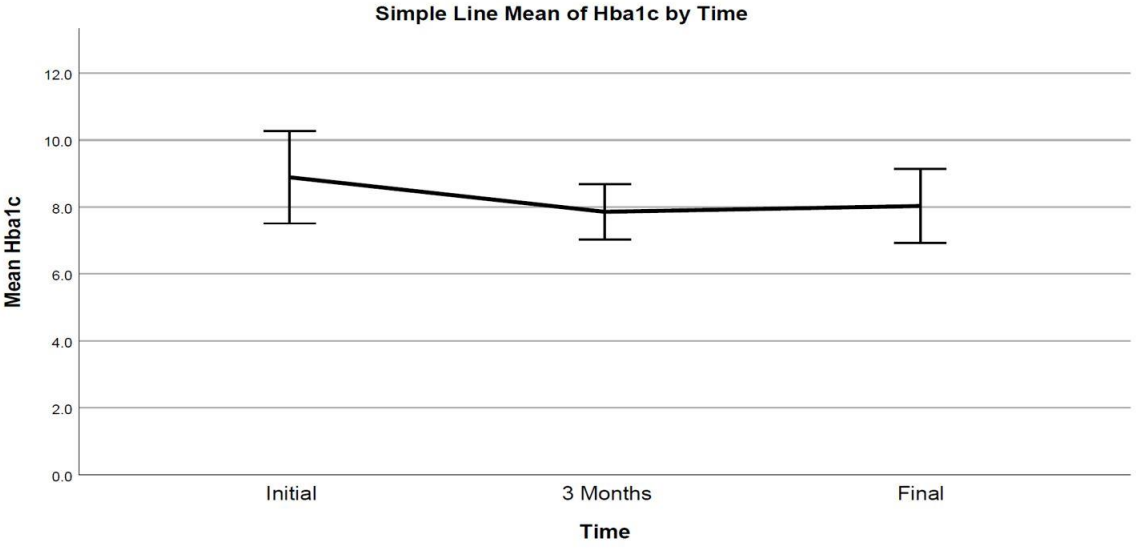


**Figure 1. Changes in mean HbA1c over time in patients treated with SGLT2 inhibitors**

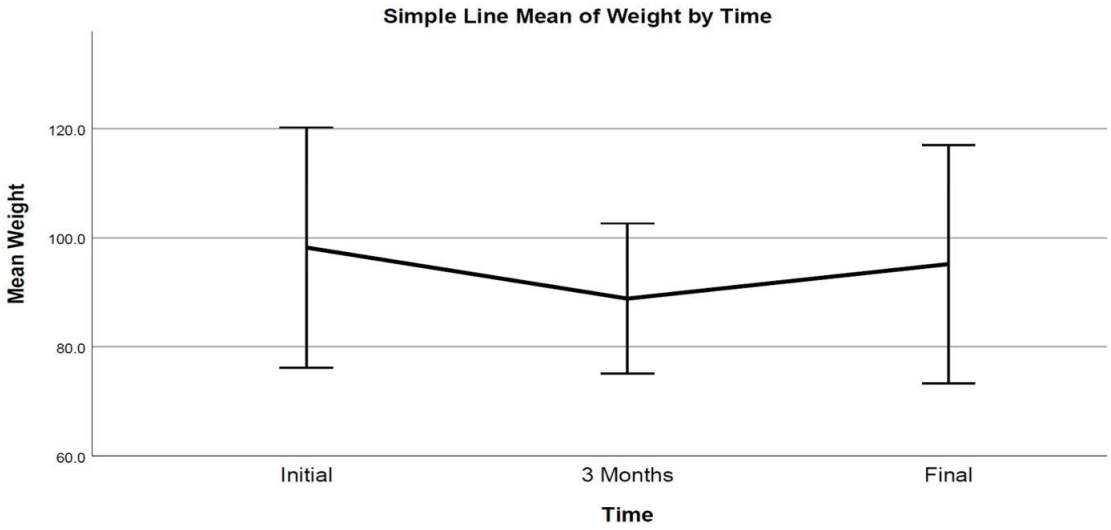


**Figure 2. Changes in weight over time in patients treated with SGLT2 inhibitors**

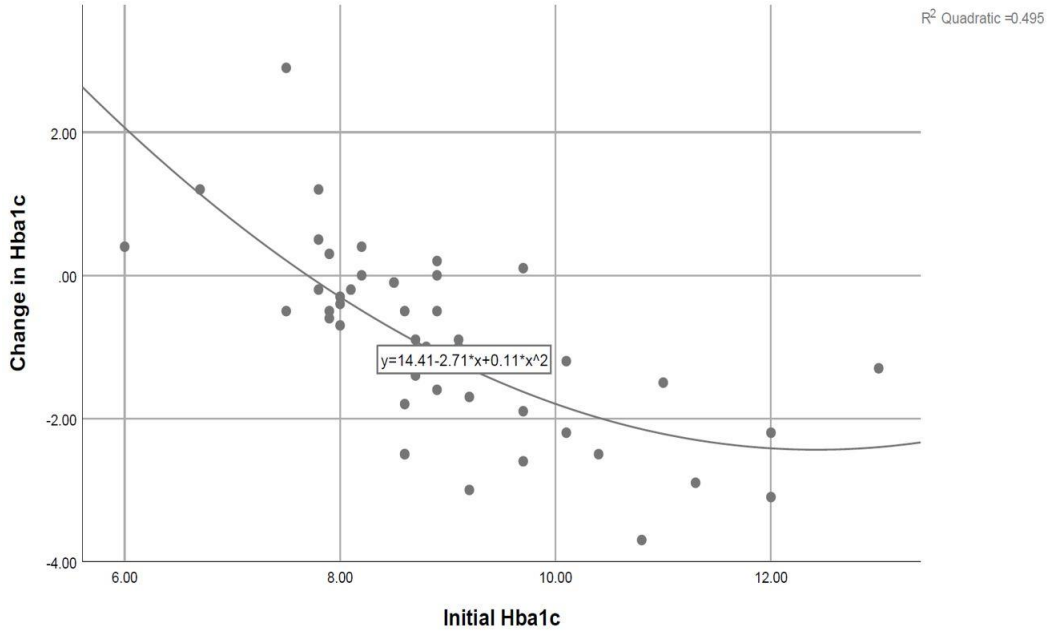


Figure 3. Simple scatter of change in HbA1c by initial HbA1c

**Background**

Sodium–glucose co-transporter 2 (SGLT2) inhibitors are new group of medications which reduce glucose reabsorption in the proximal tubule leading to decrease in plasma glucose.[1] In addition to glycaemic control, SGLT2 inhibitors improve the body weight and blood pressure (BP).[2,3]

Although SGLT2 inhibitors are well tolerated, they are associated with an increased risk of lower urinary tract and genital infections, as well as dehydration, urinary frequency, diabetic ketoacidosis, and bone fractures. [4,5,6,7]

This is a retrospective descriptive study assessing the safety and efficacy measures of SGLT2 inhibitors in a real -world public diabetes outpatient setting.

**Method**

This is a retrospective study analyzing data from 50 patients with type 2 diabetes (T2DM) who were treated with dapagliflozin or empagliflozin in the diabetic clinics across Eastern Health, between October 2014 and February 2018.

All statistical computations were performed using SPSS version 23.0. Descriptive statistics were analysed followed by T tests, Pearsons and ANOVA correlations and Multivariate analysis.

**Results**

The mean age of the participants was 57.24 years, 52% were women and 60% of patients received Dapagliflozin. The SGLT2 inhibitor was stopped in 34% of the patients due to genital and urinary tract infection, worsening of glycaemic control, weight gain or polyuria (Table.1). No significant change noted in renal function.

Significant decrease noted in Hemoglobin A1c (HbA1c), weight and diastolic BP (DBL), ALT and GGT over time, as well as a significant increase in HDL cholesterol level (Table 2, Figures 1,2). Change in HbA1c was related to initial HbA1c and independent of age, weight or initial renal function (Figure 3).

**Discussion**

The efficacy parameters of SGLT2 inhibitors have again been shown in this study. Despite the significant benefits in glycaemic control, weight, blood pressure and HDL cholesterol levels, the SGLT2 inhibitor was discontinued in nearly 1 out of 3 patients, mainly due to side effects.


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## 253

## Postpartum rhythm and blues: paraganglioma masquerading as hypertension and pre-eclampsia in pregnancy


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Paragangliomas (PGLs) are rare neuroendocrine tumours derived from the autonomic nervous system paraganglia. We present a 28-year-old woman diagnosed with a large inoperable mediastinal PGL after presenting with persistent postpartum hypertension. She had four pregnancies each complicated by hypertension and pre-eclampsia, the last requiring emergency caesarean section and intensive care to control refractory hypertension and pre-eclampsia. Nine months later she was investigated for persistent hypertension associated with 20kg weight loss, lethargy and spells of diaphoresis and palpitations. Family history was notable for PGL in both her father and paternal grandmother. Subsequent investigation found markedly elevated urinary normetanephrine 16,382 nmol/d (NR 600-3300) and dopamine 16,407 nmol/d (NR 375-3500). CT showed a 6-cm posterior mediastinal mass with avid uptake on $^{68}$Ga DOTATATE PET/CT and left atrial wall involvement on cardiac MRI. There was no evidence of metastases or other tumours. Phenoxybenzamine was commenced. At thoracotomy the mass was inoperable as it invaded the left atrial wall. Biopsy confirmed PGL and immunohistochemistry staining for succinate dehydrogenase B (SDHB) was negative consistent with a high likelihood of a *SDH* subunit germline mutation. She is now undergoing radionuclide therapy, $^{177}$Lutetium Octreotate (Lutate) and remains on phenoxybenzamine and metoprolol.

Most PGLs are diagnosed in the third to fifth decade[1,2], almost half are associated with an inherited syndrome[3,4], and about one quarter of catecholamine-secreting PGLs are malignant[4]. Surgical resection is the mainstay of treatment. One third of resected PGLs recur within five years[5]. External beam radiotherapy, radionuclide and chemotherapies may be used alone or in combination for inoperable or malignant disease. Hereditary PGL due to SDH deficiency is associated with poorer prognosis compared with other mutations with younger age of onset and higher malignancy rates (21 – 79%)[6,7]. This case highlights the importance of investigating persistent postpartum hypertension, and recognising the classic symptoms of catecholamine secreting tumours.


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## 254

## Takotsubo cardiomyopathy – A case report in a patient with metastatic phaeochromocytoma receiving steroids with peptide receptor radionuclide therapy


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*2. Nuclear Medicine Department, The Queen Elizabeth Hospital, Woodville South, SA, Australia*

*3. Endocrine and Metabolic Unit, The Queen Elizabeth Hospital, Woodville South, SA, Australia*

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*5. Intensive Care Unit, The Queen Elizabeth Hospital, Woodville South, SA, Australia*

*6. Department of Anaesthesia and Intensive Care, University of Adelaide, Adelaide, SA, Australia*

*7. Cardiology Unit, The Queen Elizabeth Hospital, Woodville South, SA, Australia*

Metastatic phaeochromocytoma (MP) is a rare and complex condition. Management is twofold: controlling excess catecholamine secretion to minimise cardiovascular morbidity, and controlling tumour progression. We present a case of non-familial MP in a 55 yo man, ECOG 0. The original 6cm right adrenal phaeochromocytoma was completely resected, with low volume, non-operable local-regional recurrence subsequently diagnosed. He was managed on phenoxybenzamine and atenolol but intermittently experienced severe cardiac symptoms due to catecholamine excess, requiring hospitalisation.

Upon biochemical progression and worsening blood pressure control, he was referred for Peptide Receptor Radionuclide Therapy (PRRT) with $^{177}$Lutetium OctreoTate (LuTate). Baseline echocardiogram was normal. Standard premedication (dexamethasone and ondansetron) was administered prior to his first therapeutic dose of LuTate. Within 24 hours, he suffered cardiovascular instability, severe hypertension and atrial fibrillation, requiring stabilisation at a tertiary ICU including adjustment of pharmacotherapy to prazosin and metoprolol. LuTate-induced catecholamine surge was presumed. He proceeded to make a complete recovery.

Prior to the second dose of PRRT, he received a variation in premedication (dexamethasone and palonesetron) although LuTate was not administered. A rapidly developing hypertensive crisis again occurred, culminating in oliguria and acute pulmonary oedema. Plasma metanephrines rose to 17813pmol/L (RR<900) with NT-Pro BNP 12439ng/L (RR:0-124) with transthoracic cardiac echocardiogram demonstrating severe cardiac failure and apical hypokinesis. Aggressive therapy resulted in normalisation of the severe myocardial dysfunction.

Final diagnosis was of Takotsubo Cardiomyopathy (TCM) , secondary to underlying MP and additional pharmacological triggers.

This case required cohesive, multidisciplinary care.

Key issues for review:

1. Understanding of potential crisis triggers, including exogenous corticosteroid administration and PRRT, in patients with MP
2. Optimal pharmacotherapy for prevention and treatment of hypertensive crises in patients with MP, in the absence of recognised guidelines.
3. Management of Takotsubo Syndrome including Beta blockade in patients with MP.

**255**

## Management dilemmas with denosumab: rebound vertebral fractures during a planned dental procedure 12 days post pre-empted delayed denosumab dose

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Denosumab is a potent, well-tolerated osteoporosis treatment, which is conveniently administered six-monthly. To minimise the potential adverse effect of osteonecrosis of the jaw (ONJ), dental review before commencement is generally advised. Should an invasive dental procedure be necessary after denosumab therapy has already been commenced, The Australian Dental Association has recommended waiting six months after the last denosumab dose [1]. Given organisational issues and delays in healing, any prolongation prior to recommencement of denosumab could increase the risk of rebound vertebral fractures [2]. Indeed, authoritative societies are advising clinicians to avoid interruption in denosumab therapy unless a final bisphosphonate dose is administered [3].

We present a memorable case in point: an 80 year old female with known osteoporosis and no previous fractures had her denosumab dose withheld prior to a planned tooth extraction scheduled to occur at the 6 month time point. The dental procedure was performed six months and twelve days after her last dose of denosumab. Whilst the dental chair was being lowered, the patient experienced acute lower back pain. Imaging revealed new wedge compression fractures of L1 and L2. Upon referral to our Osteoporosis clinic, she was diagnosed with rebound vertebral fractures during a treatment break from denosumab, and commenced on teriparatide. She has since experienced no further fractures.

The need to balance two potential adverse effects of denosumab is exaggerated in the elderly, a group most affected by both osteoporosis and tooth decay [4]. Commonly considered is the risk of ONJ in those with poor dentition requiring dental intervention, the risk of which is increased by continued treatment [5]. Equally concerning, however, is the risk of accelerated bone loss and rebound vertebral fractures should therapy be interrupted. Our case highlights this management dilemma.

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**256**

## Testicular size as a reflection of masculinity

**Mark Ng Tang Fui[1, 2], Rudolf Hoermann[2], Mathis Grossmann[1, 2]**

*1. Austin Health, Heidelberg, Victoria, Australia*

*2. Medicine, University of Melbourne, Heidelberg, Victoria, Australia*

Importance: Measurement of testicular size is a routine part of the assessment of men presenting with hypogonadism and has long been considered a sign of masculinity

Objective: To determine whether testicular volume is correlated with biochemical and clinical characteristics of masculinity

Design: Cross-sectional study.

Participants: 89 obese men with a total testosterone level <12nmol/L participating in a previously described RCT (ClinicalTrials.gov NCT01616732).

Measurements: Testicular volume was measured by an orchidometer as an average of both testes and total testosterone by LCMS/MS. Men completed the ageing male symptoms score (AMS) and international index of erectile function 5 (IIEF5). Handgrip was measured by a dynamometer, physical function testing included the 15m rapid walking, timed up and go, stair ascent and descent with a weighted vest.

Main Outcomes: 89 men participated with median [IQR] age of 53.1y [47.6, 59.2, weight of 116kg [105, 129] and total testosterone of 7.0nmol/L [6.1; 7.9]. The mean testicular volume was 18mL [10; 20]. Testicular volume was not correlated with total or free testosterone, or FSH but was weakly negatively correlated with LH ($r = -0.160$ $p = 0.037$). Testicular volume was negatively correlated with body fat mass ($r = -0.212$, $p = 0.005$) and BMI ($r = -0.120$, $p = 0.010$) but not correlated with age. Testicular volume was positively correlated with IIEF5 ($r = 0.201$, $p = 0.021$) but not correlated with handgrip strength, the battery of physical function tests or AMS.

Conclusions: Among obese men with lowered testosterone, testicular volume is associated with, to a small degree, biochemical and clinical markers of masculinity.

**257**

## A curious case of ketoacidosis

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Lactation ketoacidosis is a rare but serious complication of carbohydrate restriction in breastfeeding women. We report the case of an otherwise well 26-year-old Caucasian female, 8 weeks post-partum, who presented to the Emergency Department with a four-day history of abdominal pain and progressive shortness of breath. Initial investigations revealed a severe high anion gap metabolic acidosis (pH 6.97, $HCO_3^-$ 5, $pCO_2$ 22, anion gap 27, base excess -25.5, glucose 4.0). Capillary ketones were elevated at 6.3 mmol/L.

In an attempt to assist weight loss post-partum, she had commenced a low carbohydrate diet (<50 grams/day) 17 days prior, with 7 kg weight loss. There was a further reduction in oral intake in the days prior to presentation to ED. She had been exclusively breastfeeding since delivery.

Following recognition of ketoacidosis, the patient was commenced on an insulin and dextrose infusion and transferred to ICU. Other causes of high anion gap metabolic acidosis were excluded. Lactate was 1.0 mmol/L. Serum ketones normalised 25 hours after presentation. She was advised to cease breastfeeding during the acute admission but was given advice to increase her carbohydrate intake and continued breastfeeding post-discharge.

### Discussion

Lactation ketoacidosis is a rare condition, with twelve reported cases published in the medical literature (1-12). Most cases have been reported in first three months post-partum. Symptoms are usually non-specific, with nausea, vomiting, malaise and abdominal discomfort. Low carbohydrate intake, either intentionally or through fasting, is a common precipitant. Treatment incorporates intravenous dextrose and resumption of carbohydrate intake.

Lactation ketoacidosis results when energy intake and hepatic gluconeogenesis are unable to match the increased energy requirement of lactation. If sufficient energy intake is not maintained, a hypoglycaemic, hypoinsulinaemic state results, resulting in adipose tissue breakdown, and ketone body formation.

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**258**

## Title: Licorice-induced apparent mineralocorticoid excess and normal pressure hydrocephalus

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A 51 year old post-menopausal woman presents to the Emergency Department with severe headaches, hypertension, hypokalemia and metabolic alkalosis. Following a thorough history, it was found that she had been consuming a herbal tea to aid in restoring her fertility, containing various herbal extracts including glcyrrhiza glabra, a root containing glycyrrhizinic acid. We present a case of licorice-induced apparent mineralocorticoid excess causing hypokalaemia, hypertension, oedema and normal pressure hydrocephalus.

**259**

## The effectiveness of Liraglutide (Saxenda) for weight loss real world data from a community clinic

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**Background**

High dose liraglutide (Saxenda) has been shown to be effective for weight loss management. At present, it is only available on a private script. Its usefulness may be limited by its cost and side effect profile. We report our experiences with the use of liraglutide in managing obese patients from a community endocrinology clinic. Data was obtained over three years and expressed as mean ± SD.

**Results**

42 patients (34 females, 8 males) were studied (age 51.5± 11.3 years, BMI 39.4± 6.0). Duration of use was from one to thirty-six months, with majority over 4 to 6 months. A majority received co-administered metformin (93%) but only 36% had diabetes at the beginning. Throughout therapy, patients were instructed to stay on the liraglutide dose most tolerable for them. As a result, 1.2mg, 1.8mg and 3.0mg doses were used by 12 patients each, and 3 patients had used daily doses of 0.6mg and 2.4mg. 88% reported decrease in food intake as a result of liraglutide. 44% had experienced side effects namely nausea, constipation. Mean weight loss achieved was 6.8± 6.1kg. Weight loss correlated significantly with duration of use (P=0.002) and with reduced food intake (P=0.007), but not with dose, side effects, sex, use of metformin, age, or starting weight.

**Conclusion**

Liraglutide is effective for weight loss management in a community clinic. Its effect is likely to be achieved through reduction in food intake and is more effective with longer duration of use. This report suggests that a smaller treatment dose may be feasible and cost-effective.

**260**

## A pituitary mimic manifesting as cardiac tamponade

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INTRODUCTION:

Pituitary disorders are a common endocrine problem. Rarely non-endocrine pathology can manifest with pituitary symptoms, leading to delays in accurate diagnosis and treatment.

CASE:

We report a case of a 46-year-old female, with a 30-pack-year smoking history, who presented with unilateral visual disturbance and headaches. This was on the background of chronic diarrhoea and weight loss. She also reported polyuria, polydipsia, spontaneous galactorrhoea and amenorrhea since cessation of contraception five months prior. She had preserved visual field testing.

Bloods revealed an early morning cortisol of 274 nmol/L[N 140 – 640], ACTH 24 ng/L[N 10-50], TSH 1.4 mU/L[N 0.3-4.5], IGF-1 22nmol/L[N 8.3-32], and Prolactin 1570 mU/L[N 71-566]. A 24-hour urine collection confirmed polyuria with an output of 3.6 litres. MRI noted a pituitary mass(18 x 21 x 16mm) with no other abnormalities. She was subsequently commenced on carbegoline. 12 days later she presented with vomiting and new transaminitis. Her admission was rapidly complicated by respiratory distress and hypotension, with urgent echocardiography revealing cardiac tamponade. 800mL of blood-stained fluid was drained by emergency pericardiocentesis. Repeat prolactin had normalised (8 mU/L). Serial MRI during her admission

revealed interval increase in the pituitary mass with encroachment into the suprasellar cistern and small areas of necrosis within the lesion. Cytology from pericardial fluid showed non-small cell carcinoma with subsequent pan computed tomography revealing a right apical lung lesion, extensive mediastinal adenopathy and an adrenal metastasis.

DISCUSSION:

Pituitary metastasis is rare, with an occurrence rate between 1-3.6% (1). Breast and lung cancer are the most common sources (1,2). Even rarer are symptomatic presentations of pituitary metastasis, with one series suggesting 7% (2).

CONCLUSION:

This case highlights a common endocrine problem masquerading as metastatic malignancy which manifested as cardiac tamponade. Diagnosis can often be delayed due to constitutional malignant symptoms that can mimic pituitary dysfunction.


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**261**

## Hypothyroidism presenting with synchronous intracerebral haemorrhage and cardiac tamponade


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BACKGROUND:

Untreated hypothyroidism can lead to fluid retention and increase bleeding risk, which in extreme cases can manifest as cardiac tamponade.

CASE:

A 66 year old female with chronic atrial fibrillation on rivaroxaban, hypertension, diabetes and a previous history of untreated Hashimoto's disease, presented with progressive symptoms of heart failure. Echocardiography demonstrated a moderate pericardial effusion without features of tamponade. 24 hours into her admission she had new left sided hemiparesis, with CT brain showing a right parietal lobe intraparenchymal haemorrhage. Following this diagnosis, she deteriorated with evidence of respiratory distress and subsequent PEA cardiac arrest. Bedside echo showed progressive effusion with tamponade. Emergency pericardiocentesis was performed, with 1 litre of blood-stained fluid being drained.

Biochemistry revealed a TSH of 53 mU/L (N 0.3-4.5) and free T4 <3.2 pmol/L (N 7-17). She was subsequently commenced on regular thyroxine 100mcg daily, but due to limited adherence she was transitioned to thrice weekly thyroxine administered by community nurses.

DISCUSSION:

Untreated hypothyroidism is well known to cause heart failure symptoms, with pericardial effusions occurring in 3-6% (1). Cardiac tamponade as a presentation is however, rare. Bleeding or thrombosis can also occur in the setting of hypothyroid induced coagulation and platelet dysfunction (2). Spontaneous intracerebral haemorrhage is even rarer than cardiac tamponade. We surmise that poor renal clearance of her rivaroxaban, compounded by increased bleeding tendency from chronically untreated hypothyroidism contributed to her intracerebral haemorrhage and hastened the development of cardiac tamponade. Although daily thyroxine is ideal, in patients with suboptimal adherence, increased doses of thyroxine can be taken less frequently due to the long medication half-life.

CONCLUSION:

This case highlights the extreme multi-organ manifestations of untreated hypothyroidism. Avoiding rare life-threating complications of hypothyroidism can be overcome with judicious and early thyroid replacement.


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**262**

## Hypoparathyroidism-independent hypocalcaemia in severe hypomagnesaemia.

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A 77yo Caucasian female was admitted for investigation of dysphagia. Gastroscopy, biopsy and imaging revealed metastatic small-cell carcinoma of the oesophagus. Her past history included post-surgical hypoparathyroidism from early adult life after thyroidectomy for probable multinodular goitre. She was normocalcaemic (total Ca++ 2.57mmol/L, albumin 39g/L) taking calcitriol 0.25µg bd without calcium supplements.
She was treated with chemotherapy including carboplatin. She developed severe hypomagnesaemia (0.47mmol/L; N: 0.70-1.10) (a recognised complication of platinum-based drugs due to injury to the distal convoluted tubule) but also symptomatic hypocalcaemia (total Ca++ 1.40, albumin 28, corrected Ca++ 1.64). Supplementation with calcium and increased calcitriol alone was ineffective but normocalcaemia was restored with both intravenous and oral MgSO4.
Chemotherapy was continued in 3 week cycles with carboplatin on Day1 maintaining normocalcaemia with concurrent iv infusions of 10g MgSO4 followed by oral magnesium supplements. Additionally oral calcium was given days 1-7 in each cycle. She achieved a partial remission of her malignancy but then developed progressive disease requiring palliative care. She passed away 8 months after her initial presentation.
It is well-accepted that PTH secretion is magnesium-dependent. Hypomagnesaemia also induces resistance to PTH. Our patient was hypoparathyroid but normocalcaemic on presentation. Possible explanations for her hypocalcaemia include alteration of the normal heteroionic exchange of Ca++ and Mg++ at the bone surface with increased Mg++ release in exchange for increased skeletal uptake of Ca++ (1) or a possible role of Mg++ in regulation of vitamin D action in bone or gut.
Hypoparathyroidism is now an uncommon complication of thyroid surgery. However platinum-containing drugs are used commonly in chemotherapy. This case highlights the necessity to consider repletion of magnesium in patients receiving platinum especially in those with known hypoparathyroidism.

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**263**

## Sugar High: An unusual case of hyperglycaemia

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**Introduction:** In a patient with type 1 diabetes, who is insulinopenic, the hyperosmolar hyperglycaemic state with suppressed ketones is a rare presentation. In the insulinopenic state counter-regulatory hormones at high concentrations (glucagon, adrenaline and cortisol) increase the action of hormone sensitive lipase, releasing free fatty acids from adipose tissue predisposing to diabetic ketoacidosis (DKA) through beta-oxidation and conversion to ketone bodies. We report a patient who in the setting of intermittent insulin adherence with methamphetamine use and acute on chronic renal impairment presented with Hyperosmolar Hyperglycaemic State (HHS) instead of DKA.

**Case:** A 36-year-old Caucasian male with type 1 diabetes and established micro and macrovascular complications including nephrotic range proteinuria, was brought into the Emergency Department obtunded. He presented febrile (38$^{o}$C), tachycardic (112 beats per minute), hypertensive (BP 240/110 mmHg) and dehydrated. Laboratory investigation results revealed a pH: 7.3 a normal anion gap 16 mmol/L, venous glucose 82 mmol/L and ketones 0.66 mmol/L. Increased serum osmolarity of 345 mOsmol/L. Creatinine 504 umol/L baseline Creatinine 280 umol/L and hyperkalaemia (K: 6.3mmol/L).

He was diagnosed to have a hyperosmolar hyperglycaemic state (HHS) complicated by acute on chronic kidney disease (CKD) in the setting of methamphetamine use.

We propose the following mechanism for this:

1. Renal impairment reduces insulin clearance and subsequently increases its half-life. Ketosis suppression requires 1/10 of insulin required for hyperglycaemia suppression1.
2. Suppression of glucagon a hormone secreted by alpha cells of the pancreas and enteroendocrine cells in the gut by cocaine and amphetamine regulated transcript (CART). CART is a pancreatic peptide released in response to methamphetamine suppresses glucagon release.

**Conclusion**: In the setting of acute on chronic renal failure with methamphetamine use the counter regulatory hormone suppression is the proposed link in supressing ketoses and predisposing to hyperosmolar hyperglycaemia state in susceptible patients with Type 1 Diabetes.

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**264**

## Hidden in plain sight an unusual presentation of growth hormone excess

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This case describes a 32-year-old mother of two with an unusual and challenging presentation of acromegaly. The patient did not have the classical features of acromegaly, but presented with elevated prolactin (2653mIU/L), oligomenorrhoea and galactorrhoea. She had an elevated IGF-1 139nmol/L and growth hormone 30mIU/L, which failed to suppress on oral glucose tolerance. Initial MRI brain showed a solid-cystic macroadenoma (47 x 22 x 19mm) with optic chiasm compression and bilateral cavernous sinus involvement. Formal visual field testing was normal.

The patient underwent surgical resection followed by stereotactic radiotherapy (50.4Gy in 18 fractions). Histopathology showed positive immunohistochemistry for chromogranin, growth hormone and prolactin. Despite multimodal treatment including lanreotide 120mg monthly and cabergoline 0.5mg weekly, her acromegaly remains resistant with persistently elevated IGF-1 and GH.

In patients with acromegaly, 30-40% have hyperprolactinaemia, which may represent either 'stalk effect' or true co-secretion from mammosomatotroph cells in the pituitary[1,2]. In cases of growth hormone and prolactin co-secretion compared to growth hormone hypersecretion alone, adenomas are larger and classical acromegalic features are less pronounced[2]. There is increased menstrual disorders and galactorrhoea leading to earlier presentation in women[2]. It is unclear if cosecretion of prolactin significantly alters morbidity and mortality in acromegaly.

In the treatment of acromegaly, current guidelines recommend surgical management as first line with adjuvant radiotherapy or medical therapy in residual disease[3]. Somatostatin analogues (SSA) are commonly used for medical therapy. Pasireotide, a second generation SSA and pegvisomant (a growth hormone receptor antagonist) have achieved good outcomes[3]. Dopamine agonists also have a role, with prolactin co-secretion a positive predictor of response[3]. Combination therapy with SSA and pegvisomant is reported[3] and a recent case report induced biochemical remission with combination pasireotide, pegvisomant and cabergoline[4]. This case is an unusual presentation of acromegaly and it is hoped that with the use of immunohistochemical markers including SSTR expression to predict response to medical therapy and the use of newer agents will result in biochemical remission.


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## 265

## Endocrine Therapy in Women with Early Breast Cancer – Experience of a Tertiary Centre Combined Endocrinology-Oncology Breast Cancer Service


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Publish consent withheld

## 266

## Androgen replacement for male hypogonadism after PBS restrictions of 2015


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As of April 1 2015, the PBS implemented new criteria for the prescription of testosterone with key differences from prior criteria. In September 2016, the Pharmaceutical Benefits Advisory Committee reported that in the 12 month period since this amendment there was a vast decline in the number of prescriptions filled for testosterone. Our study aimed to review the effect of these changes on local practices at a tertiary endocrinology outpatient service.

A retrospective chart review was conducted to identify all outpatient referrals to the Sunshine Coast Endocrinology service for management of hypogonadism in the two-year period since the PBS restrictions were implemented and determine to what extent patients were now excluded as a result of the changes. All endocrinology referrals from 1 April 2015 to 30 June 2017 were screened from which 173 patients met inclusion criteria. Demographics, biochemistry, indication for testosterone replacement and relevant comorbidities were examined.

Of the 173 outpatients, a smaller proportion had established testicular or pituitary pathology, while the majority (126, 72.8%) of patients had no established disorder. Of those patients with no established disorder, by strict interpretation, only 3 patients (2.2%) meet current PBS criteria, whereas 56 (40.3%) would have met the pre-2015 criteria. Fewer patients (35.3% vs 55.4%) meet the lower biochemistry requirements (i.e. two morning testosterone levels <6mmol/L vs <8mmol/L). 60.9% had a BMI >30, 26.2% were taking opiates, 15.9% were older than 70. In addition, 17.3% were in fact less than the required age of 40. Of the three patients meeting PBS criteria, two had untreated depression while the third patient had obstructive sleep apnoea and alcohol dependence.

By strict application of the revised criteria, it is apparent that very few patients with low testosterone values will continue to meet PBS inclusion in the absence of an established pituitary or testicular disorder.

## 267

# MEN4, the MEN1 mimicker; the discovery of a novel pathogenic variant in the *CDKN1B* gene.

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***CASE***

LM, a 42-year-old Lebanese woman, was referred for investigation of MEN1 syndrome. LM was diagnosed with a parathyroid adenoma aged 33 and a prolactinoma aged 42. LM's relevant family history includes a sister diagnosed with a parathyroid adenoma. The result of germline testing of the *menin* gene was inconclusive, with no pathogenic variant identified. Subsequently, utilising a next generation sequencing gene panel, a pathogenic variant in *CDKN1B* (c.179G>A, p.Trp60Ter) was identified, confirming MEN4 syndrome. This variant results in a premature stop codon, leading to a truncated CDKN1B protein with predicted loss of CDKN1B function.

***MEN4***

Multiple endocrine neoplasia (MEN) refers to a group of autosomal dominant disorders that increases the likelihood of developing endocrine and non-endocrine tumours. Approximately 5-10% of patients who present with a MEN-1 like phenotype do not have mutations of the menin gene. Studies have found that up to 3% of this population harbour a *CDKN1B* mutation resulting in MEN4. The prevalence of this very rare disease is thought to be less than 1/million with less than 20 cases documented in the literature.[1,2]

*PHENOTYPE:* As with MEN1, primary hyperparathyroidism is the predominant phenotypic feature occurring in 80% of patients, followed by pituitary neoplasia in 37%, and less commonly gastropancreatic neuroendocrine tumours and adrenal neoplasia. These manifestations occur later in life and are less aggressive than MEN1.[2,3]

*GENETICS & TUMORIGENESIS:* MEN4 is caused by a germline mutation in the tumour suppressor gene *CDKN1B.* Interestingly, it does not always follow Knudson's 'two-hit' hypothesis. *CDKN1B* is located on chromosome 12p13.1 and codes for the protein p27. It plays an inhibitory role as part of the CDKI family of genes, which result in cell cycle arrest. Mutations of this gene therefore trigger uncontrolled cell cycle progression.[3] A common pathway for tumorigenesis between MEN1 and MEN4 has been suggested whereby *CDKN1B* is transcriptionally regulated by menin through epigenetic mechanisms.[4]

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## 268

# A case of a large adrenal myelolipoma in a patient with congenital adrenal hyperplasia

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**CONTEXT**

Myelolipomas are benign neoplasms of the adrenal glands that consist of both adipose and hematopoietic tissue which are usually small and have a prevalence of 0.1% in autopsy studies (1). Although adrenal masses occur in 11% of all Congenital Adrenal Hyperplasia(CAH) patients, only 6.5% of these tumours are Myelolipomas (2).

Myelolipomas are usually discovered incidentally, and the malignant potential of an incidental adrenal mass is proportional to its size (3). However several case reports of large Myelolipomas are described in patients with CAH (4).

**CASE DESCRIPTION**

A 42-year-old man with CAH who had reasonable disease control on long term Prednisone therapy presented to his gastroenterologist with severe colitis. Disease control of colitis was not achieved by either steroidal or non steroidal therapy. An incidental 18cm left adrenal mass was found on MR Enterography with mixed areas of solid and fat density. A malignant adrenal lesion (liposarcoma) could not be ruled out on imaging characteristics alone. There was no evidence of adrenal hormone hyper secretion on biochemical testing and the mass did not increase in size on short duration serial imaging. The mass was resected completely together with the spleen and descending colon due to the strong suspicion of adrenal malignancy. Surgical histology revealed an Adrenal Myelolipoma. He proceeded to have a stormy post operative course

**CONCLUSION**

The case highlights that patients with CAH may present with incidental adrenal tumours that are both large and benign such as Myelolipomas. In these patients the size of an adrenal mass lesion alone is a poor predictor of malignant potential. Increased awareness of such cases in CAH patients is required .


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## 269

## Acquired osteosclerosis secondary to signet-ring cell adenocarcinoma


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Publish consent withheld


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## 270

## Clinical outcomes and factors that contribute to long-term remission after pituitary surgery in patients with Cushing's disease: experience from two Australian Tertiary Hospitals.


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**Introduction:** Cushing's disease (CD) is associated with high mortality rate especially with persistent disease. [1, 2] Our aim was to identify predictors of remission using our long-term follow-up data on CD patients.

**Method:** All histories of patients with treated CD at RMH and RAH between 1990-2016 were reviewed. A binary regression model was used for statistical analysis.

**Results:** Eighty-seven patients had long term clinical outcome available. Mean follow-up period was 9 years (IQR 2.7-14.4). Thirty patients (34%) were male and mean age of diagnosis was 45 years (IQR 35-57). Macro-adenoma were more common in males (50% vs 21%). Osteoporosis rate was highest (50%) in males with low testosterone level (< 6nmol/L). Median weight loss was 10kg at 1 year follow-up (IQR 4-12) but this wasn't sustained in the long-term. After repeated operations, a higher rate of diabetes insipidus (41% vs 24%, p value=0.04) and CSF leak (11% vs 4%, p value=0.04) were seen but not SIADH (6%). Mortality in the cohort was low (6%). Remission was achieved in 43 patients (49%) after first surgery and the rate was higher

(60%) for surgeries performed between 2007-2016, although mean follow-up time was shorter: 6.1 years (IQR 1.9-8.7) vs 3.4 years (IQR 1.2-6.3). Overall, factors associated with achieving clinical remission post initial surgery included: micro-adenoma (OR 8.41, p value=0.03), age > 35 years (OR 4.36, p value=0.01) and initial surgery performed between 2007-2016 (OR 4.9, p value=0.001). Identification of micro-adenoma on initial MRI (p value=0.31) and level of 24 hour urinary free cortisol (p value = 0.28) weren't found to be associated with clinical outcome.

**Conclusion:** In our study, higher rates of DI and CSF leak were seen with repeated pituitary operations. Factors associated with remission post initial surgery in long term follow-up include micro-adenoma, age >35 years and operation performed between 2007-2016.

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## 271

## Clinical characterisation of patients with Acromegaly: A single centre experience

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**Introduction:** Acromegaly leads to unfavourable metabolic complications and mortality.[1] The aim of this study was to clinically characterize patients with acromegaly and to examine outcomes.

**Method:** All histories of patients with treated acromegaly at a single tertiary hospital between 1970-2017 were reviewed.

**Results:** Sixty-eight patients were included. Thirty-one patients (45%) were females and the mean age at diagnosis was 45 years (IQR 37-56). A high proportion of patients (81%) had macro-adenomas and 6 (9%) had tumours that co-secreted prolactin and growth hormone. The most common symptoms reported were altered facial appearance (85%), enlargement of hands and feets (81%) and headache (57%). Hypertension (38%), diabetes mellitus (24%) and sleep apnoea (22%) were also frequently reported. Hypogonadism (testosterone level < 6nmol/L) was present in 32% of males, although osteoporosis was uncommon (3%). Fifty-four patients (79%) had long-term clinical outcome documented with a mean follow-up period of 13 years (IQR 4.7-22.7). Mortality was low (9%). Following initial surgery, sustained remission was achieved in 23 patients (43%), ten patients (19%) had disease relapse and 25 patients (46%) had persistent disease requiring adjuvant medical and/or radiotherapy. In total, eleven patients required more than one operation and 23 patients (42.6%) received radiotherapy. The incidence of SIADH (4%), CSF leak (4%) and diabetes insipidus (6%) were low post initial surgery, however 16 (30%) developed DI after subsequent surgery. Sixteen patients (30%) required long term thyroxine replacement, 12 (22%) needed cortisol replacement and 13 males (45%) received testosterone replacement. Initial IGF-1 level but not GH level was negatively associated with remission rate post initial surgery. (OR 0.51, p value=0.05)

**Conclusion:** Macroadenomas were common amongst patients with acromegaly at this centre and metabolic complications such as hypertension, diabetes mellitus and sleep apnoea were prevalent. Initial IGF-1 level but not GH-level was negatively associated with long-term remission post initial surgery.

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## 272

## Hypertension in adrenocortical carcinoma: lessons learned

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A 71 year old female was referred to Endocrinology Clinic after presenting to Emergency with bitemporal headache and blood pressure 200/80mmHg. She had a history of pregnancy induced hypertension aged 27 and essential hypertension diagnosed aged 40. At age 57, she experienced her first episode of hypertensive urgency; at the time, screening for endocrine causes of hypertension was negative but computed tomography (CT) of the abdomen was undertaken and revealed a 4cm adrenal mass. This was resected and histopathology showed adrenocortical carcinoma (ACC). Post-operatively her hypertension remained well-controlled until her re-presentation in July 2017.

Screening for hyperaldosteronism, hypercortisolaemia and phaeochromocytoma was once again negative. Given the history of ACC, repeat CT abdomen was arranged and surprisingly revealed a left lingular lobe mass. Biopsy of the mass was consistent with metastatic ACC, which prompted further biochemical investigation for a hormonal cause of hypertension. An extended steroid panel showed elevations in progesterone 1.25 nmol/L (<0.32), 17-hydroxyprogesterone 2.6 nmol/L (<2.0), 17-hydroxyprenenolone 33nmol/L (<6.8), dehydroepiandrostenedione-sulphate 4475 nmol/L (27.0-2440 nmol/L), 11-deoxycorticosterone 8.1 nmol/L (<0.57) and 11-deoxycortisol 10.3 nmol/L (<1.0). The solitary metastasis was resected in October 2017 with ensuing normalisation of all hormone levels and blood pressure.

11-deoxycorticosterone (DOC) is a steroid precursor to aldosterone which can bind to and activate the mineralocorticoid receptor. DOC-secreting ACC is an extremely rare cause of secondary hypertension. In the current case, the close temporal relationship between exacerbation of the patient's hypertension and incidence of ACC prompted further investigations which revealed DOC secretion as the cause of hypertension. An understanding of the cause of DOC hypersecretion in ACC, along

with improvements in assay techniques, have now enabled the identification of biomarkers of adrenal malignancy which may improve the specificity of preoperative diagnosis of ACC and prevent unnecessary adrenalectomy.


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## 273

## Navigating Medication Availability: Combination Fluconazole and Metyrapone to Treat Ectopic Cushing's Syndrome


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Introduction. Small cell lung cancer (SCLC) is a neuroendocrine tumour with the capacity to secrete a number of polypeptide hormones including ACTH resulting in a Cushing's syndrome (CS). ACTH-secreting SCLC is associated with a poorer prognosis than SCLC alone. Although critically important, the management of hypercortisolaemia in this context is challenged by the lack of availability of first line option ketoconazole, and the expense and toxicity profile of other anti-adrenal agents. There is little experience using alternative options.

Case. A 63-year-old female with metastatic SCLC (involving pleura, bone and liver) was diagnosed with ectopic ACTH secretion after presenting with severe hypokalaemia, hypertension and hyperglycaemia. She was unsuitable for resection of primary lung tumour and at diagnosis, her condition was deemed incurable. She was not fit to undergo bilateral adrenalectomy. Ketoconazole was unavailable. Hypertension was controlled with spironolactone 100mg bd. Metyrapone 500mg tds improved morning serum cortisol levels from 1274nmol/L to 222nmol/L. Serum cortisol rose to 1887nmol/L after metyrapone was inadvertently withheld. Metyrapone 500mg tds was restarted with fluconazole 200mg bd and serum cortisol levels improved again to 502nmol/L then remained stable. This combination of ketoconazole, metyrapone and spirolactone allowed a reduction in potassium supplementation from 160mmol intravenous and 124mmol oral potassium chloride, to 72mmol potassium chloride orally daily. Disease course was complicated by pulmonary embolism, and the patient passed 4 months after SCLC diagnosis.

Conclusion. This is the first report of combined use of metyrapone and fluconazole in the management of ectopic Cushing's syndrome related hypercortisolaemia. This combination is a suitable well-tolerated option especially when traditional options are unavailable.

## 274

## Characterising baseline motivation and engagement in healthy lifestyle behaviours in participants in the testosterone for type 2 diabetes prevention in men (T4DM) Study


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Background: Beneficial lifestyle changes are difficult to implement in overweight men at risk of diabetes. The impact of motivation on facilitating engagement in healthy lifestyle behaviours is incompletely understood.

Aim: Characterisation of a questionnaire to characterise levels of motivation and willingness to change, in relation to healthy lifestyle behaviours.

Participants: 605 of 1,007 men 50-74 years with waist ≥95cm, testosterone ≤14nmol/L, and impaired glucose tolerance (IGT)/newly diagnosed type 2 diabetes enrolled in T4DM (ACTRN12612000287831), randomised to testosterone vs placebo for two years with background lifestyle intervention.

Methods: Dedicated questionnaire administered at randomisation comprising motivation and behavioural domains. Relevant items were compared with SF12 and Physical Activity questionnaires.

Results: On scale 1 (low)-10 (high), motivation was rated (median) 8 and willingness to change 8. Over a 14-day period, men reported engagement in healthy activities on (median) 5 days, moderate physical activities 6 days, vigorous physical activities 2 days and quality time with friends/family 9 days. Overall effort to engage in these activities was rated 3/10.

Self-rated physical health (median score 7/10) correlated with quality of life by SF12 score (r=-0.57, p=<0.001). Self-reported engagement in moderate and vigorous physical activity correlated with corresponding Physical Activity questionnaire responses (r=0.60, p=<0.001; r=0.47, p=<0.001 respectively). Motivation correlated strongly with willingness to change (r=0.75, p=<0.001) but only modestly with engagement in healthy behaviours (r=0.15, p=0.001).

Baseline testosterone did not correlate with motivation (p>0.05) but was positively correlated with engagement in vigorous physical activity (difference 0.07 nmol/L/day, p=0.025).

Conclusions: Men participating in T4DM with IGT/newly diagnosed diabetes self-report high motivation and willingness to change, but moderate engagement with healthy lifestyle behaviours. Key elements from the motivation and behavioural questionnaire correlated strongly with similar questions from validated instruments. Further research is needed to translate motivation into improved engagement in healthy lifestyle behaviours in men at risk of diabetes.

**275**

## Parathyroid carcinoma during pregnancy

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Case description: We report a case of 37 year-old Thai woman with a peak serum calcium of 3.6 mmol/L in her third pregnancy. She had previously had hypercalcaemia in two previous pregnancies over a 6-year period but no past history of nephrolithiasis, fractures or renal impairment and no previous investigations. Previous pregnancies were uncomplicated. In this pregnancy, she was first found to have parathyroid (PTH)-mediated hypercalcaemia at 8 weeks gestation with serum calcium of 2.94 mmol/L and serum PTH 73.3 pmol/L, vitamin D 30 nmol/L. She was first referred for management of hypercalcemia at 32 weeks gestation. A 24-hour urinary calcium excretion and fractional excretion calcium were both elevated excluding familial hypocalciuric hypercalcaemia. Hypercalcemia was refractory to saline diuresis with frusemide, and calcitonin. Induction of labour occurred at 37 weeks Her baby had transient hypercalcaemia which normalised after 36 hours. Maternal hypercalcaemia persisted despite the use of pamidronate 1mg/kg. Further investigations including a Tc99m Sestimibi scan, showed low level increased tracer uptake at the lower pole of the right thyroid lobe with FNA confirming a parathyroid lesion. Bone densitometry showed osteopenia in the lumbar spine and femoral neck and osteoporosis in the left wrist. A right inferior parathyroidectomy was performed 13 months postpartum. Histopathology showed a 16x14x10mm encapsulated nodule with invasion to thyroid gland and areas of fibrosis. Immunohistochemistry was negative for parafibromin and positive for PGP 9.5, diagnostic for parathyroid carcinoma, low grade. Serum calcium normalised postoperatively while on maintenance dose of cholecalciferol and calcium carbonate.

Conclusion: Parathyroid carcinoma is a rare cause of hypercalcaemia. The diagnosis can be difficult due to overlapping features with benign adenoma but the use of immunohistochemical markers are diagnostic. The insidious presentation over seven years in a young female is unusual.

| Weeks of Pregnancy | Serum Calcium (mmol/L) | Treatment |
|---|---|---|
| 32 | 3.10 | Hydration, vitamin D 5000 |
| 33 + 2 days | 3.02 | Frusemide 20mg d |
| 33 + 4 days | 2.93 | |
| 33 + 5 days | 3.15 | Frusemide 20mg |
| 34 | 3.03 | |
| 35 + 1 day | 3.25 | Calcitonin 100 units<br>Vitamin D IM 100,000 |
| 35 + 3 days | 3.14 | |
| 35 + 4 days | 3.24 | |
| 35 + 6 days | 3.44 | Calcitonin 400 units I |
| 36 | 3.0 | |
| 36 + 4 days | 3.3 | Calcitonin 500 units I |
| 36 + 5 days | 3.62 | Calcitonin 600 units I |
| 36 + 6 days | 3.33 | |
| 37 + 1 day | 3.14 | Induction of labour, c |
| Day 1 post partum | 3.24 | Pamidronate 60m |
| Day 2 post partum | 3.22 | |

**276**

## Isolated post-prandial hypoglycaemia and a negative 72 hour fast – an unusual case of proinsulinoma

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**Case**

A 45 year-old man was referred to the Endocrinology clinic with 3-months history suggestive of post-prandial hypoglycaemia (PPH), including one episode resulting in syncope and facial injury. Sugary drinks precipitated these episodes. He was otherwise healthy and has not had gastric or fundoplication surgery. There is a family history of paternal uncle with pancreatic cancer, and grandmother with hyperparathyroidism.

75gOGTT confirmed the diagnosis of proinsulinoma, with symptomatic hypoglycaemia (2.3mmol/l) occurring at 120minutes, associated with failure of suppression of insulin and proinsulin (544.2mIU/l and >100pmol/l respectively). Intriguingly, 72-hour fast did not precipitate hypoglycaemia (BGL 5mmol/l at start to 3.4mmol/l at 72hours with low beta-hydroxybutyrate 2.2mmol/l).

Imaging confirmed an intensely DOTATATE-avid 27x26x26mm head of pancreas lesion. Selective arterial calcium stimulation (SACS), however, returned with discordant localisation to the pancreatic tail and also indicated liver metastasis. Biopsy performed via endoscopic ultrasound (EUS) of the pancreatic head lesion further confirmed a well-differentiated insulinoma. As liver lesions were not identified on DOTATATE-PET, MRCP and EUS, a pancreatico-duodenectomy with intra-operative ultrasound has been planned for June'2018. Diazoxide was commenced in the interim with good effect.

**Discussion**

To our knowledge, there have been less than ten cases of insulinoma reported with both isolated PPH and negative 72-hour fast. Mechanisms hypothesised include (1) predominance of Glut-2 expression[1], (2) over-expression of GLP1 receptors[2], and (3) prolonged half-life of insulin after a significant insulin surge[3]. Despite only 6% of insulinomas presenting with exclusively post-prandial symptoms[4], insulinoma should be considered in the differentials for PPH after common causes are excluded.

Majority of insulinomas are benign. This case will require long-term observation due to several factors suggestive of malignancy including early presentation, markedly elevated proinsulin (>40% total insulin)[5], and positive SACS for liver metastasis with negative imaging.

Further operation details, immunohistochemistry, and post-operative outcome will be discussed during the presentation.

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**277**

## The whole is greater than the sum of its parts: synthesised triple-assessment of thyroid nodules optimises pre-operative risk-stratification

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**Introduction:**

Accurate risk-stratification of malignancy risk of thyroid nodules best occurs with integration of clinical factors, ultrasound features and cytology results[1]. An illustrative case is presented.

**Case presentation:**

A 53 year old female presented for review of an incidentally discovered thyroid nodule. Clinical examination revealed a firm thyroid nodule on the right without lymphadenopathy.

Cytology, performed prior to specialist review, showed a cellular aspirate with atypical follicular cells in sheets, without colloid, classified as Bethesda IV “Suspicious for Follicular Neoplasm”.

Specialist neck-ultrasound identified a large right upper pole thyroid nodule (23x21x24mm) which was markedly hypoechoic. The margin was grossly lobulated. There was no extrathyroidal extension or calcification. Vascularity was normal. A capsule was not seen.

Ultrasound features were not typical of a follicular lesion, which are usually isoechoic with an identifiable capsule. Marked hypoechogenicity of a solid lesion suggests dense hypercellularity, and gross lobulations are a high-risk feature, suggesting invasion. Together with the cytology findings (cellular aspirate, Bethesda IV) and clinical findings (firm nodule) a pre-operative diagnosis of follicular thyroid cancer (FTC) was made.

Histopathology revealed a 25mm widely-infiltrative lesion with gross lobulations and no capsule. Microscopy showed mixed infiltrative and expansile growth pattern, fused microfollicular structures and areas of solid tumour cell sheets, peripheral irregular infiltrating strands of tumour cells and perineural and lymphovascular invasion, consistent with an unencapsulated, widely invasive FTC.

**Conclusion:**

This case illustrates that synthesis of complementary information obtained from clinical presentation, cytology and ultrasound yields greater diagnostic information than any modality in isolation. Lobulation and hypoechogenicity are typical high risk features on ultrasound, although not usually associated with follicular pathology, and are classically demonstrated on both ultrasound and gross imaging in this case.

**278**

## Pharmacological and surgical treatment of non-fertility outcomes in polycystic ovary syndrome: an overview of systematic reviews

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Background

Polycystic ovary syndrome (PCOS) affects up to 13% women and is associated with significant complications. The quality of evidence supporting the recommendations on treatment of non-fertility outcomes in PCOS is unknown.

Objective

To summarise and appraise the methodological quality of systematic reviews and meta-analyses evaluating pharmacological and surgical treatments for non-fertility outcomes in PCOS.

Methods

A literature search from MEDLINE, EMBASE, CINAHL PLUS, and PROSPERO was performed from inception until 15th of September 2017. Article selection, data extraction, and quality appraisal of included reviews were performed in duplicate. A narrative synthesis of the findings was conducted.

Results

This overview included 31 reviews. The quality was low for seven, moderate for sixteen, and high for eight reviews. Two reviews assessed psychological outcomes. Metformin improved anthropometric (seven of ten reviews), metabolic (four of fourteen reviews), and endocrine outcomes (three of twelve reviews). Thiazolidinediones improved metabolic (two of five reviews) and endocrine outcomes (one of five reviews) but worsened weight gain (five of five reviews). Combined oral contraceptive pill (COCP) improved clinical hyperandrogenism (two of four reviews). Statins improved lipid profile (three of three reviews) and testosterone level (two of three reviews). There was no conclusive evidence regarding the use of other interventions.

Conclusions

There is reliable evidence regarding the use of metformin and COCPs in women with PCOS but not for other interventions. There is significant gap in knowledge regarding the management of psychological outcomes in women with PCOS which needs further evaluation.


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**279**

## Pituitary abscess or a Rathke's cleft cyst?


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**CASE:** A 68-year-old female with a 4 year history of panhypopituitarism requiring thyroxine, cortisol and demospressin replacement secondary to a suspected Rathke's cleft cyst(RCC), presented with worsening vision and headaches. MRI of the pituitary demonstrated enlargement of the known cystic pituitary lesion with compression of the optic chiasm. She underwent transphenoidal surgery (TSS) which revealed frank pus in the sella. Histopathology showed features of chronic inflammation and suppuration in keeping with an abscess. No organisms were seen on gram stain or .

Eight months after TSS she represented with headaches, visual disturbance and a left sixth nerve palsy. There were no symptoms of sepsis. MRI demonstrated recurrence of this cystic lesion.

Further TSS revealed pus in the lesion. Histopathology of the resected tissue showed a RCC with surrounding chronic inflammation demonstrated by an epithelial lining adjacent to inflammatory infiltrate, fibrous tissue and proteinaceous material. Gram stain and culture again did not identify any organism. Patient was treated with oral trimethoprim/sulfamethoxazole for a period of 4 weeks. Repeat imaging showed re-accumulation of cyst fluid. A trial of high dose glucocorticoid steroids could be considered to treat secondary hypophysitis.

**Discussion**: Pituitary abscess is a rare cause of a pituitary mass. Clinical features are variable and include headaches and pituitary hypofunction ( over 50% cases), visual disturbance (25 - 45% cases) and fever (33 – 44%).[1, 2] MRI imaging may demonstrate a rim enhancing lesion in the pituitary.[3] Cultures are often negative. Abscesses often occur secondary to an underlying pituitary lesion such as a RCC. Both abscesses and hypophysitis have been described to occur secondary to RCC and must be differentiated based on clinical, radiological, histological and microbiological findings. [4]


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**280**

## Dihydrotestosterone and Testosterone in a cohort of hyperandrogenaemic women with Polycystic Ovarian Syndrome, Congenital Adrenal Hyperplasia and Androgen-secreting Tumours


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**Background**

Hyperandrogenaemia such as that seen in Polycystic Ovarian Syndrome (PCOS) is a common presentation in women of reproductive age. However, PCOS is a diagnosis of exclusion and late-onset congenital adrenal hyperplasia (CAH) and rarely androgen-secreting tumours (AT) need to be considered. Dihydrotestosterone (DHT) may help to differentiate these groups of women with hyperandrogenism. Increased 5-alpha reductase activity has been reported in PCOS.

**Method**

Serum “androgen profile” which includes Testosterone (T), DHT, Androstenedione and 17-Hydroxyprogesterone by LCMSMS Xevo TQ-S (Waters Corporation, Milford, MA) with prior liquid-liquid phase extraction is offered at PathWest QEII for biochemical investigation of women with hyperandrogenism. An audit was undertaken on all androgen profiles requested from 1st January 2016 to 1st January 2018. Results from women above the age of 16 with T ≥2.0 nmol/L in the follicular phase were grouped according to clinical diagnoses of PCOS, CAH or AT. Women on oral contraceptive pills and Testosterone therapy were excluded. A total of 106 patients were analysed: 84 with PCOS (79.2%), and 11 each (10.4%) with CAH or AT.

**Results**

Serum DHT was increased in 16 patients with PCOS (19%), 4 with CAH (36.3%) and 5 with AT (45.4%). After adjustment for age, T was significantly lower in both PCOS (p=0.001) and CAH (p=0.008) compared to those with AT. Serum DHT was also significantly lower in both PCOS (p=0.005) and CAH (p=0.004) subjects than those with AT. The median ratio of T:DHT in PCOS was lower than CAH and AT.

**Conclusion**

Both T and DHT were significantly higher in the AT group than the PCOS or CAH group. The evidence of a lower T: DHT ratio was demonstrated in PCOS group compared to CAH or AT group, which suggests increased 5-alpha reductase activity in PCOS women.

**281**

## A rare complication of Hashimoto's Thyroiditis

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**Case**

61 year old female was referred for an incidental 25mm right thyroid lobe nodule on neck ultrasound while investigating for a posterior neck lipoma. She has a 3 year history of Hashimoto’s Thyroiditis (HT) and hypothyroidism on Thyroxine 50mcg replacement. Thyroid ultrasound demonstrated atypical features with fine needle aspiration (FNA) indicating a poorly amorphous lymphoid population with no colloid or thyroid component raising the possibility of thyroid lymphoma. Right thyroid lobectomy was performed with histopathology confirming follicular lymphoma Grade 1-2 arising from a background of HT. Haematology review is pending.

**Discussion**

Primary thyroid lymphoma (PTL) is rare, accounting for ~1-2% of extranodal lymphomas with the majority of cases being diffuse large B-cell lymphoma (DLBCL) followed by mucosa-associated lymphoid tissue (MALT) lymphoma, while follicular lymphoma only accounts for ~10% of cases.[1,2] It predominantly affects middle-aged women, as in our case.[1,2] Patients with HT have a greater than 60-fold increase risk of developing PTL , with lag time of HT to PTL diagnosis between 18 months and 9 years.[1,2,3] It is hypothesised that chronic antigenic stimulation of the lymphocytes predisposes cells to lymphomatous transformation.[1,2]

An enlarging goitre with background of HT should raise suspicion of PTL.[4] Traditionally core-needle or surgical biopsies were performed due to difficulty in distinguishing thyroiditis from low -grade PTL.4 With advances in immune-phenotypic analysis, the accuracy of FNA has improved.4 Once PTL diagnosis is established, it is staged as per Ann Arbor Staging criteria.4 Localised and indolent disease such as MALT and follicular lymphoma are usually treated with radiotherapy.[4,5] Surgery has not been shown to add any benefit to radiotherapy alone other than relief of compressive symptoms.[4,5] Disseminated or aggressive disease including DLBCL, is treated with combined chemotherapy and radiotherapy.[4,5] From the SEER Database, PTL over 32 years of follow-up have median overall survival of 9.3 years.[6]

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**282**

## Diabetic ketoacidosis and hypertriglyceridaemic pancreatitis in undiagnosed type 2 diabetes mellitus - a case report and literature review of the management of severe hypertriglyceridaemic pancreatitis

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**Introduction:** The triad of diabetic ketoacidosis, severe hypertriglyceridaemia, and acute pancreatitis is rarely seen.[1] Management of hypertriglyceridemic pancreatitis (HTGP) includes a fat free diet and lipid-lowering pharmacotherapy. Plasmapheresis, insulin and heparin are often considered in severe HTGP to lower triglycerides more rapidly.

**Case Report:** A 34-year-old man with no past medical history and BMI 37.6kg/m2, presents drowsy, febrile and tachycardic. Investigations reveal a non-anion gap metabolic acidosis (pH 7.26), glucose 81mmol/L, ketones 5.6mmol/L, lipase 3590U/L and triglycerides 91mmol/L. HbA1c was 14.1% (131mmol/mol), C-peptide 0.93nmol/L, Anti-GAD <5U/ml and IA2-antibodies <8U/mL. He was diagnosed with Type 2 Diabetes Mellitus. Intravenous fluids and insulin were commenced. Given the marked hypertriglyceridemia and severity of pancreatitis, plasmapheresis was implemented. Within 12 hours triglycerides were 15.3mmol/L. He had a long, complicated admission including multiple pancreatic necrosectomies. On discharge he had good glycaemic control on Metformin alone and having lost 37kg. Metformin was ceased four months later. His HbA1c was 5.3% (34mmol/mol) and fasting triglycerides 1.4mmol/L.

**Discussion:** There is a lack of randomised trials on HTGP management. In severe disease, heparin, insulin and plasmapheresis are often considered. Heparin only transiently increases lipoprotein lipase (LPL) to reduce triglycerides followed by depletion and deficiency of LPL.[2] Its use is now controversial. Insulin activates LPL and intravenous therapy is preferred in severe disease for faster lowering of triglycerides.[3] Plasmapheresis rapidly reduces triglyceride levels but mortality and morbidity benefits remain unclear.[4,5] Timing of plasmapheresis appears crucial with early implementation required for maximal benefit.[4-6] Case series comparing insulin to plasmapheresis demonstrate greater reductions in triglycerides with plasmapheresis but longer hospital stay and no mortality difference.[7,8] Although there are no definitive guidelines, insulin, especially in diabetics, is often favoured for simplicity and cost. However, some authors suggest considering plasmapheresis in very severe disease or failure to respond to other therapy within 24-48 hours.[9,10]

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**283**

## Socio-economic risk factors for hypoglycemic episodes in young Sri Lankan adults with diabetes

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Introduction:

Hypoglycemic episodes (HEs) are a major treatment related side effect among patients with diabetes. It's a risk factor for cardiovascular adverse events and affects quality of life.

Aims:

To identify socio-economic risk factors for HEs among young adults with diabetes.

Methodology:

A sample of 1007 young Sri Lankan adults with diabetes (age 20- 45 years) were randomly selected and their socio-economic details such as ethnicity, educational level, income and details on HEs were recorded. Correlation between socio-economic variables and HEs were analyzed using Pearson Chi square analysis.

Results:

Overall 42.3% were males. Mean age was 36.6 (±5.8) years. Mean fasting blood sugar and HbA1c were 165.6 (±69.3) mg/dl and 8.0% (±2.0%) respectively. Patients who had never experienced a HE and those who were experiencing less than one HE per month overall were 42.2% and 67.5% respectively. Daily hypoglycemia was reported in 4.9%. A history of hospital admission for hypoglycemia was present in 3.5%. Only 21.7% of males reported one or more HEs per month while 40.3% of females reported the same ($p<0.01$). One or more HEs per month were recorded in less patients with Indian Tamil ethnicity

(25%) than Sinhala (30.6%), Sri Lankan Tamil (44.4%) or Muslim (44.8%) ethnicities (p<0.05). Only 19.4% of patients with a monthly income over 25,000 LKR (158 USD) developed one or more HEs per month while 35.8% of patients with an income less than this developed the same (p<0.01). Incidence of hypoglycemia in patients educated up to GCE Ordinary level exam (37.6%) was twice that of those who had had a higher education (19.5%) (p<0.01).

Conclusion:

Female gender, ethnicity, monthly income <25,000 LKR and low education level are risk factors for HEs in young adults with diabetes. Closer follow up and adjustment of treatment regimens may be indicated in these high risk categories.

**284**

## A rare case of an intra-cavernous carotid aneurysm masquerading as a pituitary adenoma

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Introduction:

Pituitary tumors are the commonest type of intracranial tumors with a prevalence of 5–20% according to autopsy studies. In contrast, intracranial aneurysms are rare. Failure to make the correct diagnosis can lead to catastrophic consequences.

Case report:

A 69 year old previously healthy female presented with progressive intermittent headache for 3 years. There was no diurnal pattern of symptoms, associated vomiting or visual disturbance. She was clinically euthyroid and denied galactorrhea, postural dizziness or limb weakness. On examination visual fields were normal and she had no papilledema or other focal neurological deficits. Thyroid profile was suggestive of secondary hypothyroidism [TSH 1.2 mIU/L (0.4–4.0), free T4 0.6 ng/dL (0.9–1.7) and free T3 3.5 pmol/L (3.5–6.5)]. Perimetry showed a right homonymous inferior quadrantanopia. Further investigation showed low cortisol levels (4.03 µg/dL) and markedly raised prolactin level of 1634 mU/L (< 400 mU/L). Thyroxin and hydrocortisone replacement therapy were commenced. An MRI scan of the head was performed and a mass lesion in the sellar region was found, which was reported as a pituitary macroadenoma. Patient was referred for neurosurgery. On re-evaluation by the neurosurgeon, doubt was cast on the nature of the tumor due to the multilayered and 'halo' like appearance of the lesion on MRI. A CT angiogram was performed and a large aneurysm measuring 19.9 mm × 21.5 mm was discovered arising from the cavernous portion of the left internal carotid artery. The patient eventually underwent endosaccular coiling and stenting and made an uncomplicated recovery without recurrence of symptoms during follow-up.

Conclusion:

Attempt of trans-sphenoidal surgery for a pituitary tumor would have had catastrophic consequences in this patient. The rare possibility of an intra-cavernous carotid aneurysm should always be kept in mind in evaluating a patient with a mass lesion suggestive of a pituitary tumor.

**285**

## 1,25-dihydroxyvitamin D-associated hypercalcemia in a metastatic pancreatic neuroendocrine tumour

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Hypercalcaemia is a common complication of malignancy, occurring in 20 to 30 percent of cases. Hypercalcaemia is occasionally seen in neuroendocrine tumours (NET) and is primarily attributed to secretion of parathyroid hormone-related peptide ( PTHrP) from tumours. We present a case of hypercalcaemia in a metastatic pancreatic NET which was associated with increased circulating 1,25-dihydroxyvitamin D. Only one other case has been reported of hypercalcaemia with elevated 1,25-dihydroxyvitamin D in neuroendocrine tumour.

A 53yo female presented with asymptomatic hypercalcaemia with a serum calcium of 3.35mmol/L. Parathyroid hormone (PTH) was appropriately suppressed at 0.6pmol/L. She had a mildly elevated PTHrP of 2.9 ( normal < 2pmol/L), 25-hydroxyvitamin D of 63mmol/L and inappropriately elevated 1,25-dihydroxyvitamin D of 389pmol/L ( 60-200). Computer tomography detected a 11x 5cm mass in the body and tail of pancreas with multiple hepatic metastases. Biopsy of her hepatic lesions was consistent with a neuroendocrine tumour, with positive staining of Cam5.2, chromogranin A and synaptophysin. Ki67 staining was 3%. Distal pancreatectomy and splenectomy were initially performed. The patient had persistent hypercalcaemia despite treatment with bisphosphonate therapy, denosumab and prednisolone. Hepatic embolization was followed by a two stage liver resection. Her treatment-resistant hypercalcaemia persisted with a calcium of 3.31mmol/L with a nearly five-fold elevation of circulating 1,25-dihydroxyvitamin D (924pmol/L) until all her hepatic metastases were resected. After her last resection, her calcium normalised to 2.40mmol/L and her 1,25-dihydroxyvitamin D decreased to 162pmol/L. Lanreotide 120mg 4 weekly was commenced to achieve delay in tumour recurrence and 1,25-dihydroxyvitamin D levels have remained stable 6 months post operatively at 215pmol/L.

**286**

## False positive Iodine-123 (123-I) metaiodobenzylguanidine (MIBG) scintigraphy in large adrenocortical neoplasm

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Iodine-123 (123-I) metaiodobenzylguanidine (MIBG) scintigraphy has a high sensitivity of 85-96% and specificity of 95-100% for the detection of phaeochromocytoma. False positive result can occur in younger patients with small adrenal lesions with moderate, often bilateral uptake. Only four reported cases have described a false positive MIBG study in large adrenocortical adenoma. Our case describes an example of a false positive MIBG in a large adrenocortical neoplasm.

An 18yo male was found to have a large incidental adrenal mass. He had a background of left frontal anaplastic oligodendroglia managed previously with surgical resection, chemotherapy and radiation therapy at the age of 8. Computed tomography showed a left suprarenal mass measuring 78x 56x 17mm. The mass has numerous vessels coursing through it towards a central necrosis. There was washout of the lesion in the delayed scan. These features were suggestive of phaechromocytoma. Blood pressure remained within normal parameters . The adrenal mass was non-functioning with normal plasma metanephrines and normetanephrines, 24 hour urine metanephrines and normetaphrines. Aldosterone to renin ratio was also normal. MIBG scan showed an irregular, intense tracer accumulation localised to the large left adrenal mass, also suggestive of pheochromocytoma. Left adrenalectomy was undertaken after two weeks of alpha blockade. Histology revealed an 85 x 80 x 60mm mass with yellow friable areas suggestive of central necrosis. The tumour was composed of large epithelioid and polygonal cells with pleomorphic nuclei. Immunohistochemistry stained positively for Calretinin, Melan A, CAM5.2 and AE1/AE3 and was negative for Synaptophysin, Chromogranin A, SOX10, PAX8, Inhibin and HepPAR1. The overall Ki67 proliferation index was approximately 2% with the focal area approaching 5%. These findings were consistent with adrenal cortical neoplasm and not pheochromocytoma. MLH1 mutation was detected on genetic testing which is associated with Lynch syndrome related cancers.

**287**

## Current pattern of primary aldosteronism diagnosis: delayed and complicated

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**Background**:

Primary aldosteronism (PA), also known as Conn's syndrome, is the most common specifically treatable and potentially curable cause of hypertension. It has a prevalence of 3.2% to 12.7% in primary care and up to 30% in referral centres based on mostly overseas studies. There is limited data regarding the epidemiology and diagnosis of PA in Australia.

**Objectives:**

To analyse the referral pattern and disease characteristics of hypertensive patients referred to the Endocrine Hypertension Service (EHS) at Monash Health.

**Methods**:

Clinical data of 87 patients who attended the EHS from May 2016 to May 2017 was collected prospectively. Each patient completed a questionnaire covering socio-demographic, medication and comorbidity information. Referral sources and management outcomes were obtained from hospital medical records.

**Results**:

The majority of referrals (77%) were derived from tertiary centres, with only 23% from primary care. Only 3% of referrals to the EHS were made at first presentation of hypertension, while 61% had already had hypertension for over 10 years. Amongst the 62 patients diagnosed with PA by the EHS, 55% were on at least 3 antihypertensive medications, and 42% had associated end-organ damage. Adrenalectomy in 14 patients with aldosterone-producing adrenal adenomas led to 100% biochemical cure while targeted medical treatment in 37 patients led to significantly improved blood pressure control with fewer antihypertensive medications.

**Conclusion**:

The current diagnosis of PA is suboptimal – its delayed diagnosis results in end-organ damage which requires complex management and complicates the evaluation process of PA. Given that appropriate management of PA produced significant clinical and biochemical improvement, we postulate that there is a need to increase awareness of PA in primary and tertiary care so that an earlier diagnosis can be made to achieve optimal patient outcomes.

**288**

## Role of alert sticker in improving detection of neonatal hyperthyroidism among pregnant women with Graves' disease

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**Background:**

The relationship between maternal Graves' disease and neonatal hyperthyroidism is well established. Maternal Thyroid Receptor Antibodies (TRABs) over 3 times the upper limit of normal can result in fetal and subsequent neonatal hyperthyroidism, causing significant morbidity and mortality. As this is not detected on Guthrie testing (which, being designed for congenital hypothyroidism, tests only Thyroid Stimulating Hormone), complete thyroid function testing (TFTs) is imperative for at-risk neonates.

In 2016 at the ESA ASM, we presented a case of missed neonatal hyperthyroidism after such testing was not undertaken.

This case prompted our implementation of a Graves' disease alert sticker in January 2015, to highlight relevant medical files where complete neonatal TFTs are indicated. We audited this intervention and now present the results.

**Methods:**

Obstetric patients with Graves' disease attending our Endocrinology in Pregnancy Clinic between January 2011 and June 2016 were identified from medical records. Neonates of patients with TRAB titres above 5 IU/L after 16 weeks were evaluated for whether follow-up TFTs were performed at birth, day 2-7 and day 10-14. Comparison was made of data before and after the intervention.

**Results:**

Prior to implementing the Graves' disease alert sticker, of three patients with TRAB titres above 5 IU/L, only one neonate received full TFTs at birth, 2-7 days and 10-14 days post-delivery. Another had TFTs done at birth, while the remaining neonate did not have any TFTs performed. Post implementation, of three patients with TRAB titres above 5 IU/L, three neonates had complete TFTs at birth, 2-7 days and 10-14 days post-delivery.

**Conclusion:**

Following introduction of a Graves' disease alert sticker all at-risk neonates have undergone complete TFTs. We appeal to other centres to trial a similar approach. Looking forward, introduction of the electronic medical record may facilitate such endeavours; and will require auditing in due course.


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**289**

## Addisonian crisis and pancytopenia as first presentation of Addison's disease: a case report


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23-year-old previously well man, with family history significant for autoimmunity, presented after unconscious collapse with a 6month history of anorexia, 3kg weight loss and lethargy. On arrival, he was alert, hypotensive with blood pressure of 60/50mmHg, tachycardic but afebrile. Examination revealed only mild hyperpigmentation in scar tissue.

Investigations suggested adrenal insufficiency with a critically low serum cortisol of 18nmol/L(68-327nmol/L), evidence of hypoaldosteronism with a sodium 120mmol/L, potassium 5.7mmol/L, elevated renin >500mIU/L(4.4-46mIU/L) and a low-normal aldosterone 102pmol/L(61-978pmol/L). Adrenal CT was unremarkable. ACTH measured 6hours after administration of 100mg intravenous hydrocortisone was low-normal at 9ng/L(7.2-63.3ng/L). He had pancytopaenia with haemoglobin of 105g/L(130-170g/L), leucocyte count of $3.1x10^9$/L(4-$10x10^9$/L) and platelets of $103x10^9$/L(150-$410x10^9$). Low reticulocyte count of <0.5% suggestive of bone marrow suppression. Biochemistry showed subclinical hypothyroidism (TSH 17.56mIU/L(0.27-4.2mIU/L), T4 14.8pmol/L(12-22pmol/L)). Notably, anti-TPO antibodies were negative.

He improved rapidly with intravenous rehydration and hydrocortisone. He was discharged 4days later on hydrocortisone 20mg morning, 10mg afternoon and fludrocortisone 0.1mg daily.

After 2weeks, he had clinically improved and his TSH reduced to 10.29mIU/L. His pancytopaenia normalised (haemoglobin 130g/L, leucocyte count $6.8x10^9$/L and platelets $148x10^9$/L) indicating a possible reactive aetiology. Autoimmune screen showed an elevated antinuclear antibody of 1:160 speckled pattern. Vitamin B12, HIV serology and Epstein-bar virus were normal. Adrenal antibodies and repeat pre-dose ACTH are pending.

Pancytopaenia is a rare complication of endocrinopathies of unclear pathophysiology. It is associated with hypopituitarism in the majority of cases and rarely with primary hypothyroidism (1,2,3,4) and primary adrenal insufficiency (2,4,6). In studies in which bone marrow aspiration was performed, they revealed bone marrow hypocellularity (1,4,7,8,9), however pancytopaenia often improves before bone marrow aspiration is performed, as was in our case. Several in vitro studies show glucocorticoids stimulation of haematopoiesis (10,11,12). In our case, pancytopaenia resolved with steroid replacement alone in a patient with adrenal insufficiency.

**290**

## Calf circumference as a clinical marker of sarcopenia in women

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**Background:** Sarcopenia is defined as low skeletal muscle mass (SMM) and muscle function. It is associated with adverse health outcomes such as increased falls and fracture risk; decreased bone mineral density; prolonged hospital stays; increased risk of death and disability; discharge to a facility after hospital stay; and, increased burden on the economy. [1,2,3]

**Aim:** To examine the relationship between calf circumference (CC) and SMM and to assess the suitability of CC as a simple, clinically useful measuring tool of SMM for the diagnosis of sarcopenia in middle-aged and older women.

**Methods:** Data from 135 female participants aged 40-97 years old were analysed in this quantitative study. Measurements taken from each participant included anthropometry, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA) and measurements of their calf, thigh and mid-upper arm circumference (cm). European cut off values[1] were used to diagnose sarcopenia in our patients which include DEXA appendicular SMM / height$^2$ <5.5kg/m$^2$, muscle strength <20kg, and BIA skeletal muscle index/height $^2$ <6.42kg/m$^2$.

**Results:** Forty-seven women in the study were diagnosed with sarcopenia, 77 normal SMM, and 11 had inconclusive values. Regression analysis showed the strongest relationship between appendicular SMM and lean body mass impedance, lean body mass anthropometry and CC. In receiver operating characteristic analysis, the optimal calf circumference cut-off values for predicting sarcopenia was 33.6cm (sensitivity 80.9% specificity 75.3%) with p-value = <0.01, NPV=0.866 and PPV=0.667. Ninety-one percent of patients with sarcopenia had a calf circumference <35.1cm and 90.9% of those without sarcopenia had a calf circumference above 31.6cm.

**Conclusion:** Calf circumference was positively correlated with appendicular SMM, with the suggested cut off value of ≤33.6cm being a good predictor for sarcopenia.

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**291**

## Body composition in elderly women with hip fracture

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**Introduction:**

Sarcopenia is an age-related decline in muscle mass and function. Studies have shown the association between sarcopenia with increased morbidity and mortality. Additionally, sarcopenia serves as an entry point into the physical cycle of frailty, a separate but overlapping entity in which frail individuals are susceptible to adverse health outcomes and impaired quality of life.

Hip fracture patients with sarcopaenia have increased risk of poor outcomes following hospitalisation. Whilst osteoporosis is a known risk factor for fractures, the association between sarcopenia and fracture risk is increasingly recognised.

Our aims in this study was to compare a group of women with hip fracture and controls in terms of:

1. The relationship between anthropometric variables and lean body mass
2. The relationship between age and lean body mass
3. The difference in lean body mass as assessed by anthropometry, CT thigh and bioelectrical impedance analysis

**Methods:** Women age > 60 years old who presents with a hip fracture were recruited for the study. For comparison, women above the age of 60 awaiting hip replacement or well women in the community were enrolled.

**Results:**Women in the hip fracture group were older (80.70 ±11.30 vs 71.64 ± 5.51 years, p value 0.004), had a lower Body Mass Index (26.42 ± 5.14 vs 30.22 ± 7.54, p value 0.089)

and were lighter. Women awaiting hip replacement and in the community had higher lean muscle mass (8.079 ± 2.40 vs5.78 ± 3.60 kilograms, p value 0.033) compared to women with hip fracture.

**Conclusion:**Women with hip fracture have lower lean muscle mass compared to controls.

**292**

## Twenty-four-hour urinary sodium and aldosterone excretion in hypertensive patients may indicate underlying primary aldosteronism

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**Objectives:** Primary aldosteronism (PA) is an under-diagnosed cause of hypertension characterised by autonomous aldosterone production with renin suppression and an elevated aldosterone:renin ratio (ARR). PA may be confirmed by an oral salt-loading test where 24-hour urinary aldosterone excretion (UAE) remains elevated (>33.3nmol/d) after 3 days of high salt intake with urinary sodium (UrNa) >200mmol/d. Given the high sodium intake in our community, we hypothesise that PA may be diagnosed, or at least suggested, by an elevated aldosterone level in a routine 24-hour urine sample.

**Methods:** A retrospective analysis of 24-hour UrNa and UAE measurements from 151 patients (20 with confirmed PA, 131 without known PA) with corresponding plasma aldosterone and renin levels was performed. The clinical and biochemical data were obtained from Monash Health medical records. Statistical significance was set at $p<0.05$.

**Results:** Twenty-four-hour UrNa and UAE met salt-loading criteria for PA in 5 of 20 PA patients (25%) and 28 of 131 patients without known PA (21%). Of the 131 without known PA, 85 had UrNa < 200 mmol/L of whom 14 had renin < 4.4mU/L. A suppressed plasma renin in the absence of high sodium intake is not physiological and should prompt further testing for PA. Urinary sodium may also be important for the interpretation of a normal plasma renin. In the setting of low urinary sodium, renin may be falsely normal (or un-suppressed), leading to a normal ARR and therefore mask the underlying hyperaldosteronism. This was observed in 3 patients with confirmed PA who had ARRs in the normal range.

**Conclusion:** PA is common but infrequently diagnosed. It is important to maximise the utility of common tests in facilitating its diagnosis. Our study demonstrates that 24-hour urinary sodium and aldosterone measurements can affect the interpretation of plasma aldosterone and renin and aid PA detection.