Endocrinology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

BMD = bone mineral density; **HR** = hazard ratio; **QOL** = quality of life; **TID** = three times daily; **TSHoma** = TSH-secreting pituitary adenoma

Welcome to the fifteenth edition of Endocrinology Research Review.

Highlights of this Review include: a comprehensive review and critical analysis of data for treatment of hypothyroidism with thyroid hormone formulations; a large, retrospective study investigating the impact of surgery and radiotherapy in patients with TSHoma; and a case study detailing successful use of radio frequency ablation to treat an ectopic ACTH-secreting tumour in a patient with severe hypercortisolism.

We hope you find the selection for this month's edition useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards

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Calcitonin measurement in aspiration needle washout fluids has higher sensitivity than cytology in detecting medullary thyroid cancer

Authors: Trimboli P et al

Summary: The authors of this retrospective multicentre cohort study aimed to evaluate aspiration needle washout calcitonin measurement (FNA-CT) in comparison to cytology for diagnosis of medullary thyroid cancer (MTC). Subjects were 36 patients with MTC lesions. 52 controls had elevated serum calcitonin, biopsy and non-medullary lesions. Median FNA-CT was 2,000 pg/ml (range 58-10,000) in subjects with MTC, in comparison to 2.7 pg/ml for controls (range < 2-13), $p < 0.001$. 100% sensitivity and specificity for predicting MTC lesions was obtained using a cut-off value of 29.6 pg/ml. In contrast, MTC was predicted with 56.8% sensitivity using cytology (21/37 lesions). 14 lesions classed as benign or non-conclusive with cytology were identified as MTC using FNA-CT, and this diagnosis was confirmed histologically. In their conclusions the authors note that this was the first multicentre case series to demonstrate superiority of FNA-CT over cytology for diagnosis of MTC, and recommend FNA-CT for all patients with elevated calcitonin undergoing biopsy.

Comment: This article follows hard on the publication of a large international study of 313 patients, including Australian data, showing that cytology alone has low sensitivity in the preoperative diagnosis of MTC. (Essig Jr GF et al. Endocr Pract 2013; 19:920-927). This current Italian study extends this international data to indicate the value of needle-wash calcitonin to diagnose MTC when serum calcitonin is high and suggests that a sample for this testing should be taken routinely when performing FNB of a thyroid nodule.

Reference: Clin Endocrinol 2014; 80(1):135-140
http://onlinelibrary.wiley.com/doi/10.1111/cen.12234/abstract

Thyroid function tests and mortality in aged hospitalized patients

Authors: Iglesias P et al

Summary: The aim of this 7-year prospective observational study was to examine associations between thyroid hormone levels and mortality in hospitalised, elderly subjects. Participants (n = 404) were patients aged > 65 years who were admitted to the geriatric department of a single Spanish hospital during 2005. Thyroid function tests (TSH, fT3 and fT4) were conducted on admission, and subjects were followed-up for 7 years. Total mortality rate during the study period was 80%. Serum TSH, fT3 or fT4 levels in the first tertile were significant predictors of reduced survival time. Significant predictors of all-cause mortality were: history of cancer (HR 1.6, 95% CI 1.12-2.28, p = 0.009); age (HR 1.03, 95% CI 1.01-1.06, p = 0.003); and serum fT3 levels (HR 0.72, 95% CI 0.63-0.84, p < 0.001). In subjects where cause of death was known, 30.2% died of cardiovascular disease. Serum fT3 was a significant predictor of cardiovascular mortality (HR 0.76, 95% CI 0.63-0.91, p = 0.004). In conclusion, the authors found that lowered thyroid hormone levels in hospitalised elderly patients were associated with increased long-term all-cause mortality, and that low serum fT3 levels were associated with all-cause and cardiovascular mortality.

Comment: It was shown many years ago that low fT3 and especially low fT4 predicts lower acute survival in critical illness (Slag et al. JAMA 1981; 245:43). The main findings of the current study are the high rate of low T3 syndrome (73%) on hospital admission for a wide range of medical diagnoses in elderly patients and that a single measurement of fT3 can predict short and longer term mortality: a mean fT3 3.5 pM vs. 4.0 pM predicts a median survival time of 3 months versus 19 months. Other diagnoses were made purely by the *in-vitro* thyroid function test pattern: overt hyperthyroidism 2.2%, subclinical hyperthyroidism 2.0%, and overt hypothyroidism 1%. These interpretations should be treated with caution because of the wide range of transient non-thyroidal illness-related changes other than low T3 syndrome, particularly low TSH (Chosich N et al. Thyroidol 1989; 2:79).

Reference: JCEM 2013. Epub ahead of print. DOI: 10.1210/jc.2012-4096
http://jcem.endojournals.org/content/98/12/4683.abstract

Treatment with thyroid hormone

Authors: Biondi B and Wartofsky L

Summary: This large, comprehensive review provides a critical analysis of treatment of hypothyroidism with thyroid hormone formulations. Subject matter includes an evaluation of the available thyroid hormone formulations, and their appropriate use for primary and central hypothyroidism in patients of all ages from infants to the elderly, including those with co-morbid conditions, and during pregnancy and birth. The review discusses LT4 requirements according to factors including sex, age, menstrual status, body mass and lean body mass. Key causes of under-treatment, including medication compliance, timing of medication administration and poor absorption are reviewed, as are the consequences of TSH suppression resulting from over-treatment. New evidence is also examined, including data supporting treatment of mild thyroid hormone deficiency; indications for combined T3/T4 therapy in some hypothyroid patients; and indications for TSH suppression with LT4 in patients with euthyroid multinodular goitre and differentiated thyroid carcinoma. The use of thyroid hormone therapy for the treatment of patients with obesity, severe cardiac disease, dyslipidaemia and other non-thyroidal disease is discussed.

Comment: This is a comprehensive, authoritative review by two acknowledged international experts (80 pages and 638 references). It is clearly an excellent critical review of the literature and a very valuable source of key references. It will undoubtedly be cited frequently over the next decade.

Reference: Endocr Rev 2014. Epub ahead of print. DOI: 10.1210/er.2013-1083
http://tinyurl.com/k64rmys

Thyrotropin-secreting pituitary adenomas: outcome of pituitary surgery and irradiation

Authors: Malchiodi E et al

Summary: Evaluating the impact of surgery and radiotherapy on hormonal control and tumour mass in subjects with TSH-secreting pituitary adenomas (TSHoma) was the objective of this retrospective multicentre study. Subjects were 70 patients with TSHoma (70% macroadenoma). Mean follow-up was 64.4 months (range 3-324). Surgery was carried out in 97%, and radiotherapy in 27% of these. Post-surgical normalised thyroid function was observed in 75%, and normal pituitary imaging plus normal hormonal profile was observed in 58%. Within 2 years of surgery pituitary deficiencies were recorded in 9%, and hormonal or tumoural recurrence in 3%. There was no improvement in outcomes with pre-surgical medical treatment. Hypersecretion was controlled with radiotherapy for 37% of subjects within 2 years. Novel pituitary deficits occurred in 32% between 18-96 months. Normalised thyroid function was observed in 80% of subjects at the final follow-up, 20% were receiving medical treatment (85% somatostatin analogue monotherapy, 15% with the addition of methimazole). 80% of subjects with disease control received surgery only, 20% received surgery plus radiotherapy. The authors conclude that surgery remains the first line therapy for TSHoma, and is associated with very low rates of recurrence. Somatostatin analogue treatment and radiotherapy are effective methods for controlling hyperthyroidism and tumour growth in patients with unsuccessful surgery.

Comment: TSHomas are rare and individual centres therefore have difficulty in acquiring a substantial experience - so this large retrospective study of the response to therapy of TSHomas is important. It provides a strong evidence base for the standard approach of initial surgery where possible, radiotherapy and somatostatin analogue treatment. Adjunctive therapy with cabergoline, and with a thionamide for thyroid hormone excess, was found of value in some patients.

Reference: J Clin Endocrinol Metab 2014. Epub ahead of print. DOI: 10.1210/jc.2013-4376
http://tinyurl.com/k2hyxs8

Effects of Odanacatib on BMD and safety in the treatment of osteoporosis in postmenopausal women previously treated with Alendronate

Authors: Bonnick S et al

Summary: This randomised, placebo-controlled clinical trial assessed the effects of ondancatib on bone mineral density (BMD) and biomarkers of bone turnover in post-menopausal women, previously treated with alendronate. Subjects were 240 post-menopausal women aged ≥ 60 years with low BMD following ≥ 3 years of alendronate therapy. Low BMD was defined as T-score ≤ 2.5 and > -3.5 in subjects without prior fracture, or ≤ 1.5 and > -3.5 with prior fracture, and was assessed by dual-energy x-ray absorptiometry. Bone sites studied were total hip, femoral neck, trochanter and lumbar spine. Subjects received ondancatib 50 mg weekly or placebo for 24 months, with BMD assessments at baseline, 6, 12 and 24 months. Biomarkers, measured at baseline, 3, 6, 12, 18 and 24 months, were serum C-telopeptides, urinary N-telopeptides and serum N-terminal propeptides of type 1 collagen, and serum bone-specific alkaline phosphatase. Active therapy with ondancatib was associated with significantly greater gains in BMD from baseline to 24 months in comparison to placebo; 1.7, 1.8, 0.8 and 2.3% at the femoral neck, trochanter, total hip and lumbar spine respectively. Ondancatib significantly increased serum C-telopeptides of type 1 collagen vs. placebo. Similar safety profiles were observed for both groups. The authors concluded that ondancatib is associated with improved BMD in post-menopausal women with low BMD following alendronate therapy.

Comment: Cathepsin K is a lysosomal collagenase found predominantly in osteoclasts which can cleave collagen in its triple helix form. A rare genetic condition, pycnodysostosis, with an osteopetrosis-like phenotype, is due to cathepsin K deficiency. Cathepsin K is also found in multinucleate giant cells e.g. Langerhans cells, macrophages and fibroblasts. It has a role in thyroglobulin processing, and is a kininase that may have a role to limit bronchospasm in asthma. Odanacatib is a potent cathepsin K inhibitor and a potent, and relatively selective and reversible inhibitor of bone resorption. This trial shows efficacy on BMD and an apparent beneficial effect on fracture rate (4.9 vs. 13.2%, 6/122 vs. 16/121 events). It was originally forecast for registration in 2013 but publicly undisclosed safety concerns have led to a phase III extension study, so whether the safety concerns are substantive must await the evaluation of the extension study when completed. This current trial showed a 9% discontinuation rate for the active drug versus a 3.3% rate on placebo.

Reference: J Clin Endocrinol Metab 2013; 98(12):4727-35
http://jcem.endojournals.org/content/98/12/4727.abstract

Two years of Denosumab and Teriparatide administration in postmenopausal women with osteoporosis (the DATA extension study)

Authors: Leder BZ et al

Summary: This paper reports 2-year outcomes from the DATA randomised controlled clinical trial. 94 post-menopausal women with osteoporosis received monotherapy with denosumab (60 mg/6 monthly) or teriparatide (20 µg/day) or both in combination for 24 months. The goal of the study was to evaluate the potential for additive BMD benefits with combination therapy. BMD was measured at the lumbar spine, femoral neck, total hip and distal radius. Biomarkers of bone turnover were also assessed. Combination therapy was significantly more effective than monotherapy with either drug for BMD at the lumbar spine, 12.9 ± 5.0% vs. 9.5 ± 5.9% for teriparatide ($p = 0.01$) or 8.3 ± 3.4% for denosumab ($p = 0.008$). Results were similarly in favour of combination therapy at the femoral neck, 6.8 ± 3.6% vs. 2.8 ± 3.9% and 4.1 ± 3.8% for teriparatide ($p = 0.003$) and denosumab ($p = 0.008$) respectively, and at the total hip, 6.3 ± 2.6% vs. 2.0 ± 3.0% for teriparatide and 3.2 ± 2.5% for denosumab ($p < 0.001$ for both). In conclusion, 24 months of combination therapy with teriparatide plus denosumab is more effective than either treatment alone for improving BMD in post-menopausal women with osteoporosis.

Comment: It cannot be assumed that combination pharmacological treatment for osteoporosis will be additive for BMD improvement or even that it may not detract. In this study of 94 post-menopausal women with osteoporosis, the lumbar spine increment with the combination of teriparatide and denosumab was greater than for either therapy alone but not additive, and for the femoral neck was approximately additive. The study was not powered for fracture rate changes but if BMD is accepted as a surrogate marker of fracture risk then this combination may offer an advantage to patients at high risk of fragility fracture.

Reference: J Clin Endocrinol Metab 2014. Epub ahead of print. DOI: 10.1210/jc.2013-444
http://tinyurl.com/lzzacef

Cushing's syndrome due to a bronchial ACTH secreting carcinoid successfully treated with radio frequency ablation

Authors: Corsello SM et al

Summary: The authors of this paper present a case study detailing the use of radio frequency ablation (RFA) to treat an ACTH-secreting bronchial carcinoid tumour in a patient with symptoms of Cushing's syndrome. The patient, a 43 year old female, presented with severe symptoms of hypercortisolism, which had been rapidly worsening over a three-month history. Cushing's syndrome resulting from ectopic ACTH production was indicated by hormonal tests, and imaging detected an 8 mm pulmonary nodule in the middle right lobe. The patient responded poorly to ketoconazole therapy and therefore lobectomy could not be carried out at that time. As an alternative, RFA was used to thermally ablate the tumour. The patient demonstrated a rapid response to therapy, and consequent decline in levels of ACTH and cortisol. PET scanning showed a complete response to treatment. At 6 weeks post-ablation a right middle lobectomy was successfully completed. Histologic analysis revealed a 0.7 cm ACTH-secreting bronchial carcinoid tumour. The authors conclude that RFA of ACTH-secreting bronchial carcinoid tumours induces rapid symptom control and should be considered for patients in whom surgery is contraindicated.

Comment: Cushing's syndrome of such severity that medical control is needed before surgical treatment is a major challenge in endocrinology. This problem is compounded by failure of ketoconazole therapy to improve hypercortisolism as in this case, where CT-guided electrode placement into the primary tumour allowed RFA over 12 minutes with temperatures at the electrode tip of 90-115 C with consequent marked hormonal improvement allowing a VATS lobectomy with tumour resection at 6 weeks. RFA is now widely available in major hospitals so this sequence of therapies is a useful management addition.

Reference: J Clin Endocrinol Metab 2014. Epub ahead of print. DOI: 10.1210/jc.2013-4359
http://tinyurl.com/nsy29zr

Ketoconazole in Cushing's disease: Is it worth a try?

Authors: Castinetti F et al

Summary: This retrospective multicentre study aimed to determine the efficacy and tolerability of ketoconazole monotherapy for the treatment of Cushing's syndrome using historical data from 200 patients. Median ketoconazole dose was 600 mg daily (final dose). Normal urinary free cortisol levels were observed in 49.3% of subjects, a decrease of ≥ 50% occurred in 25.6%, and 25.4% were unchanged. Poor tolerability led to discontinuation of ketoconazole in 20.5%. 13.5% of subjects had mild elevation of hepatic enzymes, and 2.5% had major elevations. No incidences of fatal hepatitis occurred. Ketoconazole was used as a pre-surgical treatment in 20% of subjects. In this group, 40-50% demonstrated improved control of hypertension, hypokalaemia and diabetes. Prior to surgery, urinary free cortisol was normal in 48.7%.

Comment: This review indicates that ketoconazole can be an effective agent to control hypercortisolism in Cushing's syndrome, but there is a significant proportion (20%), who will not tolerate the agent, and a minority (2.5%), that experiences major hepatic enzyme elevation indicating the need for frequent expert review and testing. Oral ketoconazole has been deregistered by the TGA from 1 December 2013 following the EMA recommendation in July 2013 to suspend ketoconazole in Europe, and FDA revisions to the product's indications and safety warnings about liver and adrenal gland problems. The FDA has maintained the registration and supply of ketoconazole so it may be possible to import the drug for individual patient use for Cushing's syndrome. Fluconazole has had very limited use as an alternative agent (Riedl et al. Eur J Endocrinol 2006; 154:519) but its use may now need to be explored. Of other agents for medical management of Cushing's syndrome, aminoglutethimide is no longer available, metyrapone may be of some benefit (Jeffcoate et al. BMJ 1977; 2:215), etomidate in low dose infusion has efficacy (Schulte et al. J Clin Endocrinol Metab 1990; 70:1426) and there is experience of using low dose mitotane in Cushing's disease going back over 30 years (Baudry et al. Eur J Endocrinol 2012; 167:473) but it can persist in tissues for up to 20 months compromising safety of a subsequent pregnancy (Leiba et al. Ann Endocrinol (Paris) 1989; 50:49.)

Reference: J Clin Endocrinol Metab 2014. Epub ahead of print. DOI: 10.1210/jc.2013-3628
http://tinyurl.com/lvcuf2t

Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of Addison's disease

Authors: Øksnes M et al

Summary: The objective of this prospective, randomised, multicentre, open-label crossover clinical trial was to compare oral administration of hydrocortisone with continuous subcutaneous hydrocortisone infusion (CSHI) in patients with Addison's disease. 33 patients were randomised to oral hydrocortisone TID or CSHI for three months, with assessments at baseline, 8 and 12 weeks. The primary outcome measure was morning ACTH level. Subjects receiving CSHI demonstrated normalised morning ACTH levels and 24 hour salivary cortisol curves. Urinary concentrations of glucocorticoid metabolites were similar to normal patterns with CSHI but not with oral therapy. CSHI resulted in improvement in some QOL domains of vitality. Subjects in both groups showed no improvement in sleep parameters, using either subjective or objective measures. The authors conclude that CSHI in patients with Addison's disease resulted in ACTH and cortisol concentrations close to those observed under normal circadian rhythms, without negative consequences for glucocorticoid metabolism.

Comment: Although after 60 years of adrenal steroid replacement therapy for Addison's disease the overall impression is that the great majority of patients have done very well on conventional therapy with twice- or thrice-daily oral replacement therapy, there is evidence, at least in a minority, of decreased QOL, increased cardiovascular risk, increased osteoporosis risk, and increased mortality. It is also known that conventional therapy neither normalises ACTH, particularly in the morning, nor serum cortisol levels which can be high shortly after a dose and low hours later. Whether a treatment regimen that more closely mimics physiological values would improve QOL or reduce any of the perceived risks is unknown. This three month open-label crossover study in 33 Addisonian patients (of 55 screened) using an insulin pump for subcutaneous delivery of hydrocortisone shows that a pattern closely resembling the physiological form can be achieved, and reports an improvement in QOL during the infusion arm, but the low statistical power and the open study design limit the strength of this observation. The patients were not selected for subjective ill health. The results of this study justify further research into this form of replacement therapy especially in those who report impaired QOL on conventional therapy but use of this treatment outside of controlled trials is not yet indicated.

Reference: J Clin Endocrinol Metab 2014. Epub ahead of print. DOI: 10.1210/jc.2013-4253
http://tinyurl.com/kjwr7dm

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Selection and review of the research has been carried out independently by Professor Duncan Topliss, MB BS Hons, MD, FRACP, FACE.

Professor Duncan Topliss is Director of the Department of Endocrinology and Diabetes at the Alfred Hospital Melbourne, Professor of Medicine in the Department of Medicine Monash University and a past-President and Life Member of the Endocrine Society of Australia. He has served on the editorial board of the Journal of Thyroid Research and Clinical Endocrinology and is a frequent reviewer for Clinical Endocrinology, Thyroid, and other endocrine journals. Professor Topliss heads the Diabetes Clinic at the Alfred Hospital, has a long-term interest in diabetes prevention and management and has been an investigator on several major international diabetes trials. He has a wide interest in clinical endocrinology including osteoporosis, pituitary and adrenal disease and endocrine hypertension and has over 25 years of experience in the management of thyroid disease and thyroid cancer. His other interests are drug regulation and safety, and he is a member of the Australian Advisory Committee on the Safety of Medicine and the Australian Advisory Committee on Pharmaceutical Medicines of the Therapeutic Goods Administration.

