Endocrinology Research Review™

Making Education Easy

Issue 16 - 2014

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Abbreviations used in this review:

ACTH = adrenocorticotrophic hormone;
DTC = differentiated thyroid cancer;
FNAC = fine needle aspiration cytology; **FT4** = free thyroxine;
PCOS = polycystic ovary syndrome; **QoL** = quality of life;
Tg = thyroglobulin; **TPO-Ab** = thyroid peroxidase antibody;
TSH = thyroid-stimulating hormone

Welcome to the sixteenth edition of Endocrinology Research Review.

Highlights of this Review include a study of selenium supplementation in euthyroid thyroid peroxidase antibody positive women which found although supplementation improved selenium status, there were no benefits with regard to thyroid hormone or thyroid antibody status. We also report on an interesting study which finds that androstenedione, the immediate precursor for testosterone, may be a more sensitive biomarker for androgen excess in women with PCOS, and importantly, identified an association between androstenedione and insulin sensitivity which may help predict metabolic risk in this cohort. Finally, we have included a comprehensive and valuable review of primary and secondary adrenal insufficiency, well worth keeping as a reference for clinicians who manage patients with these challenging and life-threatening disorders.

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,

Professor Cres Eastman

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Radiocontrast-induced thyroid dysfunction: is it common and what should we do about it?

Authors: Hudzik B & Zubelewicz-Szkodzińska B

Summary: The use of radiocontrast-enhanced imaging, in particular for computed tomography and coronary angiography, has become more prevalent in recent years. This review discusses issues surrounding radiocontrast-induced thyroid dysfunction in relation to intravenous, intraarterial and enteral (endoscopic retrograde cholangiopancreatography) routes of administration for iodine-containing contrast media. Topics covered include prevalence and types of thyroid dysfunction, identification of at-risk patient groups, methods of prophylaxis and possible treatments.

Comment: This is a good review. The tolerable upper limit of iodine intake is 1,100 ug per day for healthy euthyroid people, established by experimental work several decades ago, and accepted by NHMRC, WHO and most international medical bodies. However, exposure to much larger doses of iodine are well tolerated by most healthy people because of the auto-regulatory system in the thyroid, namely the Sodium Iodide Symporter which down-regulates and temporarily inhibits iodine uptake into the thyroid. This is known as the Wolf-Chaikoff effect. In people with underlying thyroid disease, such as autoimmune thyroiditis and autonomous multinodular goitres, the auto-regulatory system may be disabled exposing the thyroid to iodine excess and the subsequent development of either hypothyroidism or hyperthyroidism. This may also occur uncommonly in people with no evidence of underlying thyroid disease. These issues are discussed in this review as well as the documentation of the "massive iodine loads" administered to patients undergoing diagnostic and therapeutic radiographic imaging studies. The incidence of thyroid dysfunction resulting from exposure to iodine excess through radiocontrast administration has been estimated at between 0.05% and 5% of patients. The authors conclude it is important for clinicians to recognise that administration of radiocontrast agents may cause thyroid dysfunction and that high risk patients, particularly elderly ones with cardiovascular disease, should be identified before scanning to prevent iodine-induced hyperthyroidism.

Reference: Clin Endocrinol 2014;80(3):322-7
http://onlinelibrary.wiley.com/doi/10.1111/cen.12376/abstract

Cortisol secretion from adrenal adenomas discovered as incidentalomas is responsive to ACTH

Authors: Olsen H et al

Summary: 80 consecutive patients with adrenal incidentalomas, and 50 with unilateral adenomas, were included in this retrospective study which aimed to examine whether adenoma secretion of cortisol is responsive to ACTH. Baseline measurements of cortisol and ACTH were compared to those following a 1-mg overnight dexamethasone suppression test (DST), and the cortisol response to ACTH calculated. Three groups were defined on the basis of basal ACTH; >3.0 pM (n=29); 2.0-2.9 pM (n=9); <2.0 pM (n=12). Cortisol was not significantly different between groups at baseline, however lower basal ACTH was associated with a greater cortisol response to ACTH, was negatively correlated with adenoma size (p=0.03), and positively correlated with adenoma attenuation at unenhanced CT (p=0.04).

Comment: Patients discovered to have an incidental adrenal adenoma (incidentaloma) are routinely tested for hypersecretion of adrenal hormones as part of the routine workup. In this study of 80 patients with incidental adrenal adenomas the investigators found that patients with low basal ACTH exhibited increased cortisol responses to ACTH and that the response to ACTH correlated with the size and attenuation of the adenoma on CT scanning, thereby providing indirect evidence that the adenoma is the source of the increased cortisol secretion. Cortisol secretion from adrenal adenomas therefore seems to be responsive to ACTH, which is contrary to the general view that these tumours are non-secretory. The investigators postulated that the increased cortisol response to ACTH may change the cortisol set-point of the HPA axis and could be a pathogenic factor in metabolic and skeletal complications of subclinical hypercortisolism. They recommend that the cortisol response to ACTH should be measured in future studies of subclinical hypercortisolism as it may prove to be a useful criterion for diagnosing this condition.

Reference: Clin Endocrinol 2014;80(3):335-41
http://tinyurl.com/m4a3dy7

Selenite supplementation in euthyroid subjects with thyroid peroxidase antibodies

Authors: Eskes SA et al

Summary: This randomised, placebo-controlled, double-blind clinical trial assessed the use of selenium supplementation in euthyroid thyroid peroxidase antibody (TPO-Ab) positive women in the absence of thyroid medication. Subjects were randomised to sodium selenite (200 ug/day, n=30) or placebo (n=31) for 6 months. Assessments, including TSH, FT4, TPO-Ab, selenium, selenoprotein P and QoL were carried out at baseline, 3, 6 and 9 months. Selenium supplementation increased serum selenium and selenoprotein P, but did not alter TPO-Ab, TSH or QoL. In conclusion, selenium supplementation in euthyroid TPO-Ab-positive women may improve selenium status, but has no impact on thyroid hormone status, TPO-Ab status or QoL.

Comment: Selenium supplements are currently in vogue for the treatment of patients with auto-immune thyroid disorders (AITD) especially Graves' orbitopathy and Hashimoto's disease, as several well conducted therapeutic trials have demonstrated benefit. However not all trials have shown benefit. The presence of TPO-Ab antibodies in euthyroid patients carries a significant risk of ultimately developing hypothyroidism, albeit at a rate of between 2 and 5% per annum. It follows that if one can delay the inflammatory process it may prevent the onset of hypothyroidism in these patients. In this report of a randomised placebo-controlled double-blind clinical trial of selenium supplementation (200 ug sodium selenite daily) administered to TPO-Ab positive subjects the investigators could not demonstrate an effect on TPO-Ab, TSH or QoL in these patients. One possibility for the negative study is that these patients in the Netherlands were iodine replete whereas most previous studies have been performed in mildly iodine deficient countries. In conclusion, the evidence for routine prescription of selenium supplements to patients with AITD remains uncertain.

Reference: Clin Endocrinol 2014;80(3):444-51
http://onlinelibrary.wiley.com/doi/10.1111/cen.12284/abstract

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Selection and review of the research has been carried out independently by Professor Creswell J. Eastman *AM. MB.BS.MD.FRACP.FRCPA. FAFPHM. ACCAM*

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Professor Eastman was the founding Head of the Department of Endocrinology and Diabetes at Westmead Hospital. He is a former President of the Endocrine Society of Australia and the Asia Oceania Thyroid Association. He is the Patron and Principal Medical Adviser for the Australian Thyroid Foundation. He has directed major research and public health projects into Iodine Deficiency Disorders (IDD) in Australia, Malaysia, Indonesia, Laos, Cambodia, the Philippines, Thailand, the Pacific Islands, China and Tibet. He is Vice Chairman and Asia Pacific Regional Coordinator for the International Council for Control of Iodine Deficiency Disorders (ICCIDD).

Mild iodine deficiency in women after spontaneous abortions living in an iodine-sufficient area of Czech Republic

Authors: Jiskra J et al

Summary: The investigators in this prospective, non-randomised follow-up study assessed the impact of iodine status on reproductive health in 171 women after spontaneous early abortion (SpA). Subjects with thyroid disease were excluded. Urinary iodine concentrations, TSH, FT4, TPO-Ab and thyroid ultrasound were obtained at 2-8 weeks (median 4) following early SpA and compared to those from an age-matched control group. Follow-up continued for a median of 38 months (range 12-47). Relationships between iodine status, reproductive health and other measured parameters were investigated using multivariate regression analysis. Urinary iodine concentration was lower in the SpA group vs. controls (92.0 vs. 117.8 µg/l, p<0.001), and more women in this group were mildly iodine deficient (58.0 vs. 31.5%, p <0.001). However, no associations were observed between iodine status, thyroid hormone or antibody status and reproductive health, including rates of successful pregnancies or obstetric complications.

Comment: The goal of this study undertaken in the Czech Republic was first, to ascertain if the prevalence of iodine deficiency was greater in women who had suffered early SpA compared with age-matched controls and secondly, to evaluate the relationship between mild iodine deficiency and several different parameters of thyroid function and finally, to establish if the urinary iodine excretion after SpA had any predictive effect on women's subsequent reproductive health. The proposition was that moderate to severe iodine deficiency during pregnancy is a known cause of hypothyroidism or isolated hypothyroxinaemia leading to an increased incidence of SpA.

Reference: Clin Endocrinol 2014;80(3):452-8
http://onlinelibrary.wiley.com/doi/10.1111/cen.12298/abstract

Impact of early vs late postoperative radioiodine remnant ablation on final outcome in patients with low-risk well-differentiated thyroid cancer

Authors: Tsirona S et al

Summary: This retrospective study assessed the impact of late vs. early postoperative radioiodine remnant ablation (RRA) on outcomes in patients with stage 1 differentiated thyroid cancer and near-total thyroidectomy. Mean age at diagnosis was 49.3 years (range 18-79). Subjects in the early group (n=50) received RAA at <4.7 months (median 3.0, range 0.8-4.7), whereas those in the late group (n=57) received RAA at > 4.7 months (median 6.0, range 4.8-30.3). Post-RAA for the early and late groups respectively, remission rates were 88 vs. 91.2%, persistence rates were 12 vs. 1.8%, and recurrence rates were 0 vs. 7%. Following further radioiodine therapy (n=11) or watchful waiting where required, all subjects were in remission at latest follow-up (median 87.3 months, range 23.3-251.6).

Comment: Standard treatment for well differentiated thyroid cancer for most patients in Australia is total thyroidectomy followed by radioactive iodine (RAI) ablation of any residual thyroid tissue. Prior to the availability and demonstrated effectiveness of pre-treatment Thyrogen® stimulation, the vast majority of patients waited several weeks without thyroxine replacement until the endogenous serum TSH rose to a sufficient level to ensure optimal uptake of RAI. Waiting times are often significant for limited inpatient facilities. In addition, it has generally been believed that delayed administration of RAI may prejudice long term survival as demonstrated in patients with metastatic disease. As these authors state, the impact of delayed RAI for patients with minimal disease, which is the case for the majority of newly diagnosed thyroid cancer patients, is unclear. In this small study of just over 100 patients treated for well differentiated thyroid cancer, half were treated within 3 months, and the other half delayed until 6 months. No difference was found in outcome between the two groups. While of clinical interest, the limitations of this study, including retrospectivity, no controls, and arbitrary dosages of RAI, limit the conclusions to be drawn. Nonetheless it is reassuring that it is unlikely that we are harming our patients if they have to wait up to 6 months for RAI treatment.

Reference: Clin Endocrinol 2014;80(3):459-63
http://onlinelibrary.wiley.com/doi/10.1111/cen.12301/abstract

Unstimulated highly sensitive thyroglobulin in follow-up of differentiated thyroid cancer patients

Authors: Giovanella L et al

Summary: This meta-analysis examined the diagnostic performance of highly sensitive serum thyroglobulin (Tg) assays (functional sensitivity ~ 0.1 ng/ml) as an indicator of relapse in differentiated thyroid cancer. A total of 9 papers (6 retrospective, 1 prospective, 1 not described) comprising 3,178 patients (mean age 40-52 years) were included in the analysis. 8 studies utilised the automated immunochemiluminometric Tg Access assay (Beckman Coulter), and 3 used the manual ELISA EIASON TgCa (IASON GmbH). Data including numbers of true-positives, false-positives, true-negatives and false-negatives for serum Tg were obtained. Stimulated Tg was used as a reference standard.

Comment: The authors conducted a meta-analysis of published papers to assess the diagnostic performance of highly sensitive serum Tg assays in monitoring management of patients treated with thyroxine suppressive therapy after total thyroidectomy, with or without radioiodine ablation. They found that when the suppressed serum Tg was <0.1 ng/ml it accurately predicted that stimulated Tg will be <1ng/ml, providing a negative predictive value of 97% which this tells us that residual disease is very unlikely and not worth further investigation by stimulation tests. By contrast, if the suppressed TSH is >0.1 ng/ml, the positive predictive value is less certain, and further investigations will need to be undertaken. As highly sensitive Tg assays are generally not readily available we need to consult with our clinical chemistry colleagues to improve access to this test.

Reference: J Clin Endocrinol Metab 2014;99(2) Epub 27 November, 2013
http://press.endocrine.org/doi/abs/10.1210/jc.2013-3156

Adrenal insufficiency

Authors: Charmandari E et al

Summary: Deficiencies in the production or action of glucocorticoids result in adrenal insufficiency. The authors of this comprehensive review have summarised current understandings of primary and secondary adrenal insufficiency in terms of epidemiology, aetiology, pathophysiology, clinical manifestations, diagnosis and management.

Comment: This review of primary and secondary adrenal insufficiency is comprehensive and valuable to clinicians managing patients with these challenging, life threatening disorders. The authors provide detailed information on all of the common and rare causes of adrenal insufficiency, but the vast majority of patients with primary adrenal insufficiency (Addison's disease) encountered in clinical practice are due to autoimmune adrenalitis. They emphasise that the preclinical time course of this disorder can span many years and the initial adrenal destruction is within the zona glomerulosa which is characterised by high plasma renin activity and diminished aldosterone production followed by progressive glucocorticoid deficiency. The review provides helpful information on laboratory parameters and their interpretation, as well as adrenal hormone replacement dosages and management strategies. The review is worth keeping as a reference article to be consulted when faced with problems in the management of these patients.

Reference: Lancet Epub 4 February, 2014
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61684-0/fulltext

Hyperandrogenemia predicts metabolic phenotype in polycystic ovary syndrome

Authors: O'Reilly MW et al

Summary: This prospective cohort study examined the utility of the androgen precursor androstenedione to predict metabolic dysfunction in polycystic ovary syndrome (PCOS). Subjects were 86 women with PCOS and 43 controls matched by age and BMI. Investigations included serum androgen measurement using tandem mass spectrometry and 24-hour urine androgen excretion using gas chromatography/mass spectrometry. Subjects received oral glucose tolerance tests and were assessed for insulin resistance. Women with PCOS had significantly higher serum androgen levels than controls (p<0.001) and these were positively correlated with the free androgen index and total androgen metabolite excretion (all p<0.001). 100% (n=56) of PCOS subjects with elevated testosterone also had elevated androstenedione. Serum androstenedione was strongly negatively correlated with insulin sensitivity.

Comment: PCOS is defined by the clinical triad of anovulation, insulin resistance, and androgen excess. As the authors of this study emphasise, it is not clear to clinicians which androgens should be measured, what constitutes normal reference ranges, and which analytical technique should be used. Further, they remind us that we do not know if different patterns of biochemical hyperandrogenemia define distinct PCOS subgroups in terms of metabolic risk. Measurement of serum testosterone is the most commonly used diagnostic test for hyperandrogenaemia but has several well-known limitations. These investigators examined the hypothesis that androstenedione, the immediate precursor for testosterone, could be a more sensitive marker for the biochemical detection of androgen excess. Androstenedione is secreted by both the ovaries and adrenals, and is also derived from dehydroepiandrosterone (DHEA) by enzymatic conversion in peripheral tissues. In this study of 86 women with PCOS, each androgen in serum was measured by liquid chromatography/tandem mass spectrometry (LC-MS). Serum androstenedione was elevated in 76 of 86 women (88.3%) with PCOS compared with an elevated testosterone in 56 of 86 (65%) and 2.3% and 11.6% of controls respectively. They conclude that serum androstenedione is a more sensitive marker of androgen excess than serum testosterone in women with PCOS. In addition, the study revealed a strong negative association between serum androstenedione and insulin sensitivity which may provide a new tool for predicting metabolic risk in PCOS women. While steroid assay by LC-MS is superior to immunoassay, the lack of widespread availability of this analytical technique limits its use in routine clinical practice.

Reference: J Clin Endocrinol Metab 2014;99(2) Epub 7 January, 2014
http://press.endocrine.org/doi/abs/10.1210/jc.2013-3399

Determination of the optimal time interval for repeat evaluation after a benign thyroid nodule aspiration

Authors: Nou E et al

Summary: This long-term study examined the optimal timing for repeat evaluation of cytologically benign thyroid nodules. Subjects (n=1,369) included all patients attending a single clinic over an 8-year period who had initially benign cytology following fine needle aspiration cytology (FNAC) of thyroid nodules ≥1cm. Mean follow-up period (from the initial FNAC to thyroidectomy, death or the most recent clinic visit) was 8.5 years (range 0.25-18). No deaths due to thyroid cancer occurred during follow-up. 18 malignancies were identified and removed at a mean follow-up time of 4.5 years. No metastatic disease was identified in this group, and all subjects with an initial false-negative FNAC had survived to a mean of 11 years follow-up at the time of publication. The authors suggest that repeat thyroid nodule evaluation should be undertaken 2-4 years following initially benign FNAC.

Comment: Thyroid nodules are common and readily identified by ultrasound examination with thyroid cancer confirmed or excluded by FNAC. As the authors of this study state, cytological interpretation is not flawless, and because the false-negative rate is not negligible, a repeat FNAC is frequently recommended when there is uncertainty and some authorities routinely recommend repeat FNAC for thyroid nodules initially diagnosed as benign (American Thyroid Association Guidelines). The major concern for clinicians is false-negative cytology leading to a missed diagnosis of malignancy and potentially preventable fatal outcome. In this retrospective study from the Brigham and Women's Hospital in Boston, the authors examined the records of over two thousand patients evaluated for thyroid nodules by FNAC undertaken between 1995 and 2003. They were attempting to determine the optimal timing for repeat assessment of patients initially diagnosed with falsely benign cytology and consequent disease related mortality due to a missed diagnosis. It is notable that 24% of their cohort with benign nodules ultimately pursued surgery for a variety of poorly defined reasons. The study revealed that following initial benign FNAC from a clinically relevant (≥1 cm) thyroid nodule, zero deaths (0%) were found to be attributable to thyroid disease or thyroid cancer during an average follow up of 8.5 years. However 18 false-negative FNAC results (1.3%) were confirmed in their cohort. The mean time from the initial benign cytology to the surgical removal of carcinoma in these 18 patients was 4.5 years (range 0.3–10). The authors have concluded that benign cytology alone, when obtained via ultrasound-guided FNAC in clinically relevant thyroid nodules, excludes the most dangerous and harmful of thyroid malignancies. They recommend that asymptomatic, low-risk patients with nodules unlikely to cause structural compromise can typically be recommended for repeat assessment in 2–4 years time. While these results provide some assurance, these recommendations should be interpreted in the context of the individual patient's clinical state and the experience of the clinicians caring for such patients.

Reference: ***J Clin Endocrinol Metab 2014;99(2) Epub 25 November 2013***
http://press.endocrine.org/doi/abs/10.1210/jc.2013-3160

