Endocrinology Research Review™

Making Education Easy

Issue 18 - 2014

In this issue:

Abbreviations used in this review:

DTC = differentiated thyroid carcinoma; **FT4** = free thyroxine; **GH** = growth hormone; **GO** = Graves' orbitopathy; **LT4** = levothyroxine; **OR** = odds ratio; **PHPT** = primary hyperparathyroidism; **RAIT** = radioactive iodine treatment; **TSH** = thyroid-stimulating hormone; **TSH** = thyroid-stimulating hormone; **TSHR** = thyroid-stimulating hormone receptor

Welcome to the eighteenth issue of Endocrinology Research Review.

In this issue we report on a meta-analysis of vitamin D supplementation in patients with primary hyperparathyroidism and vitamin D deficiency which appears to show that this is a safe and effective treatment strategy. We include the startling results of a postal survey investigating development of impulse control disorders, including hyper-sexuality, in patients with dopamine agonist-treated prolactinomas, and we profile an assessment of selenium levels in patients with Graves' orbitopathy with interesting findings which suggest that decreasing selenium levels may parallel increasing severity of orbitopathy.

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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Sexual dimorphism and thyroid dysfunction: a matter of oxidative stress?

Authors: Fortunato RS et al.

Summary/Comment: The greater frequency of thyroid disorders in females, particularly but not exclusively for autoimmune thyroid disease, is well known but the mechanisms are not. In this review the authors put forward the hypothesis that one of the underlying mechanisms is an oestrogen induced redox imbalance in the thyrocyte rendering the thyrocyte more vulnerable to damage from oxidative stress. The hypothesis is founded on good experimental evidence showing differences between male and female thyrocyte redox balance and oestrogen increasing hydrogen peroxide (H_2O_2) production within thyroid cells. In the past, many investigators have postulated a causal link between free radical accumulation in thyroid cells and subsequent cell atrophy related to decreased glutathione peroxidase (GPX) production exacerbated by lack of selenium, an essential cofactor for GPX. One could speculate that the observed beneficial effect of selenium supplementation in patients with autoimmune thyroid disorders may be related to positive effect on decreasing redox imbalance. Further research is required to address these questions.

Reference: J Endocrinol 2014;221:R31-R40
http://joe.endocrinology-journals.org/content/221/2/R31.abstract

Effect of 25 (OH) D replacements in patients with primary hyperparathyroidism and coexistent vitamin D deficiency on serum 25(OH) D, calcium and PTH levels

Authors: Shah VN et al.

Summary: This meta-analysis and review evaluated the safety of vitamin D replacement in patients with primary hyperparathyroidism (PHPT) and vitamin D deficiency. Ten studies comprising a total of 340 subjects were included in the analysis. Vitamin D replacement increased in serum 25(OH)D (+55.3 nmol/L, 95% CI 33.3 to 77.3) and reduced serum parathyroid hormone (PTH) (-3.5 pmol/L, 5.8 to -1.2), but serum calcium (-0.08 mmol/L, -0.2 to 0.03) and urinary calcium (0.72 mmol/L/24 hr) were unchanged (p=0.2). In conclusion the authors found vitamin D replacement in subjects with PHPT and vitamin D deficiency decreased serum PTH without causing hypercalcaemia or hypercalciuria.

Comment: The question of safety and efficacy of Vitamin D supplementation given to patients with PHPT has previously been commented on in Research Reviews. Clinicians who monitor patients with PHPT, prior to or in place of surgery, are frequently challenged by this issue and express concern that vitamin D supplementation may increase hypercalcaemia and hypercalciuria in patients with PHPT. This reported meta-analysis examines this issue and confirms that vitamin D supplementation provided to PHPT patients is safe and effective in lowering parathyroid hormone levels and does not escalate hypercalcaemia and hypercalciuria. While the authors make the point that we lack randomised clinical trials testing this question, the evidence is strong that vitamin D supplementation appears to be beneficial in lowering serum PTH and calcium levels and decreasing urinary calcium excretion and is therefore a safe and effective strategy to pursue in patients with PHPT.

Reference: Clin Endocrinol 2014;80(6):797–803
http://onlinelibrary.wiley.com/doi/10.1111/cen.12398/abstract

Cluster of cardiometabolic risk factors in children with GH deficiency

Authors: Capalbo D et al.

Summary/Comment: Growth hormone (GH) deficient adults have a significantly increased risk of developing cardiovascular disease. Whether this risk applies to GH deficient children has been uncertain. This interesting and comprehensive, prospective case-control study measured a wide range of cardiovascular risk factors in 71 GH deficient (GHD) children before and 2 years after treatment and compared them with a control group. The GHD children exhibited higher levels of serum total and LDL cholesterol, triglycerides, homocysteine, leptin and fibrinogen, but no differences were found in adiponectin or high sensitivity CRP levels. Two years of GH therapy lowered these risk factors in the GHD children. Adiponectin levels were significantly increased in the GH treated groups, possibly indicating decreased hyperinsulinaemia and insulin resistance. While it is possible that the beneficial effects of GH therapy on cardiovascular risk factors could translate into decreased rates of cardiovascular disease in later life only time and longer term trials will provide those answers.

Reference: Clin Endocrinol 2014;80(6):856–862
http://onlinelibrary.wiley.com/doi/10.1111/cen.12393/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).

Impulse control disorders in patients with dopamine agonist-treated prolactinomas and nonfunctioning pituitary adenomas

Authors: Bancos I et al.

Summary/Comment: The putative causal relationship between dopamine agonist (DA) therapy and the development of impulse control disorders (ICD) in patients with Parkinson's disease is well known, but there are very few reports in the endocrine literature about the incidence of ICD in prolactinoma patients treated with DA drugs such as cabergoline and bromocriptine. The current study used a postal survey with self-reporting of ICD symptoms and behaviour in 77 prolactinoma patients, with past or present treatment with a DA, and compared the responses with a survey of 70 patients with chromophobe adenoma who had not been treated with a DA. The startling result was the high prevalence of ICD behaviours on self-reporting in both groups, but the major finding was an almost 10 fold increase in hyper-sexuality in men treated with a DA, but this did not occur in women. A postal study of this nature with data being reliant on self-reporting creates a level of scepticism and leaves many questions unanswered. Regardless of the uncertainty, the lessons for clinicians managing patients requiring DA therapy are first to inform their patients at the outset of these possible adverse effects and then to ensure active monitoring as many patients will not voluntarily report suffering from an ICD.

Reference: Clin Endocrinol 2014;80(6):863–868
http://onlinelibrary.wiley.com/doi/10.1111/cen.12375/abstract

Serum selenium status in Graves' disease with and without orbitopathy

Authors: Khong JJ et al.

Summary: The authors of this prospective case-control study aimed to determine whether serum selenium levels were lower in patients with Graves' disease (GD) with or without orbitopathy. Subjects were 198 Australian endocrine/ophthalmology clinic attendees with Graves' disease of whom 101 had Graves' orbitopathy (GO). GO was associated with significantly lower mean serum selenium than GD; 1.10 ± 0.18 μM vs 1.19 ± 0.20 μM, p=0.001. This difference remained following adjustment for age, smoking status, thyroidectomy, radioactive iodine treatment and residential location. Selenium levels appeared to be correlated with severity of GO, with the lowest levels (1.09 ± 0.18 μM) observed in severe, sight-threatening GO. The authors concluded that, "relative selenium deficiency may be an independent risk factor for orbitopathy in patients with Graves' disease".

Comment: The beneficial effect of selenium supplementation in patients suffering from GO has been demonstrated in approximately a third of treated patients. It is not clear if the benefit is independent of the individual patient's selenium balance. This collaborative Australian study measured plasma selenium levels in 101 patients with Graves' orbitopathy and compared them with 97 without Graves' orbitopathy. The interesting finding was a significantly lower plasma selenium level in the patients with GO and that decreasing selenium levels paralleled increasing severity of GO. These findings suggest that selenium levels may, in an as yet unknown way, be involved with the development and severity of GO. This study adds some more to unravelling the relationship between selenium and GO. The practical message is that clinicians should consider measuring serum selenium concentrations in patients with GO before arbitrarily commencing therapeutic selenium supplementation.

Reference: Clin Endocrinol 2014;80(6):905-10
http://onlinelibrary.wiley.com/doi/10.1111/cen.12392/abstract

Management of neonates born to women with Graves' disease

Authors: Besançon A et al.

Summary/Comment: Neonatal hyperthyroidism is a serious disorder accompanied by a significant level of morbidity and if not recognised early in the neonatal period and treated with antithyroid drugs it can be fatal. Thankfully it is now a relatively rare disorder as there is high level of awareness that the offspring of women suffering from Graves' disease during pregnancy are at risk of this complication. In this prospective observational French study, of 68 neonates born to women with Graves' disease none of the neonates born to women who were thyroid receptor antibody (TRAB) negative suffered from neonatal hyperthyroidism. Of the 33 neonates born to TRAB positive mothers, 24 (73.7%) had TRAB measured in cord blood and 7 subsequently suffered hyperthyroidism. Therefore the presence of TRAB in cord blood indicates the baby is at risk, but the level of FT4 at between 3 and 4 days after birth was predictive of the development of neonatal hyperthyroidism. This study reinforces what we already know and adds some new information in that TRAB testing should be done in women with present or past Graves' disease before conception if possible, early on during pregnancy and around 22 weeks gestation (recommendations from American Endocrine Society Guidelines). Each pregnancy should be managed individually on its merits if the mother is TRAB positive. The authors of this study confirm that it is essential to measure the TRAB level in foetal cord blood and if TRAB positive the neonate has a 30% chance of developing hyperthyroidism. In their study an elevated FT4 level between 3 and 7 days, but not at birth, was highly predictive for developing hyperthyroidism. These are helpful management guidelines.

Reference: Eur J Endocrinol 2014;170:855-62
http://www.eje-online.org/content/170/6/855.abstract

Association between L-thyroxine treatment, GH deficiency, and radiological vertebral fractures in patients with adult-onset hypopituitarism

Authors: Mazziotti G et al.

Summary: This Italian cross-sectional study, conducted in 74 subjects with adult-onset hypopituitarism and severe growth hormone deficiency (GHD), aimed to investigate relationships between radiological vertebral fractures and LT4 replacement doses. Radiological vertebral fractures were observed in 31.1% of subjects and were associated with untreated GHD (p=0.02); higher serum FT4 (p=0.03); higher daily LT4 dose (p=0.005); and longer duration of hypopituitarism (p=0.05). Under multivariate analysis, factors independently associated with fractures were untreated GHD (OR 4.27, 95% CI 1.27-14.33, p = 0.01) and LT4 dose (OR 4.01, 1.16-14.39, p=0.03). The authors concluded that fracture risk may be increased by relative overtreatment with LT4 in some patients with hypopituitarism.

Comment: Previous large studies of adults suffering from hypopituitarism and GHD have shown an increased risk of fractures. Surprisingly the largest study database (Pharmacia and Upjohn Metabolic database –KIMS) did not show increased fracture risk in hypopituitary patients treated with thyroxine and/or glucocorticoid replacement therapy. Intuitively one would think the risk should increase with increasing dosages of thyroxine and glucocorticoids. The conclusion from the KIMS database has been that the increased fracture risk was due to GHD alone. By contrast, this small cross-sectional Italian study of hypopituitary patients with GHD, reported an independent relationship between increased vertebral fracture risk and daily thyroxine replacement at higher dosages (mean 1.35 μg/kg body weight), compared with replacement at lower dosages (mean 0.93 μg/kg body weight). Most clinicians managing such patients should now be more aware that excessive thyroid hormone replacement therapy in hypopituitary patients may increase fracture risk, which is what we would expect.

Reference: Eur J Endocrinol 2014;170:893-9
http://www.eje-online.org/content/170/6/893.abstract

Clinical relevance of thyroid-stimulating autoantibodies in pediatric Graves' disease

Authors: Diana T et al.

Summary/Comment: This large cross-sectional, retrospective study was undertaken to establish if thyroid receptor stimulating antibody concentrations (TSAb) measured by a new commercial bioassay method are of greater diagnostic and prognostic relevance than results from widely available automated thyroid binding inhibitory (TBII) assays in paediatric patients suffering from Graves' disease with or without Graves' orbitopathy (GO). Many studies of diagnostic and prognostic relevance of TBII in children as well as adults have been reported in the literature. In this study of a paediatric population, the investigators claim excellent sensitivity, specificity, and reproducibility of this novel TSH receptor antibody bioassay. In addition to being a useful biomarker for disease activity, they claim TSAb results also correlated with the presence of GO independent of thyroid function, suggesting a possible causal role of TSAb in the immunopathogenesis of GO and in the development of the clinical phenotype of thyroid eye disease with proptosis. The unique advantage of bioassays over binding assays is their ability to measure the functional activity of the Ig and therefore to distinguish predominantly stimulating or blocking (or neutral) TSHR antibodies. Thus measurement of TSAb can prove useful when TBII may be misleading due to a preponderance of "blocking" rather than "stimulating" antibodies. As the TSAb method employed in this study is a new commercial one available in several countries it is likely to be available in Australia in the near future.

Reference: JCEM 2014;99(5):1648-55
http://press.endocrine.org/doi/abs/10.1210/jc.2013-4026

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

Authors: Øksnes M et al.

Summary/Comment: It is well accepted that orally administered glucocorticoid replacement therapy in patients with Addison's disease (AD) is satisfactory for maintenance of good health, but far from ideal in restoring normal physiological pituitary-adrenal function. This multicenter, crossover, randomized clinical trial of continuous subcutaneous hydrocortisone infusion (CSHI) compared the effects of 3 months on CSHI with 3 months on thrice-daily oral hydrocortisone conventional therapy (OHC) in AD patients. The ACTH level, as a marker of overall glucocorticoid effects and regulation, was the primary outcome. Safety and effects on other metabolic parameters, quality of life and sleep were secondary end points. This study showed that CSHI safely reestablished the circadian cortisol rhythm and normalised morning ACTH levels in AD patients, contrasting with the typical daytime cortisol peaks and troughs and elevated morning ACTH seen with OCH. CSHI restored glucocorticoid metabolism close to normal, however, the evidence for improved sleep and quality of life was lacking. Despite this advance, we remain some way from achieving ideal glucocorticoid and mineralocorticoid replacement in AD but this report suggests a trial of CSHI may be warranted in the small minority of AD patients who cannot be stabilised on conventional oral therapy.

Reference: JCEM 2014;99(5):1665-74
http://tinyurl.com/pkldyhh

Radioiodine ablation of postsurgical thyroid remnants after treatment with recombinant human TSH in patients with moderate-to-severe Graves' orbitopathy

Authors: Moleti M et al.

Summary: This prospective, randomised, single-blind study compared the efficacy of ^{131}I thyroid ablation following total thyroidectomy and recombinant human TSH stimulation (Tx-RAI) vs thyroidectomy alone (Tx) in 40 patients with moderate to severe GO. At 12-month follow-up, improvement in GO was observed in 70 vs 20% of the Tx-RAI and Tx subjects respectively. Inactive GO was observed in 75 vs 30% of Tx-RAI and Tx subjects respectively ($p<0.01$).

Comment: There have been several studies testing the hypothesis that GO responds quickest and best to total thyroidectomy followed by radioactive iodine ablation of any thyroidal remnant. This strategy is based on the theoretical postulate that total thyroid ablation, by removing both thyroid-orbit cross-reacting autoantigens and autoreactive T lymphocytes, would be beneficial in improving outcomes of GO. The results of this study indicate that postoperative radioiodine ablation is more effective in the short term (24 months) than thyroidectomy alone in inducing earlier and steadier improvement in patients with moderate-to-severe GO treated with intravenous glucocorticoids. Longer follow-up indicated no significant difference in outcomes. The authors state that further studies investigating the overall benefits and risks of this procedure are warranted before any conclusions can be drawn. A unique contribution from this study was the finding that recombinant TSH pretreatment before administration of radioactive iodine was safe and effective, obviating the need to withhold thyroxine replacement for several weeks before giving radioactive iodine.

Reference: JCEM 2014;99(5):1783-9
http://press.endocrine.org/doi/abs/10.1210/jc.2013-3093

The impact of iodinated contrast agent administered during preoperative computed tomography scan on body iodine pool in patients with differentiated thyroid cancer preparing for radioactive iodine treatment

Authors: Young S et al.

Summary: The authors of this large retrospective review investigated the appropriate time interval between preoperative CT with iodinated contrast agents (ICA) and commencement of radioactive iodine treatment (RAIT). Subjects were 1,023 patients with differentiated thyroid carcinoma. There were no significant differences in urinary iodine excretion (UIE) between patients with the shortest time interval from CT to spot iodine measurement (31-60 days) and those with intervals of 61-90, 91-120, 121-50 or 151-180 days ($p<0.05$). The authors concluded that in this cohort there was no difference in UIE at 1 month or 6 months post-CT with ICA and therefore delays of 3-4 months before commencement of RAIT should be reconsidered.

Comment: This study provides useful information to clinicians managing thyroid cancer patients and scheduling radioactive iodine therapy after total thyroidectomy. A preoperative neck CT scan to identify metastatic cancer in cervical lymph nodes is being increasingly advocated in guidelines from expert groups. The downside to this procedure has been the recommendation to wait 3 to 4 months before administering radioactive iodine to ensure clearance of excessive iodine accumulated from the contrast agent given at the time of scanning. This study of over 1,000 patients who underwent a preoperative CT scan with iodine containing contrast agents had effectively cleared the iodine load within 1 month indicating that it is not necessary to wait 3 to 4 months before scheduling radioactive iodine therapy. Before implementing a new regimen suggested by this study it would still be wise to check urine iodine excretion in each patient before giving radioactive iodine.

Reference: Thyroid 2014;24(5):872-877
http://online.liebertpub.com/doi/abs/10.1089/thy.2013.0238

