Endocrinology Research Review™

Making Education Easy

Issue 6 - 2013

In this issue:

Welcome to the sixth issue of Endocrinology Research Review.

Among the papers selected for this edition is an interesting study reporting a significant association between BMI and tumour size, extrathyroidal invasion and advanced stage of papillary thyroid cancer. A French study in pregnant ewes found exposure to BPA in utero resulted in a 30% decrease in thyroxine levels in newborn lambs raising further concerns about the adverse effects on thyroid function of maternal and fetal exposure to BPA.

Two review articles are also included in this edition. One addresses the difficulties clinicians face with dosing and side effects of radioiodine (^{131}I) therapy for the treatment of benign thyroid diseases. The second reviews the role of selenium and the thyroid gland and may be important to the clinician managing patients with autoimmune thyroid disorders.

We hope you find the selections for this issue interesting and we look forward to receiving your comments and feedback.

Kind Regards,

Professor Cres Eastman
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Associations between body mass index and clinico-pathological characteristics of papillary thyroid cancer

Authors: Kim HJ, et al

Summary: This study retrospectively analysed 2057 patients with PTC to examine the association between BMI and disease recurrence. Patients were grouped according to BMI based on the WHO standardised categories; underweight (BMI <18.5 kg/m^2), normal weight (BMI 18·5–24·9), overweight (BMI 25·0–29·9) and obese (BM ≥30).

The authors reported a 5-kg/m^2 increase in BMI was associated with PTC tumours larger than 1 cm, with microscopic extrathyroidal invasion, and with advanced tumour-node-metastasis. The association was independent of confounding variables such as gender, age, serum TSH, total cholesterol and fasting glucose level. Forty-three patients (2·1%) experienced recurrence during the median 84 month follow-up. The authors found no significant differences in recurrence of PTCs among BMI groups.

Comment: The rationale for this large retrospective study carried out in Korea was to test the hypothesis that certain environmental factors such as body weight and increased BMI may be associated with the increasing incidence of papillary thyroid cancer, occurring not only in Korea, but also documented in many other countries throughout the world. They asked the question "is there an association between excess weight and prognostic factors"? They found a statistically significant association of higher BMI with larger tumour size, extrathyroidal invasion and advanced stage of papillary thyroid cancer that is interesting and intriguing. Given these associations, it is surprising that there was no association between BMI and persistent disease or disease free survival. It is not clear why excess body weight would be associated with larger and more aggressive tumours, but excess adiposity and increased cancer risk has been reported for many different types of cancer, so thyroid cancer is another one to add to the list and much more research is required to provide insights into possible causal relationships.

Reference: Clin Endocrinol (Oxf) 2013;78(1):134-40
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2012.04506.x/abstract

Abbreviations used in this issue:

ACTH = adrenocorticotropic hormone; **BMD** = bone mineral density; **BMI** = body mass index; **BPA** = bisphenol A; **CAH** = congenital adrenal hyperplasia; **DTC** = differentiated thyroid cancer; **GH** = growth hormone; **GPX** = glutathione peroxidase; **ICCIDD** = International Council for the Control of Iodine Deficiency Disorders; **IGF-1** = insulin-like growth factor-1; **^{131}I** = Iodine-131; **OR** = odds ratio; **PreDEq** = prednisolone dose equivalent; **PTC** = papillary thyroid cancer; **PTH** = parathyroid hormone; **T_4** = thyroxine; **Tg** = thyroglobulin; **TPOAb** = thyroid peroxidase antibodies; **TSH** = thyroid stimulating hormone; **UIC** = urinary iodine concentration; **WHO** = World Health Organisation

Selenium and the thyroid gland: more good news for clinicians

Authors: Drutel A, et al

Summary: This review looks at the role of selenium status on the development of thyroid pathologies and the value of selenium supplementation in autoimmune thyroid disorders. The authors review the impact of selenium supplementation in patients with Hashimoto's disease, in pregnant women with anti-TPO antibodies and Graves' disease. The article also addresses the risk of side effects following long-term selenium supplementation.

Comment: This is a very interesting and important review article that may ultimately be important to the clinician managing patients with autoimmune thyroid disorders. Selenium is an essential trace mineral that is found in the chemical form selenocysteine in highest concentrations in the thyroid gland, presumably because the thyroid expresses several specific selenoprotein enzymes that are essential for the synthesis of thyroid hormones. The principal selenoproteins are the enzymes, GPX and the deiodinases. An important function of GPX is to act as an antioxidant and so protect thyroid tissues from oxidative damage by toxic free radicals.

The authors review several studies demonstrating the benefit of selenium supplementation in the management of autoimmune thyroid disorders. For example, selenium supplementation has been shown to potentiate the activity of selenoproteins decreasing inflammation within the thyroid gland decreasing anti TPOAb levels and improving thyroid morphology. Whether this has any long-term beneficial effect in patients with Hashimoto's disease remains to be established. Of more clinical relevance is the evidence from a recent randomised, double-blind, placebo-controlled trial showing significant improvement in orbital information in patients with Graves' orbitopathy. There is also some evidence that selenium supplementation may prevent or ameliorate postpartum thyroiditis. The review emphasises the point that plasma or serum selenium concentrations do not reflect intra-thyroidal concentrations of selenium and consequently assays of blood selenium levels are not recommended in routine clinical practice. They also caution that excessive selenium supplementation may precipitate type II diabetes.

Reference: Clin Endocrinol (Oxf) 2013;78(2):155-64
http://onlinelibrary.wiley.com/doi/10.1111/cen.12066/abstract

Glucocorticoid treatment regimen and health outcomes in adults with congenital adrenal hyperplasia

Authors: Han TS, et al

Summary: Glucocorticoid treatment regimen impacts on health outcomes were assessed in this cross-sectional study of 196 adult CAH patients. Glucocorticoid dose was converted to PreDEq using published formulae for treatment comparison. The study reported patients on dexamethasone had lower androgens and adrenocorticotropic hormone but greater insulin resistance compared with those receiving hydrocortisone or prednisolone. The study also found that partial correlation analysis (adjusted for age and sex) showed PreDEq weakly correlated with blood pressure and androstenedione and that mutation severity was associated with increased PreDEq.

Comment: This article may be helpful to clinicians who look after patients with CAH where appropriate choice of therapy and optimal metabolic control are often difficult to achieve. The authors of this paper have previously reported the health status of adult patients in the UK suffering from CAH and surprisingly found a higher prevalence of metabolic abnormalities than anticipated. Obesity, hypercholesterolaemia, insulin resistance, osteopaenia and osteoporosis occurred in a high proportion of patients. There was a wide variety of glucocorticoids prescribed for therapy; the commonest being prednisolone, hydrocortisone and dexamethasone, individually or in combination. Most would agree that the goal of therapy in CAH is to replace deficient cortisol and prevent the consequences of androgen excess while avoiding glucocorticoid overtreatment. However, there are no controlled drug trials in adults with CAH so choice of steroid and mode of therapy comes mainly from clinical experience.

Despite several limitations to the current study there is some useful information for clinicians managing adult patients with CAH. For example, while dexamethasone - most commonly used in this country as a pre-bedtime therapy to suppress overnight ACTH secretion - was the most potent glucocorticoid in lowering adrenal androgen production, it caused more severe insulin resistance than either prednisolone or hydrocortisone. Surprisingly, the study reported that increasing the glucocorticoid dose did not necessarily lead to better disease control and was frequently associated with a worse metabolic profile. In conclusion, as clinicians practising in this field are well aware there is much trial and error in achieving good metabolic control while preventing adverse effects from glucocorticoid therapy.

Reference: Clin Endocrinol (Oxf) 2013;78(2):197-203
http://onlinelibrary.wiley.com/doi/10.1111/cen.12045/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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Outcome of multimodal therapy in operated acromegalic patients, a study in 115 patients

Authors: Albarel F, et al

Summary: This retrospective 10-year study evaluated initial and long-term outcomes of newly diagnosed acromegalic patients. Remission was assessed using GH nadir after oral glucose tolerance test <0·4 µg/l and normal IGF-1 at 3 months and at the end of the follow-up (median 41 months). The authors reported 90·9% of patients had controlled disease at the end of follow-up, 49·5% of patients were in long-term remission after surgery alone and 2·0% of patients experienced recurrent disease. Multivariate predictors of 3-month remission included mean GH at diagnosis, tumour invasion and surgeon report of incomplete or uncertain macroscopic resection. Multivariate predictors at diagnosis of long-term remission included mean GH level, adenoma size and absence of pituitary deficit.

Comment: This report from France is a retrospective study of outcomes in 109 patients treated by transsphenoidal surgery for acromegaly between 1997 and 2007. It is generally agreed that the goals of therapy in acromegaly are to lower the serum IGF -1 levels to within the normal reference range for age and to decrease the serum growth hormone down to less than 1 mcg/L after a glucose load and transsphenoidal surgical resection is the preferred first choice of therapy when growth hormone producing tumours are deemed resectable. Outcomes from transsphenoidal surgery are dependent upon selection of patients and the experience and skill of the operator. The results from this clinic are comparable with many other reports from clinics experienced in this form of therapy. It reinforces the view that acromegaly is best treated by transsphenoidal surgery by experienced operators and only if this fails should one consider medical therapy or radiotherapy.

Reference: Clin Endocrinol (Oxf) 2013;78(2):263-70
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2012.04492.x/abstract

Thyroid function and the metabolic syndrome in older persons: a population-based study

Authors: Heima NE, et al

Summary: These researchers investigated the association between serum TSH and the metabolic syndrome in Dutch older persons. The study cohort of 1187 subjects (590 men and 597 women) aged between 65 and 88 years were assessed for metabolic syndrome and serum TSH levels. Metabolic syndrome prevalence was 34.2% and mean serum TSH was 1.9mU/l. Subjects in the upper quartile with a serum TSH level above 2.28mU/l had a significantly increased prevalence of metabolic syndrome compared with subjects in the lowest quartile with a serum TSH below 1.04mU/l. The researchers reported the OR was 1.62 (95% CI 1.15–2.32) after adjustment for confounders; age, sex, alcohol use, total physical activity, and smoking.

Comment: The metabolic syndrome comprises a group of risk factors that predispose to cardiovascular disease and includes central obesity, a raised serum triglyceride level, decreased HDL cholesterol level, insulin resistance, impaired fasting glucose level and hypertension. Over the past decade several studies have explored the relationship between thyroid function and metabolic syndrome attempting to determine if minor disturbances in thyroid function are associated with increased risk of developing cardiovascular disease. A similar study to this, also performed in the Netherlands, was published in the Journal of Clinical Endocrinology and Metabolism in 2007 and showed that a lower free T4 level was significantly associated with four components of the metabolic syndrome. In the present study the researchers have shown that patients with a higher serum TSH within their normal reference range have a higher prevalence of metabolic syndrome. This finding is not original and has been reported in several other publications in recent years. Some clinicians have interpreted these findings as more evidence for treating patients with marginally elevated serum TSH levels classified as suffering from subclinical hypothyroidism. More prospective studies are necessary to clarify whether or not such patients should be treated with thyroxine to decrease development of cardiovascular diseases.

Reference: Eur J Endocrinol 2012;168(1):59-65
http://www.eje-online.org/content/168/1/59.abstract

Maternal and fetal exposure to Bisphenol A is associated with alterations of thyroid function in pregnant ewes and their newborn lambs

Authors: Viguié C, et al

Summary: This French study assessed ewe maternal and fetal exposure to BPA and its main metabolite BPA-glucuronide and the impact of exposure on thyroid function. Ewes were treated with BPA (5mg/kg/day subcutaneous) or vehicle from day 28 until the end of pregnancy. The team found unconjugated BPA did not accumulate in pregnant ewes, and its concentration was similar in the newborns and their mothers. In amniotic fluid and cord blood BPA-glucuronide concentrations were about 1300-fold higher than those of BPA. The team also reported a 30% decrease in total thyroxine concentrations in BPA-treated pregnant ewes and in the cord and the jugular blood of their newborns.

Comment: There has been a recent resurgence in the identification of specific chemicals that may function as endocrine disruptors. These chemicals can interfere with the endocrine system and produce adverse developmental, reproductive and immune disorders in humans and animals. Greatest risk occurs during prenatal and early postnatal development. A plasticiser, BPA, that is found in every day plastic food and drink containers as well as many other domestic products, has recently been incriminated as the causative agent in decreasing thyroid hormone levels in newborn male offspring of women who had high concentrations of BPA in their urine.

This current study from France undertaken in pregnant ewes showed that exposure to BPA in utero resulted in a 30% decrease in thyroxine levels in newborn lambs. Whether this can be extrapolated to humans remains to be determined but raises further concerns about the adverse effects on thyroid function of maternal and fetal exposure to BPA.

Reference: Endocrinology 2013;154(1):521-8
http://endo.endojournals.org/content/154/1/521.abstract

Therapy of hypoparathyroidism with PTH(1–84): A prospective four-year investigation of efficacy and safety

Authors: Cusano NE, et al

Summary: This study examined the effect of 4 years of PTH(1–84) treatment in 27 subjects with hypoparathyroidism with prospective monitoring of calcium and vitamin D requirements, serum and urinary calcium, serum phosphorus, bone turnover markers, and BMD. Treatment with PTH(1–84) reduced supplemental calcium requirements by 37% and 1,25-dihydroxyvitamin D requirements by 45%. Seven subjects (26%) ceased 1,25-dihydroxyvitamin D completely. Serum calcium concentration remained stable, and urinary calcium and phosphorus excretion declined. Lumbar spine BMD increased by 5.5 ± 9% at 4 yr while femoral neck, total hip and distal radius BMD remained stable. There was a significant increase in bone turnover markers, reaching a 3-fold peak from baseline values at 6–12 months, returning to steady-state levels at 30 months.

Comment: The authors of this article remind us that hypoparathyroidism is a disorder characterised by hypocalcemia and efficient PTH and is the only classic endocrine deficiency for which the missing hormone (PTH) is not yet an approved therapy. Instead, we have to rely upon the age-old remedies of vitamin D and calcium supplementation to maintain normal calcium levels in the blood. Previous reports have shown that short term treatment with recombinant PTH 1-84 appears safe and effective in treating hypoparathyroidism, but there are no long-term safety and efficacy data. This study reports data on patients treated on alternate days for up to 4 years with injectable PTH 1-84 in an open label trial without a control group. There seems little doubt that treatment was safe and effective but not entirely free of adverse effects including episodes of mild hypercalcaemia, musculoskeletal, gastrointestinal and genitourinary complaints. Many patients were required to continue with vitamin D and calcium supplementation. Therefore, the likelihood of approval and widespread usage of recombinant PTH replacing traditional vitamin D and calcium supplementation for correction of hypoparathyroidism seems some way off.

Reference: J Clin Endocrinol Metab 2013;98(1):137-44
http://jcem.endojournals.org/content/98/1/137.abstract

Life expectancy is reduced in differentiated thyroid cancer patients ≥ 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients

Authors: Verburg FA, et al

Summary: The all-cause mortality rate in DTC patients was compared to that of the general population in this prospective database study. The study cohort of 2011 DTC patients were treated in a German hospital from 1980–2011. All patients received total thyroidectomy with subsequent ^{131}I ablation, except for those with an isolated papillary microcarcinoma. The authors concluded that life expectancy was not significantly reduced in 86% of DTC patients (TNM stages I, II, or III). Patients who were at least 45 yr old at diagnosis and had extensive perithyroidal invasion, lateral cervical lymph node metastases, or distant metastases showed a clearly reduced life expectancy (TNM stages IVa, IVb, and IVc). The loss of life expectancy was significantly greater in patients over 60 yr of age at diagnosis compared to for those aged 45–59 yr in all groups.

Comment: This retrospective study from a single Cancer Centre in Germany looked at the records of over 2000 patients treated for DTC to see if the all-cause mortality rate in DTC patients compares to that of the general population. All of their patients had been treated by thyroidectomy and subsequent ^{131}I ablation. What they concluded is reasonably well known that life expectancy is not significantly reduced in the vast majority of DTC patients treated by surgery and radioactive iodine but reduces in patients over the age of 45 with extensive local invasion, cervical lymph node metastases and/or distant metastases. There was no difference between males and females. A shortcoming of this study was that they did not report the effect or influence of thyroxine suppressive therapy on life expectancy. They comment that the large number of patients treated with an ablative ^{131}I therapy was not associated with an unexpected excess mortality. However there were no control patients to make a comparison. The authors acknowledge that their patients were treated at a single tertiary referral Cancer Centre and therefore the results cannot be extrapolated to other centres. Nonetheless, the data provides comfort to patients treated for DTC.

Reference: J Clin Endocrinol Metab 2013;98(1):172-80
http://jcem.endojournals.org/content/98/1/172.abstract

Percutaneous ultrasound-guided laser ablation is effective for treating selected nodal metastases in papillary thyroid cancer

Authors: Papini E, et al

Summary: This pilot study assessed the effectiveness and safety of ultrasound-guided laser ablation for nonsurgical treatment of small-size neck metastases of PTC. The study participants included 5 patients with previous total thyroidectomy and neck dissection for PTC, with eight new lymph node metastases. The team monitored Tg and ultrasound changes of the lymph nodes 6 and 12 months after laser ablation and found a single laser ablation treatment induced progressive volume reduction of the eight metastatic lymph nodes. The mean serum Tg on levothyroxine decreased from 8.0 ± 3.2 ng/ml to 2.0 ± 2.5 ng/ml at 12-month control ($P < 0.02$ vs baseline). In three patients Tg levels were undetectable at 12-month control.

Comment: This report recommends that percutaneous ultrasound guided laser ablation joins radiofrequency ablation and ultrasound guided percutaneous ethanol injection as an alternative treatment to surgical removal of selective nodal metastases of papillary thyroid cancer. This may have a place when repeated neck surgery is required for radioiodine resistant nodal metastases to avoid surgical complications of multiple neck explorations. The present study was an experimental trial in 5 patients with local recurrences of papillary thyroid cancer in three different Italian thyroid centres. In a pilot study the researchers treated one individual with the laser therapy and then surgically excised the metastatic lymph node two weeks later confirming that the node was necrotic and all tumour cells had been eliminated. They emphasise that while their treatment was effective in this very small series of patients, mini invasive techniques are only occasionally associated with an anatomical or biochemical cure for cancer. Nonetheless, the technique may have a place in the treatment of patients who are not suitable for surgery or in debulking unresectable anaplastic tumours. Quite rightly, long-term controlled trials are necessary to define the role of this treatment in the management of metastatic thyroid cancer.

Reference: J Clin Endocrinol Metab 2013;98(1):E92-7
http://jcem.endojournals.org/content/98/1/E92.abstract

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Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100–299 µg/L: A UNICEF/ICCIDD study group report

Authors: Zimmerman MB, et al

Summary: This cross-sectional study of children aged 6 to 12 years (n=2512) in 12 countries evaluated the Tg response to both low- and high-iodine intake by analysing the levels of UIC, TSH, total T_4, Tg, and thyroid antibodies. The investigators reported Tg concentrations showed a clear U-shaped curve over a range of iodine intakes. There was a significantly higher prevalence of elevated Tg values in children with iodine deficiency (UIC <100 µg/L) and iodine excess (UIC >300 µg/L) when compared with iodine-sufficient children. There was no significant change in the prevalence of elevated Tg, TSH, T_4, or thyroid antibodies comparing children within the UIC ranges of 100–199 vs 200–299 µg/L.

Comment: Measurement of UIC is a surrogate for dietary iodine intake because approximately 90% of ingested iodine appears in the urine within a day or two of ingestion. Therefore, measurement of UIC is the simplest and best means of defining iodine intake in a population. The WHO and ICCIDD have provided population UIC guidelines for definition of iodine deficiency, iodine sufficiency and iodine excess. In this multi-country study the investigators have tested the hypothesis that serum Tg measurement is a potential alternative means of assessing population iodine deficiency. While their data indicates that serum TG is a very sensitive marker of iodine deficiency and excess it is unlikely that this test will replace UIC for population iodine studies as it is more invasive and more expensive than urine testing.

Reference: J Clin Endocrinol Metab 2013 Jan 23 [Epub ahead of print]
http://jcem.endojournals.org/content/early/2013/01/23/jc.2012-3952.abstract

Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome

Authors: Bonnema SJ, et al

Summary: This review article of radioiodine (^{131}I) therapy of benign thyroid diseases addresses the difficulties clinicians face with treatment dosing and side effects. The authors discuss the complexity of dosing due to factors such as imprecise measurement of the ^{131}I biokinetics and internal dosimetric factors including thyroid follicle size. The methods of stimulating thyroid ^{131}I uptake are also addressed. The authors conclude that no single factor reliably predicts the outcome from ^{131}I therapy.

Comment: The senior author of this review is one of the major proponents in the world for the use of radioiodine therapy for benign thyroid disease and in more recent times has published widely on the use of such therapy for non-toxic multinodular goitre after pre-stimulation with recombinant TSH (Thyrogen). This review is comprehensive and helpful to clinicians but provides little in the way of new insights to assist the clinician in the calculation and application of specific doses of ^{131}I. Most clinicians find dosimetry unhelpful and rely on empiric methods. This review emphasises that the likelihood of permanent hypothyroidism is inevitable for Graves' disease patients treated with ^{131}I and that ^{131}I therapy may exacerbate thyroid eye disease. However, the authors state that despite numerous studies no single factor reliably predicts the outcome from therapy. Without good clinical trial data most clinicians rely upon their own experience and their own institutional protocols for treating benign thyroid disease with radioactive iodine. There is no new information in this review that is likely to change an individual clinician's practice.

Reference: Endocr Rev 2012;33(6):920-80
http://edrv.endojournals.org/content/33/6/920.abstract