Endocrinology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

IGF-1 = insulin-like growth factor 1
NF-PNET = non-functioning pancreatic neuroendocrine tumours
QOL = quality of life

Welcome to the fourteenth edition of Endocrinology Research Review.

Highlights of this Review include yet another excellent clinical research report from Dr Peter Laurberg's group in Denmark where they have examined relationships between antithyroid drug exposure and birth defects in over 800,000 live-born children; an investigation into appropriate thyroxine doses for women diagnosed with new onset hypothyroidism during pregnancy and; important information on the short to medium term efficacy and safety of denosumab therapy for osteoporosis. We hope you find the selection for this month's edition useful in your practice. We look forward to receiving your comments or feedback.

Kind Regards,

Professor Cres Eastman
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Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency

Authors: Ameri P et al

Summary: This two-part study examined the effects of oral vitamin D supplementation on circulating IGF-1 levels, and the clinical relevance of this in subjects with growth hormone (GH) deficiency. Adults, mean age 61.9 years, who received oral vitamin D3 supplementation (5,000 or 7,000 IU/week) for 12 weeks had significantly improved 25-hydroxyvitamin D levels (+12.7 and +13.1 ng/ml respectively, both $p < 0.001$ vs. baseline). IGF-1 levels also increased in the 7,000 IU group. In a group of 69 subjects with GH deficiency, there was a significant positive correlation between 25-hydroxyvitamin D levels $\geq$ 15 ng/ml and circulating IGF-1 $\geq 50^{th}$ percentile, OR 4.4 (95% CI 1.0-18.8, $p < 0.05$). In conclusion, improving vitamin D status in GH deficiency may result in increased IGF-1.

Comment: Here is another report on vitamin D and its association with yet another physiologic function. The investigators have shown that vitamin D supplementation given in pharmacological doses to older healthy subjects for 12 weeks significantly increases IGF-1 levels. Equally Vitamin D supplementation improved IGF-1 levels in GH deficient patients. Whether this a physiological or pharmacological effect is not clear and further studies are needed to assess if the effect is of long term benefit.

Reference: Eur J Endocrinol 2013; 169:767-772
http://www.eje-online.org/content/169/6/767.abstract

Endocrinology Research Review™

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

Creswell Eastman is the Principal of the Sydney Thyroid Clinic, Clinical Professor of Medicine at the University of Sydney and a practising Consultant in Endocrinology and Public Health Medicine.

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).

Stimulated Thyroglobulin at Recombinant Human TSH-Aided Ablation Predicts Disease-Free Status One Year Later

Authors: Melo M et al

Summary: This prospective, observational study recruited 293 consecutive patients with differentiated thyroid carcinoma and no distant metastases who received total or near-total thyroidectomy followed by ablation under rhTSH or endogenous TSH stimulation. It aimed to determine the value of serum thyroglobulin (Tg) levels at the time of ablation in predicting disease-free status 1 year post therapy. Tg at ablation was an independent negative predictor of detectable disease in both the rhTSH group (90% negative predictive value) and the control group (95% negative predictive value).

Comment: This study addresses an important clinical question in managing patients with low-risk, well-differentiated thyroid cancer. The 293 patients in the study treated surgically by total thyroidectomy were then given an ablative dose of radioactive iodine, either after stimulation with recombinant TSH or endogenous TSH stimulation by withholding thyroid hormone replacement therapy. The investigators measured serum Tg to the TSH stimulation and not surprisingly found that a lower stimulated Tg level before radioiodine ablation was a good predictor of a favourable prognosis. It is this reviewer's experience that the stimulated Tg level should be measured before ablation and is a measure of the completeness of the surgical removal of functioning thyroid tissue and may vary from one surgeon to another.

Reference: J Clin Endocrinol Metab 2013; 98(11):4364-4372
http://tinyurl.com/lreylhf

Birth Defects After Early Pregnancy Use of Antithyroid Drugs

Authors: Andersen SL et al

Summary: This Danish study examined associations between birth defects and antithyroid drug (ATD) treatment during early pregnancy utilising a nationwide registry of 817,093 live births. Prevalence of birth defects by exposure was: 8.0% propylthiouracil (PTU, n = 564), 9.1% methimazole/carbimazole (MMI/CMZ, n = 1,097); 10.1% MMI/CMZ and PTU, shifted in early pregnancy (n = 159); 5.4% use of ATDs but not during pregnancy (n = 3,543); 5.7%; no ATD use (n = 811,730). Types of defects differed between ATDs.

Comment: Hyperthyroidism due to Graves's disease is said to complicate 0.1% to 0.4% of pregnancies and if untreated poses significant risks to maternal and foetal welfare. Preferred antithyroid drugs used during pregnancy include MMI (not available in Australia), CMZ and PTU. These are all effective therapies but each of them crosses the placenta. This article is yet another excellent clinical research report from Dr Peter Laurberg's group from Aalborg in Denmark where they have examined birth defect outcome data in over 800,000 live-born children. 0.22% of children were born to mothers treated with MMI/CMZ and 0.07% born to mothers treated with PTU. Most patients were treated with MMI and only a small number with PTU, reflecting preference for treatment with MMI/CMZ. 1.6% of these babies developed malformations, attributable to antithyroid drugs, consistent with a dominant, but not exclusive, embryopathy involving the gastrointestinal tract, and also aplasia cutis. The pattern for birth defects in children whose mothers were treated with PTU was different. Overall this study corroborates previous studies linking maternal treatment with MMI/CMZ and birth defects, but also suggests an increased prevalence of birth defects in children exposed to PTU. The authors state that while it is imperative to treat overt hyperthyroidism in pregnant women, treatment with PTU before pregnancy and during the first trimester is the preferred option as recommended by current international guidelines.

Reference: J Clin Endocrinol Metab 2013; 98(11):4373-4381
http://jcem.endojournals.org/content/98/11/4373.abstract

The Effect of Three or Six Years of Denosumab Exposure in Women With Postmenopausal Osteoporosis

Authors: Bone HG et al

Summary: The authors reported 6-year results from the FREEDOM randomised, controlled, open-label extension study of the safety and efficacy of denosumab in women with post-menopausal osteoporosis. 4,550 subjects received either denosumab throughout (denosumab group), or placebo for the initial 3 years, followed by denosumab to 6 years (crossover group). The denosumab group experienced cumulative gains from baseline in bone mineral density (BMD) of 15.2% (lumbar spine) and 7.5% (total hip). The crossover group had BMD gains of 9.4% (lumbar spine) and 4.8% (total hip) and fracture rates comparable to those in the denosumab group. Jaw osteonecrosis was observed in 6 subjects, and atypical femoral fracture in 1.

Comment: This report, authored appropriately by Dr Bone and colleagues, provides us with important information on the short to medium term efficacy and safety of denosumab therapy for osteoporosis. Cumulative 6 year gains in bone density and reduced fracture incidence data are reassuring in confirming the efficacy of this treatment. However, it should be noted that serious side effects such as osteonecrosis of the jaw and atypical femur fractures occurred in a small number of patients as has been previously reported with bisphosphonate therapy and clinicians should be aware of these potential, but rare, adverse effects.

Reference: J Clin Endocrinol Metab 2013; 8(11):4483-4492
http://jcem.endojournals.org/content/98/11/4483.abstract

Cognitive Development in Congenital Hypothyroidism: Is Overtreatment a Greater Threat Than Undertreatment?

Authors: Bongers-Schokking JJ et al

Summary/Comment: Treatment and follow-up of children with congenital hypothyroidism (CHT) has drastically changed over the last 35 years, but there is still no consensus on optimal thyroid hormone replacement therapy. The older reference ranges for T4 (130–156 nmol/L) and TSH (< 10 mU/L) are quite different from the more recently proposed guidelines; free T4 upper normal range of 18–30 pmol/L, TSH 0.5–4.5 mU/L, or normal adult range. However, a positive effect of these changes on the eventual cognitive outcome has not been proven. The authors of this study set out to find out if early overtreatment compared with undertreatment influenced cognitive development by age 11 in children treated for congenital hypothyroidism. There is a large body of literature showing under-treatment has a negative effect on cognitive development in these children. In this prospective, longitudinal study of cognitive development the authors have found that with early-treated CHT, overtreatment during the first 2 years, characterized by free T4 concentrations above the reference range, has an important adverse effect on cognitive outcome at 11 years. They hypothesize that severe postnatal over-treatment initially advances CNS maturation but later causes a premature arrest of this development, resulting in irreversible damage, as has been demonstrated in animal experiments. On the other hand, they emphasize that postnatal undertreatment leads to delayed CNS maturation, delayed fiber formation and myelination defects also causing irreversible brain damage. They conclude that "our results suggest that over-treatment is a greater risk than under-treatment and should be avoided as much as possible. Early treatment with frequent monitoring is mandatory. To initiate treatment, we recommend keeping free T4 concentrations within the reference range, in the case of our cohort 17–29 pmol/L. This can be achieved with low levothyroxine dosages, decreasing the risk for over-treatment. Using the upper half of the TSH reference range, i.e. 3.3–5.7 mU/L for our CHT cohort rather than the normal TSH reference range also could decrease the risk of overtreatment".

Reference: J Clin Endocrinol Metab 2013; 98(11):4499-4506
http://jcem.endojournals.org/content/98/11/4499.abstract

Iodine concentrations in milk and in urine during breastfeeding are differently affected by maternal fluid intake

Authors: Andersen SL et al

Summary/Comment: The population of Denmark has long been mildly iodine deficient but mandatory iodisation of salt has recently been introduced in an attempt to correct this problem. As the authors point out, breast fed infants are entirely dependent on an adequate quantity of iodine in breast milk to ensure normal thyroid function and optimal brain development. In this study the investigators have measured maternal urinary iodine excretion as a surrogate marker for maternal iodine intake. They have also tested to see if it correlated with breast milk iodine concentration and if maternal fluid intake influenced urinary iodine excretion. The investigators have shown that the maternal urine iodine excretion in spot urine samples is not a good predictor of breast milk iodine concentration, but that 24 hour urine samples correlate better. The most important finding is that these Danish breastfeeding mothers are mildly iodine deficient and iodine supplementation is recommended to correct the iodine deficiency. While there is very little data available on iodine nutrition for breastfeeding women in Australia, because iodine deficiency is common in pregnant women, the NHMRC recommends breastfeeding mothers should be taking an iodine supplement of 150 µg/day.

Reference: E-pub ahead of print. doi:10.1089/thy.2013.0541
http://online.liebertpub.com/doi/abs/10.1089/thy.2013.0541

Is empirical radioactive iodine therapy still a valid approach in patients with thyroid cancer and elevated thyroglobulin?

Authors: Rosario PW et al

Summary: 24 patients with papillary thyroid cancer, no evidence of metastatic disease but elevated Tg after initial therapy, underwent empirical radioiodine therapy and post-therapy whole-body scanning. 23 had no ectopic uptake, and 15 had mild uptake (< 5%) in the thyroid bed. 1 patient had pulmonary metastases detected by whole-body scanning, 2 others developed metastases during mean follow-up of 22 months. The authors concluded empirical radioiodine therapy should be restricted to patients with documented progression of serum Tg.

Comment: This small study attempts to address a difficult clinical question of "should patients who have been treated for thyroid cancer who have a mildly elevated serum thyroglobulin level but no evidence of metastatic disease on ultrasound, CT and FDG-PET scanning be given an empirical, large, therapeutic dose of radioactive iodine". While one should be cautious in interpreting the data from a small study of only 24 patients, the fact that only one patient initially, and two patients subsequently during longer follow-up, proved to have metastases as a cause for the detectable Tg. The reason for the mildly elevated Tg level in the majority of patients was residual thyroid tissue in the thyroid bed. Therefore, in this study the answer to the question is that the empirical use of large therapeutic dose of radioiodine for patients with mildly elevated serum thyroglobulin without evidence of metastatic disease is generally not warranted.

Reference: E-pub ahead of print. doi:10.1089/thy.2013.0427
http://online.liebertpub.com/doi/abs/10.1089/thy.2013.0427

Moderate weight loss is sufficient to affect thyroid hormone homeostasis and inhibit its peripheral conversion

Authors: Agnihothri RV et al

Summary: This longitudinal study assigned 77 subjects (47 overweight/obese) to 12-months of individualised dietary restriction aimed at achieving 5-10% weight loss in order to examine the effects of moderate weight loss on thyroid hormone levels. Baseline thyroid hormone levels correlated with fat mass. Following weight loss, serum T3 decreased significantly (112.7-101.8 ng/dL, $p < 0.001$) in correlation with weight loss ($R = 0.294$, $p < 0.001$). No significant changes in serum TSH or free T4 were observed. In those who lost ≥ 5% body weight the T3:T4 ratio decreased significantly ($p = 0.02$).

Comment: This study looked at changes in thyroid hormone levels in obese and overweight volunteers who participated in a 12 month longitudinal study of moderate dietary restriction aimed at achieving 5 to 10% weight loss. The small decrease of approximately 10% in serum T3 without any significant change in serum TSH or free T4 levels is in keeping with many previous human studies showing decreased peripheral conversion of T4 to T3 in response to caloric restriction with a compensatory increase in serum reverse T3 production. The physiological relevance of these changes remains unknown as is the case with similar observations, but of much greater magnitude, in patients with non-thyroidal illness.

Reference: E-pub ahead of print. doi:10.1089/thy.2013.0055
http://online.liebertpub.com/doi/abs/10.1089/thy.2013.0055

Adequate Levothyroxine Doses for the Treatment of Hypothyroidism Newly Discovered During Pregnancy

Authors: Abalovich M et al

Summary: This retrospective study examined 77 subjects with hypothyroidism newly discovered during pregnancy to determine appropriate LT4 doses for normalisation of TSH levels to ≤ 2 mIU/L in trimester 1 or ≤ 3 mIU/L in trimester 3. Women with sub-clinical hypothyroidism (SCH) required a significantly lower LT4 dose (1.31 ± 0.36 µg/kg/day) compared to those with overt hypothyroidism (OH, 2.33 ± 0.59) $p < 0.0001$. Women with SCH and baseline TSH > 2.5 (1st trimester) or > 3 (3rd trimester) required a significantly lower LT4 dose (1.20 ± 0.39 µg/kg/day) compared to those with SCH and TSH > 4.21 mIU (1.42 ± 0.31) $p < 0.014$. Mean time to euthyroidism with appropriate LT4 dosing was similar in women with SCH (6.06 ± 3.3weeks) and OH (5.3 ± 1.8).

Comment: Recent guidelines for management of SCH and OH during pregnancy promulgated by the American Endocrine Society (De Groot et al. J Clin Endo Metab 2012; 97:2543-2565) and also the American Thyroid Association, recommend commencement of thyroxine replacement therapy to ensure serum TSH is kept below 2.5 mIU/l in the first trimester and 3.0 mIU/ in the middle and last trimesters. Dr Abalovich (who is a member of the expert guidelines committee) and colleagues have performed a retrospective analysis of pregnant patients treated with thyroxine (64 with SCH and 13 with OH). As one would expect, OH women required a significantly higher dose of thyroxine 2.33 µg/kg body weight/day compared with 1.31 µg/kg body weight/day for SCH women and those with TSH levels between 2.5 and 4.2 mIU/l required less than those with serum TSH levels between 4.2 and 10.0 mIU/l. The results of this study confirm what most experienced clinicians already know from managing thyroid hormone replacement for hypothyroidism in pregnant women. However their 7 recommended thyroxine dosages based on serum TSH level and body weight are of practical assistance in managing these women.

Reference: Thyroid 2013; 23(11):1479-1483
http://online.liebertpub.com/doi/abs/10.1089/thy.2013.0024

Cortisol diurnal rhythm and quality of life after successful medical treatment of Cushing's disease

Authors: van der Pas R et al

Summary: 17 patients with Cushing's disease underwent stepwise medical therapy with pasireotide, cabergoline and ketoconazole for 80 days, followed by continued medical treatment or surgery. 6/12 patients with baseline disturbance had restoration of cortisol diurnal rhythm (CDR), however quality of life (QOL) remained significantly impaired in comparison to literature-derived controls and did not change significantly over the course of the study.

Comment: This study from the Netherlands assessed the benefits of medical therapy aimed at normalising cortisol secretion on QOL in 17 patients suffering from Cushing's disease. They were able to normalise urine free cortisol levels in 15 of 17 patients but this was not accompanied by improved QOL in the short term. The shortcomings of this study were the small number of patients and the relatively short duration of the study - as most clinicians caring for patients with Cushing's disease will confirm, even after successful surgery it may take many months or even years for patients to recover QOL. Nonetheless the study does confirm that appropriate medical therapy can be effective in managing Cushing's disease as a prelude to surgery or when surgery cannot be undertaken.

Reference: Pituitary 2013; 16(4):536-544
http://link.springer.com/article/10.1007/s11102-012-0452-2

Large, Single-Dose, Oral Vitamin D Supplementation in Adult Populations: A Systematic Review

Authors: Kearns MD et al

Summary: This comprehensive review and meta-analysis evaluated 30 studies of large, single dose, oral vitamin D supplementation in adults. Serum 25-hydroxyvitamin D was consistently increased by large single doses of vitamin D, with optimal improvements from doses of vitamin D3 of ≥ 300,000 IU. Bone health and extra-skeletal outcomes were also improved. The authors recommend vitamin D3 single dosages of ≥300,000 IU to improve vitamin D status and suppress parathyroid concentrations for ≤ 3 months.

Comment: Vitamin D deficiency is widespread in most populations but potential adverse biological events remain to be documented despite a huge literature on the subject. Most clinicians will recognise that long-term compliance with daily vitamin D supplementation is poor and most patients abandon taking the supplement with time. Compounding chemists in Australia offer parenteral vitamin D in doses of 500,000 to 600,000 IU per injection and this form of replacement is becoming more popular. In this review the authors report that vitamin D3 in doses of 300,000 IU is effective in reversing vitamin D deficiency and secondary hyperparathyroidism for up to 3 months. They caution use of individual parenteral D3 supplements in excess of 500,000 IU per injection.

Reference: E-pub ahead of print. DOI:10.4158/EP13265.RA
http://tinyurl.com/mrbfmqp

Observational Study of Natural History of Small Sporadic Nonfunctioning Pancreatic Neuroendocrine Tumors

Authors: Gaujoux S et al

Summary/Comment: This article reporting a useful evolving paradigm for managing small, nonfunctioning, incidentally discovered, pancreatic neuroendocrine tumours (PNETS) was accompanied by an editorial that emphasizes a wide spectrum of biological behavior in these tumours from slow growing to highly aggressive malignancies that rapidly metastasize. Functioning PNETs are characterized by the hormone(s) they secrete and are treated primarily by surgery wherever possible. By contrast, non-functioning PNETs are often silent and asymptomatic and as these authors state "one of the main challenges in PNET management, especially with a small nonfunctioning tumor, is accurately assessing the tumor's natural history, i.e. to predict the risk of malignancy and outcome". Despite many different studies, specific prognostic factors have remained elusive. What we can conclude from this study is that asymptomatic sporadic non-functioning PNETs, especially those smaller than 2 cm in size, have excellent long-term survival, despite a 10% risk of nodal metastasis reported in most surgical series, and that conservative management is preferable to surgical intervention. The authors of this report emphasize that if undertaking a watchful-waiting strategy one must be certain of the diagnosis of non-functioning PNET, proven by either FNAC or positive somatostatin receptor imaging. While every case must be managed on its own merit this report provides reassurance that for proven small (< 2 cm tumours) non-functioning PNETs, a conservative non-surgical strategy is safe and effective in most patients.

Reference: J Clin Endocrinol Metab 2013; 98(12):4784-9
http://jcem.endojournals.org/content/98/12/4784.long