Endocrinology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AIH = autoimmune hypothyroidism
AUC = area under the curve
HT = Hashimoto's thyroiditis
PCT = papillary thyroid carcinoma
RR = relative risk
SIR = standardised incidence ratio
SPM = secondary primary malignancy
ST = bilateral subtotal thyroidectomy
TPP = thyrotoxic periodic paralysis
TRAb = TSH-receptor antibody
TT = total thyroidectomy

Welcome to the thirteenth edition of Endocrinology Research Review.

Highlights of this Review include Taiwanese data from a large population-based study which demonstrate a different pattern of secondary primary malignancies in subjects with primary thyroid cancer in comparison to European populations. We also include a meta-analysis comparing complication rates from total and subtotal thyroidectomy in Graves' hyperthyroidism, and a 10-year prospective observational study from Taipei that provides useful data on thyrotoxic periodic paralysis in an Asian population.

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 Duncan Topliss

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Plasma-free vs deconjugated metanephrines for diagnosis of phaeochromocytoma

Authors: Pamporaki C et al

Summary: This study compared plasma levels of free vs. deconjugated normetanephrine and metanephrine as biomarkers for the diagnosis of phaeochromocytoma. Subjects were 198 patients with phaeochromocytoma, 528 patients initially suspected of the disorder but with normal follow-up for ≥ 2 years, and 262 normotensive and hypertensive controls. Plasma concentrations of metanephrines were measured using liquid chromatography with electrochemical detection. In patients with phaeochromocytoma, the plasma concentrations of free normetanephrine and deconjugated normetanephrine respectively were 17 and 10 x greater than in controls. Free vs. deconjugated normetanephrine levels were 72% higher, $p < 0.001$. Relative increases in free and deconjugated plasma metanephrines were similar. Free normetanephrine was superior for diagnostic performance vs. deconjugated, with sensitivity of 97 vs. 92% ($p = 0.002$); specificity of 93 vs. 89% ($p = 0.012$); and AUC of the receiver operating curve 0.986 vs. 0.965 ($p < 0.001$). In conclusion, for the diagnosis of phaeochromocytoma, the use of free plasma metanephrines is superior to that of deconjugated plasma metanephrines.

Comment: Measurements of plasma or urinary metanephrines (metanephrine and normetanephrine), the O-methylated extraneuronal metabolites of catecholamines, provide superior tests for diagnosis of phaeochromocytoma than other tests and are currently recommended for initial screening. This study establishes that measurements of plasma concentrations of free normetanephrine and metanephrine are superior to the deconjugated metabolites for the diagnosis of phaeochromocytoma. Metanephrines in plasma or urine can be measured as free metabolites or after a deconjugation step involving either acid hydrolysis or enzyme-catalysed conversion of the sulphate conjugates to the free metabolites. The free fractions of metanephrines are formed in considerable amounts in adrenal medullary chromaffin cells, whereas the sulphate-conjugated metabolites are formed from the free amines by the actions of sulphate transferase 1A3, an enzyme located primarily in the gastrointestinal tract. The free metanephrines are cleared rapidly from the circulation so that their concentrations are low. In contrast, deconjugated metanephrines are cleared slowly. Therefore, plasma levels of the deconjugated metabolites are 15- to 30-fold higher than the free metabolites and much easier to measure, but given the additional technical requirements of a deconjugation step and the lack of commercially available sulphate-conjugated metabolites for both calibration and quality control purposes, there is no overall benefit in measurements of deconjugated over free metanephrines.

Reference: Clinical Endocrinology 2013; 79:476–483
http://tinyurl.com/m88ctra

BRAF mutation positive papillary thyroid carcinoma is less advanced when Hashimoto's thyroiditis lymphocytic infiltration is present

Authors: Marotta V et al

Summary: Lymphocytic infiltration is a feature of Hashimoto's thyroiditis (HT), and is also commonly seen in patients with papillary thyroid carcinoma (PTC). The authors of this study investigated the role of BRAFV600E mutation and lymphocytic infiltration on prognosis in 146 patients with a histologic diagnosis of PTC. Cytology samples were analysed by direct-and pyro-sequencing in order to detect BRAFV600E mutation. The presence of lymphocytic infiltration was confirmed using microscopic assessment of histological samples. Laboratory results and clinical findings were correlated. Factors associated with HT lymphocytic infiltration in patients with PTC were: female gender; smaller tumours; less likelihood of extra-capsular extension; earlier TMN stage; and BRAFV600E mutation positivity. Subjects with PTC and BRAFV600E mutation were more likely to be female; have less likelihood of extra-capsular extension; and earlier TMN stage. The authors conclusions were that HT lymphocytic infiltration is protective for PTC progression, regardless of BRAFV600E status.

Comment: In Endocrinology Research Review earlier this year we featured a report of an increased prevalence of histological HT in PTC, OR 2.8, and improved recurrence-free follow-up, HR 0.6, (Lee et al. Eur J Endocrinol 2013; 168:343-349). The association may be due to selection bias by histological diagnosis, as it is not seen in population-based fine-needle biopsy studies (Jankovic et al. J Clin Endocrinol Metab 2013; 98:474-482). In the study in this edition, even in BRAF V600E mutation positive tumours, the association was with less-advanced cancer. This is similar to Dvorkin et al. (J Clin Endocrinol Metab 2013; 98:2409-14) who, in a retrospective study of PTC found a 14.2% prevalence of HT with PTC and an association with less aggressive cancer and improved long term outcome. Lun et al. (Otolaryngol Head Neck Surg 2013; 148:396-402) have also found that, while there was an association of HT with PTC, this was with less advanced cancer. So while the association itself remains uncertain, the concomitant presence of HT appears to have a favourable prognosis.

Reference: Clinical Endocrinology 2013; 79:739–746
http://tinyurl.com/k3paeyb

Total thyroidectomy vs bilateral subtotal thyroidectomy in patients with Graves' disease

Authors: Zhenying G et al

Summary: This meta-analysis used prospective randomised, controlled clinical trials of total thyroidectomy (TT) vs. bilateral subtotal thyroidectomy (ST) in subjects with Graves' disease to determine relative complication rates from the two procedures. Outcomes evaluated were relative risk (RR) for: recurrent hyperthyroidism; progression of ophthalmopathy; development of temporary or permanent hypoparathyroidism; temporary or permanent recurrent laryngeal nerve palsy; and post-operative bleeding. 4 trials comprising 674 patients were included. TT was superior to ST for risk of recurrent hyperthyroidism (RR 0.14, 95% CI 0.05-0.41, $p < 0.01$), but was associated with higher rates of temporary hypoparathyroidism (RR 2.66, 95% CI 1.89-3.73, $p < 0.01$). No between-group differences in risk of permanent hypoparathyroidism (RR 2.30, 95% CI 0.78-6.76, $p = 0.13$); temporary (RR 1.08, 95% CI 0.47-2.48, $p = 0.85$) or permanent recurrent laryngeal nerve palsy (RR 1.54, 95% CI 0.41-5.73, $p = 0.52$); post-operative bleeding (RR 0.32, 95% CI 0.05-1.96, $p = 0.22$); or ophthalmopathy progression (RR 0.92, 95% CI 0.5-1.71, $p = 0.8$) were observed for TT and ST respectively. The authors conclude that total thyroidectomy should be preferred over bilateral subtotal thyroidectomy for patients with Graves' disease.

Comment: Total thyroidectomy rather than subtotal thyroidectomy has become the favored procedure in many centres in Australia and elsewhere to treat Graves' hyperthyroidism. This is exemplified by the report of Al-Adhami et al. in Aberdeen, (J Otolaryngol Head & Neck Surg 2013; 42:37), of a shift in practice from before 1991 of almost all subtotal thyroidectomies to almost all total thyroidectomies since 2008. This review from China of four prospective series shows that total thyroidectomy in expert hands is not associated with an increase in permanent hypoparathyroidism, or recurrent laryngeal nerve dysfunction, and of course, has a negligible recurrence rate. Furthermore the idea that subtotal thyroidectomy avoids long-term need for replacement thyroxine therapy is incorrect, as shown by the data from Al-Adhami et al. where the progression to hypothyroidism by 5 years post-operation was over 50%, presumably due to the progressive autoimmune damage in the residual thyroid. Total thyroidectomy is now the surgical treatment of choice for Graves' hyperthyroidism.

Reference: Clinical Endocrinology 2013; 79:739–746
http://tinyurl.com/mr9z5md

Serum selenium is low in newly diagnosed Graves' disease

Authors: Bülow Pedersen I et al

Summary: The aim of this Danish population-based study was to compare serum selenium values in patients with recently diagnosed autoimmune thyroid disease and normal controls. Subjects were 97 individuals with Graves' disease and 96 with autoimmune overt hypothyroidism (AIH), plus 92 euthyroid individuals with high serum thyroid peroxidase antibodies and 830 controls. The primary outcome measure was difference in serum selenium concentrations. Participants with Graves' disease had significantly lower serum selenium than controls (89.9 vs. 98.8 µg/l, $p < 0.01$). Differences remained significant after controlling for age, sex, mineral supplementation, smoking, region and time of sampling. In contrast, serum selenium was comparable in subjects with AIH vs. controls (98.4 vs. 98.8 µg/l, $p = 0.86$) in the linear model, but significantly lower with multivariate analysis ($p = 0.04$). Euthyroid individuals with elevated serum thyroid peroxidase antibodies had comparable serum selenium levels to controls ($p = 0.27$). The authors conclude that recently diagnosed autoimmune thyroid disease, in particular Graves' disease, is associated with low serum selenium.

Comment: This case-control study reports a modest lowering of serum selenium at diagnosis of Graves' hyperthyroidism, and in overt AIH when adjusted by multivariate analysis. The effect of restoration of euthyroidism was not examined. The effect of selenium supplementation in autoimmune thyroid disease remains uncertain. There are conflicting data (Schomburg. Nat Rev Endocrinol 2011; 8:160-171 and Anastasilakis et al. Int J Clin Prac 2012; 66:378-83) but selenium supplementation has been reported to improve mild/moderate Graves' ophthalmopathy (Marcocci et al. New Engl J Med 2011; 364:1920-1931.) Smoking lowers serum selenium values (Arnaud et al. Br J Nutr 2006; 2:313) and this study also found lower serum selenium with smokers, but the interaction between smoking, selenium, and Graves' hyperthyroidism is unclear. The effect of selenium supplementation on Graves' hyperthyroidism itself has not been examined but a trial (GRASS) is planned (Watt et al. Trials 2013; 14:119).

Reference: Clinical Endocrinology 2013; 79:584–590
http://tinyurl.com/kpxdtfe

A ten-year analysis of thyrotoxic periodic paralysis in 135 patients

Authors: Chin-Chun C et al

Summary: This 10-year prospective observational study from Taipei enrolled 135 subjects with thyrotoxic periodic paralysis (TPP) in order to study the symptomatology of thyrotoxicosis and evaluate the factors precipitating attacks of TPP. Following an attack the severity of thyrotoxicosis was evaluated using the Wayne's index. Oral glucose loading tests were carried out after recovery where possible. In this consecutive cohort males ($n = 130$) heavily outnumbered females ($n = 5$). TPP attacks were most common in the summer and autumn, and 70% occurred in the morning. Factors precipitating attacks of TPP were identified in only 34% of subjects. These included: high carbohydrate load; upper respiratory tract infection; exercise; high salt diet; steroids and bronchodilators. Only 1 third of subjects had a personal or family history of hyperthyroidism. Following glucose loading, insulin-induced acute hypokalaemia ($K+ 4.47 \pm 0.6$ mmol/l) with re-paralysis in occurred in 18% of subjects. The authors' conclusions were that in most cases of TPP the signs and symptoms of thyrotoxicosis are subtle and clear precipitating factors are lacking. They suggest that as well as hyperinsulinaemia, other insulin-independent mechanisms may be involved in the pathogenesis of TPP.

Comment: This prospective observational study shows that TPP is almost entirely seen in Chinese males without a personal or family history of hyperthyroidism, mostly manifesting on summer and autumn mornings, with only one third having clear precipitating factors. Most importantly, less than 20% had overt hyperthyroidism, so TPP must be considered in any acute weakness in a Chinese male.

Reference: Eur J Endocrinol 2013; 169:529-536
http://tinyurl.com/myljvh5

Determinants of serum T4 and T3 at time of diagnosis in nosological types of thyrotoxicosis

Authors: Carlé A et al

Summary: This Danish population-based study examined thyroid hormone levels at time of diagnosis in subjects with thyrotoxicosis and identified associated risk factors. All patients diagnosed with primary overt thyrotoxicosis between 1997 and 2000 ($n = 1,082$) were prospectively identified and classified 10 nosological types. Multivariate analysis was used to identify correlations between serum T3 and T4 levels and factors including: age; sex; iodine levels; smoking status; alcohol intake; iodine supplementation; co-morbidities; and TSH-receptor antibody (TRAb) status. Subjects with Graves' disease had higher serum T3 and higher T3:T4 ratios compared to those with non-Graves' thyrotoxicosis, and a strong negative correlation between age and thyroid hormone level. Also in Graves' patients, severe iodine deficiency was associated with lower thyroid hormone levels. Biochemically mild thyrotoxicosis was observed in both TRAb-negative Graves' subjects, and in older patients with toxic nodular goitre. Sex; smoking status; iodine supplementation; alcohol intake; and co-morbidities were not associated with thyroid hormone levels in thyrotoxicosis. The authors conclude that young age, TRAb-positivity and higher iodine intake are associated with biochemical disruption at the time of diagnosis in patients with Graves' disease.

Comment: No surprises here but worthwhile confirmation in a modern, substantial, population-based cohort. The observations that Graves' hyperthyroidism and younger age are associated with higher thyroid hormone levels at diagnosis, and TRAb negativity and iodine deficiency with lower levels, accords with common experience.

Reference: Eur J Endocrinol 2013; 169:537-545
http://tinyurl.com/knoosp4

Second primary malignancies following thyroid cancer

Authors: Lu CH et al

Summary: The aim of this large population-based study from Taiwan was to quantify the incidence and risk of secondary primary malignancies (SPMs) following primary thyroid cancer in a cohort of Asian subjects. Standardised incidence ratios (SIRs) and cumulative incidence rates for SPMs were calculated using data in 19,068 subjects (14,863 female) with primary thyroid cancer obtained from the nationwide Taiwanese cancer registry. During 134,678 person/years of follow-up, 3.38% of subjects developed ≥ 1 SPM. In comparison to the general population, study participants had an increased risk of developing SPMs; SIR 1.33 (95% CI 1.23-1.44). Cancers with an elevated risk profile in this population were salivary gland, nasopharynx, lung, thymus, leukaemia, lymphoma, breast, bladder and brain. The risk of developing SPMs was highest in patients ≤ 50 years and for the 5 years post- thyroid cancer diagnosis. Median overall survival for participants who did and did not develop SPMs was 4.73 and 23.28 years respectively.

Comment: These data from Taiwan show a different pattern of SPMs in an Asian population in comparison with studies in Europeans. The risk was higher earlier after diagnosis of the thyroid cancer suggesting that this was not a long-term effect of radioiodine treatment, but this was not specifically examined. Subramanian et al. (Thyroid 2007; 17:1277) in a meta-analysis of SPM after thyroid cancer found a relative risk of 1.25, and this increased risk was related to radioiodine therapy by Sawka et al. (Thyroid 2009; 19:451). An increase of SPM in USA SEER data was shown over 40 years correlating with an increase in use of radioiodine ablation (Iyer et al. Cancer 2011; 117:4439).

Reference: Eur J Endocrinol 2013; 169:577-585
http://tinyurl.com/mqo32zl

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

Professor Duncan Topliss is Director of the Department of Endocrinology and Diabetes at the Alfred Hospital Melbourne, Professor of Medicine in the Department of Medicine Monash University and a past-President and Life Member of the Endocrine Society of Australia. He has served on the editorial board of Journal of Thyroid Research and Clinical Endocrinology and is a frequent reviewer for Clinical Endocrinology, Thyroid, and other endocrine journals.

Professor Topliss heads the Diabetes Clinic at the Alfred Hospital, has a long-term interest in diabetes prevention and management and has been an investigator on several major international diabetes trials. He has a wide interest in clinical endocrinology including osteoporosis, pituitary and adrenal disease and endocrine hypertension and has over 25 years of experience in the management of thyroid disease and thyroid cancer. His other interests are drug regulation and safety: he is a member of the Australian Advisory Committee on the Safety of Medicine and the Australian Advisory Committee on Pharmaceutical Medicines of the Therapeutic Goods Administration.

Surgery for 'asymptomatic' mild primary hyperparathyroidism improves some clinical symptoms postoperatively

Authors: Blanchard C et al

Summary: Assessing post-parathyroidectomy symptom improvement in subjects with mild primary hyperparathyroidism was the aim of this prospective, non-randomised study. 116 subjects with mild (asymptomatic) hyperparathyroidism had their non-specific symptomatology evaluated with a 22-item questionnaire before surgery, and again postoperatively at 3, 6 and 12 months. Surgery resolved hyperparathyroidism in 98% of subjects. At 12 months post-surgery 12 of the 22 questionnaire items were improved. The largest benefits were observed in patients < 70 years of age and those with preoperative serum calcium levels ≥ 2.6 mmol/l. The authors concluded that post-operative symptom improvement in patients with mild primary hyperparathyroidism is maintained for at least 12 months, and that improvement is greatest in those with higher preoperative serum calcium levels, and those of a younger age.

Comment: This prospective non-randomized uncontrolled study reports resolution of 12/22 non-specific symptoms by questionnaire and is held to support parathyroidectomy for apparently asymptomatic hyperparathyroidism, especially in patient less than 70 years of age and with serum calcium more than 2.6 mmol/L, but the possibility that patients' answers were influenced by the desire to please the doctor, and to affirm their choice to have surgery cannot be ruled out. An authoritative review of asymptomatic primary hyperparathyroidism has recently been published (Silverberg et al. J Clin Densitom 2013; 16:14-21). Most do not evolve to classical hyperparathyroidism. Cortical bone mineral density is reduced at the distal radius, and to a lesser extent at the hip but there are no specific data on fracture risk. Preclinical predictors of adverse cardiovascular outcome have been found but no definitive endpoints have yet been reported. Subjective muscle weakness has been reported but there is little objective data (Rolighed et al. World J Surg 2013; Oct 8 epub ahead of print). The assessment of possible neurocognitive dysfunction in mild primary hyperparathyroidism is challenging (Grant and Velusamy. J Clin Endocrinol Metab 2013; Nov 7 epub ahead of print). Current data are heavily confounded; indeed neuropsychiatric symptoms were excluded as a current indication for surgery at the most recent International Conference on Asymptomatic Hyperparathyroidism.

Reference: Eur J Endocrinol 2013; 169:665-672
http://tinyurl.com/k6ht68u

Parathyroid hormone changes following denosumab treatment in postmenopausal osteoporosis

Authors: Makras P et al

Summary: The authors of this prospective study aimed to describe the effects on parathyroid hormone of denosumab when combined with different calcium/vitamin D regimes. Participants were 47 post-menopausal women who required initiation or continuation of therapy for osteoporosis. Following administration of denosumab, subjects received either daily calcium carbonate (1 g) plus colecalciferol (800 IU) for 6 months (Group A), or a double dose during month 1 and standard dosing for the remainder (Group B). Subjects in Group A had significantly higher parathyroid hormone levels at 1 and 6 months, and significantly decreased calcium levels at 1 but not 6 months in comparison to Group B. The authors conclude that following administration of denosumab a decrease in parathyroid hormone levels should be expected. They suggest further research into this effect is needed.

Comment: A dose-dependent increase in PTH persisting to month 6 post-dose, and a transient decrease in serum calcium, are well-documented in pre-clinical and clinical studies of denosumab, due to inhibition of osteoclast maturation and activity, despite standard supplementation of elemental calcium of 600 mg daily and colecalciferol 800 IU daily. In this study double dose supplementation prevented this PTH rise. It is unclear if these changes have any adverse consequences on bone quality, but it is important to be aware of raised PTH during denosumab therapy. High dose denosumab, as used to reduce skeletal events in prostate cancer, can be associated with hypocalcaemia especially if hypovitaminosis D is not corrected before therapy. Denosumab can be an effective off-label treatment of resistant humoral hypercalcaemia of malignancy.

Reference: Clinical Endocrinology 2013; 79:499–503
http://tinyurl.com/kkupjv3