Endocrinology Research Review™

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In this issue:

Abbreviations used in this issue:

DEXA = dual-energy X-ray absorptiometry; **eGFR** = estimated glomerular filtration rate; **FT3** = free triiodothyronine; **FT4** = free thyroxine; **HR** = hazard ratio; **LT4** = levothyroxine; **PNET** = pancreatic neuroendocrine tumour; **PTC** = papillary thyroid cancer; **TPOAb** = thyroid peroxidase antibody; **TSH** = thyroid-stimulating hormone; **ULN** = upper limit of normal.

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Welcome to issue 37 of Endocrinology Research Review.

This month is truly a global issue with publications from countries including China, Italy, the UK and of course Australia all featured. Highlights include Australian research in which clusterin shows promise as a biomarker for progression of diabetic kidney disease amongst patients with type 2 diabetes. We feature a useful report providing insights into diagnosis and treatment of the rare autoimmune disorder primary lymphocytic hypophysitis, and informative clinical practice guidelines for the management of women and girls with Turner syndrome. Finally, subcutaneous testosterone injection appears safe and effective, and is preferred to intramuscular injection, amongst female-to-male transgender patients.

We hope you find the selection for this month's issue useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards

Professor Cres Eastman

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Urine clusterin/apolipoprotein J is linked to tubular damage and renal outcomes in patients with type 2 diabetes mellitus

Authors: Kim SS et al.

Summary: The aim of this small prospective study was to examine associations between urine clusterin/apolipoprotein J (Apo J) and development or progression of diabetic kidney disease amongst subjects with type 2 diabetes. Participants were patients with type 2 diabetes (n = 159) and non-diabetic controls (n = 20) with eGFR ≥ 60 mL/min/1.73 m^2 who were followed up for a median of 3.0 (1.0-5.9) years. Annual rate of decline in eGFR was the primary outcome measure, with persistent albuminuria and development of chronic kidney disease ≥ stage 3 as secondary outcomes. Subjects with type 2 diabetes had significantly higher baseline urine clusterin levels compared to controls, and this was correlated with urine tubular damage markers. Urine clusterin levels were positively correlated with annual rate of decline in eGFR in an analysis adjusted for clinical confounders, and under multivariate analysis were associated with development of chronic kidney disease ≥ stage 3 and persistence/progression of albuminuria. The authors conclude that urine clusterin has potential as a predictive biomarker for progression of diabetic kidney disease amongst patients with type 2 diabetes.

Comment: Detection of microalbuminuria is currently considered to be the earliest sensitive marker of diabetic nephropathy. The search for other serum and urine biomarkers for earliest detection of renal damage, and monitoring of the decline in renal function of patients suffering diabetic nephropathy, has yielded several potential chemical markers including a glycoprotein called clusterin, also known as apolipoprotein J (Apo J), that is expressed ubiquitously in various metabolic tissues and body fluids. Clusterin is rapidly induced in the kidney and urine in response to kidney injury and has been hailed as a potential biochemical marker for monitoring deterioration in renal function in diabetic patients. The authors of this study provide new evidence of a relationship between urine clusterin and tubular damage markers and identify urine clusterin as an early indicator for tubular damage in type 2 diabetic subjects. In addition, they show that urine clusterin is linked to the stage of chronic renal disease and albuminuria as an indicator of progression in the early stages of nephropathy in type 2 diabetic patients. We need to be cautious in interpreting the data as it was a small study, conducted over a short timeframe, and requires more research on a larger scale before consideration as diagnostic biomarker. Nonetheless it may well be a new and helpful biomarker for detection and monitoring of renal damage in patients with type 2 diabetes.

Reference: Clin Endocrinol (Oxf). 2017;87(2):156-64

Abstract

Serum phosphorus levels and fracture following renal transplantation

Authors: Aleksova J et al.

Summary: These Australian authors conducted a single centre, retrospective, cross-sectional analysis of renal transplant recipients who had been referred for DEXA scanning, in order to assess fracture risk factors in this cohort. The patient population (n = 46) had a mean age of 56 years and a mean of 6.7 years post-transplantation. The proportion of subjects with any fracture was 35%; 52 patients with 79 fractures, 40 fractures following transplantation. The most common fracture site was ankle/foot (48%). Factors associated with fractures in univariate and multivariate regression analysis following adjustment for age, gender, weight, eGFR and pre-transplant fracture history included lower serum phosphorus levels (p = 0.011) and declining femoral neck *T*-score (p = 0.042). Serum phosphorus levels remained significantly associated with fracture risk independent of femoral neck *T*-score, parathyroid hormone levels, parathyroidectomy status and prednisolone use.

Comment: While bone and mineral disorders are very common in end-stage kidney disease and difficult to manage in patients on dialysis, renal transplantation usually reverses these problems. However, increased fracture risk, particularly hip fracture rates, persists after transplantation. This retrospective study from Melbourne explored the relationship between lower serum phosphorus levels and fracture risk in transplant recipients and confirmed fracture risk was increased and that there was a relationship between lower serum phosphorus levels, declining femoral neck *T*-scores and an association with fractures. It is well known that renal phosphate wasting occurs in chronic renal failure due to high levels of the two phosphaturic hormones, FGF-23 (fibroblast growth factor-23) and parathyroid hormone and that this renal phosphorus loss continues in the early post-transplantation mediated by persistently high levels of FGF-23 and parathyroid hormone. As these mediators decline with time after successful transplantation, the mechanism for hypophosphataemia remains obscure. As the authors state, there is currently insufficient evidence to guide phosphorus replacement after transplantation, and prospective studies are required to establish optimal phosphorus levels and determine the safety and therapeutic benefit of phosphorus replacement to prevent increased fracture risk.

Reference: Clin Endocrinol (Oxf). 2017;87(2):141-8
Abstract

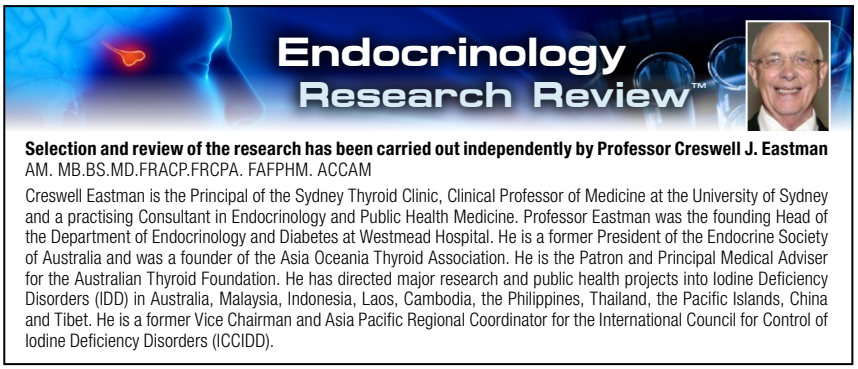
Incidence and prognostic value of serotonin secretion in pancreatic neuroendocrine tumours

Authors: Zandee WT et al.

Summary: These investigators aimed to determine the incidence of serotonin secretion amongst patients with pancreatic neuroendocrine tumours (PNETs), and the prognostic impact of this on overall survival (OS). Subjects were 255 patients with PNETs who had undergone 24-hour urinary 5-HIAA (5-hydroxyindoleacaetic acid) excretion testing. Serotonin secretion was defined as 5-HIAA excretion > 3x ULN (50 µmol/24 hours). Carcinoid syndrome was diagnosed in 0.8% (n = 2) of the study cohort, and non-symptomatic serotonin secretion in 7.8% (n = 20). The presence of serotonin was confirmed by immunohistochemical staining in 28.6% of serotonin secreting PNETs; all controls returned negative results. Under univariate analysis serotonin secretion was a negative prognostic factor for OS (HR 2.2; 95% CI 1.27. 3.81). However the only factors predicting OS under multivariate analysis were chromogranin A levels > 10x ULN (HR 1.81; 1.10, 2.98) and non-specific enolase > ULN (HR 3.51; 2.26, 5.46).

Comment: The carcinoid syndrome is most often associated with liver metastases from low-grade small intestinal neuroendocrine tumours but is seen rarely in patients with multiple PNETs. By contrast, finding small increases in serum serotonin and urinary 5-HIAA concentrations is not unusual when investigating patients suffering from a PNET adding a further degree of cost and complexity to the diagnosis and management of such patients. In this reported population of 255 patients with mainly Stage 4 PNETs and elevated chromogranin-A levels, who were screened for carcinoid syndrome, only two patients (0.8%) had the carcinoid syndrome. While carcinoid syndrome was rare, 28% of tumours showed serotonin synthesis on immunohistochemical staining and 7.8% had some evidence of increased serotonin production. Screening of patients with PNETs for increased serotonin secretion is not currently incorporated in published guidelines and this report is in keeping with these guidelines that the testing is not necessary.

Reference: Clin Endocrinol (Oxf). 2017;87(2):165-170
Abstract



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 was a founder of 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 a former Vice Chairman and Asia Pacific Regional Coordinator for the International Council for Control of Iodine Deficiency Disorders (ICCIDD).

Primary lymphocytic hypophysitis: clinical characteristics and treatment of 50 cases in a single centre in China over 18 years

Authors: Wang S et al.

Summary: In this report by Chinese investigators, a cohort of patients with primary lymphocytic hypophysitis were studied retrospectively in order to gain insights into the diagnosis and treatment of this rare disorder. Subjects comprised 50 patients (28 diagnosed histologically, 22 diagnosed clinically) attending a single centre between 1999 and 2016. Amongst this cohort, 72% were also diagnosed with central diabetes insipidus (CDI), 60% with hypogonadotropic hypogonadism, 26% with adrenal insufficiency and 22% with IGF-1 axis defects. Under imaging, 96% exhibited thickening of the pituitary stalk and 78% both intra- and suprasellar expansion. Glucocorticoid therapy was associated with improvements in anterior pituitary function, but none of the studied covariates were significantly associated with improvements in CDI or recurrence.

Comment: Lymphocytic hypophysitis is a rare, autoimmune disorder presenting most commonly in late pregnancy or early in the postpartum period and is characterised by swelling of the pituitary, the pituitary stalk and posterior pituitary. It may also occur in men and is most often confused with a pituitary adenoma or an infiltrative disorder. The commonest functional abnormality is CDI and the disorder may be labelled idiopathic CDI. However, multiple pituitary hormone deficiencies may occur in association with CDI as detailed in this report of a large series from China adding more information to what is currently in the literature. As expected, CDI occurring in 72% was the most common endocrine manifestation of the disorder followed by hypogonadotrophic hypogonadism in 60%. Thickening of the pituitary stalk was the most common imaging abnormality in association with intrasellar and suprasellar expansion. The message is that a comprehensive diagnostic assessment of both anterior and posterior pituitary function is indicated in patients with suspected lymphocytic hypophysitis. They also confirmed that our conventional treatment with high dose glucocorticoid therapy was of significant therapeutic benefit.

Reference: Clin Endocrinol (Oxf). 2017;87(2):177-184
Abstract

Seasonal variations in TSH serum levels in athyreotic patients under L-thyroxine replacement monotherapy

Authors: Gullo D et al.

Summary: This Italian cohort study compared seasonal fluctuations in serum thyroid hormone levels amongst euthyroid and hypothyroid subjects living in a temperate climate. Monthly measurements of TSH and thyroid hormones were gathered in a group of LT4-treated athyreotic patients (n = 3,934) and euthyroid controls (n = 11,806). The only seasonal variation observed amongst the euthyroid group was a small increase in FT3 during winter (+2.9%, $P < 0.001$). Amongst athyreotic patients, TSH levels were significantly increased during winter and FT4 levels were significantly decreased. In a small sub-study of athyreotic subjects on a stable LT4 dose (n = 119), comparisons of thyroid hormone levels were also made between the coldest (December-March) and hottest (June-September) months. Serum TSH fluctuated from 0.80 mU/L in the coldest months to 0.20 mU/L during the hottest. Respective values for FT4 and FT3 were 16.3 vs 17.8 pmol/L and 3.80 vs 4.07 pmol/L.

Comment: Thyroid hormones and the sympathetic nervous system are the important thermogenic regulatory mechanisms in the adaptation to temperature variation in many animal species. By contrast, many experimental studies have been undertaken examining putative changes in thyroid hormone secretion and metabolism in response to changes in ambient temperatures without much evidence for a role for thyroid hormones in humans. Certainly in areas with a temperate climate, the occurrence of TSH and thyroid hormone seasonal changes is insignificant. This report from Italy has taken another approach in examining a possible role for thyroid hormones in human thermoregulation. They compared TSH values in different months of the year in a large series of healthy euthyroid individuals and also in a large series of athyreotic patients undergoing constant LT4 replacement treatment. Their data showed a small, but significant difference, in the seasonal serum TSH pattern between euthyroid subjects and LT4-treated athyreotic patients. The median serum TSH levels exhibited a circannual trend characterised by higher levels in winter than in summer while both FT4 and FT3 serum values were lower in the winter. They admit the mechanism underlying the seasonal changes in thyroid homeostasis in LT4-treated athyreotic patients is not clarified by their study**.** While we cannot dismiss the data, the possibility of multiple confounding factors causing the observed variations undermines the credibility of their conclusion that 'physicians and endocrinologists treating athyreotic patients should consider this evidence and evaluate the risk of undesired hyperthyroidism in summer and of mood deterioration related to thyroid hormone decrease in winter'.

Reference: Clin Endocrinol (Oxf). 2017;87(2):207-215
Abstract

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

Authors: Gravholt CH et al., on behalf of the International Turner Syndrome Consensus Group

Summary: Between 25 and 50 per 100,000 females are diagnosed with Turner Syndrome, a chromosomal disorder which has multiple, and often severe, impacts on patients throughout their lifespan. This international, consensus guideline covers five key areas of care in the management of patients with Turner Syndrome. These include diagnostic and genetic issues; growth and development through childhood and adolescence; congenital and acquired cardiovascular disease; transition and adult care; and other comorbidities and neurocognitive issues.

Comment: Turner syndrome is a rare disorder usually diagnosed and managed by paediatric endocrinologists but eventually transitioned to the care of adult endocrinologists and a multidisciplinary clinic to manage the multiple disorders associated with this disorder. This guideline will be very helpful in managing the transition and long-term care of these patients. For example, the guideline provides useful advice on management of growth hormone therapy, early attention to assisted reproduction where possible, and finally, female hormone replacement therapy. It is emphasised that congenital heart disease occurs in approximately 50% of girls with Turner Syndrome who face a lifelong heavy burden of both congenital and acquired cardiovascular disease, with consequent increased mortality and morbidity. The list of annual checks that are indicated for Turner Syndrome patients are provided in the guideline (Table 8.) and is recommended to all clinicians caring for these patients.

Reference: Eur J Endocrinol. 2017;177(3):G1-G70
Abstract

Epitope-specific antitumor immunity suppresses tumor spread in papillary thyroid cancer

Authors: Ehlers M et al.

Summary: These authors carried out analysis of tumour epitope-specific immunity amongst patients with papillary thyroid cancer (PTC) in order to determine correlations with outcomes. Subjects were 150 patients with PTC, 40 with Hashimoto's thyroiditis and 21 healthy controls. HLA typing was also carried out in 27,239 healthy, Caucasian subjects. Patients with PTC had increased levels of thyroid peroxidase and thyroglobulin-specific CD8+ T cells vs healthy controls (both $P < 0.005$). Similar results were seen for those with Hashimoto's thyroiditis. Risk of distant metastasis was affected by some HLA haplotypes in patients with PTC. Risk was reduced amongst HLA-DQB1*03 positive subjects; risk ratio 0.170 (95% CI 0.037, 0.755; $P < 0.005$), and increased amongst those who were HLA-DRB1*03 and HLA-DQB1*02 positive; relative risk ratios 4.400 (1.378, 14.05; $P < 0.05$) and 3.692 (1.102, 12.38; $P < 0.05$) vs other haplotypes.

Comment: Hashimoto's thyroiditis is commonly found in patients operated on for PTC and a possible aetiological link has been suggested because of this frequent co-existence. Some researchers have shown an improved prognosis for PTC in patients who also have Hashimoto's, suggesting some form of immunologically determined protective effect against the malignancy. The aim of this present study from Germany was to characterise tumour epitope-specific CD8+ T cell immunity in PTC patients and to correlate these results with their clinical course. What appeared to be the most interesting and relevant findings were the HLA typing results, with the risk of developing distant metastases being much lower in HLA-DQB1*03–positive patients, contrasting with a higher risk of developing distant metastases in HLADRB1* 03–positive patients. If confirmed by other investigators in larger series this may have some value in determining prognosis in patients with PTC.

Reference: J Clin Endocrinol Metab. 2016:jc20162469
Abstract

Effect of moxonidine on the aldosterone/renin ratio in healthy male volunteers

Authors: Ahmed AH et al.

Summary: This prospective investigation aimed to determine the effect of moxonidine on the plasma aldosterone/renin ratio (ARR). Twenty, normotensive, non-medicated male volunteers received moxonidine 0.2 mg/day for 1 week and 0.4 mg/day for the following 5 weeks. Baseline, 1 and 6 week, seated, mid-morning measurements were undertaken for plasma aldosterone (high-performance liquid chromatography-tandem mass spectrometry), direct renin concentration, plasma renin activity, cortisol, electrolytes and creatinine in addition to urinary aldosterone, cortisol, electrolytes and creatinine. Moxonidine therapy did not alter plasma aldosterone levels or ARR based on either direct or plasma renin levels at 1 or 6 weeks. No changes in urinary measures vs baseline were observed at either timepoint.

Comment: There is increasing evidence that primary hyperaldosteronism is a commonly overlooked cause of hypertension due in large part to the diagnosis not being considered, particularly if the serum potassium level is normal. When the diagnosis is considered inappropriate testing procedures are frequently employed. The recommended screening test for hyperaldosteronism is the plasma aldosterone/renin ratio, but there are many confounding factors to consider when interpreting the results of this test, especially the effects of anti-hypertensive medication the patient may be taking. In this Australian study the researchers tested the effect of a centrally-acting anti-hypertensive agent (moxonidine) on healthy male volunteers and found no significant changes in plasma renin or aldosterone levels leading them to recommend that moxonidine therapy may be a good option when screening patients for hyperaldosteronism who are unable to discontinue other anti-hypertensive medications. While this is an interesting preliminary and potentially very useful finding, further studies are required to test it out in females as well as males and patients with proven hyperaldosteronism.

Reference: J Clin Endocrinol Metab. 2017;102(6):2039-43
Abstract

TPOAb and thyroid function are not associated with breast cancer outcome: evidence from a large-scale study using data from the taxotere as adjuvant chemotherapy trial (TACT, CRUK01/001)

Authors: Muller I et al.

Summary: These UK researchers utilised data from a large, phase III study of taxotere as adjuvant chemotherapy in women with breast cancer (TACT) in order to investigate the prognostic significance of thyroid autoimmunity in this cohort. Subjects were 1,974 adult women with available stored plasma and either node-positive breast cancer, or early, high-risk, node-negative disease. Prior treatments had included chemotherapy (100%), radiotherapy (88.4%), hormonal therapy (69.8%) and trastuzumab (2.4%). Disease-free survival was not predicted by thyroid peroxidase antibody (TPOAb) status (unadjusted HR 0.97; 95% CI 0.78; 1.19, p = 0.75) or hypothyroid vs euthyroid status (1.15; 0.79, 1.68; p = 0.46) or hyperthyroid vs euthyroid status (1.14; 0.82, 1.61; p = 0.44). Similarly no impacts of thyroid autoimmunity were observed on overall survival or time-to-recurrence.

Comment: Is there an association between breast cancer occurrence and outcome and benign thyroid disease, particularly autoimmune thyroid disease? This is a commonly asked question in clinical practice, but the answer is not straightforward as several reviews and meta-analyses have been published with different conclusions. In this large UK study of breast cancer patients treated by surgery and multiple other adjuvant therapies no association was found between disease-free-survival in these patients and thyroid parameters such as TPOAb, FT4 and TSH levels. In addition there was no evidence that TPOAb positivity was more common in the breast cancer sufferers compared with the general population but the study was not strictly designed to test this proposition. It appears very unlikely that coexisting thyroid disorders have any significant effect on breast cancer occurrence and outcome.

Reference: Eur Thyroid J. 2017;6:197–207
Abstract

Subcutaneous injection of testosterone is an effective and preferred alternative to intramuscular injection: demonstration in female-to-male transgender patients

Authors: Spratt DI et al.

Summary: This retrospective, cohort study, conducted via the outpatient clinic of a single academic medical centre, aimed to determine the safety and efficacy of subcutaneous testosterone in female-to-male transgender patients. Subjects were 63 adult female-to-male transgender patients (53 premenopausal) who volunteered to trial subcutaneous rather than intramuscular testosterone cypionate or enanthate (initial dose 50 mg weekly). Subcutaneous testosterone doses of 50-150 mg weekly (median 75-80 mg) were effective in achieving and maintaining serum testosterone levels within the normal male range for all patients, regardless of BMI (range 19.0 to 49.9 kg/m^2). Amenorrhea occurred in 51/53 premenopausal patients, and serum total estradiol levels < 50 pg/mL in 35. 9/63 participants reported mild and transient local injection site reactions. Amongst subjects who switched from intramuscular to subcutaneous testosterone therapy all preferred the latter.

Comment: This interesting report of the practicability and efficacy of self-administered subcutaneous injections of testosterone, tested in 63 patients undergoing female-to-male transgender therapy, shows that weekly injections of testosterone 50 mg (cypionate or enanthate in oil) achieved desired blood levels and were preferred to other methods of administration of the hormone. Providing that further studies confirm the efficacy of subcutaneous testosterone injections in males, this method of replacement therapy will provide another option for hypogonadal men requiring long-term testosterone therapy, particularly those men who struggle with painful, intramuscular injections.

Reference: J Clin Endocrinol Metab. 2017;102(7):2349-55
Abstract

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