4.1 Gestational Thyrotoxicosis

This is a transient mild hyperthyroidism that occurs early in pregnancy and is not due to intrinsic thyroid disease. HCG which peaks during the first trimester stimulates the TSH receptor elevating T4 levels and suppressing TSH.It is seen in 10-15% of pregnant women and occurs with multiple gestations,hyperemesis gravidarum,h.mole,hyperplacentosis and familial gestational thyrotoxicosis. The last named is due to a mutation in the TSH receptor which makes it hypersensitive to normal or mildly elevated levels of HCG.

The symptoms of gestational thyrotoxicosis are nausea and vomiting which resolve spontaneously by 20 week gestation. The more severe form is hyperemesis gravidarum which is characterized by severe nausea and vomiting, dehydration, weight loss of upto 5kg and ketonuria. Treatment with an antithyroid drug is not indicated because the symptoms subside spontaneously with normalizing of T4 levels by 14-20 week gestation. In some patients serum TSH may remain suppressed or below normal after normalization of serum T4. The main differential diagnosis is from Grave's hyperthyroidism. This condition manifests frequently with both pre pregnancy and pregnancy symptoms. Nausea and vomiting are mild whereas goitre, ophthalmopathy,thyroid peroxidase antibody and TSH receptor antibodies are more common. Further ultrasonography reveals vascular goitre. On the contrary, gestational thyrotoxicosis has no goitre or ophthalmopathy,no peroxidase or TSH receptor antibodies and the vascularity is normal.

Ref: Sisodia K P and Mestman J H Endocrine Pract,2010;16:118/129

4.2 What is the significance of elevated PTH levels after parathyroidectomy?

A significant number of patients are reported to exhibit a normal calcium concentration but a PTH level above the reference range, as long as 15 years after parathyroidectomy.

Surgeons who use intra operative PTH measurements look for greater than 50% decrease in the PTH concentration from the base line pre operative level and a decrease in the PTH level into the defined reference range as evidence of successful parathyroidectomy. Despite inra- operative PTH concentrations meeting these parameters, 9-62% of patients later exhibit normocalcaemic PTH elevation anywhere from 1 week to 5 years after surgery.

This post operative PTH elevation with normal calcium levels can be predicted by the following

1. Higher pre operative PTh levels
2. Higher pre operative Ca levels
3. Larger parathyroid adenomas
4. Those with more severe bone disease as shown by lower pre operative 25-OH-Vit D levels and higher Alkaline phophatase, Osteocalcin and propeptide type 1 collagen levels.
5. A decrease in serum Ca from post operative day 1 to day 7 whereas those with normal post operative PTH levels exhibited stable Ca levels during this period

The mechanism of this PTH elevation maybe due to form of PTH resistance or due to Vit D deficiency.

Comment: An elevated post operative PTH concentration does not indicate surgical failure if the serum Ca levels are normal. It has also been shown that routine post operative supplementation with Ca and Vit D may decrease the risk of post operative PTH elevation.

Ref: Viskobing D M Endocr Pract 2010Jan/ Feb; 16 (1) : 112-117

4.3 A new treatment for persistant hyperinsulinaemic hypoglycaemia (HH)- Nifedipine

HH may occur with overdose of exogenous insulin or oral hypoglycaemic agents. It is also seen with solitary insulinomas and nesidioblastosis (islet cell hyperplasia) . Recently HH has also been reported following Roux-en –Y gastric bypass surgical procedure for weight reduction.

Partial Pancreatectomy has been the therapy of choice for HH following gastric bypass. Calcium channel blocking agents have been successful in the treatment of infantile HH . Sustained release Nifidipine has been successful in treating this hypoglycaemia. The mechanism of HH in gastric bypass patients has been ascribed to nesidioblastosos or diffuses β cell hyperplasia or dumping syndrome. The β cell hyperfunction may be due to rapid gastric emptying and rapid presentation of chyme to the terminal ileum, producing excess GLP-1 stimulating the growth of insulin producing islet cells. Apart from surgery and Nifidipine,Octreotide,Diazoxide and a combination of Verapamil and Acarbose have also been reported to be effective. Diabetes develops in upto 40% of patients who undergo partial pancreatectomy.
HH may occur upto 26 years after gastric bypass.

Ref: Guseva N et al Endocr Pract 2010 Jan/Feb 16(1): 107-111

4.4 What is the significance of very low HbA1c?

The normal HbA1c in healthy non diabetic patients with normal Hb levels is 4-6.5%. In certain conditions however the HbA1c may be low and may not accurately reflect blood glucose levels over the past 2-3 months. These include Hb variants such as sickle cell anaemia, β Thallasaemia minor, haemolyssis secondary to medications, autoimmune processes or mechanical Trauma such as that secondary to prosthetic heart valves. In this scenario, glycaemic control is best assessed by measuring serum fructosamine.

Ref: Danescu L G et al Endocr Pract 2010 Jan /Feb; 16 (1); 89-92

4.5 Primary pigmented nodular adrenal disease (PPNAD) – A cause of Cushing"s syndrome (CS).

PPNAD is a rare cause for CS. It is characterized by normal sized adrenal glands containing multiple small pigmented cortical nodules that function autonomously- i.e ACTH independent. It occurs in persons younger than 30 years and has an insidious onset. Some patients may present only with osteoporosis. It may be familial or sporadic and can also occur as part of the Carney complex - an autosomal dominant multiple endocrine neoplasia syndrome characterized by skin lesions, cardiac myxomas and endocrine disease.

Plasma cortisol levels are elevated with low ACTH levels. CT and MRI reveal normal sized adrenal glands which may not appear nodular. Bi lateral adrenal venous sampling will show elevated levels of cortisol in both right and left adrenal veins compared to the levels in the IVC. At operation multiple small 1-5 mm black and brown superficial nodules are observed in both adrenal glands. The differential diagnosis should exclude exogenous glucocortcoid exposure. 2/3 rd of patients have a paradoxical rise in urinary free cortisol excretion with high dose Dexamathasone. Bi lateral adrenalectomy with steroid replacement is recommended. Patients with ACTH independent Cushing's syndrome in whom adrenal adenoma and ACTH independent macronodular adrenal hyperplasia have been excluded on imaging, should be subjected to bi lateral adrenalectomy as PPNAD is the most likely cause. It is associated with mutations in the PRK AR1 gene.

Ref: Hackman K L et al Endocr Pract 2010 Jan/Feb ;16(1):84-88

4.6 Does Exenatide induce acute pancreatitis?

The US FDA has reported 36 cases of presumed pancreatitis associated with Exenatide. They had no history of recent trauma or ERCP did not take alcohol and had no biliary calculi. The abdominal CT reveals a diffusely and mildly enlarged pancreas particularly in the head and body with surrounding oedema consistent with pancreatitis. A serum lipase level 3 times above the upper limit of normal confers 99% specificity for pancreatitis. An elevated serum creatinine increases lipase values.

Apart from Exenatide other drugs causing pancreatitis include Frusemide, Lisinopril, Lovastatin, Sertraline, Metformin, Glimepiride and Gliclazide.

Most recently, Dore et al published an assessment of cohorts of 27996 Exenatide initiators and 16276 Sitagliptin initiators and approximately equal numbers of matched Metformin and Gliburide initiators. During follow up upto 1 year, acute pancreatitis occurred in 0.13% of patients treated with Exenatide and 0.12% in patients treated with Sitagliptin.
In comparison with Metformin and Gliburide the early risk was 1.0 for both drugs.
The mechanism for this adverse drug reaction is unknown. Exenatide antibodies developed in 40-50% of patients using the drug. These antibodies might cross react in susceptible patients with various pancreatic antigens.

Comment: In any diabetic patient with acute pancreatitis exenatide must be ruled out as the cause and its use discontinued, even though the risk seem to be the same as for Glibenclamide, Metformin and Sitagliptin.

Ref: Aeiob W A et Al 2010 Jan/Feb; 16(1):80-83

4.7 A new risk for fractures by falling - Bi focal lenses

When obstacles on the ground are viewed through the lower segment of multifocal glasses, vision can be blurred, and depth perception can be impaired. This is especially so when walking down the stairs. This observation presumably explains the observation that older adults who wear multifocal glasses are at elevated risk of falling. Looking down to descend a stairway or to step over obstacles can be precarious.

Comment: Patients with osteopenia have an increased risk of fragility fracture**.** If the BMD score is less than -2.0 (Age inappropriate) then treatment is recommended. If the BMD z score is between -1.0 and -2.0 (Age appropriate) then the indications for treatment is only if there are significant risk factors for fracture. These commonly include family history of osteoporosis, age>65, female sex, thin habitus, poor muscle strength and frailty, poor coordination, drugs that lead to osteoporosis, poor vision and neurological diseases. To this must now be added wearing of bifocals.

Ref: Menant J C et al J Am Geriatr Soc 2009 Oct;57:1833

4.8 Gastric bypass (GBP) Vs Banding (B) - A Randomized Trial

Roux en Y GBP and adjustable gastric banding are the two most common bariatric procedures. In a randomized trial from California, 197 obese patients underwent either laparoscopic GBP or laparoscopic banding. They were followed up for efficacy and surgical complications.

No deaths had occurred at 90 days in either group. Major complications were more common after GBP than after banding, both during days 1-30 (6% vs. 2%) and after 30 days(26% vs. 12%).Major complications after GBP were primarily bowel obstruction and anastamotic strictures. On average GBP patients had lost a greater proportion of excess weight than had banding patients at 4 years (68% vs. 45%). Treatment failures (Failure to lose more than 20% of excess weight occurred less commonly with GBP than with banding (0% vs 17%).

Comment: This randomized trial confirms that weight loss is greater after GBP than after Banding. Because GBP is more invasive, the higher early complication rate is expected. However this study's higher rate of long term complications with GBP (especially strictures) is not consistent with previously reported observational data. The discrepancy could reflect either technical surgical issues or differing thresholds for evaluating patients with symptoms that suggest strictures. GBP should be undertaken by experienced surgeons in high volume units.

Ref: Nguyen N T et al Ann Surg 2009 Oct;250:631

4.9 Gabapentin (G) –Nortriptylline (N) combination therapy for Painful neuropathy (PN)

G and N are first line drugs for neuropathic pain, but each has limited efficacy and dose limiting side effects. Whether these drugs which have different mechanisms of action, might be more effective in combination than as monotherapy was studied.

56 patients with either painful Diabetic neuropathy (PDN) or post herpetic neuralgia (PHN) were randomized to 3 groups for 6 weeks.

1. Gabapentin upto 1200mg tid
2. Nortriptylline 50mg bid
3. Combination therapy

Patients could continue to take Paracetamol , NSAIDs , or long acting opioids but could not undertake pain relief procedures such as nerve blocks , acupuncture etc during the trial.
At the maximum tolerated dose, mean reduction in pain intensity was significantly greater withy combination therapy (53%) vs. N (39%) vs. G (31%). Patients also had significantly less interference with sleep when taking the combination. The maximum tolerated dose of N & G

were significantly lower when the drugs were taken in combination than as monotherapy. Dry mouth occurred significantly more often with the combination or N monotherapy.

Comment: Patients with painful neuropathy (diabetic or herpetic) might benefit from combination therapy with G & N when either agent fails to provide adequate relief as monotherapy.

Ref: Gilron I et al Lancet 2009 Oct10 ; 374:1252

4.10 Does timing of Thyroxine dosing matter?

Food is said to interfere with absorption of Thyroxine. A randomized cross over trial enrolled 65 patients who were taking stable doses of levo thyroxine (LT4) for hypothyroidism or thyroid cancer to study this assumption. Each patient received three 8 week courses of LT4 taken at different times daily- at least one hour before breakfast, after overnight fasting with breakfast or at bed time (at least 2 hours after the last meal of the day).

The mean TSH levels were 1.06 with the fasting regime, 2.9 when taken with breakfast and 2.2 at bed time. These differences pair wise were statistically significant.

Comment: These findings suggest that LT4 is absorbed most completely and reliably in the morning, after overnight fasting -at least 1 hour before breakfast. Therefore there is no place for taking Thyroxin at other times once daily nor in divided bid or tid dosing schedules.

Ref: Bach-Huynh T G et al J Clin Endocrinol Metab 2009 Oct ;94:3905

4.11 Diabetics with stable angina – which is better – Medical therapy or prompt revascularization (PCI or CABG)?

The BARI 2 D trial involved 2,368 patients with Type 2 DM and stable CAD. The diabetes was treated by either insulin, sulphonylureas, metformin or rosiglitazone to achieve a target A1c < 7%. The cohort was randomized to either medical therapy or to PCI/ CABG. The 5 year survival rate was 88% in all treatment groups. Freedom from major CV events were also similar. Compared to medical therapy, neither PCI nor CABG was associated with a mortality benefit.

Comment: These results failed to demonstrate a firm advantage of revascularization over medical therapy in patients with stable CAD. These findings reinforce those of the COURAGE trial, which supported medical therapy as a reasonable initial approach to these patients.

Ref: Frye R.L. et al N.E.J.Med 2009 Jun 11; 360: 2503.
Boden W.E. et al IBID : 2570.

4.12 What are the changes in cardiac risk factors during perimenopause?

Perimenopause is the period of one year preceding and one year after the menopause. Post menopausal women have higher risk for CV events than do pre menopausal women. 3,000 perimenopausal women were followed up for 9 years. Annual measurements for risk factors were undertaken.

TC, LDLC and apo B levels all increased during the perimenopause. HDLC peaked around the time of the last menstrual period and then declined. All other risk markers followed a simpler linear model consistent with effects of chronological aging.

Comment: In this analysis, lipids underwent substantial, presumably detrimental changes from the year before to the year after the final menstrual period.

Ref: Mathews K.A. et al J. Am. Coll. Cardiol. 2009 Dec 15/22; 54: 2366.

4.13 Do inhaled steroids affect bone density?

In the TORCH trial, patients with moderate to severe COPD were randomized to receive inhaled steroids (Fluticasone) , Beta agonist (salmeterol) , combination therapy or placebo. Now in a substudy of 658 TORCH participants, researchers report serial measurements of bone mineral density (BMD) for 3 years.

At base line, 18% of men and 30% of women had osteoporosis. During 3 years of follow up mean BMD declined by 2-3% from baseline in each of the randomized groups, with no significant difference between the inhaled steroid, placebo or salmeterol only groups.

Comment: In this 3 year randomized trial, the extent of declining BMD was no greater with inhaled steroids than with salmeterol only or placebo groups. Whether the decline in BMD would accelerate with longer use of inhaled steroid therapy – compared with other therapies, is unclear. Another observation is that patients with advanced COPD were at high risk for osteoporosis and many of them might be candidates for bisphosphonate therapy regardless of whether they receive inhaled steroids.

Ref: Ferguson G.T et al Chest 2009 Dec; 136: 1456.

4.14 Will weight loss in obese men with obstructive sleep apnoea (OSA) be beneficial?

63 obese men in a single Swedish center with BMI 30 – 40, age 30 – 65, with moderate to severe OSA (apnoea – hypopnoea index [AHI] , > 15 events per hour) , treated with continuous positive airway pressure (CPAP) were evaluated. 30 of these were assigned to a very low energy liquid diet (550K cal/d) for 7 weeks followed by 2 weeks of gradual reintroduction of normal food. The control group of 33 men maintained their usual diet for 9 weeks. After 9 weeks, the mean weight loss in the intervention group was 20Kg lower than that in the control group and the AHI was 23 events per hour lower in the dieting group. 5 men in the intervention group were disease free (AHI<5) and 15 had mild OSA whereas all but one control patient continued to exhibit moderate to severe OSA.

Comment: Weight loss is effective for diminishing OSA and might allow some patients to discontinue CPAP, which often is not tolerated well.

Ref: Johansson K et al BMJ 2009 Dec 3; 339:4609.

4.15 A new action of Oxytocin (O)

O is known to affect uterine function. In recent years it has been found to be a neurotransmitter that enhances behaviours that reflect both trust and generosity. Those with a single nucleotide polymorphism of the gene for O has been found to make people who are cooler under stress.
Ref: Rodrigues S.M. et al Proc. Natl. Acad.Sci. USA 2009 Dec 15; 106: 21437.

4.16 Can women become pregnant during the perimenopausal period?

The risk for conception during the perimenopausal transition phase was investigated in 108 women. The percentage of anovulatory cycles was found to exceed 60%. However 25% of cycles longer than 60 days were found to be ovulatory. The mean day of ovulation was also found to be later than normal. Gonadotrophin levels were found to be higher even during ovulatory cycles.

Comment: Live births are quite uncommon in women who are older than 40 because the pregnancy rate is markedly poor and the rates of spontaneous and induced abortions are higher among women in this age group. However the results of this study indicate that sexually active women who do not desire pregnancy should continue to use contraception until after menopause and elevated FSH levels do not preclude ovulation.

Ref: O'Connor K.A. et al . Menopause 2009 Nov/Dec; 16: 1178.

4.17 Vitamin D deficiency – beyond bone disease

In the past decade, Vit D deficiency in both children and adults has been found not only in developing nations but also in developed nations like the USA. It has been shown that the adverse health effects of Vit D deficiency could extend well beyond bone disease. These include

1. Excess risk for cancer, particularly colon, prostate and breast.
2. Hypertension.
3. Autoimmune diseases eg: multiple sclerosis, Type 1 diabetes.
4. Other diseases.
5. Increased cardiovascular mortality.
6. Increased all cause mortality.

In the 2004 NHANES, from 6,275 children who were randomly selected and Vit D levels estimated, it was found that S 25 hydroxy Vit D levels were less than 15ng/ml in 9% (Vit D deficiency) and levels 15 – 29 ng/ml in 61% (Vit D insufficiency). The survey also showed that 25 hydroxy D levels were related inversely to **systolic BP** and **plasma glucose** in children in their teens.

In another study, in 1,300 randomly selected older adults (age 65 – 88), 50% were found to have 25 hydroxy D levels of less than 20ng/ml. In this age group, **BMD, Bone turn over markers and serum PTH levels** were adversely affected when the 25 hydroxy D levels dropped lower than 20ng/ml.

A meta analysis of 8 randomized trials showed that higher doses of daily Vit D supplements (700 – 1,000 iu) **lowered risk for falling** by 19% presumably because of **better muscle strength**. Previous research suggested that high dose supplementation also **prevents fractures.**

Ref: Komaroff A.L. J Watch 2010 Jan 1; 30:1.

4.18 Atypical fractures in long term bisphosphonate (BP) users

BPs lower overall risk for fractures in osteoporotic women. However an unusual type of femoral fractures has been described in a few long term BP users (average 9 years). These fractures are bilateral , femoral, subtrochanteric or involving the femoral shaft which may occur as fragility fractures (resulting from falls from standing height or lower). Normal fractures are intertrochanteric or involve the femoral neck. The subtrochanteric fractures have a unique appearance, with a spike or beak configuration and cortical thickening at the fracture site. This beaking with a thick cortex is highly correlated with prolonged BP use (mean 7 years).
Comment: These reports suggest that a small sub group of women could be susceptible to atypical femoral fractures after prolonged BP use. Suppression of bone turnover and accumulation of micro damage is a postulated mechanism.

Ref: Capeci C.M. and Tejwani N.C. J . Bone. Joint. Surg. Am.2009 Nov; 91 : 2556.
Lenart B.A. et al Osteoporosis Int. 2009 Aug; 20: 1353.

4.19 Oral Bisphosphonates (BP) and osteonecrosis of the jaw (ONJ)

ONJ is a well described complication of high dose iv BP therapy for cancer. Can low dose oral BP prescribed for osteoporosis cause ONJ?

Several case series have been published in which ONJ occurred during oral BP therapy, this latest report from Italy involves 24 women. The women were mean age 72, had been taking oral BPs (mainly alendronate) for 11 – 40 months. The triggering event for ONJ was usually tooth extraction or dental implant. The mandible was affected more commonly than the maxilla. The lesions eventually healed in nearly all cases.

Comment: Case series like this do not in themselves prove cause and effect. The American Society for Bone and Mineral Research note that clear evidence is lacking for a causal relation between oral BPs and ONJ.

Ref: Favia G et al J.Rheumatol. 2009 Dec ; 36: 2780.

4.20 For how long can life style intervention prevent diabetes?

In 2002, the Diabetes Prevention Programme (DPP) reported that, compared with placebo, intensive life style intervention or metformin in 3,200 overweight adults with impaired glucose tolerance (IGT) lowered the incidence of diabetes by 58 and 31% respectively. Patients who had completed the 3 year DPP study were enrolled into the 6 year unblinded DPP Outcomes Study (DPPOS). During a one year bridge period, all patients were offered a 16 session life style curriculum and thereafter 3 monthly life style reinforcement sessions. Those initially randomized to metformin continued to receive twice daily open labeled metformin.

During the 6 year DPPOS follow up, the incidence of newly diagnosed diabetes was similar in all three groups. No rebound occurred in diabetes incidence in the life style and metformin group during follow up. However extension of life style intervention to metformin and placebo recipients seemed to lower incident diabetes in those groups. The net relative reduction in diabetes incidence during the full 10 years was 34% in the life style group and 18 % in the metformin group compared with the placebo group.

Comment: This study demonstrates that life style interventions can lower diabetes incidence for many years. Additional follow up will determine whether these interventions also attenuate microvascular and macrovascular morbidity and mortality.

Ref: DPP research group, Lancet 2009 Nov 14; 374: 1677.

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