

1.1 What are the metabolic changes which occur in the decade before diabetes appears – both normoglycaemic and prediabetic phases ?

67,538 non diabetic British Civil servants were followed up for a mean 13 years. They had metabolic analysis at base line and at 6 and 11 years later. 505 developed diabetes during the study. During the 13 years of observation, participants who did not develop diabetes had slight rises in FPG and post glucose load levels, constant insulin secretion and slight decline in insulin sensitivity. By comparison, future diabetics began their study with significantly higher mean fasting and post glucose load levels, lower insulin sensitivity and higher insulin secretion. In this group, FPG levels rose slowly until about 2 years before the diagnoses of diabetes and thereafter increased rapidly. Post glucose load levels began to rise 5 years before diagnosis, stabilized for several years and began to increase rapidly about 2 years before diagnosis.

Comment: Patients destined to develop diabetes have insulin resistance and secretion which increases gradually over many years, followed by a short term rise and then rapid decline in Beta cell function. This process begins years before the patients even meet the criteria for prediabetes. There may be a window of opportunity for preventive interventions during this period. 75 g glucose 2 hour OGT may be more sensitive to detect the change than FPG.

Ref: Tabak A.G. et al Lancet 2009 June 27; 373 : 2215.

1.2 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, with 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.

1.3 What are the changes in cardiac risk factors during perimenopause?.

Perimenopause is a 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 was 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.

1.4 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 are 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.

1.5 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 passage (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.

1.6 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 unflappable under stress.

Ref: Rodrigues S.M. et al Proc. Natl. Acad.Sci. USA 2009 Dec 15; 106: 21437.

1.7 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.

1.8 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, 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.

1.9 Atypical fractures in long term bisphosphonate (BP) users.

BPs lower overall risk for fractures in osteoporotic women. However unusual type of femoral fractures have 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 Tejawani N.C. J . Bone. Joint. Surg. Am.2009 Nov; 91 : 2556.

Lenart B.A. et al Osteoporosis Int. 2009 Aug; 20: 1353.

1.10 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.

1.11 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.

1.12 HbA1C for diagnosis of diabetes – AACE and ACE statements.

1. The ADA endorses the use of A1C of 6.5% or higher as a primary criterion for the diagnosis of diabetes.

2. The rationale for this decision is based on data showing that **Retinopathy** occurs in individuals with an A1C > 6.5% at approximately the same rate as in individuals who are diagnosed on the basis of the current fasting and post challenge glucose criteria. A 10% risk for retinopathy has historically served as the bench mark for diagnosing the presence of diabetes.

3. The advantages of A1C for diagnosis include the following:

a) Does not require the patient to be fasting.

- b) Can be done at any time.
- c) Simpler to perform than the 2 hour GTT.
- d) Less dependent on the patient's health status at the time of blood sampling.

4. The disadvantages are:

- a) Identifies about 20% fewer people as diabetics than do the existing criteria based on fasting and OGT levels.
- b) More expensive.
- c) Standardized criteria of assay are not followed universally but will be implemented soon.

The AACE and ACE support these recommendations for the use of a confirmed A1C as an available option to diagnose diabetes with the following recommendations.

1. The A1C should be considered as an additional optional diagnostic criterion, not the primary criterion for the diagnosis of diabetes.
2. They suggest the use of traditional glucose criteria for diagnosis when feasible.
3. A1C is not recommended for diagnosing Type 1DM.
4. A1C is not recommended for diagnosing gestational diabetes.
5. A1C may be misleading in several ethnic populations as in African Americans.
6. A1C may be misleading in the setting of various haemoglobinopathies, iron deficiency, haemolytic anaemias, Thalassaemias, spherocytosis, and severe hepatic and renal disease.
7. They endorse only standardized, validated assays for A1C testing.
They do not endorse ;
1. A1C for diagnosis of pre diabetes or for those patients at risk for diabetes.

They support an A1C of 5.5% - 6.4% as a **screening test for prediabetes**, if it leads to measurement of an FPG or OGT for diagnosis.

Ref: Endocr.Pract. 2010 March/April 16 (2): 155 – 156.

1.13 Thyroid hormone (TH) levels in childhood obesity.

The phenomenon of **overweight** in children and adolescents is defined as a BMI > 85th but < 95th percentile while **obesity** is defined by a BMI > 95th percentile. The prevalence of these in childhood has increased over the past 4 decades and is a risk factor for increased risk of obesity in adulthood.

In a retrospective study, the prevalence of an elevated serum TSH level in children and adolescents with obesity was compared with their non obese peers. After exclusion of Hashimoto's thyroiditis, 10.8% of children with obesity were found to have a TSH level > 4 m.i.u/l although in none of them did it exceed 7.5 m.i.u/l. The total T4 and free T4 levels were normal while the free T3 may be elevated. This may be diagnosed as subclinical hypothyroidism or T3 hyperthyroidism, but the question has been raised whether the elevated TSH is contributing to the obesity or whether it is a consequence of it. It appears to be the latter.

Both the elevation in serum TSH levels and the increased T4 to T3 conversions resulting in elevated freeT3, which occur in obese appear to be modulated by leptin. Overfeeding is accompanied by an increased serum T3 while when obese subjects are fasted, the reverse is true. In anorexia nervosa – the opposite of obesity – both the serum TSH and T3 concentrations are low and increase with weight regain. These findings provide strong evidence that these thyroid functional abnormalities are a consequence of and not the cause of obesity. In fact in patients with severe hypothyroidism (mean TSH level 349 m.i.u/l) adequate thyroid replacement resulted only in a mean weight loss of 2.3Kg. Further in children and adolescents, mild abnormalities such as TSH < 7.5m.i.u./l frequently resolved spontaneously.

When should thyroid function be assessed in overweight and obese children?. The following indications are recommended.

1. In a child whose growth rate is decelerating.
2. In a child with enlarged thyroid gland.
3. A strong family history of thyroid disease.
4. Symptoms suggestive of thyroid disease.

The children with overweight and obesity should be treated with limitation of calorie intake and increase of calorie expenditure. Thyroid hormone should not be given routinely for obese children but limited to dose with clinical and lab evidence of hypothyroidism.

Ref: Carswell J.M. et al Endocr.Pract 2010 Mar/April; 16 (2): 157 -158.

1.14 Hypophysitis – some aspects.

1. May present as a space occupying lesion.
2. Autoimmunity is the commonest cause.
3. They may be granulomatous, Xanthomatous or necrotizing.
4. May present with GRH deficiency but LH deficiency is commoner.
5. Suprasellar extension, cavernous sinus invasion and involvement of sinuses may occur.
6. Typical MRI features are , enlarged and enhanced pituitary gland, thickened expanded infundibulum and stalk up to the hypothalamus.
7. Deficiency of any single pituitary hormone or combination may be seen.
8. Current or recent pregnancy, Diabetes insipidus, hypopituitarism of rapid onset or out of proportion to the size of the pituitary lesion and associated autoimmune diseases are indicative of hypophysitis.
9. The enlarged sellar mass is contrast enhancing, homogeneous, symmetrically enlarged with a relatively low signal on T1 weighted and high signal on T2 weighted images.
10. Complete resolution over time of inflammation, radiologic abnormalities and endocrine dysfunction may occur spontaneously or with use of steroids in a therapeutic trial or use of hydrocortisone as cortisol replacement therapy.
11. Chronic hypophysitis, granuloma formation and fibrosis may be observed in some.
12. All cases should be investigated for a possible underlying systemic disease.
13. Unlike pituitary adenoma, additional medical therapy may be appropriate in the absence of visual compromise and includes anti inflammatory agents such as corticosteroids or methotrexate.
14. Relapses may occur after withdrawal of steroid therapy.
15. If pituitary surgery has been initiated, intra operative frozen section should be done and if hypophysitis is confirmed, decompression of the sella turcica without causing hypopituitarism, rather than extensive debulking of the lesion is adequate.
16. Radiotherapy has been used in treatment infrequently although gamma knife radio surgery with low dose irradiation may be effective.
17. Long term follow up is mandatory.

Ref: Anandakrishnan S. Endocr.Pract. 2010 March/April; 16 (2): 159 – 161.

1.15A new treatment for lipodystrophy and the metabolic syndrome - Metreleptin.

Lipodystrophy may be congenital or acquired, partial or Metreleptin may produce its effects by reducing hyperphagia with decreased satiation time and increased satiety time. Leptin also regulates fatty acid metabolism in cells other than adipocytes and directly stimulates fatty acid oxidation in adipose tissue and liver, leading to decreased insulin resistance. The decreased insulin resistance may also be due to the decreased hepatic lipid content (80%) and decreased intramyocellular content by 33%.

In NASH, six months of treatment led to significant histologic improvements in steatosis and ballooning degeneration in conjunction with reductions in the NASH activity score by 60%, whereas fibrosis was unchanged.

Metreleptin improves immunity and T cell function and reproductive function such as irregular menstrual cycles. It also decreased proteinuria and hyperfiltration in those with diabetic nephropathy.

Inflammatory reactions at injection sites and flu like symptoms may follow metreleptin injections. The potentiation of cancer cell growth and T cell lymphomas are being studied. Antibodies to the drug may develop.

Metreleptin is currently an investigative medication and not available for routine clinical use. The FDA authorizes metreleptin to be given to patients with severe lipodystrophy and metabolic abnormalities in need of additional therapeutic options – ie, having inadequate metabolic control with use of currently available standard therapies for diabetes and hypertriglyceridaemia.

Ref: Oral E.A. and Chan J.L. *Endocr. Pract.* 2010 Mar/Apr; 16: 324 – 333.

1.16 Does route and type of HRT for menopause affect the risk for venous thrombo embolism (VTE)?.

Risk for idiopathic VTE is greatest during the first year of post menopausal HRT. 80,000 French women, mean age 54, were studied prospectively for 10 years comparing transdermal oestrogen with progestogen vs oral oestrogen + progestogen. 549 first VTE events occurred. “Past users” and “never users” had similar VTE risk. Users of oral, but not transdermal (patch or gel) oestrogen had substantially higher risk for VTE than did “never users” - HR 1.7. No significant association was found between VTE and concomitant micronized progesterone (Prometrium), Pregnane derivatives including Medroxyprogesterone acetate (Provera) or Nortestosterone derivatives including Norethindrone acetate. However, the “Norpregnane” derivatives – Normegestrol acetate and Promegestone **were** associated with significantly higher VTE risk.

Comment: Although this is an observational study, it suggest that transdermal oestrogens are safe in regard to VTE risk. Oral oestrogens increase the risk, the possible mechanism being that it can raise levels of thrombogenic factors. This study also provides reassurance that progestogens apart from Nor pregnane derivatives, when prescribed with transdermal oestrogen do not raise VTE risk.

Ref: Canonico M. et al *Arterioscler. Thromb. Vasc Biol* 2010 Feb; 30: 340.
Cushman M. *IBID* :136

1.17 Are non traumatic rib fractures in elderly men a risk factor for future fracture at multiple sites?.

Rib fractures are the most common non spine fractures that occur in elders. In the prospective Osteoporotic Fractures in Men Study, it was sought to determine the epidemiology and prognosis of rib fractures in nearly 6,000 older men, age over 65.

During a mean follow up of 6.2 yrs, rib fractures were the most common non spine fracture that occurred. A history of rib fracture at baseline was associated with significantly elevated risks for new rib (HR 2.7) hip (HR 2.1) and wrist (HR 2.1) fractures.

Comment: Rib fracture at base line in older men is associated with an elevated risk for future fractures at multiple sites.

Ref: Barrett – Connor E. et al *BMJ* 2010 March 15th .

1.18 In unexplained recurrent miscarriage, does Aspirin alone or combined with Heparin help?.

5% of women experience two or more miscarriages. 50% of such women have no identifiable cause. It is postulated that many of these result from unrecognized clotting disorders and anti thrombotic therapy is sometimes administered to women with this problem.

364 Dutch women with 2 or more unexplained miscarriages and who were attempting to conceive or were pregnant less than 6 weeks gestation were randomized to receive low dose aspirin – 80mg/d + low molecular weight heparin, aspirin alone or placebo. The overall live birth rate was 54% with no significant difference among the 3 groups.

Comment: This study provides good evidence that anti thrombotic therapy should not be advocated for unexplained recurrent miscarriage.

Ref: Kaandorp S.P. et al NEJ Med 2010 Apr 29; 362: 1586.

1.19 Do Bisphosphonates(BP) cause atypical femoral fractures?.

Several uncontrolled case series have described atypical sub trochanteric or femoral shaft fractures after long term BP therapy. The presumed mechanism is over suppression of bone turnover preventing repair of microfractures. These reports however do not establish causality. Researchers have now examined whether an excess of such fractures occurred in 3 previously published randomized trials of BP therapy for osteoporosis. The analysis was supported by the makers of Alendronate and Zoledronic acid.

The trials included 7,800 BP recipients and 7,500 placebo recipients. 3,900 received Zoledronic acid yearly for 3 years, 3,200 received Alendronate for 4 years and 660 received Alendronate for 10 years. Overall 6 BP recipients and 4 placebo recipients experienced subtrochanteric or femoral shaft fractures – a non significant difference.

Comment: This report provides reassurance that intermediate term use of BPs does not elevate risk for atypical femoral fractures. Because of lingering uncertainty about longer term exposure to BPs , some experts recommend a “ drug holiday” after 5-10 years of BP therapy.

Ref: Black D.M. et al NEJ Med 2010 May 13; 362: 1761.
JCEM 2010; 95 : 1555.

1.20 Pioglitazone (P) vs Vitamin E (E) for Non Alcoholic Steato Hepatitis (NASH).

Earlier studies have suggested that P and E can lead to improvements in NASH. 247 non diabetic NASH patients were randomized to either P - 30mg/d or E – 800 iu/d or placebo for 96 weeks in a multicenter double blind trial. The primary outcome was a composite score of histological features of NASH (Fatty infiltration, ballooning, inflammation, necrosis and fibrosis). Results were as follows.

1. E was better than placebo (43 vs 19%, P = 0.001) but P was not.
2. E significantly attenuated hepatocellular ballooning.
3. Both E and P significantly lowered SGPT and SGOT levels.
4. Neither P or E improved fibrosis.

Comment: This study shows that E is superior to placebo in non diabetic NASH. P seemed to improve histology somewhat and liver enzymes.

Ref: Sanyal A.J. et al NEJ Med 2010 May 6; 362: 1675.