2.1 A new treatment for diabetic painful neuropathy (DPN) – Botulinum toxin (BT) transdermal injections.

BT has inhibitory effects on biochemical mediators of neuropathic pain. This it does independently of its known neuromuscular effects. 20 patients were randomized to receive intradermal BT type A – 12 injections spaced in a 3 x 4 grid on the dorsum of each foot – or saline placebo. 12 weeks later each patient crossed over to the other treatment. Mean pain scores decreased by about 2.5 points in the BT group vs 0.5 points in the placebo group – a significant difference.

Comment: This is an expensive and labour intensive intervention. Further confirmatory large scale trials are required.

Ref: Yuan R.Y. et al Neurology 2009 Apr 28; 72 : 1473.

2.2 Prevention of diabetes – a new drug – Voglibose.

Life style modification (LSM) and pharmacological interventions with metformin, rosiglitazone or acarbose have prevented progression from impaired glucose tolerance (IGT) to Type 2 diabetes. LSM is more effective but more labour intensive and less sustainable than drug interventions. A manufacturer supported randomized Japanese trial evaluated voglibose, an alpha glucosidase inhibitor similar to acarbose.

1,800 patients who had IGT and atleast one other diabetes risk factor received voglibose or placebo t.i.d along with diet and exercise and followed up for 3 years. The trial was stopped at 48 weeks. Voglibose recipients progressed to diabetes less vs placebo (3.6% vs 9.4%). More patients taking voglibose reverted to normoglycaemia (59% vs 46%). Side effects mainly GIT, occurred more often with the active drug.

Comment: Alpha glucose inhibitors prevent progression from IGT to diabetes. They may be particularly effective with Asian diets which contain more carbohydrates than Western diets.

Ref: Kawamori R. et al Lancet 2009 May 9 ; 373 : 1607.
Sheen A.J. IBID: 1579.

2.3 What happens to abnormal TSH levels in children?.

A population based study of about 1 million children was undertaken in Israel. 121,000 of these had a TSH taken and repeated within 5 years. The age range of the children was 6 months to 16 yrs. Those with low initial levels had normal levels on the 2nd test in 79%.

Those with mildly elevated TSH (5.50 – 10.0 miu/l) 74% had normal levels on the 2nd test.
Those with highly elevated TSH (>10miu/l) 40% had normal levels on the 2nd test.
Female sex and TSH levels > 10miu/l were significantly associated with persistently elevated TSH levels in multivariate analysis.

Comment: Most TSH abnormalities normalized with time. A second test is mandatory in children with elevated TSH levels.

Ref: Lazar L et al J.C.E.M. 2009 May ; 94: 1678.

2.4 Microdose transdermal oestrodiol (MTO) for preventing bone loss.

In a double blind randomized study of 340 post menopausal women (mean age 66) , the cohort received either daily MTO 0.014 mg (menostar) or daily 60mg of Raloxifene for 2 years. All women had intact uteri and lumber spine osteopenia.

Lumber spine BMD increased from base line by 2.4% in the MTO group and by 3% with Raloxifene. Total hip BMD also increased significantly more in those taking raloxifene than in those taking MTO (1.8% vs 0.4%). Resorption markers also decreased more in the raloxifene group. Endometrial and breast changes were similar and minimal in both groups.

Comment: Raloxifene seems to be better than MTO in preventing bone loss. MTO however is a reasonable alternative for women who have BMDs that are low but are insufficient to meet the indications for the use of approved antiresorptive agents.

Ref: Schaefers M. et al Menopause 2009 May/June: 16 : 559.

2.5 Fenofibrate in diabetes- does it reduce amputation rates (FIELD study)?

10,000 patients with DM not on lipid lowering therapy were randomized to daily fenofibrate 200mg or placebo for 5 years. The primary outcome of first MI or CV death were not different in the 2 groups. However, fenofibrate recipients had significantly less progression of albuminuria and fewer retinal laser procedures.

The tertiary end point of this FIELD study was non traumatic lower limb amputations. This occurred less often in the group that received fenofibrate (0.9% vs 1.4%). This was mainly in below ankle amputations. There was no effect in above ankle amputations. This effect of fenofibrate on amputation risk was independent of dyslipidaemia and glycaemic control. The NNT to prevent one amputation was 197 but the NNT was only 25 for patients with previous foot ulcers and albuminuria.

Comment: The aggregate results of the FIELD study suggest that fenofibrate

a) inhibits progression of albuminuria.
b) Decreasesd requirement of retinal laser procedures.
c) Decreased below ankle amputation rates due to microvascular disease especially in patients with previous foot ulcers and albuminuria.
d) This effect is independent of glycaemic and lipid control.

Ref: Rajamani K. et al Lancet 2009 May 23; 373 : 1780.

2.6 Are acupuncture or Chineese herbal combinations effective in reducing hot flushes in post menopausal women?.

The effects of acupuncture + self care (Soy herbs, physical activity, relaxation techniques) vs self care alone was studied in 248 post menopausal women. At 12 weeks women in the acupuncture group reported greater reductions in hot flush frequency and intensity ($P < 0.001$) and greater improvement in somatic symptoms and sleep quality.

Another study in 217 post menopausal women evaluated 2 doses of MF 101 (5g or 10g daily) , which is a combination of 22 Chineese herbs that is not approved for clinical use or licenced as a herbal product in the US. MF 101 b inds equally to both Alpha and Beta oestrogen receptor but activates only oestrogen receptor Beta pathways. It thus acts like a SERM. At 12 weeks, hot flush frequency decreased by 48% in women who received the higher 10g daily dose while those who received placebo decreased by 37% (P=0.05) and the proportion of women with > 50% reduction in hot flush frequency was 16% higher than in the placebo group (P=0.03). MF 101 was associated with slight increases in endometrial thickness.

Ref: Borud E.K. et al Menopause 2009 May/June; 16: 484.
Soares C.N. IBID : 434 (also 458 and 428).

2.7 Fructose – Is it suitable for diabetes?

Fructose is unique because despite its sweetening power, it has a low glycaemic index, making it comparable to unrefined complex carbohydrates. Fructose regulates its own transporter (GLUT 5). Its metabolism is by fructokinase which is in part insulin dependent. It is found in fruits, honey, cooking sugar, sweetened drinks, diabetic jam and in manufactured foods that used fructose syrup or crystalized fructose.

It use has risen sharply over the last four years parallel to the prevalence of obesity, diabetes and hypertension. It is now known that fructose can contribute to the metabolic syndrome, insulin resistance, increased triglycerids, abdominal obesity, increased BP due to activation of the RA system, hyperuricaemia, oxidative stress, endothelial dysfunction, glomerular lesions and hepatic steatosis. These effects appear not to be due to excessive caloric intake, but rather to the specific metabolism of fructose.

All these findings place fructose in an ambiguous position, with possible beneficial effects on glycaemic balance but probable harmful effects in terms of metabolic and cardio vascular disease. The maximum daily consumption in diabetic subjects is 50g of fructose, provided it is used in place other carbohydrates.

Comments: The correct intake of fructose appears to be "neither too little nor too much. It is best not to exceed a fructose intake of 50g/d in diabetes.

Ref: Schlienger JL Int J Metab 10 June 2009

2.8 Dose dual blockage with ACE inhibitors +ARBs improve nephro protection?

ACE inhibitor (ACEI) mono therapy may sometimes result in an escape phenomenon resulting in angiotensin I accumulation leading to angiotensm II generation. Dual blockage leads to a small additional decrease in BP compared to mono therapy. This incremental fall in BP is only a fraction what is commonly observed with addition of a CCB or a thiazide diuretic added to an ACEI. The dual blockade was not successful in heart failure patients also. A meta analysis found no reduction in all cause mortality but only a reduction in heart failure hospitalizations. More patients discontinued medication in the combination arm because of increase in creatinine , hyperkalaemia and hypotension. No data at present exists showing a cardio protective effect of dual blockade compared with ACEI in coronary artery disease.

Nephrologists and diabetologists use the combinations because they reduce the proteinuria by 25% more than either drug alone. However the estimated GFR decreased more with the combinations than with ramipril (ONTARGET) alone. The primary composite renal outcome of the combination therapy – dialysis, doubling of serum creatinine and death increased significantly more (ONTARGET trial). The secondary renal endpoint of dialysis or doubling the serum creatinine was also significantly more with combianation therapy.

Comments: These findings strongly argue against a nephro protective effect of dual RAS blockade. Whether combination therapy would be more successful in advanced proteinuric chronic kidney disease is at present unknown.

Ref: Widimsky J Eur Cardiol J 4 May 09

2.9 Adiponectin (A) – Is it a truly cardio protective adipokine?

A increases insulin sensitivity via its effects in liver and muscle. It enhances glucose and fatty acid oxidation and suppresses hepatic glucose synthesis. It also has anti inflammatory and atheroprotective properties. It increases nitric oxide productions, suppresses adhesion molecules expressions by endothelial cells, monocyte adhesion to the endothelium and foam cell formation.

High adiponectin levels were associated with lower risk for MI and for developing diabetes and other coronary events. These findings have not been corroborated in the British Regional Heart Study.

Comments: It would probably be safer to consider that adiponectin is primarily associated with Type 2 DM and metabolic syndrome and that its relationship with CAD requires clarification.

Ref: Karastergiou J & Kaski JC Eur Cardiol J 20 April 2009

2.10 Primary prevention of CV events in diabetes – is aspirin useful?

In a meta analysis of 6 randomized controlled trials involving more than 10,000 patients, investigators determined the effects of aspirin (100-650mg/d) in patients with diabetes but without preexisting CV disease.

Compared with placebo or no treatment, aspirin did not lower risk for major CV events (MI, Stroke or CV deaths) or allcause mortality. When the outcomes were assessed individually, aspirin did not lower risk for MI, Stroke or CV death. However after stratification by sex, aspirin substantially lowered risk for MI in **men** (RR 0.57) but not in women.

Comments: The ADA in 2010 Clinical Practice Recommendations says "Consider aspirin therapy (75-162mg/d) as a primary prevention strategy in those with type 1 or type 2 DM at increased CV risk (10yr risk >10%). This includes most men >50yrs of age or women >60yrs of age who have at least 1 major additional risk factor (family history of CVD, HT, Smoking, dyslipideamia or albuminuria). However this meta analysis does not support **routine** use of aspirin for primary prevention **except for prevention of MI in men with diabetes.** The editorialists recommend that clinicians focus on minimizing CV risk factors before recommending aspirin for primary prevention of CV events. Potential benefits of aspirin for primary prevention should be weighed against potential harms such as GI bleeding.

Ref: De Berardis G et. al. BMJ 2009 Nov 6
Haynes R et. al. BMJ 2009 Nov 6

2.11 Insulin vs Oral therapy for newly diagnosed type 2 DM

Patients with newly diagnosed type 2 DM are usually started on oral agents and insulin administered only if glycaemic control remains inadequate after prolonged multi drug oral therapy.

In a trial of 58 such patients (mean A1c = 10.8%) researchers compared early insulin therapy and triple oral therapy. After a 3 months run in period during which all patients received insulin and metformin to normalize A1c levels, patients were randomized to receive insulin (NovoMix 70/30 bd) + metformin or a combination of metformin, glibenclamide and pioglitazone. At 3 yrs mean A1c level was 6% in both groups. Mean weight gain was slightly more with triple oral therpy (7.2 vs 4.5 kg ; P =0.09) hypoglycaemic episodes, quality of life and treatment satisfaction did not differ significantly between groups.

Comments: Early insulin therapy can be well received by patients with newly diagnosed type 2 DM. Fears of excessive weight gain and hypoglycaemia with early insulin therapy compared with multiple oral agents are not warranted. These patients however are not typical because insulin was given for the first 3 months and therefore avoided prolonged glucose toxicity which would have been present for a long time if orals were started from day 1. Wider adoption of early insulin therpy may preserve beta cell function.

Ref: Lingvay J et. al. Diabetes Care 2009 Oct;32:1789

2.12 Ghrelin – some aspects.

Three peptides are critical players in growth hormone (GH) production. They are GH releasing hormone (GHRH), somatostatin (S) and GH releasing peptide Ghrelin.

Ghrelin is expressed in the hypothalamus, pituitary, stomach, upper GIT, Kidney and the CVS. A subset of gastric oxyntic cells are now known to cosecrete both Ghrelin and Motilin. Ghrelin act via the Type 1a secretagogue receptor to stimulate GH secretion 5 – 20 fold. It stimulates GHRH release and inhibits somatostatin action. Mutations of the Ghrelin receptor are associated with short stature. Therefore Ghrelin analogues may have utility in the treatment of short stature and GH deficiency states if GHRH release and somatotrope function are preserved. Ghrelin levels are increased in starvation, fasting between meals, ongoing weight loss after gastric bypass surgery, end stage liver and kidney disease, malnutrition and cachexia. Conversely nutrient intake (CHO > protein > fat), obesity, hypogonadism, insulin and somatostatin reduce plasma Ghrelin levels. **Ghrelin is the only systemically active appetite hormone known.** Appetite enhancement is antagonized by inhibitors of neuropeptide Y, Agouti related peptide and Orexin. Appetite is potentiated by inhibitors of the anorexigenic peptides melanocortin or CRH.

Ghrelin inhibits insulin secretion and Ghrelin receptor blockers (GRBs) enhance insulin secretion and improve glucose control. Ghrelin is also produced in **Islet epsilon cells**.

Ghrelin stimulates upper GI motility and Ghrelin analogues are under evaluation as prokinetic agents for treatment of gastroparesis and post operative ileus.

Ghrelin also inhibits fat oxidation, induces weight gain, reduces diastolic BP and increases cardiac output. Frailty and congestive heart failure are two further exploratory therapeutic applications of Ghrelin.

Comment:

1 Key features of Ghrelin.

- Widely expressed in stomach, brain, pituitary and pancreas.
- Receptors - nearly ubiquitous.
- Potent GH secretagogue.
- Enhances appetite, reduces insulin secretion, stimulates GI motility.

2. Potential application of Ghrelin analogues.

a) Ghrelin agonists.

- Increase anabolism in cachectic states.
- Stimulates motility in disorders such as gastroparesis and ileus.
- Promote appetite in anorexic states such as anorexia nervosa and post chemotherapy.
- Increase linear growth in short stature when GHRH is present.
- Decrease diastolic after load in patients with heart failure.

b) Ghrelin antagonists.

- Increase glucose induced insulin secretion in Type 2DM.

Ref: Endocrinology Update Mayo Clinic 2008 ,3 (3); 1-2.

2.13 Gestational diabetes (GD) – some aspects.

The targets for GD are

a) Capillary fasting glucose < 5.3mmol/l. (95mg/dl).
b) One hour post prandial Plasma glucose < 7.8mmol/l (140mg/dl).
c) Two hour post prandial plasma glucose < 6.7mmol/l (120mg/dl).

Obesity is an independent factor influencing outcome in GD women treated with diet but not in those with insulin.

Outcomes are also dependent on the foetal abdominal circumference measured by ultrasound. A circumference above the 75th percentile requires intensive treatment.

Lowering of mean maternal glucose to < 4.8mmol /l (86mg/dl) is associated with small for gestational age (SGA) babies.

Capillary glucose values during treatment with metformin and / or insulin is related strongly and independently to the primary outcome composite of neonatal outcomes, maternal pre eclampsia and frequency of large for gestational age (LGA) infants. The fasting capillary glucose predicted neonatal complications while the post prandial capillary glucose related to risks of pre eclampsia and LGA infants. When metformin is used, supplemental insulin should be used readily if glucose targets are not achieved.

Ref: Rowan J.A. et al Diabetes Care 2010 Jan ; 33 (1): 9-16.

2.14 Is insulin glargine safe in pregnancy?.

Insulin glargine is a long acting insulin analogue that acts for 24 hours and is peakless. Beef and Pork insulins used earlier were shown to cross the placenta via the formation of insulin antibody complexes, leading to foetal macrosomia despite excellent glycaemic control. The possible consequences of transplacental transfer of insulin analogues such as glargine include teratogenecity, immunogenecity and mitogenecity. Further glargine has a 6-8 fold increased affinity for the IGF -1 receptor. Such growth promoting properties may lead to increased foetal growth and other mitogenic effects should insulin cross the placenta.

In a recent study, insulin glargine was shown not to cross the human placents to a measurable extent if the sc dose did not exceed 0.3 U/Kg. This is perhaps due to the placenta possessing receptors for insulin as well as a capacity for rapid degradation by insulin degrading enzymes.

Ref: Pollex E.K. et al Diabetes Care 2010 Jan; 33 (1): 29 – 33.

2.15 What are the indications for the use of metformin in prediabetics?.

Progression from prediabetes can be prevented or delayed by life style change and / or medication. The ADA issued a consensus statement recommending early identification and preventive treatment in high risk individuals. The following are recommended for treatment with metformin in addition to life style modification which includes weight loss and physical activity.

Individuals with both IFG and IGT + 1 additional risk factor (age < 60, BMI > 35, family history of diabetes in first degree relative, elevated triglycerides, reduced HDLC or A1C > 6.0%).

This prevention of progression is important because 25 – 39% of patients with IFG or IGT go on to develop diabetes over a period of 5-10 years. Further prediabetes alone is associated with an increased risk for cardiovascular disease and microvascular complications. Other agents which prevent progression are Acarbose (risk reduction – RR = 25%), Rosiglitazone (RR = 62%) and Orlistat (RR = 56%), but they have many side effects when given for long periods and expensive too. Therefore Metformin is the leading candidate for preventive treatment.

In addition to prevention of progression to diabetes, emphasis should also be made to treat comorbid conditions such as hypertension, hyperlipidaemia and obesity. Other conditions such as metabolic syndrome, NASH, polycystic ovarian disease and gestational diabetes also warrant preventive metformin therapy. Delaying or preventing diabetes with metformin is cost effective.

Ref: Rhee M.K. et al Diabetes Care 2010 Jan; 33 (1): 49 -54.

2.16 What are the associations of microalbuminuria (MA) in pregnancy?

MA in early pregnancy is associated with a four fold increased risk of developing pre eclampsia. Early MA is also associated with pre term delivery (delivery before 34 weeks). A1C values during pregnancy are also highly predictive of both pre eclampsia and pre term delivery. A trial of antihypertensive treatment in normotensive microalbuminuric pregnant women to prevent pre eclampsia is recommended.

Ref: Jensen D.M. et al Diabetes Care 2010 Jan; 33 (1): 90 – 94.

2.17 Truncal pruritus (TP) – a new symptom of diabetic neuropathy.

An itching sensation is thought to be transmitted by small unmyelinated sensory fibres. Pruritus may therefore reflect some abnormality of the peripheral nerves. A study of 2,656 diabetics and 499 non diabetics was undertaken. The incidence of TP in diabetic subjects was significantly higher than in age matched non diabetic subjects. Presence of abnormal sensations in the feet and absent ankle reflexes were independent risk factors for TP. The prevalence of TP in diabetics was 12% which is 4 times of that of non diabetic subjects. These patients also had impaired blood pressure response to a head up tilt test and impaired heart rate variability during deep breathing. Since these are evidence of sympathetic dysfunction, it is plausible that TP is also a manifestation of autonomic neuropathy.

Ref: Yamaoka H. et al Diabetes Care 2010 Jan; 33 (1): 150 – 155.

2.18 A new risk factor for vertebral fractures (VF) – endogenous secretory receptor for advanced glycation end products (esRAGE) in Type 2 diabetes.

Type 2 diabetics have an increased risk for hip fracture and for vertebral fractures. The BMD in diabetics at any site fails to assess the risk of VF, suggesting that bone quality may be more important than bone density in defining bone strength in Type 2 DM. Bone quality is known to be determined by bone architecture, turnover, accumulation of micro damage, mineralization and properties of bone matrix proteins such as collagen. Pentosidine is one of the well known advance glycation end products (AGEs), and its bone content in spontaneous diabetic rats has been shown to increase concurrently with the onset of diabetes, resulting in impaired mechanical properties of the bone despite normal BMD. Serum Pentosidine levels are associated with the presence of VF in post menopausal diabetic women independent of BMD.The serum levels of esRAGE and esRAGE to Pentosidine ratio are more useful that BMD for assessing the risk of VF in Type 2 diabetics. The serum levels are negatively associated with the presence of VF. The levels were significant in both sexes. The mechanism of AGEs is that they inhibit the synthesis of Type 1 collagen and osteocalcin in primary osteoblasts and the secretion of PTH from the parathyroid cells. They also impair bone matrix production and mineralization of osteoblasts.

Ref: Yamamoto M et al Diabetes Care 2009 Dec:32 : 2263 – 2268.

2.19 For diabetics with multi vessel coronary artery disease which is better – CABG or Stenting?.

The BARI (1996) study showed that the 5yr mortality rates for diabetics receiving angioplasty were double those for CABG. In this era of drug eluting stents which is the better procedure?.

The CARDia trial included 510 diabetics randomized to CABG or stenting. Drug eluting stents accounted for 71% of the stent procedures. Results at 1 yr showed that the primary end point (a composite of death, MI, stroke and repeat revascularization) was met in 11% of CABG and 17.5% of stent patients (P = 0.04) which thus favours CABG. When revascularization was removed from the composite, the secondary end point (Death, MI and stroke) was met in 10.2% of CABG and 11.6% of the PCI group(P = 0.63) – not significant.

Comment: Although CABG has its advantages, stenting may now be considered a reasonable strategy in diabetic patients with multivessel disease. However multiple stenting is expensive and further revascularization may make it even more exorbitant.

Ref: **Kapur A et al J Am Coll Cardiol 2010; 55:432-440**

2.20 Pheochromocytoma (P) – some aspects.

P is frequently diagnosed nowadays before symptoms develop because of genetic screening for hereditary endocrine syndromes or incidental discovery of an adrenal mass on CT or MRI. 5% of all adrenal incidentalomas have been proved to be Pheos. 50% of all Pheos are initially detected as incidentalomas, often without spells or hypertension. If a Pheo is responsible for classic Pheo spells, then the biochemical tests are always unequivocally abnormal ie increases more than 5 times the upper limit of the reference range. However, in the asymptomatic patient with P, fractionated metanephrines and catecholamines may be in the normal range because the neoplasm has been detected in the prebiochemical phase. In this case the diagnosis of P can only be made by the characteristics of the imaging technique. The typical P appears as a dense (Hounsfield units > 20) vascular mass with slow contrast wash out (< 50% at 10 mts after contrast) compared with the much more common adrenocortical adenoma which is usually hypodense (Hounsfield units <10) and has a rapid contrast wash out (> 50% at 10 mts).

Plasma fractionated metanephrines have a 15% false +ve rate, usually because increased plasma normetanephrine component. 97% of patients with plasma normetanephrine concentrations (when taken alone) above the upper limit of the reference range do not have a Pheo.

False +ve biochemical results may result from the following drugs.

- Tricyclics.
- L-dopa.
- Ethanol withdrawal.
- Clonidine withdrawl.
- Antipsychotics.
- Prochlorperazine.

When CT / MRI is negative but suspicion of P is very strong, an I 123- MIBG scan is indicated. The normal adrenals takes up this scan and the intensity of the uptake is usually asymmetrical. An adrenal gland should never be resected on the basis of asymmetrical adrenal uptake of MIBG unless the uptake pattern correlates with a vascular adrenal mass on CT.

Ref: Endocrinology Update Mayo clinic 2009; 4 (4): 1-3.

Compiled by :- Dr. Henry N. Rajaratnam
MD, FCCP, FRCP (Lond), (Hon) FRACP, (Hon) FSLCGP, FACE