Almost 30 years ago at the annual Banting lecture, Dr G M Reaven stated that the core of Met-S is insulin resistance.

Focusing on certain core aspects of this complex pathophysiology, Prof R DeFronzo stated that there are eight factors that progressively march you from Met-S into the complicated realm of clinical disease. He terms these the ‘ominous octet’. From the time of diagnosis to the clinical presentation, is an average of three years when a patient could present with type 2 diabetes mellitus, symptomatic cardiovascular disease, sleep apnoea, fatty liver disease, arthritidies and malignancies. The problem is that by the time one has diagnosed Met-S, 10%-12% of patients already have retinopathy and 15% have peripheral neuropathy.

**THE ‘HATEFUL EIGHT’**

The ‘hateful eight’, (a la Mr Q Tarintino) starts with:

1. Muscle insulin resistance, when glucose in no longer utilised or stored as glycogen and there is an increase in gluconeogenesis (cori cycle) with a rise in post prandial glucose and with the start of muscle atrophy.

2. Liver gluconeogenesis with rise of fasting glucose and the release of triglycerides as VLDL and the start of steatosis.

3. Pancreatic beta cell apoptosis with up to 80% cell loss before the clinical presentation. This is related to TX-NIP and amylin (amyloid polypeptide) islet cell destruction.

4. Adipocyte fat storage lipolysis and change to adipokine secretion of tumour necrosis factor TNF-a, interleukin -6 IL -6, resistin, plasminogen activator inhibitor-1 and decrease in adiponectin. Leptin is secreted and very resistant to its anorexigenc effects and it has been shown to be predictor of cardiac disease in Met-S.

5. Change gut microbiota with increased polysaccharide absorption and loss if incretin effect with reduced glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide increase.

6. Pancreatic alpha cell stimulation with hyperglucaemia with resultant fasting hyperglycaemia.

7. Increased renal glucose reabsorption in proximal tubules via sodium-glucose co-transporter 2.

8. Change of central nervous system hypothalamus nuclei response to feeding and satiety with polyphagia, night eating disorder and up to 30% depression. Changes in pituitary hormones with male hypogonadism and female hyperandrogenisation and increased pigmentation via MSH-a causes lentigines (freckles), acanthosis nigricans and so-called bronzed diabetes.

**Eating plan:** Recently, eating plans have been highlighted with regards to the rapid escalation in the incidence of the metabolic syndrome and type 2 diabetes mellitus. To date, the best diet is the dietary approaches to stop hypertension (DASH) diet with reduced salt intake. The Banting diet is a popular hot topic in SA and has changed the eating habits of thousands of people due to its reduction in glucose and fructose substrates and the controversial eating of high saturated fats.

Also recently, the intermittent fasting diet which causes and stimulates SIRT-1 gene, in a similar way to the use of resveratrol and thereby stimulates mitochondrial function and has anti-ageing benefits. Fasting diets cause a rise in fasting-induced adipose factor, which stimulates PPAR-gamma and causes insulin sensitivity to return.

Of all the plethora of diets, the easy rule is to cut the salt, cut the sodas, cut the sugars. Slowing down the progress from Met-S to diabetes mellitus has been documented by drinking 4-6 cups of espressed coffee per day or drinking 4-6 cups of green tea. Both without sugar.

All dairy products have been shown to be beneficial and causes weight reduction. The more fermented foods eaten such as yoghurts, cottage cheese, crème fresh, kefir, the better. Should we prescribe a diet for a patient as therapy? Diets high in garlic, watermelon and beetroot increase endothelial nitric oxide synthase and reduce blood pressure.

**Exercise:** We must walk a minimum of 150 minutes per week and a minimum 10 000 steps per day. Good exercises to reduce visceral fat and improve the immune innate and adaptive responses are the combined aerobic (cardio) and anaerobic (resistance) exercises.

Best by far is high intensity interval training. Think boxing, mixed martial arts, dancing and sprinting. High-speed efforts over a short period of time followed by slow-paced walk then again high-speed effort. This can be done with or without weight resistance. The best
form of casual exercise other than basic brisk walking is doing outdoor chores.

**Sleep:** This is the third pillar of medical wellbeing. We must sleep for between 6-8 hours per night and we must be asleep between 12h00 midnight and 05h00 am to reduce nocturnal circadian cortisol secretion. No light pollution, no TV screens switched on. Total dark rooms are best. No use of electronic devices at least 60 minutes before sleep. The blue light frequencies from screens trigger cortisol release. Simple apps such as blu-light-block are helpful. Daytime naps are associated with increased hypertension. Try to avoid antipsychotic medication to aid with sleep due to weight gain and the resultant worsening of the metabolic syndrome. Shift and night workers are particularly at higher risk of the Met-S.

**Comorbidities:** Of all the presenting conditions, the treatment of hypertension is paramount. Firstly, reduce sodium salt intake and increase potassium salt usage. Hypertension in Met-S is associated with a high renin-angiotensin stimulation and so ACE inhibitors and ARBs are first-line therapies. Co prescribed with calcium channel blockers, there has been shown a reduction in pancreatic beta-cell apoptosis by inhibiting Tx-Nip, improvement of endothelial dysfunction and renal protection.

The third arm is often diuretic use. We need to be cautious because thiazide diuretics are a cause of the Met-S, resulting in hyperuricaemia, hypokalaemia, hyperglycaemia, hypercalcaemia and dyslipidaemia. The use of indapamide is better, but there is also associated with hyperuricaemia, hypokalaemia and hypomagnesaemia. Spiractin in low doses of 12.5-25mg daily has come to the fore due to the secondary hyperaldosteronism, female hyperandrogenisation and fatty liver disease. We have been told to treat to target in both primary and secondary dyslipidaemia. Recently, the AHA simply stated: “Half the LDL!”

Statin use is controversial in Met-S in patients younger than 65 years of age. There is concern of increasing progression to type 2 diabetes mellitus and an increased incidence in dementia. There is also a 20% risk of fibromyalgic symptoms.

The fibrates have shown to increase HDL, reduce triglycerides (TG) but only result in a 25% reduction of LDL. Ezetrol add-on therapy only causes a 20% reduction. Niacin has been shown to have no response in dyslipidaemia outcomes and are often prescribed to balance HDL and TG. Omega-3 fish oils and diets high in mono-saturated fats (Mediterranean diet) with nuts, especially walnuts, and eating oily fish at least twice a week are beneficial.

In **diabetes mellitus,** avoid sulfonylureas as they cause progressive beta cell loss and progression of disease with rising of the HbA1c levels. Also delay insulin use, as it causes weight gain and has numerous hypoglycemic events. Aim to treat HbA1c <6% in Met-S due to presence of retinopathy and peripheral neuropathy early on in the disease at normal HbA1c levels.

In **obstructive sleep apnoea,** there are risks of hypertension, fatigue, arrhythmia and sudden death. Polysomnography sleep studies with nocturnal oxygen desaturation are important adjuvant therapeutic and prognostic tests. Met-S is the commonest cause of chronic fatigue syndrome.

**Fatty liver** is an important prognostic risk factor. Over 30% of patients are positive sonographically before any transaminase derangements. Treat by reducing fructose intake, as it is directly hepatotoxic. Also reduce alcohol intake as one can have nonalcoholic steatohepatitis with alcoholic steatohepatitis. To date, weight loss and glycaemic control are best therapies. Recently, the use of oral dipeptidyl peptidase-4 (DPP-4) inhibitors has been shown to reduce fatty liver. If not treated, over 33% will progress to liver cirrhosis, portal hypertension, liver failure and hepatocellular carcinoma. With weight loss, always watch out for increase in cholecystitis and/or cholelithiasis.

In **gut health,** the gastrointestinal tract endothelium is the largest immunologically active organ. There are anatomically high concentrations of lymphatics, lymph nodes and macrophages. First phase post prandially is portal flow to the liver. Gut bacteria microbiota must be balanced otherwise this leads to colonic dysbiosis. The phylae that are important are the gram positive fermentates bacillus, clostridium,
Lactobacillus and mycoplasma. 30% Must be gram-negative bacteria, which aid in digesting fibre to monosaccharides and produce vitamin K1 and K2. The oligosaccharides and fibre increase gut GLP-1.

Mice raised in germ-free environments are resistant to dietary-induced obesity and Met-S. Once they are exposed to germ full environments, they have a 60% weight gain and sudden onset of insulin resistance.

Intermittent fasting has shown to help balance gut bacteria. To aid in GIT, microbiota diets must as least have 100g fibre per day. Oligadon are immune reactants in the gut and a possible trigger of ‘leaky’ antigens.

Antibiotic stewardship is paramount. Azithromycin has recently come under the spotlight with regards to causing gut lactic acidosis. These are resistant to dietary-fibre increase gut GLP-1.

What of future possible therapies? Could faecal transplantation be foreseen? The overuse of proton pump inhibitors has raised issues around gut microbiota and an increase in Met-S.

**SPECIFIC MEDICATION**

The biguanide, metformin, remains the gold standard of treating Met-S and since 1977 the UK Prospective Diabetes Study has shown that it increases insulin sensitivity and has protective functions with regards to cardiac outcomes, especially macro-vascular events, hormonal imbalances, and certain malignancies. The problem is by three years, 50% of patients will need add-on therapy to keep HbA1c <7%. The controversy surrounding its use lies in renal dysfunction. Can one safely prescribe metformin in eGFR <35? In general, metformin is very safe, cost effective, can be used in children and has a low incidence of the dreaded lactic acidosis.

Thiazolidinediones are rarely used due to the concern over their cardiac safety. They are best in the pre-diabetic phase. They act as PPAR-gamma agonists and improve mitochondrial oxidation and have shown numerous benefits with improving insulin sensitivity, preserving beta cell function and having anti-atherogenic effects but their high cost and weight gain potential restrict their use.

The GLP-1 agonists include exenatide and liraglutide. They are gut peptides that account for the incretin effect and its benefit is weight loss and a reduction in both postprandial and fasting glucose levels, due to its dual function on beat and alpha pancreatic cells. They have shown cardio protection beyond their HbA1c-lowering ability (LEADER trials) and they are renally safe. Their use is limited by the side-effect profile of severe initial nausea, the subcutaneous route for administration, the cost and limited funding. Patients with a gene transcription TCF7L2 have an impaired response to GLP-1.

DPP-4 inhibitors are indirect enhancers of GLP-1 incretin response. They include sitagliptin, vildagliptin and saxagliptin. They are unfortunately weight neutral, but they do have favourable cardio outcomes and are safe in renal dysfunction, with very low risk for dangerous hypoglycaemia. They are synergistic when used with metformin.

SGLT2 inhibitors reduce renal reabsorption of glucose in the proximal convoluted tubules creating glycosuria. They have very good cardiac outcomes, especially the lowering of blood pressure, but there remain concerns about bladder infections, acidosis, amputation rates and fracture risks. We await their registration in SA.

**NON-SPECIFIC MEDICATIONS**

The one drug registered for weight loss is phentermine (Duromine). It has been prescribed since the 1970s and is recommended for safe short-term initial therapy for 12 weeks, as a trigger to aid weight loss by calorie intake restriction. It functions at the hypothalamic anorexigenic cocaine and amphetamine regulated transcription nuclei. Topiramate is a registered anti-epileptic and anti-migraine medication and it is often used off label for weight loss. A combination with phentermine in the US is called Qsymia, found to be synergistic in weight loss benefits.

The lipase inhibitor orlistat is the only other registered weight loss agent. It inhibits dietary fat absorption by 70%, thereby effectively causing steatorrhoea. The weight loss benefits are limited, as fat does not cause fat and there is no change in insulin sensitivity, which is the core to the Met-S. Some benefits are noted with regards to a reduction in triglyceride levels.

A dynamic vitamin essential to use in the Met-S is vitamin D. Most people should have vitamin D levels of 75-100 if they have a Met-S. This can be done using ergocalciferol 50000u biweekly or vitamin D3 2000u daily.

**SURGERY**

Surgery has shown profound weight loss with reversibility of the Met-S and even a cure of over 85% of type 2 diabetes mellitus. The one condition that tends to remain is hypertension. Limited procedures recently have come to the fore, such as the less invasive duodenal resurfacing called REVITA-1. All the surgical procedures aim to decrease high calorie absorption, lower food and glycaemic loads and result in a 10-fold increase in GLP-1.

References available on request.