SANOFI diabetes specialist weekend 2012, Cape Town

Sanofi hosted their annual specialist diabetes meeting in Cape Town in November 2012. Pieter Taljaard of Sanofi opened the meeting with a brief address, raising the concern that the number of diabetes patients in South Africa is increasing annually by 18 000. Sanofi are committed to treatment and innovation in the management of types 1 and 2 diabetes in both the public and private sectors.

It is increasingly accepted that the long-term outcomes of chronic illness are significantly improved when healthcare is managed with a team approach. The patient is integral to the team, with healthcare workers providing the support system that caters to the patient’s specific circumstances. Guidelines should serve to assist the clinician in tailoring a suitable response that considers the unique combination of circumstances any patient may have. Individualisation of patient care is paramount, not only in terms of pharmaceutical therapies but also in the allied field of psychosocial support, which encourages lifestyle alterations and therapeutic adherence.

Examining the players implicated in the pathogenesis of type 2 diabetes (T2DM), De Fronzo’s ‘ominous octet’ was often referred to during the Sanofi meeting. The implications of De Fronzo’s review for T2DM therapy are that treatment will require multiple combinations of agents to correct multiple pathophysiological defects, based on known pathogenic abnormalities in the individual rather than simple reduction in HbA1c levels. Treatment must also be started early in the natural history of T2DM if β-cell failure is to be prevented (Fig. 1).


Treating type 2 diabetes in 2012: choices based on facts

Prof Larry Distiller, endocrinologist, CDE, Houghton

Previous estimates and projections on the global prevalence of T2DM have had to be revisited due to the obesity-driven exponential increase in diabetes. The latest figures indicate more than 780 million people will have diabetes by 2025, approximately one in every 10 people on the planet.

Meeting the challenges of diabetes treatment is confounded by many factors. South Africa currently represents the third most obese population in the world, with an increase in body mass index (BMI) of 5 to 8 kg/m² over the last two decades. Healthcare workers are weighed down by the evidence, the treatment guidelines of various authorities rarely reach consensus, and protocols are becoming increasingly more complex in light of the multiple new therapeutic agents available for diabetes management.

Moreover, patient-centred care that is respectful of and responsive to the needs and values of the patient shows improved clinical outcomes. The doctor no longer dictates the therapeutic options but negotiates the route with the patient. When profiling the patient with diabetes, the doctor needs to ascertain the attitudes of the individual and what motivates him/her, the risks of hypoglycaemia
and other adverse events, the duration of diabetes and life expectancy, and the presence of microvascular disease, cardiovascular disease and other co-morbidities. Targets for HbA1c levels will differ accordingly.

Lifestyle intervention is effective; however the willpower required for lifestyle changes is often short lived. Because of this, many protocols recommend initiation of first-line therapy (usually metformin as monotherapy) on diagnosis of diabetes. This is based largely on the United Kingdom Prospective Diabetes Study (UKPDS) sub-group analysis of 342 obese patients reflecting an improved relative risk of myocardial infarction, all-cause mortality and diabetes-related deaths and end-points with earlier metformin initiation.

The side effects of metformin include gastrointestinal disturbances, vitamin B12 deficiency, and in rare cases (1:100 000) lactic acidosis. In the context of renal impairment, dose reduction or cessation of the drug is indicated.

Prof Distiller added that sulphonylureas (SU) have a small but significant benefit in terms of heart disease, although this risk–benefit in conjunction with insulin use remains uncertain. Although relatively cheap, SU have the disadvantage of increased hypoglycaemic events and weight gain. Use of glibenclamide is no longer recommended due to the risk of hypoglycaemia and the International Diabetes Federation (IDF) recommends slow-release glimepiride as the SU of choice. Prof Distiller recommended glimepiride as another reasonable alternative.

Acarbose has seen limited use in South Africa. Its cost versus its relatively weak blood glucose-lowering effect and unpleasant gastrointestinal side effects have not made it popular in this region. In terms of the thiazolidinediones, rosiglitazone has been withdrawn due to fears of increased risk of cardiovascular disease. Pioglitazone has been withdrawn from French and German markets and has a ‘black-box warning’ in the USA due to concerns surrounding increased risk of fractures and bladder cancer.

Incretin-based therapies are relatively recent additions to the treatment options available for T2DM. The dipeptidyl peptidase (DPP-4) inhibitors are all equivalent in reducing HbA1c levels (0.5–1%). They have the advantage of no hypoglycaemia, and possibly, preservation of β-cell function. The glucagon-like peptide-1 (GLP-1) agonists exhibit a 0.8 to 1.5% reduction in HbA1c level, promote weight loss and demonstrate a reduced risk of hypoglycaemia. GLP-1 agonists may also reduce cardiovascular risk, and early outcome studies indicate preservation of β-cell function and possibly β-cell regeneration.

Within the GLP-1 class, liraglutide has slight advantages over exenatide, which requires twice-daily dosing, whereas exenatide has the benefits of once-daily dosing and slightly greater reductions in HbA1c, level and body weight. Prof Distiller did question whether the benefits of small weight loss (average of 3 kg) and a slightly reduced risk of hypoglycaemia were sufficient to justify the relative cost of the use of these agents.

Insulin therapy is a vital tool in the management of T2DM, especially with the inevitable decline in β-cell function seen with the condition. All other therapies targeting insulin deficiency rely on the presence of functioning β-cells. Weight gain associated with insulin use is mostly due to achieving better glycaemic control, resulting in decreased glycosuria, as well as increased fat storage. The earlier insulin is used, the less weight gain is evident, although insulin resistance remains an issue. It is for this reason that metformin therapy is maintained.

A dose of intermediate- or long-acting insulin at bedtime to provide basal supplementation of insulin is appropriate for early initiation in the patient with some β-cell function, and may be effective for months or years. As β-cell loss progresses, boluses of short- or rapid-acting insulin prior to meals will also be required (the so-called incremental basal-plus or full basal-bolus approaches). The patient should be prepared to expect insulin therapy as inevitable at some stage of the management of his/her diabetes.

Talking about bariatric surgery, Prof Distiller pointed out that this does not represent a cure for diabetes and is not free of complications. Bariatric surgery is most effective in recently diagnosed T2DM and can be considered in those where lifestyle interventions (nutrition and activity levels) have not been effective. There is, however, an 80% redevelopment of diabetes post-surgery.

In summary, Prof Distiller concluded that doctors should be using guidelines to facilitate decision making and that these recommendations should never replace clinical judgment. Lifestyle modification is highly effective and is the essential foundation for drug therapy. There is no best therapeutic algorithm, with each of the diabetes agents having their own merits. No drug will work as well without appropriate behavioural modification.

**Dyslipidaemia in diabetes = LDL-C lowering + X (?)**

Dr Dirk Blom, head of Lipidology, Groote Schuur Hospital Lipid Unit, Cape Heart Centre, UCT

Dr Blom began by emphasising that atherosclerosis appears to be an almost inevitable complication of long-standing T2DM. Atherosclerosis manifests clinically with cardiovascular events and it is therefore not surprising that 50 to 75% of deaths in those with T2DM are secondary to cardiovascular disease. Atherosclerosis in T2DM is often diffuse with a higher plaque burden, smaller arteries and inadequate compensatory heart remodelling. Very high rates of peripheral vascular disease are also observed in patients with diabetes. Dr Blom added that the younger the patient when diagnosed with diabetes, the greater the number of life years lost, predominantly due to vascular disease.

The pathogenesis of vascular disease is complex, with manifold interactions between factors such as dyslipidaemia, hyperglycaemia and insulin resistance, hypertension, inflammation, oxidation and smoking. Two major mechanisms in the pathogenesis of atherosclerosis are endothelial dysfunction or the response-to-injury reaction, and sub-endothelial retention and accumulation of lipids, leading to what is often called the response-to-retention reaction. Thinking of T2DM as a vascular disorder with increased glucose levels rather than as a pure disorder of glucose metabolism helps to focus attention on the fact that treatment of T2DM involves much more than just controlling glucose levels.

Dr Blom is of the opinion that targeting dyslipidaemia in T2DM is a highly effective and worthwhile intervention. Lipids should be considered the ‘low-hanging fruit’ in the management of T2DM, as it is often easier to control lipids well than, for instance, achieve tight glycaemic control.

In terms of low-density lipoprotein (LDL) cholesterol, lower is better (LDL-C < 1.8 mmol/L, apoB < 0.80 g/L). LDL and remnant lipoproteins are the two most atherogenic lipoproteins and are central to the pathogenesis of atherosclerosis. The CARD5 study enrolled patients with T2DM with one added vascular risk factor who were free of
Clinically overt cardiovascular disease. The results showed an unequivocal decrease in cardiovascular events with the administration of atorvastatin over placebo.

Dr Blom used these data and those from a meta-analysis of all major statin trials to substantiate an across-the-board statin strategy for T2DM, even in the absence of cardiovascular disease or increased LDL cholesterol levels. He further stated, ‘Statins reduce almost all cardiovascular outcomes except haemorrhagic stroke and are the number one workhorse in LDL cholesterol lowering.’ Other LDL cholesterol-lowering agents include ezetimibe, which combines well with statins.

Bile acid sequestrants are not frequently used in South Africa but are interesting agents to consider in those with T2DM, as they have been shown to not only reduce LDL cholesterol but can also improve glycaemic control. Unfortunately, cholestyramine is poorly tolerated due to frequent gastrointestinal side effects. Colesevelam is better tolerated but is not available in South Africa. Colesevelam has more extensive data on glycaemic control than cholestyramine and reduces HbA1c levels by approximately 0.5%.

Aggressive management of LDL cholesterol unfortunately does not prevent all cardiovascular events. This residual risk is a major target of on-going research and therapeutic efforts. More aggressive management of dyslipidaemia may be one way to reduce residual risk. Dr Blom considered two potential management strategies. The first is to focus harder on LDL cholesterol lowering, as current interventions are often too little, too late. Earlier and more aggressive statin therapy could bring substantial benefits.

The second strategy is often referred to as comprehensive lipid management. This strategy targets other components of the atherogenic lipid phenotype, such as elevated triglycerides, low high-density (HDL) cholesterol and the presence of small, dense LDL particles.

Of the agents used in comprehensive lipid management, Dr Blom discussed fibrates and niacin, as well as some agents still in development. Data from trials of fibrate monotherapy indicate that fibrates reduce cardiovascular event rates in patients with atherogenic dyslipidaemia, but are not efficacious in high vascular-risk patient without atherogenic dyslipidaemia. Sub-group analysis of the ACCORD trial, which enrolled T2DM patients with particularly high vascular risk, indicated some benefit from adding fenofibrate to simvastatin for patients with marked dyslipidaemia, defined as triglycerides > 2.30 mmol/l and HDL < 0.88 mmol/l.

The AIM-HIGH study, examining the efficacy of niacin in atherosclerotic dyslipidaemia, was abandoned as it was seen as futile, with no improved cardiovascular outcomes evident from adding niacin as a second agent to statins. Results from the larger HPSII-THRIVE trial are pending.

In summary, Dr Blom recommended early, aggressive statin therapy. In the case of severe hypertriglyceridaemia (> 10 mmol/l) a fibrate is often required to prevent pancreatitis. There is no benefit from adding fibrates to statins in patients with T2DM who do not have marked dyslipidaemia, as defined in the ACCORD study. Dr Blom also warned against therapeutic inertia, as several surveys show that many patients remain on their initial statin dose despite not reaching their LDL cholesterol targets.

**Portions of portions: the diet debacle**

*Dr Wayne May, endocrinologist, Cape Town*

From as early as the 17th century, individuals with type 1 diabetes (T1DM) have been placed on low-carbohydrate diets to better manage their health. Diet, despite being the oldest tool in the health arsenal, remains a controversial issue and the debate around low-carbohydrate diets is currently of particular interest in South Africa, with much discussion being generated in the practice of medicine and in the social media.

Low-carbohydrate diets can be stratified according to daily carbohydrate intake. A ketogenic diet is defined as carbohydrate intake of less than 50 g daily, whereas a non-ketogenic diet may be defined as low in carbohydrates (50–130 g daily) or moderate (130–225 g daily).

Low-fat diets became popularised in the 1950s with the hypothesis that fat is the cause of heart disease, after associations were made between dietary fat and heart disease mortality. By 1986, a blood cholesterol level above 200 mg/dl was treated as a disease. Despite being a molecule that is essential throughout the body, many epidemiological studies have indicated that as levels of cholesterol and saturated fat increase, the risk of coronary death over 10 years also increases.

Migrational studies of Japanese immigrants to the USA have shown increased risk of heart disease accompanying the change to a Western diet, however no consistent evidence exists. Some dietary-intervention studies have indicated that interventional lowering of cholesterol and saturated fats in the diet is associated with a decreased risk of heart disease. In terms of the patient with diabetes, UKPDS data rates cholesterol as the strongest predictor for heart disease. The CARD study indicates that statin therapy alone can reduce the risk of heart disease in the patient with diabetes.

Dr May went on to compare benefits of low-carbohydrate and low-fat diets for the patient with diabetes. Obesity reviews indicate that in terms of weight loss, low-carbohydrate diets show better results in the short term (at six months), but within a year, weight loss will be equivalent in both low-carbohydrate and low-fat diets. Low-carbohydrate diets have the advantage of raising HDL cholesterol levels; however, at both six and 12 months, low-fat diets had the advantage in terms of LDL cholesterol levels.

Trials on the dietary prevention of diabetes have indicated that a diet low in fat and saturated fats, and high in fibre (Mediterranean diet) will delay the progression to diabetes. Why this is the case remains in the realm of speculation, although weight loss could be the predominant driving factor. Similarly, pharmaceutical agents that decrease fat intake show a delay in progression to diabetes, with associated cardiovascular benefits.

A study by Shai and colleagues’ comparing low-carbohydrate, low-fat, and Mediterranean diets indicated that the Mediterranean diet was best for fasting sugar levels. At 24 months, weight loss was superior in the low-carbohydrate and Mediterranean dietary arms.

However, adherence to a low-carbohydrate diet over the long term is difficult, with a six-year follow up indicating equivalence to low-fat diets in terms of weight loss. Low-carbohydrate diets were also found to exhibit a short-term benefit in HbA1c levels, although this was lost over time, with equivalent levels with low-fat diets at 12 months. No diet has currently shown any benefit in terms of macro- and microvascular reduction or promoting a longer life.

Few data exist for low-carbohydrate diets in T1DM. Existing studies show improved HbA1c levels, reduction in hypoglycaemic episodes and a lowering of insulin-replacement requirements. Improved HbA1c level has also been noted in low-carbohydrate diets in the young; however, there are no data on
the effects of such a diet on growth and induction of puberty.

The American Diabetes Association currently recommends that macronutrient dietary portions be individualised to the patient’s circumstances and are to be formulated by a registered dietician. Locally, SEMDSA recommends a diet consisting of < 35% fat, 45 to 60% carbohydrate and 15 to 20% protein; and for weight loss, a low-fat, low-carbohydrate or Mediterranean diet.


Diabetes in the elderly

Dr Stan Landau, physician, CDE, Houghton

Developing countries are bearing the lion’s share of new-onset T2DM in the elderly. The elderly, along with the rest of the population, are progressively tending towards obesity. In South Africa, 8% of the population is represented by people over the age of 60 years, and of the population aged 65 years and older, one in five individuals has T2DM.

Dr Landau referred to De Fronzo’s ominous octet of pathogenic mechanisms in T2DM and questioned which of these were of primary consideration in the elderly. As an example, incretin effects alter with ageing. The elderly with T2DM have greater levels of GLP-1 secretion that are poorly functional, and the activity of DPP-4 is exceptionally reduced. DPP-4 inhibition may therefore be inappropriate in this setting.

With increased insulin resistance and decreased insulin secretion, renal glucose thresholds are elevated, resulting in insidious and vague symptoms that are further compounded by the presence of co-morbidities. Data from the United Kingdom indicates that of the elderly population with T2DM, 16% are blind or have visual impairment and 25% have foot ulceration. Dr Landau advised that annual T2DM screening for people over 70 years of age is invaluable, particularly in those who are asymptomatic.

Dr Landau continued with a number of considerations in the treatment of T2DM in the elderly. He raised the point that blood pressure measurements in the elderly are more accurate when the patient is standing. Patients should be assessed for impaired cognitive function and also according to the Geriatric Depression scale. The elderly patient should be screened for osteoporosis, have a vascular risk assessment and be examined for sarcopenia. The frail, sick patient requires less aggressive T2DM therapeutic intervention as long-term cardiovascular outcomes are not a priority.

Thiazolidinediones are to be avoided because of the threat of bone fractures and falls; and glibenclamide is also inappropriate for use in the elderly. Metformin is safe and there are a number of insulin options. Hypoglycaemic events are common with insulin use and this is often due to erratic nutrition/feeding patterns. Of the DPP-4 inhibitors, vildagliptin is most appropriate in those older than 70 years, although these patients are more likely to encounter side effects and severe adverse events. Data on GLP-1 liraglutide indicate dose efficacy in patients older than 65 years, and no contraindications exist at this time.

When educating the elderly patient with diabetes, age-related factors such as poor eyesight and hearing, cognitive impairment, depression, limited mobility and access to healthcare services, and self-administration and monitoring of therapy in arthritic patients, need to be considered. It is important to set appropriate, individualised targets.

Glenda Hardy