

SANOFI specialist diabetes meeting, Cape Town

In a new direction for SANOFI, the general manager, John Fagan pointed out that not only is diabetes a key focus area for SANOFI, 'but we also need to go beyond traditional pharmaceutical research and development in our focus. Together with clinicians, we need to think about the patient first, then about the product, and do competent research and development to meet patients' unmet needs', he said. This approach is reflected in the Diabetes Division's new slogan, 'Going beyond, together'.

In the special briefing at the recent SANOFI specialist meeting held in Cape Town, John Fagan noted that the South African Government's National Health Insurance development looks more cautious, planned, and inclusive of the private sector than initially thought, which offers opportunities for both state- and privately funded healthcare organisations to improve patient care.

'The ORIGIN outcome trial with strong South African patient recruitment, which looks at early insulin therapy with glargine, will likely present first results at the 2012 American Diabetes Association (ADA) meeting and is an important diabetes care milestone for Sanofi', he concluded.

The incretins: so much attention at international meetings that a review in South Africa is timeous

Dr Larry Distiller, co-ordinator of this specialist meeting, set the pace of thorough review of topics presented at the meeting, by cautioning clinicians to evaluate incretin usage critically. 'It is clearly time to review these agents, both the GLP-1 agonists and the DPP-4 inhibitors, as their international status grows and they become more available on the South African market', he noted.

'The defining characteristic of these two classes of agents are the supra-physiological levels of GLP-1s attained by exenatide or liraglutide treatment (the GLP-1 agonists), and the physiologically stable levels of GLP-1s attained by the use of DPP-4 inhibitors. The actions of the injectable GLP-1 agonists are therefore generally more powerful than that of the oral DPP-4 inhibitors. The incretins' enhancement of glucose-induced insulin secretion and the restoration of the glucagon-suppression response are particularly relevant, as glucagon is certainly the forgotten hormone of type 2 diabetes', he said.

Referring to exenatide (twice daily), also to the more powerful once-weekly dosage not yet available in South Africa, and liraglutide (once daily), Dr Distiller noted that their promise is partially fulfilled by the fact that the reduction in level of HbA_{1c} (0.8–1% reduction depending on baseline HbA_{1c} level) is maintained over a two- to three-year period and there is a progressive and probably meaningful weight loss.

'There is considerable interest in the non-glycaemic potential benefits of GLP-1 agonists with regard to their neuroprotective and cardioprotective effects.' A real-life study in medically insured patients, the Life-Link study, has recently shown a 16% reduction in cardiovascular events in patients on exenatide', Dr Distiller noted.¹

'With regard to the ultimate promise of these agents, the increased proliferation and reduced apoptosis of β -cells, which was shown in early experimental laboratory studies, there is some evidence from HOMA studies that, for example, liraglutide is β -cell sparing, compared to thiazolidinediones (TZDs) and basal insulin. At this juncture, liraglutide appears the better option in this class

of agents, but this situation is dynamic and may change with the advent of once-weekly exenatide', Dr Distiller noted.

'With regard to the DPP-4 inhibitors', Dr Distiller said 'they work; they are mild and do not change the world, but they do work. They are weight neutral, drop HbA_{1c} levels on average by 0.7% and there is a suggestion that they preserve β -cell function. Overall their cardiovascular effects are not yet as well researched as the GLP-1 agonists', he noted.

With regard to when to use these agents, Dr Distiller noted that early use when there is still β -cell function is taken up in many algorithms, as an alternative for sulphonylureas with metformin; also in combination with insulin, following acceptable trials, and registration for use of the particular agent with insulin.

As DPP-4 receptors are widespread in the body, and despite claimed specificity of these inhibitors, Dr Distiller noted a general acceptance that these drugs have a subtle effect on the immune-surveillance system, leading to increased incidence of bronchitis, for example. With regard to the GLP-1 analogues and their risk of pancreatitis, pancreatic and thyroid cancer, there is an alert but not yet an alarm, despite the much-commented article on post-marketing surveillance',² he concluded.

From promise to gold standard

Dr Joshi, emeritus professor of Medicine, MEDUNSA

'Metformin has truly been established as the foundation, first-line therapy for type 2 diabetes', Prof Joshi noted. Derived from the *Galega officinalis* plant, galegine produced hypoglycaemia in sheep but was found to

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be too toxic for humans, leading to the production of dimethyl biguanide (metformin) and other biguanides, such as phenformin. Early use in the United States focused on phenformin, a pro-drug that was later withdrawn as it was the main culprit for the lactic acidosis observed in the 1950s.

The UKPDS study of type 2 diabetes and the global use of metformin are intrinsically related, although earlier clinical studies³ had shown that metformin works in poorly controlled diabetics, primarily, it was thought, by re-sensitising tissues to insulin. 'In a nutshell, today we regard the principle actions of metformin as increasing sensitivity of the liver to circulating glucose load, and reducing gluconeogenesis and improving insulin sensitivity peripherally. The loss of adipose tissue and its anorectic action in today's world is an additional valued benefit', Prof Joshi noted.

With relevance to current knowledge, metformin also acutely increases the plasma levels of GLP-1, not by DPP-4 inhibition but by stimulating GLP-1 production. 'Metformin has a synergistic action with the incretins, giving an increased effect when used together, compared to when either agent is used alone', Prof Joshi noted.

An important principal to note is that the reduction of cardiovascular events with oral anti-diabetic agents takes a long time to show results. 'In metformin's case, vascular protection was measurable only after chronic exposure of at least six years. Patience should be exercised with regard to this aspect; and the newer oral agents probably require studies in excess of five years to evaluate their cardio-protective benefits', Prof Joshi cautioned. 'The side effects of diarrhoea and nausea occur initially in 20% of patients, but over time and with the use of slow-release tablets, this can be greatly reduced', he added.

The known side effect of low vitamin B₁₂ levels and vitamin B₁₂ deficiency occur in 10 to 30% of patients after long-term metformin use (vitamin B₁₂ levels: deficiency < 150 pmol/l, low levels 150–220 pmol/l). 'Well-defined studies are needed in our populations and this is a clinical priority for local research', Prof Joshi pointed out. 'In principle, after a patient has been on metformin for 10 to 12 years, vitamin B₁₂ levels should be tested once a year, and if found to be low, a single dose of 1 000 mg vitamin B₁₂ should be given. This could be combined with calcium as it facilitates vitamin B₁₂ absorption, as shown in initial study findings', Prof Joshi said.⁴

The use of metformin in type 1 diabetes patients with high insulin usage is growing. Studies have shown that we could reduce doses of insulin by about 10% in patients with type 1 diabetes. A reduction in insulin doses of about 20 to 30% are observed in type 2 diabetics on higher doses of insulin.

Does exercise improve or impede glycaemic control in type 1 diabetes?

Andrew Heilbrunn began his fascinating presentation on the impact of exercise on glycaemic control in the type 1 diabetes patient, by referring to the findings of Ralph Paffenbarger's 36-year follow-up study in the 1993 article in *New England Journal of Medicine*, 'The Harvard Study'.⁵ Findings indicated that there was a dose response to exercise with a percentage reduction in risk of death from certain chronic illnesses, including cardiovascular disease and diabetes.

Up to a point, increased energy expenditure correlated with a reduction in risk of mortality. It was found that those with the highest levels of fitness had the lowest risk of cardiovascular death, in particular. The unfit non-diabetic person has twice the cardiovascular risk of the physically active individual. The unfit type 2 diabetes patient is a 'time-bomb'.

Ming Wei concluded his 15-year study ($n = 1\ 200$ type 2 diabetes patients) in 2000, by suggesting that the type 2 diabetes patient would benefit more from regular exercise than any other chronically ill patient. Data from a seven-year follow-up type 1 diabetes patient cohort study indicated that the mortality rate was 50% lower in the type 1 diabetes patient who burned 2 000 calories per week, opposed to those burning less than 1 000 calories per week.

The evident benefit of exercise on risk of mortality raises the question of how much exercise is appropriate to bring about physiological changes to decrease mortality. Answers to this question have ranged from 75 minutes per day, to 60 to 85% aerobic capacity for 30 to 60 minutes, to 60 minutes of moderate-intensity exercise (a brisk walk).

For the type 2 diabetes patient, the latest ADA and Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines recommend a minimum of 150 minutes' exercise per week, combining moderate-intensity aerobic exercise and strength/resistance training. One would think that these guidelines would be suitable for the

type 1 diabetes population. However, a large percentage of type 1 diabetes patients prefer to participate in marathons, high-intensity ball sports, body building, and some may challenge themselves with recreational climbing and diving. A fair number of these patients do not realise that there is a complex relationship between exercise and type 1 diabetes, and exercise may lead to hypoglycaemia or hyperglycaemia. This raises the question 'Does regular exercise improve or impede blood glucose control in type 1 diabetes?'

There are numerous theories as to why exercise may improve insulin sensitivity, increase muscle blood flow, increase insulin binding by muscle receptors, and increase insulin-regulating glucose transporters. However, the primary theory and benefit occurs during the 12 to 24 hours post exercise; the time for glycogen replenishment. During the course of exercise, liver and muscle glycogen stores are used as an energy source. Post exercise, the liver and muscle draw glucose from the blood to replenish the stores used during exercise. This process requires little insulin and is enzyme initiated.

Regular chronic exercise/training has a different effect to a single session of exercise and the literature suggests that patients with type 1 diabetes should exercise daily or on alternate days to improve their insulin sensitivity. However, with cessation of regular activity, insulin sensitivity is rapidly lost.

In the non-diabetic, insulin levels decrease with the onset of exercise. This allows for an increase in counter-regulatory hormones, in particular glucagon. This response leads to hepatic glucose production, and the subsequent increase in blood glucose is met by glucose uptake in the muscle. Due to this precise neuro-endocrine function, blood glucose levels remain stable under most exercise conditions.

In type 1 diabetes, the pancreas does not regulate insulin levels in response to exercise and there may be impaired glucose counter-regulation, making normal fuel regulation nearly impossible. Therefore the type 1 diabetes patient is at risk of becoming hypoglycaemic or hyperglycaemic, dependent to a great extent on the levels of circulating insulin and the duration and intensity of the exercise.

Fear of hypoglycaemia is the primary factor affecting the attitude of patients towards exercise. According to Remi-Rabasa Lohret, 2008, those individuals who best understood how insulin works in their body were shown to be less fearful of physical activity and hypoglycaemia. Furthermore,

those individuals with the greatest fear of physical activity had the poorest control of their diabetes.

The literature suggests that type 1 diabetes patients are more likely to develop hypoglycaemia when participating in low-intensity, long-duration events, due to the fact that they circulate their insulin more efficiently and they may have a blunted counter-regulatory hormonal response.

In an interesting observation, Robitaille, 2007, found that type 1 diabetes patients in the fed state used less liver and endogenous glucose and significantly more muscle glycogen when exercising for 30 to 60 minutes, in comparison to non-diabetic controls. This may have implications for post-exercise glycogen replenishment and hypoglycaemia.

Tansey *et al.*⁶ explained that performing low- or moderate-intensity endurance-type exercise postprandially resulted in an 86% chance of developing hypoglycaemia if the patient's blood glucose level was below 7.0 mmol/l before the exercise.

In McMahon's euglycaemic clamp studies in 2007, she found that patients performing endurance-type activities at 16:30 had a biphasic need for glucose infusion. The majority of glucose infusions were required during the 45 minutes of exercise and for 45 minutes post exercise. Further glucose infusion was required seven to 11 hours post exercise, which equated to between 02:00 and 04:00.

Dealing with the glucose needs during activity is not too difficult. However, dealing with the late hypoglycaemia occurring in the early morning has always been a challenge. The literature suggests that hypoglycaemic events can be reduced by exercising before breakfast and using rapid-acting insulin, as the patient will be slightly insulin-resistant at this time.

According to Riddell, 2006, exercise late in the day may lead to nocturnal hypoglycaemia, which may be unnoticed during sleep in the majority of individuals. The incidence of hypoglycaemia may be as high as 26% on the night of exercise in adolescents and children. This may be due to a child or adolescent's low glycogen-carrying capacity and blunted counter-regulatory response, and the onset of sleep may also be a factor.

The risk of hypoglycaemia can be managed by increasing carbohydrate intake before, during and after exercise. The rate of intake is dependent on body mass and the energy expenditure of the exercise.

Mr Heilbrunn recommends the article by Grimm and colleagues.⁷ This study indicates that depending on the intensity and duration of exercise, patients should take in 15 to 100 g of carbohydrate per hour during exercise, if exercise is performed at the peak effect of insulin action. Furthermore, daily insulin dosages should be decreased by 20 to 30% if exercising for one hour or more.

Hyperglycaemia may be common in exercises such as squash, high-intensity spinning or high-intensity resistance training, due to an excessive counter-regulatory hormonal response. In the non-diabetic, circulating counter-regulatory hormones decrease rapidly post exercise and insulin levels increase, allowing for rapid glycogen replenishment and therefore a rapid decrease in glucose levels.

Most type 1 diabetes patients choose to exercise during the tail effect of their insulin action, or they will decrease their insulin dosage in order to avoid hypoglycaemia. Therefore the post-exercise insulin levels may be low. With high post-exercise circulating counter-regulatory hormones and low insulin levels in the type 1 diabetes patient, the counter-regulatory response remains high and the patient's blood glucose levels may remain high for a number of hours post exercise. Competition days and extra carbohydrates will exacerbate the problem. It is suggested that one to two units of insulin prior to exercise and/or after exercise may counteract this hyperglycaemic effect.

Improvement of HbA_{1c} level with exercise has not been firmly established. The blood glucose response to exercise is not always predictable. Cardio-respiratory, metabolic and perceptual effort may be altered in type 1 diabetes and this may impair exercise performance.

In Herbst's cross-sectional, multi-centre analysis of 2006, the frequency of activity had a significant influence on glycaemic control without increasing the risk of severe hypoglycaemia. Furthermore, patients who exercised on a regular basis planned their insulin and carbohydrate adjustments more efficiently than patients exercising sporadically.

In Bernadini's study in 2004, it was observed that children participating in more than 360 minutes of competitive sport a week had significantly better glycaemic control than those children exercising less than 60 minutes per day.

Mr Heilbrunn felt that although there are many guidelines and books to refer to, our physiological understanding can help

guide individuals, but it cannot replace the importance of individuals monitoring their own blood glucose response to a particular exercise.

He concluded by saying, 'type 1 diabetes patients who exercise regularly report that they feel better, sleep better, have more energy and are more self-disciplined'. Ideally, patients should be exercising daily, or on alternate days, to maximise insulin sensitivity. Furthermore, 'patients who exercised on a regular basis planned their insulin and carbohydrate adjustments more efficiently than patients exercising sporadically. This would aid the prevention and management of hypoglycaemia.'

Review of 2001 type 2 diabetes guidelines

SEMDSA is in the process of reviewing guidelines for the management of type 2 diabetes. Dr Amod explained that this revision has been driven by two primary factors. He says, 'Currently in South Africa, many different guidelines are referred to... there is a need for an integrative national approach.' Also, new data has emerged on a number of considerations that affect the management of the diabetic patient since the 2008 primary-care guidelines were formulated. These include diagnosis of type 2 diabetes, blood pressure and lipid targets, hypoglycaemic risks, weight loss and bariatric surgery, and the dismissal of some new and some old therapeutic agents.

Dr Amod highlighted that many risk factors give rise to the widespread prevalence of type 2 diabetes and that on the whole, diabetes is a poorly managed disease with fewer than half of patients achieving target control levels. He emphasised that diabetes is not a homogeneous disease. He argues that the highly variable pathogenesis of type 2 diabetes and the varying degrees of disease manifestation are compounded by further variability within the individual patient dependant on duration and stage of his/her disease. This implies that many patients are inadequately managed at some point(s) along the timeline of their disease, in both public and private health systems.

A rigidly uniform therapeutic approach with limited therapeutic options will have limited success in managing the ever-increasing diabetic population. The majority of diabetic patients are treated at the primary-care level and there is a need to assess current therapeutic strategies, with the goal of improving blood glucose control. It is thought that the earlier inclusion

of safe agents will improve adherence and reduce the need for home glucose monitoring. This in turn would limit the number of patients needing up-referral to secondary and tertiary care. Dr Amod also pointed out that increasing evidence of caloric restriction improving insulin resistance and β -cell function raises the question of including weight-loss therapies in guidelines for the treatment of the diabetic patient.

In essence, Dr Amod emphasised that the source mechanism of diabetic disease should be the first consideration when determining therapeutic options to be employed in the management of the patient.

Contributors to the guideline review include endocrinologists and diabetologists, as well as members of DESSA, DSA, FCPSA, CMSA and the National Department of Health. Observers from funders and the pharmaceutical industry were also included. The draft document is currently up for comment, to be finalised early in 2012.

Early bariatric surgery benefits derive from acute caloric restriction

Dr Laura Blacking, Gauteng, presented an unbiased view of bariatric surgery, drawing from recent surgical reviews, which contrast early and long-term results, together with a cluster of established and emerging surgical techniques.

Not giving up on the 'lifestyle works' concept, a small new study of acute calorie restriction (600 kCal/day)⁹ was cited as providing exciting evidence that the unexpected early remission results from bariatric surgery are explained by this phenomenon.

'In this study from Newcastle-upon-Tyne, UK, Dr Lim and co-workers showed reversal of insulin resistance, and β -cell normalisation in overweight/obese (BMI 33.6 ± 1.2 kg/m²) patients with type 2 diabetes of less than four years' duration and not yet on insulin therapy when exposed to a 600-kCal/day diet for eight weeks. 'These patients still had pancreatic function, as did the patients who benefitted most on a long-term basis from bariatric surgery', Dr Blacking noted.

In a recent study⁹ of factors influencing the durability of remission of type 2 diabetes after Roux-en-Y gastric bypass, the study found that while early remission of type 2 diabetes occurred in 89% of post surgery patients, durable remission over a five-year period occurred in 57% of patients. Durable resolution of type 2 diabetes was greatest in patients who were fairly well controlled on diet or oral hypoglycaemic agents.

'This study emphasises that durable remission correlated most closely with an early stage of type 2 diabetes', Dr Blacking stressed. 'In our experience, motivated patients with weight loss also do better from alternative therapies, such as hypnotherapy with virtual gastric banding'.

'In my view, we need to target the brain to achieve successful weight loss', Dr Blacking stressed. 'The requirement from international guidelines is insufficiently emphasised that successful bariatric surgery requires a lifelong commitment to lifestyle change and follow up by a multidisciplinary team is essential. We need centres of excellence that offer this level of multidisciplinary care at both a pre- and post-operative level', she concluded.

'Sugar and high-fat foods are as addictive as alcohol and smoking.'

The long memory of diabetes: epigenetics provides new insights Diabetes complications under the spotlight

'Epigenetics provides us with an insight as to how the environment interacts with our genomes and emphasises the fact that our behaviour may impact both on our own lives as well as future generations.'

Dr Brian Kramer, CDE, Johannesburg, reviewed the development of the concept of the long-term hyperglycaemic memory of diabetes, as first explored in dogs by Dr RL Engerman, an ophthalmologist from the University of Wisconsin, USA.¹⁰ He observed that progression of retinopathy continued during good glycaemic control following a period of profound, poor glycaemic control.

'This memory effect has also been shown in diabetic patients in the DCCT-EPIC study. This emphasises the need for early metabolic control in both type 1 and type 2 diabetes if we are hoping to reduce diabetic complications', Dr Kramer noted. The explanation for the ongoing damage relates to both the role of advanced glycation end-products (AGES), which continue to drive the production of reactive oxygen species, and to the altered up or down regulation of genes due to changes in the epigenetic environment.

The abnormal genetic regulation relates to histone functioning, which is exposed to the altered cellular environment. 'Tightly packed methylated histones restrict the

availability of the DNA to be transcribed, while the acetylated histones allow unfolding, gene transcription and the production of gene products', Dr Kramer explained.

Research has shown that stress, nutrition, smoking and alcohol consumption can also change the environment of the histones; changes that can be passed on to generations of cells. 'Our investigation of polymorphisms is probably misplaced and the epigenetic environment may provide a new target for better therapeutic agents', Dr Kramer noted.

Even transient periods of 15 minutes of hyperglycaemia are sufficient to alter the epigenetic environment. Chronic exposure also alters the balance of histone methylase and demethylase enzymes, changing the genetic environment and gene expression.¹¹

'We really need better markers of glycaemic control than HbA_{1c} level, which does not describe exposure to glycaemia as well as we would like', Dr Kramer concluded.

Peripheral neuropathy: focusing on painful, diffuse, distal, symmetric polyneuropathy (DSM)

Dr Kaplan, Cape Town, presented a review of the physiology of pain with a special emphasis on painful diabetic neuropathy. He then discussed clinical and therapeutic aspects of treating neuropathy, and particularly painful diabetic neuropathy.

Diabetic neuropathy occurs in 30 to 60% of diabetic patients, varying from 54 to 59% in type 1 diabetes patients and somewhat lower in type 2 patients (37–54%). In 50% of cases of diabetic neuropathy, pain is present, which can occur early, even in patients with impaired glucose tolerance. The incidence of painful diabetic neuropathy progresses with duration of the diabetes, with a peak after 15 years.

Distal symmetric polyneuropathy is the most common form of neuropathy. Typically, it starts as a loss of sensation, affecting the feet more than the hands. As the neuropathy progresses, pain may become the dominant symptom. Often, pain occurs in the setting of a normal clinical examination. It is important to exclude other causes of neuropathy and pain, such as claudication, osteoarthritis and fibromyalgia.

'It is important to note that there may be few signs to relate to the patient's complaint of pain – examination of patient reflexes such as vibrational, temperature, sensory and soft touch measures may be normal', Dr Kaplan said. 'Typically, patients complain of

burning feet, especially at night, and lancinating pain is also a useful descriptor.'

At the very outset, it is important to try and assess the severity of pain, using the variety of severity scales available. A pain diary may also be useful, and a detailed medical history and psychosocial assessment is essential.

In treating pain, there are numerous guidelines that the clinician can follow, for example, the ADA, NICE or South African SEMDSA guidelines. 'There is no single drug panacea that works in every patient all the time. In fact there are significant unmet needs for drugs directed at the underlying nerve pathology', Dr Kaplan noted.

Most commonly, we start with a tricyclic antidepressant and progress to other available modalities. Ideal starting therapy would be the use of duloxetine or pregabalin. 'Of concern however is that these agents are not inexpensive and are not covered by medical aids. We need to initiate a process whereby painful diabetic neuropathy is included in the list of chronic conditions requiring full payment under the prescribed minimum benefits (PBM) legislation'. Dr Kaplan advocated.

'He who understands pain, understands medicine' – William Osler

Tramadol may be a useful adjuvant but should be used with caution with drugs from the group of selective serotonin reuptake inhibitors, as there may be an added serotonergic action. Anti-epileptic drugs are also useful. Dr Kaplan discussed these classes of drugs and outlined the potential of some newer agents.

In conclusion, Dr Kaplan noted that prevention is better than cure and clinical trials have shown that a reduction in HbA_{1c} level of 1% can reduce the prevalence of diabetic neuropathy by up to 30%. Once neuropathy is present, tight control of the blood sugar level also helps to reduce the severity of the symptoms, and more so in type 1 than type 2 diabetes.

The individualisation of therapy for haemochromatosis

Hepcidin, the 'ultimate' iron regulatory hormone, is the key determinant for assessing

the frequency with which venesection therapy should be used to treat haemochromatosis. 'Assays for this protein will soon be available', noted Prof Peter Jacobs.

Prof Jacobs, emeritus professor, UCT, has been involved in the early clinical assessment of iron overload since the 1960s, in association with Prof Tom Bothwell and others. He presented a view of this fascinating journey from clinical assessment to the recent determinations of the aberrant genes of iron absorption. In addition to mutations in the HFE gene, defects in four additional genes have been found to cause hereditary haemochromatosis: hepcidin, transferrin receptor 2 (TFR2), haemojuvelin (HJV) and ferroportin.¹²

'In the 1950s, Bothwell and others published the first report of the juvenile occurrence of haemochromatosis. We now know that this early clinical appearance which leads to early cardiovascular abnormalities is due to a defective haemojuvelin gene. Similarly, other manifestations reflecting a series of clinical syndromes can now be related to the individual genetic abnormality, which ultimately affects hepcidin levels', Prof Jacobs explained.

For the clinician today, Prof Jacobs advised the following:

- Imaging studies with MRI can be very helpful in assessing iron stores in the liver, pancreas and heart tissues.
- Early diagnosis and multidisciplinary support for the haemochromatosis patient involving an endocrinologist, biochemist and cardiologist is essential to prevent organ damage. Sole-practice support of a haemochromatosis patient is unwise.
- Advice to patients should be based on the underlying genetic abnormality so as to re-assure patients concerning their and their children's on-going risk. The University of Stellenbosch is involved in the local genetic studies and Prof Jacobs urged that clinicians should make use of these services to build up a picture of our South African environment.
- Fifty per cent of patients will be symptomatic of diabetes, as iron selectively destroys the β -cells of the pancreas.
- The prevalence of haemochromatosis is 1.3% in affected families; six times the prevalence in the general population.
- Therapeutic use of proton pump inhibitors,

dietary and lifestyle modifications, and iron chelates are not helpful.

- Venesection should be managed, to balance the loss of iron (venesection activates intrinsic mechanisms of iron absorption in the diet). Hepcidin measurement will in future be definitive in the balancing of a venesection programme.³

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