EDITORIAL

ORIGINAL ARTICLES

• Chronic pain: Addressing the triad of pain, sleep and depression/anxiety
• Achieving health objectives eating the vegetarian way. A Case Study - Sunjay Naidoo
• Recognising and Diagnosing Cardiac Autonomic Neuropathy in People with Diabetes
• Chronic diabetes and brain change

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SAZA.OPN.15.09.0155
Economic, political and social instability and chaos abounds. The Health Care community is not insulated from this ever-changing landscape. The incidence of Non-Communicable Disease is exploding worldwide, and in particular, diabetes and hypertension are placing an ever-increasing burden on medical costs.

In the past decade, a number of new drugs and insulins have been introduced - at present, over 200 new products are in development for the treatment of type 2 diabetes; some new molecules, others ‘me too’ products. New drugs always come at an enhanced cost. In a country like South Africa, where we try to practice ‘First World’ medicine in developing country economy, this creates very real problems, both in the private and public sectors. Notwithstanding the hype that accompanies the launch of new drugs and new insulins into the market, the obvious questions are: What are the advantages of these new products over the currently used classes, and, are these advantages worth the increased cost? Or, to put it more simply, what is the “bang you get for the buck”?

When analysed unemotionally, the answer to that question is unfortunately not exciting. Most of the newer agents are either “as good as” currently available therapies, whilst others offer, at best, a minor advantage at a massively enhanced cost. Even the so-called cardioprotective advantages of liraglutide, when analysed in the light of economic practicality, become concerning. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER®) trial showed you would need to treat 66 patients with 1.8 mg of liraglutide daily, for 3 years, to prevent one coronary event, and 98 patients to prevent one death. In real South African Rand terms, preventing one coronary event over 3 years would cost about R4, 400,000 and prevention of one death would cost around R6, 500,000. This is clearly not a viable option that can be sold to healthcare funders.

So what is the alternative? With all the pressure placed upon us by big Pharma with regard to their new ‘wonder agents’, we tend to forget that type 2 diabetes is essentially a lifestyle condition - failure to place sufficient emphasis on lifestyle change is both a recipe for therapeutic failure and a major cause of rising therapeutic costs in treating the condition. It is time for us to return to the basics. We need to be far more proactive in promoting better eating habits, exercise and lifestyle changes in our patients. Any pharmacological intervention should be in addition to, and not instead of, meaningful lifestyle improvements.

The annual CDE Postgraduate Forum in Diabetes Management (now in its 18th year), has a rich tradition of providing stimulating and vigorous debate on topical issues and challenges in diabetes care. We thank our Guest Editor for providing a thoughtful starting point for debate for this Issue of the SAJD, which will arrive ‘hot-off-the-press’ on the opening day of the Forum. If you are attending as a Delegate, we welcome you to the Forum and we look forward to spending the weekend with you, our colleagues and friends in diabetes.

Dr Stan Landau
Editor
email: StanL@cdediabetes.co.za
Glucophage® XR now provides a simple full dose spectrum solution to improve compliance:

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EDITORIAL
Dr Stan Landau with Guest Editor - Dr Larry Distiller

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Dr Jocelyn Hellig, Prof Brynne Ascott-Evans

PRESS RELEASE
Hypoglycaemia in type 2 diabetes increases the risk of
cardiovascular events
The economic burden of diabetes is increasing worldwide, with the greatest demands and increases in developing countries. Globally 415 million people have diabetes, with more than 14 million people in the African Region. The International Diabetes Federation predicts that by 2040 these figures will more than double. Three-and-a-half million South Africans (about 6% of the population) suffer from diabetes and there are many more who are undiagnosed. It is estimated that another five million South Africans have pre-diabetes, a condition where insulin resistance causes blood glucose levels to be higher than normal, but not high enough yet to be type 2 diabetes.

The need for more cost-effective insulin therapy is critical in reducing the financial burden on patients and health care systems. Biosimilars are distinctly different from generic drugs, as they are protein compounds that rely on modification for efficacy and are therefore bioequivalent rather than bioidentical. Biosimilars must follow precise manufacturing, processing and purification procedures, and are regulated to pass stringent laboratory and clinical trials before approval.

Biosimilar insulins have the potential to dramatically lower healthcare costs by delivering insulin with similar anti-glycaemic effect and adverse reaction profile to standard, more expensive insulin preparations. Biosimilar insulins have the potential to dramatically lower healthcare costs by delivering insulin with similar anti-glycaemic effect and adverse reaction profile to standard, more expensive insulin preparations. Biosimilar insulins, such as BIOSULIN, will play an ever increasing role in the management of diabetes.

In the BEST study (SAMJ July 2013) BIOSULIN 30/70 insulin was tested to confirm equivalence to other human premixed insulin preparations on the South African market. Seventy-seven subjects with type 1 (n = 18) and type 2 diabetes mellitus (n = 59) were switched from their existing human premix insulin to BIOSULIN 30/70. The change in HbA1c from baseline to 6 months was considered the primary endpoint of the study. BIOSULIN 30/70 achieved at least equivalent glycaemic control with no reported new or severe adverse events. In addition there was no significant difference in body weight in the study subjects during the 6-month period on BIOSULIN 30/70.

Despite the more complex production process and regulatory requirements for biosimilars, they offer a price reduction of between 21% and 47% of the parent insulin and analogue insulin. Increased use of biosimilar insulins has the potential for significant cost savings with no loss in patients’ glycaemic outcomes.

For more information regarding BIOSWISS and their products, please contact Laurett Correira on laurett@bioswiss-med.co.za.

References:

BIOSWISS offers a comprehensive range of human insulins in cartridge form, from the short acting BIOSULIN R, to the intermediate acting BIOSULIN N and BIOSULIN L, as well as the biphasic insulin BIOSULIN 30/70. They have 2 Biosulin insulin delivery devices, namely the YPSOMED BIOSULIN PEN, and GENISUPEN.

In addition they provide blood glucose monitoring devices and strips, GLUCOPLUS® and newly launched GLUCOPLUS P, as well as INSUPEN® NEEDLES and LORIS® SAFETY LANCETS.
INDICATIONS

Yelate is indicated for the treatment of:
- Depression as defined by DSM-IV Criteria
- Diabetic peripheral neuropathic pain (DPNP)
Introduction

Epidemiological studies indicate that the increasing worldwide prevalence of chronic pain may be as high as 20-50%. Furthermore, chronic pain is strongly associated with psychiatric comorbidities, and in particular, anxiety, depression and insomnia. Accordingly, pain is associated with decrements of many aspects of patient’s lives including physical and emotional functioning, affective symptoms and sleep problems. The negative impact is higher in patients with greater pain severity. However, there is a bidirectional relationship between chronic pain and these symptoms. Patients with somatisation, health-seeking behaviours and poor sleep are at high risk of developing chronic widespread pain. The risk increases in tandem with severity of anxiety, depression or sleep problems, and those with multiple predisposing factors are at the highest risk (Figure 1).

Therefore, clinically, it may be prudent to consider pain, sleep problems and anxiety/depression as co-existent components of a triad, where the presence of symptoms of one component should prompt investigation for the others.

Figure 1: The Unholy Triad: chronic pain, sleep impairment and anxiety-depression. Common patient descriptors
Shared anatomy of sensation, emotion and cognition

Pain perception due to injury or chronic pain states undergoes substantial processing at supraspinal levels. Pain is both a sensory event of the peripheral and central nervous systems and an experience that arises from, and which, in turn, influences processes of higher consciousness. The sensation of chronic pain specifically engages brain regions critical in cognitive and emotional regulation (Figure 2).

Peripheral pain signals travel initially from neospinothalamic and paleospinothalmic tracts in the spinal cord to the amygdala and hypothalamus, and to the thalamus from where projections connect to the anterior cingulate gyrus. These connections mediate arousal and autonomic responses to pain and affective dimensions of pain. Thalamocortical pathways project to the primary and associative somatosensory cortex to mediate sensory and discriminative aspects of pain. These areas of the cortex and cortical-insular-cingulate pathways also mediate cognitive and emotional dimensions of pain, playing a role in pain sensation and pain-related behavioural responses. Projections from the cingulate to hypothalamic nuclei mediate neuroendocrine and autonomic responses to pain, and projections to the caudate, putamen and nucleus accumbens mediate motor responses to pain. Dopaminergic pathways from the ventral tegmental area and substantia nigra pars compacta are active in negative reinforcement emotional and motor conditioning effects to noxious stimuli, whereas pathways from the hippocampus and related areas further mediate emotional, memory and expectational domains of pain. Higher order cognitive dimensions, such as expectation and associative value of pain are mediated by the lateral dorsal thalamic nucleus and amygdala, together with efferents from the lateral prefrontal, infero-medio-temporal and infero-parietal cortices.

Therefore complex hierarchic neural processing expands the sensation of painful stimuli into consciousness of internal state, external circumstance, memory and affective factors that are subjective and individual to the person experiencing the pain.

Chronic pain may be associated with atrophic changes in brain structure, similar to, but occurring more rapidly than those observed with ageing. In patients with chronic back pain, grey matter density was reduced bilaterally in the dorsolateral prefrontal cortex (DLPFC) and right thalamus. These changes were strongly related to pain characteristics, with distinct patterns depending on whether pain was neuropathic or non-neuropathic in origin. The degree of atrophy also correlated with duration of pain. However, treatment may reverse these changes and restore normal brain function. Pain management with spine surgery or facet joint injections was associated with increased DLPFC thickness, which correlated with the reduction of both pain and physical disability. Furthermore, after treatment, DLPFC activity during an attention-demanding cognitive task that was abnormal before treatment, returned to normal.

As already mentioned, a reciprocal relationship exists between pain, sleep problems and depression/anxiety. From a neurological point of view, depression is now recognised as more than just a disorder of mood. It is characterised by a complex interplay between common pathways linking the brain, hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system and inflammatory pathways. This explains how depression may be associated with significant morbidity and mortality with primary manifestations beyond those related to disturbed affect.

Figure 2: Sensory, emotional and cognitive (SEC) interactions in chronic pain
Imaging studies have demonstrated that in patients with insomnia, there is an interaction between neural networks, including a general arousal system (ascending reticular formation and hypothalamus), an emotion-regulating system (hippocampus, amygdala, and anterior cingulate cortex), and a cognitive system (prefrontal cortex) that does not fully deactivate from waking to sleep. Furthermore, these areas are characterised by reduced waking metabolism, suggesting that they are chronically sleep-deprived, and providing an explanation for daytime fatigue and increased risk of mental disorders in patients with insomnia. Chronic sleep problems and poor sleep quality are associated with a bilateral reduction in hippocampal volume, impaired verbal and visual memory and impaired frontal lobe function. Chronic insomnia is also associated with a significant risk of all-cause dementia. In patients with chronic pain, there is a bidirectional relationship where sleep disturbance occurs consequent to pain, but sleep disturbance is also associated with greater severity of perceived pain, leading, in turn, to greater impairment of functional ability and increased incidence of depression.

Clinical considerations
Because of these shared central pathways and the neurotransmitters common to pain sensation, emotion and cognition (SEC), it is rational that effective pain management should address each of the elements of this triad. Furthermore, each element may respond to both pharmacological and non-pharmacological treatments and a combination of these management approaches is recommended for each (Figure 3).

1. Pharmacotherapy
Benzodiazepines are not recommended for routine treatment of patients with pain and comorbid anxiety or sleeping disorders. They are potentially addictive, cause gait disturbance and increase the risk of falls. They are also associated with an increased risk of accidents and memory impairment. Furthermore, benzodiazepines suppress REM sleep, causing daytime fatigue consequent to poor sleep quality.

Selective serotonin reuptake inhibitors (SSRIs) are also not routinely recommended for patients with comorbid pain and depression, due to their relative lack of efficacy in this patient population.

Two classes of medications that are recommended as first-line agents for comorbid pain and depression/anxiety and the efficacy of which has been demonstrated in clinical trials, are the serotonin noradrenaline reuptake inhibitors (SNRIs) and α2δ ligands. The noradrenergic activity of the SNRI antidepressants is thought to modulate inhibitory descending pain pathways in the spinal cord and is also helpful in promoting motivation, concentration and sleep.

The α2δ ligands include gabapentin and pregabalin. Pregabalin improves pain in various chronic pain states, including fibromyalgia, diabetic peripheral neuropathic pain (DPNP), and also pain-associated anxiety and sleep disturbance. Pregabalin treatment was associated with a clinically meaningful improvement in sleep quantity and quality. Improving sleep in patients with chronic pain is also likely to improve associated anxiety and depression.

2. Non-pharmacological therapy
When one considers the link between brain and body, and the common areas of the brain and interaction between neurotransmitters involved in pain, depression, regulation of mood and emotions, sleep and executive function, it becomes clear that pharmacotherapy alone is not sufficient to manage the syndromes presenting in patients with chronic pain. Furthermore, the aim of treatment is not only to manage symptoms, but to achieve recovery - to enable the patient to flourish, to live a meaningful life. These greater aspects of ‘wellness’ - optimism, resilience, enthusiasm, happiness and wisdom - need to be addressed through teaching the patient to care for him or herself, both physically and mentally. Therefore, in addition to pharmacotherapy, non-pharmacological management aimed at improving wellness is essential.

Five specific aspects of wellness that are important to consider, are mindfulness (purposefully drawing attention to the present), sleep, exercise, nutrition and socialisation. These interventions have been demonstrated to improve quality of life, health and wellness and improve the likelihood of recovery.
Cognitive behavioural therapy
Cognitive behavioural therapy (CBT) improves clinical outcomes in chronic pain, with brain correlates that have been measured in imaging studies.

Chronic pain is associated with reduced cerebral grey matter volume and density. A comparison of anatomical MRI scans of patients with chronic pain before and after an 11-week CBT treatment showed increased grey matter in bilateral dorsolateral prefrontal (DLPFC), posterior parietal (PPC), subgenual anterior cingulate (ACC)/orbitofrontal, and sensorimotor cortices, as well as the hippocampus. These brain changes were associated with significant improvements in clinical measures and decreased pain catastrophizing. Brain correlates associated with decreased pain catastrophizing were left DLPFC and ventrolateral prefrontal cortex (VLPFC), right PPC, somatosensory cortex, and pregenual ACC. It is proposed that increased grey matter in the PFC and PPC reflects greater top-down control over pain and cognitive reappraisal of pain, and that changes in somatosensory cortices reflect alterations in the perception of noxious signals.

In a 3-week multidisciplinary treatment programme consisting of education, stretching, CBT, relaxation training and aerobic exercise, improved pain scores were associated with reduced salivary cortisol concentration. This suggests that one of the active mechanisms underlying the efficacy of this treatment approach, is an improvement in HPA axis function, with increased resiliency to stress.

Mindfulness
Mindfulness may be defined as “the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally, to the unfolding of experience moment by moment.” It involves a consciousness of sensations, perceptions, emotions and thoughts and is the attentional state that underlies all forms of meditation.

Mindfulness-based cognitive therapy (MBCT) is believed to work by reducing cognitive and emotional reactivity to stressful events and promoting resilience. It has been shown to assist in recovery from a variety of painful and psychological conditions, especially depression and anxiety.

More than half of all people with diabetes are estimated to suffer emotional distress related specifically to the condition. One in four will, at some stage, experience depression. In comparison to usual care, a mindfulness-based CBT programme has been shown to reduce stress, depressive symptoms and anxiety and improve quality of life (mental and physical) in patients with type 1 and type 2 diabetes.

Exercise
A substantial body of evidence confirms that exercise improves mood and energy levels in patients with depression, which itself is associated with tiredness and fatigue, and reduced motivation and drive.

A large Cochrane meta-analysis of 39 studies concluded that exercise improves symptoms of depression, but it needs to be continued in the longer term for the benefits to be maintained. Benefits of sustained exercise were greater than control intervention, and comparable to those achieved with psychological and antidepressant pharmacological treatments.

The mechanisms behind the effects of exercise on mood and wellbeing are complex and multifactorial, involving direct effects on monoamine synthesis and availability in the central nervous system, and regulation of pro- and anti-inflammatory pathways. Regular exercise has been shown to reverse the neurodegeneration and atrophy observed in various regions of the brain associated with depression. Furthermore, in patients with diabetes, clinical studies have demonstrated that routine exercise can prevent or delay nerve damage and dysfunction, in turn delaying or preventing the onset of symptomatic peripheral neuropathy.

Patients with diabetic peripheral neuropathy (DPN), who participated in a programme of regular aerobic and resistance exercise, reported reduced pain and neuropathic symptoms. This was associated with increased intraepidermal nerve fibre branching observable in distal and proximal lower extremity skin biopsies. In addition, aerobic exercise was associated with improvements in general fatigue, physical fatigue, peak oxygen uptake; reduced total body fat and fat mass; and an improvement in peripheral blood flow.

WILD 5: A wellness intervention programme for patients with depression and chronic pain
The Wellness Interventions for Life’s Demands (WILD) 5 is a trackable, accountable, self-directed five-element wellness programme that has been shown to significantly improve mood, function, measures of wellness and quality of life in patients with depression, anxiety and/or chronic pain. It encourages and supports daily practice of the five elements of wellness - physical exercise, mindfulness, optimizing sleep and nutrition, and improving social connectedness.

A small pilot study of the WILD 5 programme has demonstrated significant benefits of each of the five wellness interventions in a group of 47 patients with chronic
pain. The programme was associated with significant improvements in mood, emotional eating, sleep and pain scores (Table 1). Sleep duration increased on average by 36 minutes per night (p<0.001). Results were similar regardless of whether or not the patients were taking opioids.

Support materials to assist the clinician in teaching and guiding patients through the wellness interventions are available online at: www.Wild5Resources.com (password: wellnessmatters). Resource materials are provided for the initial 30 day induction period, but patients should be encouraged to continue the programme thereafter for life.

**Conclusions**
The mind is intimately involved in both the perception of, and protracted nature of chronic pain. Furthermore, the complex nature of interrelated pathways and chemical messengers within the central nervous system that interlinks chronic pain with depression, anxiety and sleep disorders, means that it is impossible to separate these pathologies into distinct clinical entities that can be addressed in isolation. In addition, broader aspects of wellness, and specifically resilience, happiness and optimism, must be addressed if the patient is to achieve a clinical outcome consistent with a meaningful quality of life.

Although still in its infancy, WILD 5 has demonstrated that, in addition to usual care, patients can be assisted to improve wellness behaviours. These changes are associated with significant improvements in pain and function, but also, and perhaps most significantly, in overall wellbeing.

*This article is based on a presentation by Prof Rakesh Jain, MD, MPH at the 6th Annual Pfizer Pforum held in Sandton, Johannesburg on Saturday 16 April 2016. Prof Jain’s visit to South Africa was sponsored by Pfizer, South Africa.*

**References on request**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rating scale</th>
<th>Pre-study score (mean)</th>
<th>Post-study score (mean)</th>
<th>Percentage change (mean)</th>
<th>P value</th>
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<td>Depression</td>
<td>PHQ-9</td>
<td>12.1</td>
<td>6.8</td>
<td>43 %</td>
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<td>Anxiety</td>
<td>GAD-7</td>
<td>10.4</td>
<td>6.3</td>
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<td>Insomnia</td>
<td>PSQI</td>
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<td>8.4</td>
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<td>Emotional (binge) eating</td>
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<td>Happiness</td>
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<td>5.1</td>
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<td>Optimism</td>
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<td>Enthusiasm</td>
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<td>&lt;0.001</td>
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<td>Resilience</td>
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<td>3.3</td>
<td>5.2</td>
<td>57 %</td>
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<td>Worst pain</td>
<td>BPI NRS (0-10)</td>
<td>5.9</td>
<td>4.8</td>
<td>18 %</td>
<td>&lt;0.001</td>
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<td>Least pain</td>
<td>BPI NRS (0-10)</td>
<td>2.8</td>
<td>2.2</td>
<td>21 %</td>
<td>&lt;0.02</td>
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<tr>
<td>Average pain</td>
<td>BPI NRS (0-10)</td>
<td>4.4</td>
<td>3.6</td>
<td>18 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain interference with activities</td>
<td>BPI NRS (0-10)</td>
<td>4.3</td>
<td>3.6</td>
<td>16 %</td>
<td>0.05</td>
</tr>
</tbody>
</table>

PHQ-9: Patient Health Questionnaire 9-item version; GAD-7: Generalised Anxiety Disorder 7-item scale; PSQI: Pittsburgh Sleep Quality Index; NRS (0-10): 11-point numeric rating scale; BPI: Brief Pain Inventory.
Reduced postmeal plasma glucose excursions

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As effective as insulin in reducing HbA₁c

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- Administered at any time within 1 hour before the 2 main meals of the day.

BYETTA® in the type 2 diabetes treatment continuum

Before Insulin, there's

Diet and exercise plus 1 or more oral therapies

Insulin therapy

References:
Sunjay Naidoo who is 30 years old, works as a strategy analyst for a large accounting firm in Johannesburg. At the time of his first consultation, ten and a half years ago, he was diagnosed with type 2 diabetes. Sunjay’s work requires him to travel to African countries for approximately one week every month. I requested his wife to join the consultation as she was responsible for the shopping and cooking for the family. As many of our patients with a Hindu tradition do, the family follows a vegetarian way of eating. Specifically, Mrs Naidoo follows a vegan diet, while Sunjay follows a lacto-vegetarian diet and occasionally eats fish outside his home.

1. Assessment

1.1 Lifestyle
Sunjay reported that although he feels tired at night, he generally sleeps well. He goes to gym 3 to 4 times per week, doing a combination of aerobic and resistance training for an hour. He was on insulin therapy using NovoMix 30 - 24 units in the morning and 16 units at night. In addition to his insulin, he was taking 20 mg of Aspavor, 1000 mg of Glucophage and 500 IU of Vitamin D daily. He tested his fasting blood glucose level approximately twice a week.

1.2 Anthropometry
I measured Sunjay’s height at 1.69 m and his weight at 88 kg. His waist circumference was 106 cm.

1.3 Pathology
Table 1 displays the results of Sunjay’s laboratory results done just before his first consultation, as well as the tests done 3 months after medical and nutrition intervention. Of concern during the first consultation, was his HbA1c and his triglyceride level.
1.4 Nutrition History
Menu 1 in Table 2 displays the nutritional analysis of Sunjay’s representative food choices for one day in the week. He would get up at 6:30 and, after his gym session, enjoy All-Bran® cereal with low-fat milk and honey. Alternatively, he would pick up a smoothie from the gym consisting of protein powder and fruit yoghurt. For lunch, he would select a tomato and lettuce bread roll or a chickpea salad from the cafeteria. On arriving home in the late afternoon, he would snack on half a bag of potato crisps, where after he ended the day with a meal consisting of Aloo Gobi (cauliflower and potato curry) and spaghetti. In terms of drinks, Sunjay would enjoy two cups of coffee (without sugar or sweetener) and water daily. He took one alcoholic drink a week. Sunjay would rather choose Marie biscuits, cereal bars, nuts, peanuts and potato crisps than chocolates as snacks. On weekends, they would order their favourite take-out, a pizza margherita, and, when visiting friends and family, Sanjay would enjoy a vegetable curry with naan bread or roti and sweets such as carrot halva and coconut barfi. On trips to African countries, Sunjay tried to make the best choices available, but found the high-calorie snacks in the bar fridge in his hotel room, difficult to resist.

Sunjay’s typical meal pattern resulted in a high intake of calories, total fat and total carbohydrate and a low intake of protein and the majority of micronutrients.

2. Nutrition Intervention
2.1 Education
Extensive nutrition education for the management of the hyperglycaemia and dyslipidaemia was undertaken with specific focus on the:

- physiology and benefits of abdominal fat loss.
- concept of a calorie deficit to achieve fat loss, with the consequent necessity of controlling the quantities of carbohydrates, fats and proteins on a daily basis.
- consumption of an adequate amount of lean protein to ensure optimal muscle synthesis and optimal appetite control, whilst creating a low glycaemic load and a low saturated fat content for all three meals.
- concept of achieving optimal blood glucose control by the consumption of high fibre, low glycaemic index (GI), whole-grain carbohydrates in controlled quantities, at the expense of refined starches and simple sugars.
- inclusion of foods rich in nutrients considered ‘at risk’ while following a lacto-vegetarian diet (Vitamins B12 and D, calcium, iron and zinc).
- controlled intake of all fats calculated to less than 35% of total energy. An added restriction of saturated fat to less than <7% was added. Preference was given to the use of unsaturated fats to help improve the dyslipidaemia.
- equal distribution of carbohydrates across three meals and snacks.

<table>
<thead>
<tr>
<th>Table 1: Comparison of metabolic markers pre- and post-medical and nutritional intervention</th>
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<tbody>
<tr>
<td><strong>Metabolic marker</strong></td>
</tr>
<tr>
<td>HbA1c (%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
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<tr>
<td>Chol/HDL Ratio</td>
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2.2 The nutritional plan
An individualized, energy controlled, nutritionally-balanced meal plan with a 7-day cycle was negotiated.

Menus were formulated to meet Sunjay’s lifestyle requirements. Recipes and a shopping list were also provided to enable his wife to prepare the meals in a tasty and delicious way. Menu 2 in Table 2 reflects the choices of dishes Sanjay could choose from for one day. Additional choices for breakfast were offered in the form of rolled oats and grapefruit. Dry beans, corn, soya and vegetables were introduced for lunch and dinner to reduce the glycaemic load of the meals, and to improve the nutritional quality of the overall meal plan. For snacks, peanuts and potato chips were replaced with fresh fruit. Pleasure foods such as Indian sweets were reserved for weekends when attending celebrations with family and friends.

On evaluation, the nutritional quality of Menu 2 (the menu negotiated and then prescribed) reflects a higher nutritional quality than that provided by Menu 1 (the way Sunjay was eating). Menu 2 provides a higher protein and lower calorie, total fat, saturated fat and carbohydrate content. The addition of protein foods and whole grains ensured that Sanjay met his requirements for the nutrients ‘at risk’ for those following a vegetarian pattern of eating.

2.3 Progress - the follow-up monitoring sessions
The purpose of the follow-up sessions was to provide advice and support for Sunjay to acquire the practical skills to implement the nutritional principles by making daily healthy food choices.

---

### Table 2 – Comparison of food and nutrient intake pre- and post-medical and nutritional intervention

<table>
<thead>
<tr>
<th>Food items – Menu 1</th>
<th>Food items – Menu 2</th>
<th>Nutritional analysis (day)</th>
<th>Menu 1</th>
<th>Menu 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breakfast</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 g All-Bran® cereal served with</td>
<td>200 g cooked rolled oats with</td>
<td>Energy (kJ)</td>
<td>9475</td>
<td>6069</td>
</tr>
<tr>
<td>300 g low fat milk and</td>
<td>125 g low fat milk,</td>
<td>Protein (g)</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>20 g honey</td>
<td>cinnamon &amp; sweetener</td>
<td>Carbohydrate (g)</td>
<td>260</td>
<td>180</td>
</tr>
<tr>
<td><strong>Lunch</strong></td>
<td></td>
<td>Total fat (g)</td>
<td>100</td>
<td>36</td>
</tr>
<tr>
<td>80 g white bread rolls with</td>
<td>Mexican bowl - salad with:</td>
<td>Saturated fat (g)</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>20 g margarine,</td>
<td>• 140 g dry beans,</td>
<td>Unsaturated fat (g)</td>
<td>71</td>
<td>25</td>
</tr>
<tr>
<td>20 g mayonnaise,</td>
<td>• 160 g corn kernels,</td>
<td>Fibre (g)</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>tomato and</td>
<td>• 60 g Guacamole and</td>
<td>Calcium (mg)</td>
<td>543</td>
<td>739</td>
</tr>
<tr>
<td>lettuce</td>
<td>onion salsa</td>
<td>Iron (mg)</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td><strong>Dinner</strong></td>
<td></td>
<td>Magnesium (mg)</td>
<td>350</td>
<td>590</td>
</tr>
<tr>
<td>260 g Aloo Gobi and</td>
<td>Tofu vegetable curry:</td>
<td>Selenium (mcg)</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>250 g Macaroni</td>
<td>• 240 g Tofu served with</td>
<td>Zinc (mg)</td>
<td>7</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td>• 80 g wild / brown rice</td>
<td>Folate (mcg)</td>
<td>259</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>• and a variety of vegetables</td>
<td>Vitamin A (RE)</td>
<td>208</td>
<td>280</td>
</tr>
<tr>
<td><strong>Snacks</strong></td>
<td>• 120 g Apple</td>
<td>Vitamin C (mg)</td>
<td>86</td>
<td>142</td>
</tr>
<tr>
<td>100 g Potato crisps</td>
<td></td>
<td>Vitamin E (mg)</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin B12 (mcg)</td>
<td>3.2</td>
<td>5</td>
</tr>
</tbody>
</table>
During his first follow-up visit, Sunjay weighed 90 kg. He gained 2 kg in weight and 2 cm around his waist. Although he improved on the quality of carbohydrates he consumed, no attention was paid to portion control. During the consultation, practical advice was provided on:

- Portion control using food models as visual aids and using measuring spoons and cups as tools.
- How to include more vegetables in an appetizing way with lunch and dinner to lower the glycaemic load of the daily meals.
- Improving the quality and the quantity of Sunjay’s snack choices.
- Practical advice to facilitate healthy choices in restaurants while travelling, as well as managing the temptation of the bar fridges in his hotel rooms.

During Sanjay’s second follow-up consultation, losses of 2.5 kg in weight and 3 cm round his waist were recorded. Both his A1C and fasting blood glucose levels had improved dramatically. To date, Sunjay mentioned that thanks to the support of his wife, he found following the healthy eating plan much easier. He finds he is less hungry and is experiencing less cravings. He weight has dropped to 80 kg and he has had a total loss of 10 cm around his waist. He also mentioned that he now finds following his gym regimen easier and more enjoyable. It was agreed with his doctor to reduce his insulin to 16 units in the morning and 8 units in the evening (a reduction of nearly 50 % in total daily dose).

Conclusion
Although Sanjay will benefit from further weight loss, the healthy way of eating has finally become part of his lifestyle. He believes the three most important qualities enabling him to implement the changes were patience, perseverance and persistence, and the sessions with the dietitian helped him to practice these.
Impressive.

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LZ-DE-08 2013 0224
Recognising and Diagnosing Cardiac Autonomic Neuropathy in People with Diabetes

Introduction
The diabetes pandemic is spreading faster than any formulae or expert can predict. Furthermore, only one third of patients with type 2 diabetes mellitus (T2DM) will achieve the recommended HbA1c target of < 7 %. Therefore, a dramatic increase in the prevalence of diabetes complications is also expected. Cardiovascular disease is the major cause of mortality in male and female patients with either type 1 diabetes mellitus (T1DM) or T2DM. The risk of sudden cardiac death is also increased in patients with diabetes mellitus (DM) (RR 2.18; 95 % CI, 1.89–2.98). It has been well-documented that patients with DM have accelerated atherosclerosis and this is most likely to be the central cause for the increase in cardiovascular morbidity and mortality. However, less clear, is the contribution of cardiac autonomic neuropathy (CAN) to the cardiovascular sequelae. Diabetic autonomic neuropathy (DAN) is one of the distinct clinical syndromes of diabetic neuropathy and CAN forms a part of the wide-spectrum of abnormalities associated with DAN. Rather than focus on all the abnormalities associated with abnormal autonomic function in patients with diabetes, this article will focus on recognising and diagnosing CAN and will use recommendations from expert opinion to suggest who should be screened.

CARDIAC AUTONOMIC FUNCTION
Anatomy
The internal physiologic homeostasis of our organs is maintained by a sympathetic and parasympathetic nerve supply. Focusing on the heart, sympathetic innervation arises from the spinal cord at the level of the 1st to the 4th thoracic vertebrae. It travels via sympathetic ganglia in the sympathetic chain and innervates the sinoatrial (SA) node, the atrioventricular (AV) node and the ventricular myocardium. Parasympathetic innervation of the heart arises in the medulla and travels via the vagus nerve to innervate the SA and AV nodes. For the heart and blood vessels, acetylcholine is the neurotransmitter at pre- and post-ganglionic parasympathetic nerve fibres, but only at pre-ganglionic sympathetic nerve fibres. Norepinephrine is the neurotransmitter at all post-ganglionic sympathetic nerve fibres going to the heart and blood vessels.
Sympathetic stimulation of the SA node increases the frequency of action potentials, thereby increasing heart rate (HR).

**Physiology**
Sympathetic stimulation of the SA node increases the frequency of action potentials, thereby increasing heart rate (HR). Parasympathetic stimulation decreases the frequency of action potentials, thereby decreasing the HR. Therefore, dual innervation of the SA and AV nodes by parasympathetic and sympathetic nerve fibres results in a push-and-pull control of the HR. Since the intrinsic rate of the SA node is about 100-110 beats per minute and the average resting HR is about 72 beats per minute, it is evident that under resting conditions, the parasympathetic supply dominates.

Ventricular contractility is almost entirely controlled by the sympathetic nervous system. Sympathetic stimulation results in the release of norepinephrine, which, after binding to β-1 adrenergic receptors and thereby activating adenylate cyclase, results in an increase in cyclic AMP. This has the effect of opening calcium channels in the plasma membrane, increasing release of calcium from the sarcoplasmic reticulum, increasing myosin cross-bridge cycling and increasing calcium pump activity in the sarcoplasmic reticulum, all of which favour enhanced contractility.

**CARDIAC AUTONOMIC NEUROPATHY (CAN)**

**Introduction**
The prevalence of CAN is difficult to assess, as variable diagnostic criteria exist. It is also influenced by patient age and duration of diabetes. Consequently, a wide spectrum of prevalence is reported in the scientific literature ranging from 1.6 to 90%. Equally complex, is the pathogenesis of CAN, which is largely driven by hyperglycaemia, causing an increase in inflammatory mediators (IL-6, TNF-α, TLR-2, TLR-4) and oxidative stress by activating the polyol, protein kinase C, hexosamine and AGE-RAGE pathways.

**Clinical implications**
Multiple abnormalities in cardiovascular and peripheral vascular function are associated with CAN (Table 1), some of which result in distinct clinical consequences for patients:
- Exercise intolerance
- Abnormal blood pressure regulation
- Orthostatic hypotension
- Resting tachycardia
- Hypoglycaemic unawareness
- Silent myocardial ischaemia
- Left ventricular dysfunction.

These abnormalities in cardiovascular and peripheral vascular function translate into dire clinical outcomes with reported 5-year mortality rates up to 50% in patients with T1DM and T2DM, with a high proportion attributed to sudden cardiac death. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, CAN strongly predicted all-cause mortality (HR 2.14; 95% CI, 1.37–3.37) and cardiovascular disease (CVD) mortality (HR 2.62; 95% CI, 1.4–4.91), independent of duration of diabetes.

### Table 1: Cardiac and peripheral vascular abnormalities associated with CAN *

<table>
<thead>
<tr>
<th>Heart</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sympathovagal imbalance</td>
<td></td>
</tr>
<tr>
<td>• Perioperative haemodynamic instability</td>
<td></td>
</tr>
<tr>
<td>• Rhythm - resting tachycardia, loss of reflex heart rate variations, prolonged QT interval</td>
<td></td>
</tr>
<tr>
<td>• Blood pressure - hypertension, orthostatic hypertension, postprandial hypotension, non-dipping, reverse dipping</td>
<td></td>
</tr>
<tr>
<td>• Exercise intolerance</td>
<td></td>
</tr>
<tr>
<td>• Impaired baroreflex sensitivity</td>
<td></td>
</tr>
<tr>
<td>• Coronary arteries – silent myocardial ischaemia, increased arterial stiffness, decreased sympathetically-mediated vasodilatation of coronary vessels</td>
<td></td>
</tr>
<tr>
<td>• Left ventricular dysfunction and hypertrophy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peripheral blood vessels</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased peripheral blood flow and warm skin</td>
<td></td>
</tr>
<tr>
<td>• Increased venous pressure</td>
<td></td>
</tr>
<tr>
<td>• Increased arteriovenous shunting and swollen veins</td>
<td></td>
</tr>
<tr>
<td>• Leg and foot oedema</td>
<td></td>
</tr>
<tr>
<td>• Loss of protective cutaneous vasomotor reflexes</td>
<td></td>
</tr>
<tr>
<td>• Increased trans capillary leakage of macromolecules</td>
<td></td>
</tr>
<tr>
<td>• Medial arterial calcification</td>
<td></td>
</tr>
</tbody>
</table>

The symptoms of CAN are non-specific and cannot be used for diagnosis. Rather, distinct cardiovascular tests are needed to make the diagnosis. Multiple tests have been used by various researchers to diagnose CAN, but the tests that have become universally accepted are those based on the blood pressure (BP) response to standing (Table 2), the response of the heart rate (HR) to deep breathing (Table 3), standing up from a supine position.

### Diagnosis and screening

The symptoms of CAN are non-specific and cannot be used for diagnosis. Rather, distinct cardiovascular tests are needed to make the diagnosis. Multiple tests have been used by various researchers to diagnose CAN, but the tests that have become universally accepted are those based on the blood pressure (BP) response to standing (Table 2), the response of the heart rate (HR) to deep breathing (Table 3), standing up from a supine position.

**Table 2: Blood pressure (BP) response to standing up from a supine position**

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Method</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>During standing, BP is maintained by an activation of the sympathetic nervous system that increases both cardiac output and peripheral vascular resistance. This test therefore assesses sympathetic function.</td>
<td>Patient lies supine for at least 5 minutes</td>
<td>Postural drop in BP&lt;br&gt; (Supine systolic BP, minus lowest systolic BP, whilst standing)&lt;br&gt; - Normal, 10 mmHg; Borderline, 11-29, Abnormal, ≥ 30</td>
</tr>
<tr>
<td></td>
<td>BP is measured three or more times, 1 minute apart, until it stabilizes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient then stands up quickly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BP is measured twice, after 60 and 120 seconds, in the standing position</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The arm in which the BP is measured should be placed horizontally at the level of the right atrium, and supported to avoid any isometric physical exercise that might increase BP. Standing with the arm hanging alongside the body may result in an overestimation of BP values (up to 10 mmHg) and may therefore reduce the sensitivity of the manoeuvre in detecting orthostatic hypotension</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Heart rate (HR) response to deep breathing**

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Method</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR varies with respiratory cycles (sinus arrhythmia) - it increases during inspiration and decreases during expiration</td>
<td>Continuous recording of heart rate (ECG)</td>
<td>Expiration-inspiration ratio&lt;br&gt;(E/I ratio - average 3 longest RR intervals expiration/average 3 shortest RR intervals inspiration)</td>
</tr>
<tr>
<td>Under parasympathetic control. Thus, this test measures parasympathetic function</td>
<td>Subject in supine or sitting position for at least 1 minute</td>
<td>Lowest normal values of E/I ratio by age:&lt;br&gt;</td>
</tr>
<tr>
<td></td>
<td>Deep inspiration to the maximum total lung capacity for 5 seconds, followed by a forced expiration down to the residual volume over 5 seconds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat 6 times in 1 minute</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to alternate the respiratory cycle is signalled directly to the patient by the operator or, preferably, by a time-keeping instrument</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Important that the subject does not change the respiratory phase before the 5 seconds have elapsed</td>
<td></td>
</tr>
</tbody>
</table>

- Normal, ≥ 15 beats; Borderline, 11-14 beats, Abnormal, ≤ 10 beats
position (Table 4) and the Valsalva manoeuvre (Table 5). These tests should be performed after an overnight fast or 2 hours after a light meal. Prior to these tests, patients should not have participated in any exercise for the previous 24 hours and should avoid caffeine, alcohol and smoking for at least 2 hours before the tests. Furthermore, the tests should not be performed during hypoglycaemia or marked hyperglycaemia. Importantly, the Valsalva manoeuvre test should not be performed in any patient with proliferative retinopathy. Expert opinion suggests that to make the diagnosis of CAN, there must be at least two abnormal tests of heart rate. The presence of orthostatic hypotension suggests severe CAN.

Recommendations from expert opinion have suggested that the following patient categories should be screened for CAN annually:

- Patients with T2DM at diagnosis
- Patients with T1DM, from 5 years after diagnosis
- Patients with diabetes and symptoms suggesting autonomic dysfunction
- Patients with diabetes before planning a programme of moderate-to-high-intensity physical exercise, especially in the presence of high cardiovascular risk
- Patients with diabetes and a history of poor glycaemic control, high cardiovascular risk and microangiopathic complications

**SUMMARY**

CAN is common and is a predictor of cardiovascular risk and sudden death in patients with diabetes. Since there are simple bedside tests to diagnose CAN, and there are some treatment options that may decrease progression of CAN and improve symptoms, it is imperative that all ‘at risk’ patients are screened annually. Knowing that a patient has CAN helps with designing therapeutic strategies and assessing risk and prognosis.

**References on request**

---

### Table 4: Heart rate (HR) response to standing up from a supine position

**Physiology**

- Initially, on standing, baroreflex-mediated vagal inhibition and sympathetic stimulation results in an increased HR to maintain stroke volume (maximum increase of HR is between the 10th and 20th beat). This is then followed by baroreflex-mediated vagal enhancement that results in a decrease in HR (occurs between the 25th and 35th beat)
- Most of the heart rate changes are due to changes in parasympathetic stimulation; therefore, this test is a measure of parasympathetic function

**Method**

- Patient lies in supine position for at least 5 minutes
- Continuous ECG recording, also blood pressure monitoring
- Ask the patient to stand up quickly, but remain relaxed, with their arms at rest alongside the body, without speaking or moving until the end of the test
- The test usually ends 30-45 seconds after standing up

**Analysis**

- 30:15 ratio
  - Normal, ≥ 1.04; Borderline, 1.01-1.03, Abnormal, ≤ 1.00

### Table 5: Heart rate (HR) response to the Valsalva manoeuvre

**Physiology**

- During straining, the rise in intrathoracic pressure causes a decrease in venous return with a consequent drop in BP and a reflex tachycardia. When the straining is released, the drop in intrathoracic pressure causes an abrupt increase in venous return with a consequent increase in BP. This often overshoots, resulting in baroreflex-mediated parasympathetic stimulation, causing a bradycardia
- This is therefore a test of parasympathetic function

**Method**

- Patient in sitting position
- Continuous ECG monitoring
- Blows with an open glottis into a mouthpiece connected to a manometer, without taking a deep breath beforehand. To maintain a constant expiratory effort equivalent to an intraoral pressure of 40 mmHg, for 15 seconds.
- After this period, the expiratory straining is suddenly released. The subject should breathe regularly and remain silent and motionless until the end of the test
- The occurring of facial flushing and plethora, and neck vein engorgement testify to the correctness of the manoeuvre

**Analysis**

- Valsalva ratio
  - Normal, ≥ 1.21; Borderline, 1.11-1.20, Abnormal, ≤ 1.10
Accord Metformin is a biguanide oral anti-hyperglycaemic agent which acts by increasing peripheral glucose utilization through increasing insulin sensitivity and decreasing hepatic and renal gluconeogenesis.¹

Accord Metformin is indicated for type 2 (non-insulin dependent) diabetes mellitus when diet has failed and especially if the patient is overweight.¹
Our understanding of the impact of diabetes on organ function has been evolving since the discovery of insulin in the 1920s. Giddy with the joy of discovery, insulin was thought to be a miracle drug that appeared to cure childhood diabetes. However, it soon became clear that although insulin prevented an early metabolic death, late complications of this progressive condition affected the eyes, kidneys, peripheral nerves, heart and vasculature, leading to serious disability and increased mortality.

The brain has been described as the final frontier of diabetes-related complications but, until two decades ago, it was largely ignored as a site for diabetes-associated end-organ-damage. However, much has changed since then.

Diabetes is a complex disorder, and several factors related either to the condition itself, treatment effects, long-term complications and comorbidities can affect the brain. Moreover, intrauterine and childhood factors, as well as socio-economic circumstances, muddy the landscape even further. Poor socio-economic status has been linked to both the development of type 2 diabetes and cognitive dysfunction (even in those without diabetes) later in life.

The relationship between diabetes and mild forms of cognitive dysfunction is quite well established (see Table 1).

For the purposes of this article, we are on fairly firm ice regarding diabetes and mild cognitive dysfunction, but we need to tread more carefully when linking diabetes and major types of dementia. The current

Table 1: The relationship between diabetes and mild forms of cognitive dysfunction

<table>
<thead>
<tr>
<th>What we know about diabetes and the brain:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diabetes is bad for your brain, but mostly it is associated with mild to moderate changes in cognition such as changes in mental speed, mental flexibility and learning</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What we are unsure about:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The exact link between diabetes and the major types of dementia</td>
</tr>
<tr>
<td>• Many mechanistic studies make pathophysiological sense, but…</td>
</tr>
<tr>
<td>• It is difficult to tease out the exact role of diabetes in dementia, as it may be judged by the company it keeps (such as hypertension and dyslipidaemia)</td>
</tr>
<tr>
<td>• Diabetes does not seemed to be linked to subjective memory complaints</td>
</tr>
</tbody>
</table>
Several large longitudinal population-based studies have shown that the rate of cognitive decline is accelerated in the elderly with type 2 diabetes.”

Diabetes mellitus is associated with changes in cognition. Age, genetics, the type of diabetes, and related comorbidities are crucial factors in the variation seen between individuals with diabetes. In people with type 1 diabetes, this association is characterised by a mild to moderate slowing of mental speed and a diminished mental flexibility. However, in type 2 diabetes, cognitive changes mainly affect learning and memory, but also mental speed and flexibility. Several large longitudinal population-based studies have shown that the rate of cognitive decline is accelerated in the elderly with type 2 diabetes. Effect sizes (see Table 2) are moderate to large in patients older than 65 years and range from 0.4 – 1.0. Smaller effect sizes (<0.5) are found in relatively younger adults (<60 years old) with type 2 diabetes. By contrast, a study on the effect of cognition in the oldest old (age at study entry 85 years) did not find an association between diabetes and accelerated cognitive decline. Whether this is a form of survivor effect or another phenomenon is unknown.

The determinants of this accelerated cognitive decline, however, are less clear; some researchers suggest that hypertension could be an important mediator, whereas others have found it associated with glycaemic control.

Crucial periods
Clinically relevant cognitive decrements in relation to the course of diabetes mainly occur during two crucial periods in life; the period of brain development in childhood, and the period when the brain undergoes neurodegenerative changes associated with ageing. Outside of these periods, cognitive decrements mainly occur in patients with substantial diabetes-related comorbidity, particularly micro- and macrovascular complications.

Early childhood
Many neuropsychological studies have shown that children with type 1 diabetes perform worse than children without the condition on measures of intelligence, processing speed, memory, and executive skills, although the magnitude of the reported effects varies. The methodological limitations of many of the early studies are a potential source of this variation. However, more recently, several well-designed longitudinal studies have found consistent evidence of lower intelligence quotient (IQ) scores, reduced mental efficiency and poorer school performance in children with type 1 diabetes.

Early onset of diabetes is known to be a potent predictor of worse cognitive outcomes in children; here, repeated episodes of severe hypoglycaemia might be a culprit. Interestingly, the role of poor glycaemic control on cognition in this age group, is less clear.

Late adulthood
Adults who develop type 2 diabetes later in life also have cognitive decrements compared with adults without type 2 diabetes; psychomotor efficiency, executive function, and learning and memory skills are often most affected.
Childhood factors strongly affect adult cognitive ability, and adverse socioeconomic circumstances early in life increase the risk of both type 2 diabetes and late-life cognitive disorders.

Studies with cognitive screening instruments, or batteries of more comprehensive neuropsychological tests, show that the rate of cognitive decline due to ageing is increased 1.5- to 2.0-fold in individuals with type 2 diabetes. Structural brain imaging studies in older adults (60 - 65 years) with type 2 diabetes, show that cerebral atrophy is more pronounced and lacunar infarctions are more common (OR 1.3 - 2.2), suggesting the role of hypertension to be a significant one. The association between type 2 diabetes and hyper-intense regions of white matter is a controversial topic. However, analyses done with sensitive volumetric techniques do indicate a modest increase in this lesion load in people with diabetes.

In a large 2010 BMJ meta-analysis, white matter hyper-intensities were found to be a predictor of stroke, dementia and death, thereby implicating them as something more than merely a radiological abnormality. The risk factors for cognitive decline and brain imaging abnormalities in older individuals with type 2 diabetes are still uncertain. Thus far, most of the available studies are cross-sectional and relate cognition and imaging findings to concurrent vascular and metabolic risk factors.

Work by Keokuk and colleagues (2015) interprets the results of cognitive function testing in adults with and without diabetes, to indicate that cognitive decrements occur secondary to diabetes itself, but other explanations are possible. Childhood factors strongly affect adult cognitive ability, and adverse socioeconomic circumstances early in life increase the risk of both type 2 diabetes and late-life cognitive disorders. Hence, cognitive decline in patients with diabetes might be a result of the same premorbid circumstances that predisposed them to diabetes.

**Crucial conditions**
The presence or development of microvascular complications is clearly linked to neurocognitive dysfunction. This is particularly seen in adult patients with type 1 diabetes, where the occurrence of microvascular complications is associated with reduced cognitive performance and cognitive decline. The mechanisms that underlie this association remain to be determined. The co-occurrence of these complications may be an index of chronic exposure to hyperglycaemia and thus, indicative of disease severity. On the other hand, it could reflect the susceptibility of an individual to hyperglycaemia-mediated damage. Alternatively, as noted in the retina, microvascular disease might be an indirect marker of changes in the microcirculation in the brain.

A much-feared factor amongst people with diabetes (and their relatives) is the occurrence of severe hypoglycaemic episodes. Thus far, the largest available prospective studies did not find long term adverse effects of severe hypoglycaemic events on cognition; however, in selected patient groups, repeated episodes of severe hypoglycaemia may have permanent adverse cognitive sequelae.

The relationship between glycaemic control, as assessed by glycated haemoglobin, and cognition, is still murky, although follow-up of the Diabetes Control and Complications Trial (DCCT) in people with type 1 diabetes, shows that poor glycaemic control is associated with an accelerated decline in the psychomotor efficiency and motor speed domains. Relatively less is known about the risk factor profile that is associated with more pronounced cognitive decrements in patients with type 2 diabetes, but hypertension, microvascular and macrovascular disease have all been implicated.

**ACCORD MIND results**
The results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes (MIND) study add further controversy to what is already a contentious field. ACCORD MIND is the first randomized study in older people with type 2 diabetes to test the effect of intensive (target HbA1c of less than 6.0 %) compared with standard glycaemic lowering strategies on cognitive domains and on structural changes in the brain. Both groups had longstanding type 2 diabetes, a high risk of cardiovascular disease, and a mean age of 62 years. Overall, the 4-year study showed no cognitive benefit in the intensive treatment group. There was a small but significant difference in total brain volume (TBV).

However, this difference does not support the use of intensive treatment to reduce brain atrophy, in view of the effects of this intervention in the main ACCORD trial: raised mortality, no overall benefit on cardiovascular disease events, an increase in hypoglycaemic events, and weight gain.
In a 2011 editorial, Biessels broke down ACCORD MIND into digestible pieces. A number of problems were encountered in the study but, despite this and the largely negative results, ACCORD MIND was an important study. It was the first large randomized trial to target cognition and abnormalities on brain MRI in people older than 55 years with type 2 diabetes. Recording of cognitive and MRI outcome was meticulous and loss to follow-up was low. The study does, however, raise important questions. What is the clinical significance of the outcomes measures? Can we now discard dysglycaemia as a treatment target to prevent cognitive decline?

**Diabetes and dementia: reasonable bedfellows?**

Although the association between diabetes and modest cognitive changes is now well established, the relationship between diabetes and dementia is an area of controversy. A causal association between type 2 diabetes and dementia is difficult to establish, owing to the number and complexity of possible risk factors and pathways.

Culprit risk factors for dementia in patients with type 2 diabetes include those that lead to the condition itself (poor lifestyle choices resulting in insulin resistance), diabetes-specific variables (hyperglycaemia, hypoglycaemia, endothelial dysfunction, inflammation, microvascular complications, and macrovascular disease), and cardiovascular risk factors (metabolic syndrome and smoking) that are associated with type 2 diabetes.

A large systemic review of population-based studies investigating the risk of dementia in diabetes mellitus (Biessels et al, 2008) concluded that in general, there is an increased risk of dementia in patients with diabetes. The increased risk includes both Alzheimer’s disease and vascular dementia, although the limitations of clinical diagnostic criteria in the classification of dementia by pathological subtype should be noted. Unfortunately, the available epidemiological data lack sufficient detail to reliably tease out specific risk factors linking diabetes to dementia.

**Underlying mechanisms**

Studies of the pathophysiological mechanisms that might suggest how diabetes-related factors and comorbid conditions can affect the brain, greatly outnumber those studies that address clinical problems. However, these studies fail to show which pathophysiological mechanism is the main driver of the association between diabetes and dementia, in a clinical setting.

In a nutshell: diabetes and its comorbidities are associated with an increased risk of atherosclerosis and stroke leading to vascular pathology in the brain. Glucose-mediated toxicity can lead to microvascular abnormalities and advanced protein glycation with oxidative stress resulting in more widespread changes in cognition and brain structure, referred to as “accelerated brain ageing”. Additionally diabetes might interfere with amyloid metabolism, giving rise to an Alzheimer’s-type pathology.

**Future research: what do our patients need?**

Cognitive dysfunction affects the ability of patients to follow complex disease management protocols, and impaired cognition also predicts cardiovascular disease and severe hypoglycaemic events.

The available trials of glycaemic control have not shown a benefit for cognitive health with tight glycaemic control, but they might have been too short to detect benefit. Even less information is available on how to manage people who have diabetes with cognitive impairment and dementia.

Studies of how or when to modify complex diabetes management regimens appropriately in cognitively impaired patients would be useful, given the risk of severe hypoglycaemia.

The symptoms of dementia associated with diabetes could differ from dementia not associated with diabetes, and studies of the effects on carers coping with the combined burden of these two diseases would be helpful.

**Summary: Much ado about everything?**

We know that diabetes is associated with milder forms of cognitive dysfunction and that some evidence shows an increased risk of dementia in people with diabetes. But, there are few detailed epidemiological data for risk factors. Some studies provide pathophysiological leads, but they do not indicate which of these leads are clinically relevant. This gap in evidence between epidemiological and mechanistic studies needs to be closed. The risk factors and mechanisms that drive the association between diabetes and accelerated cognitive decline and dementia need to be identified, before we are able to offer our patients optimum therapeutic targets and regimens. The catastrophic effect of cognitive decline and dementia on not only the health care system and work force, but on our patients and their families, should be ignored at our own peril.

**References on request**
Proprietary Name: Ryzodeg®

Scheduling Status: S3

Composition: Each ml contains insulin degludec/insulin aspart (70 % soluble insulin degludec and 30 % soluble insulin aspart) 100 units/ml.

Indications:
- Treatment of adult diabetes mellitus patients, as basal add-on to co-medication in patients who are inadequately controlled. In type 1 diabetes mellitus, Ryzodeg® should be used with short-acting soluble insulin for use at the meal times when Ryzodeg® is not used. In type 2 diabetes mellitus, Ryzodeg® should be used as an add-on to oral antidiabetic medicines. Contra-indications: Hypersensitivity to the active substances or to any of the excipients; pregnancy.

Warnings & Special Precautions: Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. Patients whose blood-glucose control is greatly improved may experience a change in their usual warning symptoms of hypoglycaemia and must be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand, or manufacturer of insulin must be done under strict medical supervision. When using Ryzodeg® in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Thiazolidinediones should be discontinued if any deterioration in cardiac function occurs. Hypoglycaemia may constitute a risk when driving or operating machinery. Pregnancy and lactation: Safety has not been established in pregnancy and lactation and Ryzodeg® should not be recommended for use during pregnancy. Dosing and Directions for Use: Ryzodeg® can be administered once- or twice-daily with the main meal(s). When needed, the patient can change the time of administration as long as Ryzodeg® is dosed with a main meal. The potency of insulin analogues, including Ryzodeg®, is expressed in units (U). 1 unit (U) Ryzodeg® corresponds to 1 international unit (IU) of human insulin and one unit of all other insulin analogues. In patients with type 2 diabetes mellitus, Ryzodeg® can be combined with oral anti-diabetic products approved for use with insulin, with or without bolus insulin. In type 1 diabetes mellitus, Ryzodeg® is combined with short-acting insulin at the remaining meals. Ryzodeg® is to be dosed in accordance with individual patients’ needs. Dose-adjustments are recommended to be primarily based on pre-breakfast glucose measurements. An adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness. Initiation: For patients with type 2 diabetes mellitus, the recommended total daily starting dose of Ryzodeg® is 10 units once-daily with meal followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, Ryzodeg® is to be used once-daily at mealtime and a short-acting insulin should be used at the remaining meals with individual dosage adjustments. The recommended starting dose of Ryzodeg® is 60 – 70 % of the total daily insulin requirements. Transfer from other insulin medicinal products: Close glucose monitoring is recommended during transfer and in the following weeks. Patients with type 2 diabetes: Patients switching from once-daily basal or premix insulin therapy can be converted unit-to-unit to once-daily Ryzodeg® at the same total insulin dose as the patient’s previous total daily insulin dose. Patients switching from more than once-daily basal or premix insulin therapy can be converted unit-to-unit to twice-daily Ryzodeg® at the same total insulin dose as the patient’s previous total daily insulin dose. Patients switching from basal/bolus insulin therapy to Ryzodeg® will need to convert their dose based on individual needs. In general, patients are initiated on the same number of basal units. Doses and timing of concurrent antidiabetic treatment may need to be adjusted. Patients with type 1 diabetes: For patients with type 1 diabetes mellitus, the recommended starting dose of Ryzodeg® is 60 – 70 % of the total daily insulin requirements in combination with short-acting insulin in the remaining meals followed by individual dosage adjustments. Doses and timing of concurrent short-acting insulin products may need to be adjusted. Flexibility: Ryzodeg® allows for flexibility in the timing of insulin administration as long as it is dosed with the main meal(s). If a dose of Ryzodeg® is missed, the patient can take the next dose with the next main meal of that day and thereafter resume the usual dosing schedule. Patients should not take an extra dose to make up for a missed dose. Ryzodeg® should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Side Effects: Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1.000 to < 1/100); rare (≥ 1/10.000 to < 1/1.000); very rare (< 1/10.000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Peripheral oedema and rare: hypersensitivity and urticaria. Pharmacological classification: A 21:1 Insulin Preparations Reg. No.: 47/21: 1/0165

In type 2 diabetes, careful control of blood glucose can help prevent or delay micro- and macrovascular complications. Initially, this may be adequately achieved with lifestyle change and oral medication, but because of the progressive nature of diabetes, characterised by gradual decline in β-cell function and density, most patients will eventually require insulin to achieve glycaemic goals. The benefits of control achieved early in the condition remain for many years, despite it becoming more difficult to maintain target glucose levels.

Hypoglycaemia limits effective diabetes management
A common limitation in achieving glucose targets however, both with oral therapies and especially as one intensifies insulin therapy, is hypoglycaemia. Hypoglycaemia not only has a negative impact on the wellbeing of the patient in the short- and long-term, it is also an important factor underlying clinical inertia.

This describes both a reluctance by clinicians to intensify therapy in patients who are insufficiently controlled on current therapies, and decreased motivation of patients to adhere to prescribed therapies.

Hypoglycaemia becomes more common with duration of therapy
Although hypoglycaemia is infrequent in early type 2 diabetes (T2DM), with longer durations of diabetes (and loss of the glucagon response to hypoglycaemia), and of insulin therapy, the incidence begins to increase, approaching that of hypoglycaemia in type 1 diabetes.

Mild hypoglycaemic events are even more common, but less reported. One prospective study reported that patients with type 2 diabetes were experiencing more than 16 mild hypoglycaemic episodes per year.

Nocturnal hypoglycaemia is especially common. Asymptomatic hypoglycaemia may be identified with continuous glucose monitoring in around 50% of patients with T2DM - the majority of episodes (74%) occur at night. Nocturnal hypoglycaemia may be suspected in patients who report morning headache, poor quality of sleep, vivid dreams or nightmares and profuse sweating in bed. Restlessness during sleep may disturb the partner.

Hypoglycaemia worsens an already increased risk of CVD
Patients with type 2 diabetes are at increased risk of cardiovascular disease (CVD). However, results of long-term studies of intensive glucose-lowering for CVD prevention have been disappointing. Tighter
glycaemic control appears to be no more effective than standard glucose reductions in reducing the risk of CVD mortality among high-risk individuals.

One hypothesis that might help to explain these observations, is the occurrence of severe hypoglycaemic episodes with intensive therapy. It has been suggested that severe hypoglycaemia is associated with a significantly increased risk of adverse vascular events and CVD mortality.7 p33a-e

Various mechanisms link hypoglycaemia to increased risk of myocardial ischaemia, acute thrombotic events and accelerated atherosclerosis, especially in an individual who is already at high risk of CVD. Hypoglycaemia induces number of adverse acute haemodynamic changes, including tachycardia, systolic hypertension, elevated cardiac output and myocardial oxygen demand, and increases the risk of potentially fatal cardiac arrhythmias. It is also associated with pro-thrombotic and pro-inflammatory effects, such as increased neutrophil and platelet activation, increased factor VII, increased C-reactive protein, vascular endothelial growth factor (VEGF) and inflammatory mediators, and reduced vasodilatation consequent to endothelial dysfunction.7 p34f,g

Clinical implications of treatment-related hypoglycaemia

From a clinical perspective, whilst it is important to achieve adequate glycaemic control, it is also desirable to avoid hypoglycaemia, especially in patients who are at high risk for CVD.7 p34h

Patients who are especially at risk include those with:
- Older age
- Longer duration of diabetes
- Concomitant medication
- Renal dysfunction
- Hypoglycaemia unawareness
- Cognitive dysfunction
- Peripheral neuropathy
- Intense glucose-lowering treatment strategies

Patients and relatives require education on the symptoms of and risk factors for hypoglycaemia, and appropriate management, should it occur.5 p55a

Where appropriate, it would be prudent to consider therapies with lower propensity to hypoglycaemia. Where insulin is required, it needs to be titrated carefully.

New insulins provide solutions to better diabetes management

Modern insulins carry a lower risk of hypoglycaemia than do older insulins.3 p160 Furthermore, progress in insulin therapy continues, allowing improved glycaemic control with fewer injections and less chance of hypoglycaemia, especially at night.8

Leading these developments, Novo Nordisk aims to make better diabetes outcomes available to all people with diabetes. Achieving target glycaemic control should not be at the expense of adverse outcomes which can be a direct result of therapy.

References
Presents a Five-Day Advanced Course in Diabetes Care for Health Professionals 2016

**DIABETES ~ THE BURDEN, THE RELIEF**

Latest estimates place the age-adjusted (20-79) comparative prevalence of Diabetes Mellitus in South Africa at 7.6% (International Diabetes Federation, 2015) and this is increasing. Up to 62% of persons with the condition are undiagnosed and at risk from disabling and life-threatening complications. Diabetes, together with its associated cardiovascular risk factors is one of the leading causes of death, either directly or indirectly, in our population.

Over the past three decades, it has become evident that good control of diabetes, as well as the common co-morbidities of hypertension and the dyslipidaemias, is vital to prevent or delay the devastating long-term complications of diabetes. To achieve this, people with diabetes need to understand their largely silent condition and the correct principles of self-care.

Health professionals often do not have access to updated approaches to a chronic, mostly self-managed condition such as diabetes ~ vital opportunities for therapeutic interaction and patient education are lost. Additionally, insight is needed into the ever-widening range of available medications and treatment strategies as well as the relationships between cardiovascular and other risk factors and diabetes.

As health services evolve, there is a move towards Team Management of Chronic Conditions. This has resulted in the rest of the Health Care Team (Nurses, Pharmacists, Dieticians, Podiatrists, Biokineticists and others) playing an ever-increasing role in diabetes care.

**WHO SHOULD ATTEND THE COURSE?**

This is an Advanced Course, and is aimed at Health Care Professionals who have a basic knowledge and understanding of diabetes mellitus. It is designed to give an extensive overview of the core principles of modern team diabetes management, so enabling the participants to understand the condition in sufficient depth, to make a real difference in the lives of people with diabetes. Pre and Post Course multiple-choice knowledge evaluation tests are administered, to allow for evaluation of the learning experience.

Attendance is also part of the contractual requirements for Practitioners wanting to open CDE affiliated “Centre for Diabetes Excellence” Branches.

**COMMENTS FROM DELEGATES TO PREVIOUS 5-DAY COURSES:**

I realise that I had been blundering around in the dark in treating my patients with diabetes and now someone has turned on the light! This a life changing Course. You have reformed my medical practice forever - General Practitioner

It was a superb Course & should result in a marked improvement in the care of people with diabetes - Registered Nurse

I enjoyed the Course thoroughly. I will manage patients with diabetes with more self-confidence. The talks were excellent, well organized and well presented - Registered Dietician

The message that you convey is that you care. The variety of topics was great. The balance between active participation and listening was great. The great teaching skills in all lectures promote learning - Registered Nurse

All speakers were excellent and displayed an impressive knowledge of their subjects. Your commitment as professionals is highly commendable. I learned a lot from this superb Course. Consequently, I will be able to treat my patients better - Medical Specialist
CPD ACCREDITED

The Course offers 34 contact hours. The Course is accredited to provide 30 CPD points for Medical Practitioners and other Healthcare Practitioners registered with the Health Professions Council of South Africa.

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Tel: +27 11 053-4400 / Fax: +27 (0)86 247-0674
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PROGRAMME SUMMARY

The Course is aligned with the latest evidence based treatment guidelines. Case studies and problem solving approaches are a vital part of the learning process.

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- Holistic Team Care Philosophy & Educational Approaches
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- Other types of diabetes including Gestational Diabetes
- Treatment of Type 1 & Type 2 Diabetes
- Psychological Adjustment to Diabetes
- Meal Planning & Nutrition in Diabetes
- The Importance of Exercise in Diabetes
- The Medical Management of Diabetic Ketoacidosis
- The Foot of the Person with Diabetes
- Acute Complications of Diabetes
- Diabetes as a Micro- & Macro-vascular Disease & Risk Factor Control
- Managed care in diabetes
- Interactive Team-facilitated Case Study Sessions
- Practical Workshop on Self Care Devices & Equipment

OUR INTERDISCIPLINARY TEAM OF COURSE LECTURERS AND FACILITATORS

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