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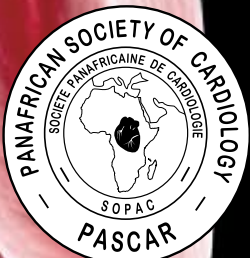
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CardioVascular Journal of Africa (official journal for PASCAR)

## International Symposium Integrated Approach to Disease Management: Endocrinology, Metabolic Disorders and Cardiac Consequences

Cape Town

6–7 March 2010





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# Report on the first international symposium, Integrated Approach to Disease Management: Endocrinology, Metabolic Disorders and Cardiac Consequences, Middle East, Russia and Africa

Cape Town, 6–7 March 2010

## Diabetes and thyroid disease interactions and their cardiac consequences

The need for an integrated approach to diabetes and thyroid disease management resulted in the organisation of a special symposium between the developing regions of the Middle East and Africa, sponsored by Merck Serono.

Experts in diabetes and thyroid dysfunction addressed the known and emerging cardiometabolic consequences of these conditions; applying new knowledge to the particular circumstances of developing regions, represented by delegates from Saudi Arabia, Iran, Lebanon, Egypt, Morocco, Russia and South Africa.

### The thyroid and type 2 diabetes

In the first keynote lecture, Prof Klaus Badenhop, Jahan Wolfgang Goethe University, Frankfurt noted that fluctuations in thyroid hormone levels, even in patients treated for their thyroid disorder, adversely affect glucose homeostasis, increasing the risk of atherosclerotic events. 'As insulin and thyroid hormones are intimately involved in metabolism at a cellular level, it is inevitable that any excess or deficit of either endocrine hormone will impact on the cardiometabolic environment.

In addition, another endocrine organ, brown adipose tissue, which stimulates thermogenesis and regulates energy homeostasis, is activated by thyroid hormones. Brown adipose tissue forms a further physiological link between diabetes, thyroid disorders and weight gain, leading to the metabolic syndrome', he noted.<sup>1</sup>

Brown adipose tissue is now also being targeted as a new therapeutic area for the treatment of obesity, as it and subcutane-

ous white adipose tissue (but not visceral white adipose tissue) have the potential to benefit metabolism by improving glucose homeostasis and increasing energy consumption.

The cardiovascular effects of thyroid hormone are exerted on heart rate, systemic vascular resistance and cardiac output (Fig. 1). The cardiovascular consequences of hypothyroidism are also well known and are summarised in Fig. 2 and Table 1.

With regard to the dual occurrence of thyroid disorders and type 2 diabetes, an interesting study from Taiwan<sup>2</sup> has found that subclinical hypothyroidism occurs quite commonly in type 2 diabetes; 7.2% of diabetes patients in this cohort of 600 patients had subclinical hypothyroidism and 3% overt

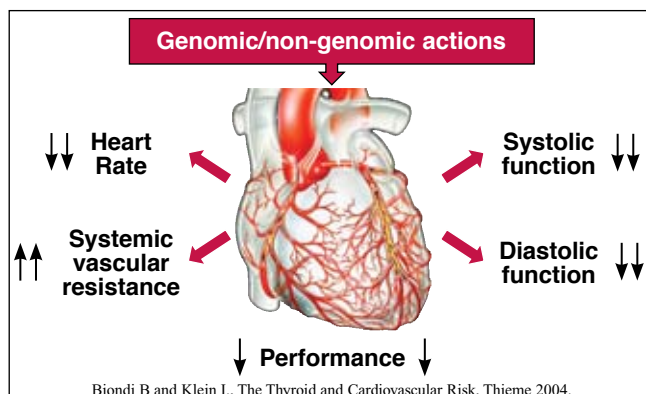
hypothyroidism, perhaps reflecting a higher level than anticipated by many physicians.

'The cardiovascular consequences of the subclinical hypothyroid state has also been substantiated in a recent meta-analysis<sup>3</sup> and with the convincing 20-year follow up of the Wickham study<sup>4</sup> which, when evaluating the cardiovascular consequences in untreated patients with subclinical hypothyroidism (SCH) and without ischaemic heart disease (IHD) at study entry, found a significantly higher incidence of IHD and IHD mortality in

**TABLE 1. CHANGES IN CARDIOVASCULAR FUNCTION IN HYPOTHYROIDISM**

	Normal range	Hypothyroidism
Systemic vascular resistance	1500–1700	2100–2700
Heart rate (beats/min)	72–84	60–80
Ejection fraction (%)	50–60	≤ 60
Cardiac output (l/min)	4.0–6.0	< 4.5
Isovolumic relaxation time (msec)	60–80	> 80
Blood volume (% of normal value)	100	84.5

Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001; **344**: 501–509



**Fig. 1. Effects of thyroid hormone on the cardiovascular system.**

- Haemodynamic changes
  - Increase in vascular resistance
    - Decreased vasodilator action of T3 and NO
  - Impaired ventricular performance
    - Changes in the expression of myocyte-specific regulatory proteins
- Increased cardiovascular risk
  - Increased risk for functional cardiovascular abnormalities
  - Increased risk for atherosclerosis

Klein I.L. The cardiovascular system in hypothyroidism. In: Braverman LE, Utiger RD, eds. *The Thyroid*. 9 ed. Philadelphia: Lippincott Williams & Wilkins, 2005: 774–780. Biondi B., Klein I. Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine* 2004; **24**: 1–13

**Fig. 2. Cardiovascular effects of hypothyroidism.**



the SCH group. These findings lost their significance when patients who had been treated with levothyroxine were included in the analysis.

The Taiwanese study,<sup>2</sup> which was undertaken to investigate the relationship between subclinical hypothyroidism and the prevalence of retinopathy, nephropathy and cardiovascular disease, showed that the higher cardiovascular events in these SCH patients are likely to be related to higher rates of nephropathy.

'It is clear from these studies that we need to identify and treat subclinical hypothyroidism in type 2 diabetes if we wish to reduce ischaemic heart disease morbidity and mortality', Prof Badenhop noted.

A recent study on the relationship between mild thyroid dysfunction in cardiac patients<sup>5</sup> has also highlighted the fact that survival rates were lower in patients with subclinical hypothyroidism and in those with low T3 levels, but were not altered in subclinical hyperthyroidism (Fig. 3).

Prof Badenhop concluded that at least 20% of diabetic patients will have some manifestations of thyroid dysfunction and this needs to be addressed in diabetes control strategies. 'Treatment goals need to be individually tailored to patient needs and profile in order to achieve physiologically adapted metabolism for lipids, glucose, heart and vascular systems', he stressed.

### Pathophysiology of type 2 diabetes

'There is a complex sequence of physio-

logical abnormalities that interact to produce the syndrome of type 2 diabetes. Understanding the pathophysiology and aligning our management of the condition to these circumstances presents an opportunity to refresh current guidelines.' This view was expressed by Prof Joshi, director of the Diabetes Care Centre, Pretoria and emeritus professor of medicine, MEDUNSA, South Africa.

'Both pancreatic  $\beta$ - and  $\alpha$ -cell dysfunction resulting from insulin resistance lies at the centre of the progression of type 2 diabetes pathology (Fig. 4), affecting the functioning of target organs – liver, muscle and adipose tissues, with resultant glucotoxicity and lipotoxicity.'

Insulin secretory defects in type 2 diabetes are characterised by abnormal patterns of basal pulsatile insulin secretion, decreased insulin capacity, decreased  $\beta$ -cell sensitivity to glucose, loss of first-phase insulin secretion in response to glucose and reduced second-phase insulin response, increased release of proinsulin and split products, morphological pancreatic changes with reduced  $\beta$ -cell mass, and amyloid deposits and defective glucose potentiation in response to non-glucose insulin secretagogues.

Beta-cell failure is also a feature of advancing age and genetic predisposition. 'Several genes have been shown to be associated with  $\beta$ -cell dysfunction in type 2 diabetes, affecting transcription factors and responsiveness to GLP-1', Prof Joshi noted.

In type 2 diabetes, there are also abnormalities related to the incretin effect,

including a deficiency of GLP-1 and resistance to the action of gastric inhibitory peptide (GIP).<sup>7</sup> The GLP-1 deficiency can already be seen in individuals with impaired glucose tolerance (IGT) and it worsens progressively with type 2 diabetes.

Highlighting the importance of the role of impaired insulin secretion, decreased muscle glucose uptake, increased hepatic glucose production and decreased hepatic glucose uptake in type 2 diabetes can aid the clinician in his management of patients over time (Fig. 4).

### The role of guidelines in optimising type 2 diabetes management

The need to monitor and up-titrate interventions in type 2 diabetes management is paramount and should be done at as rapid a pace as titration of medication allows. Also, early metformin usage needs to be expanded in many regions of the world. These views were expressed by Prof Sami Azar of the American University of Beirut Medical Centre, Lebanon in his presentation on different individual regions.

'Regions of the Middle East and North Africa (Tunisia, Morocco and Egypt) are facing a projected 81% increase in diabetes prevalence over the next 25 years, based on the 2003 International Diabetes Federation figures', Prof Azar pointed out. 'This means that the number of people with diabetes in the Middle East is set to more than double due to population growth, ageing and urbanisation trends.'

Of interest is that research on the use of metformin as initial therapy has shown

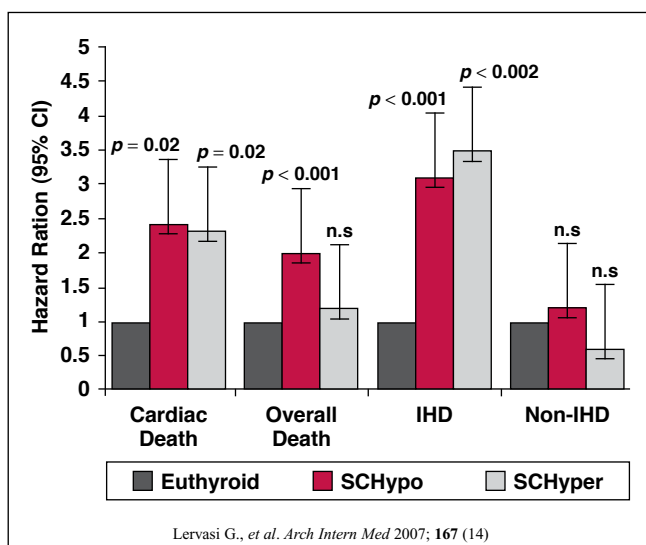


Fig. 3. Association between increased mortality and thyroid dysfunction in cardiac patients.

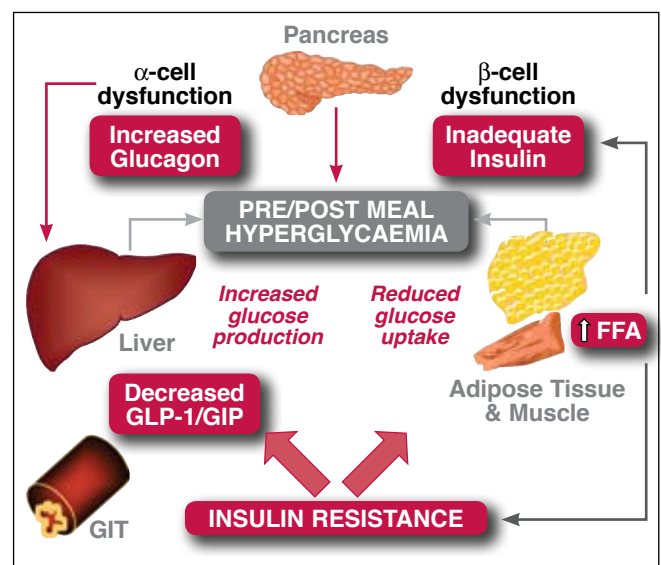


Fig. 4. Pathophysiological defects.

lower metformin initiation in the Middle East than in the United Kingdom (Fig. 5). Seeking to address cost-effective type 2 diabetes management, an expert panel of physicians in the Middle East developed an easy-to-understand and easily implementable algorithm for primary care level<sup>8</sup> (Fig. 6).

Prof Azar noted that in poorly resourced communities, the addition of sulphonylureas and other oral anti-diabetic agents is the step most often chosen. ‘The need to reinforce lifestyle message and maintain metformin therapy should be stressed at all visits, at three- and six-monthly intervals. The usage of metformin is advocated for all severities of hyperglycaemia, at all body weights and at all ages unless contra-indicated by renal disease or gastrointestinal (GI) intolerance. In the latter instance, switching to a once-daily slower-release formulation may improve GI intolerance’, Prof Azar said.

‘The recent recommendation from the American Diabetes Association to solely use HbA<sub>1c</sub> as a diagnostic measure of type 2 diabetes is problematic in Africa and many developing regions, as many patients are iron deficient and anaemic, and standardised HbA<sub>1c</sub> assays are not always available’, Prof Azar concluded.

**New therapies in type 2 diabetes management**

‘Despite more complex treatment of type 2 diabetes, which include new and more expensive drugs, we are not doing any better in achieving better glucose control for our patients.’ Expressing this view in his comprehensive update on new therapies in the management of type 2 diabetes, Dr Larry Distiller, South Africa’s champion of total care systems for diabetic patients, stressed the still unmet needs

of patients, namely: rising HbA<sub>1c</sub> levels over time, 4% β-cell loss per year, serious and fatal macrovascular consequences largely unaltered, and obesity. ‘In fact, the proportion of patients reaching HbA<sub>1c</sub> targets may well be declining and so the time for serious reflection is now’, he noted.

Concentrating on new therapies but excluding in-depth discussions on insulins, PPAR agonists and bariatric therapy, Dr Distiller noted that new forms of old drugs, such as sustained-release preparations and combinations of drugs offer the advantage of simplifying medication regimens and improving compliance. ‘We need to support patient compliance because of studies showing how increased dosage frequency to a mere twice-a-day regimen of sulphonylureas reduces compliance by a very significant 33%’, Dr Distiller added.

The new agents that focus on targeting the defective incretin hormone function in type 2 diabetes are GLP-1 analogues and DPP-IV inhibitors, which are now becoming available in developing countries. ‘The exciting aspect of the GLP-1 analogues, exenatide and liraglutide, is the prolongation of β-cell function, increasing proliferation and inhibiting apoptosis of β-cells (Fig. 7). However, to maximise their benefits to our patients, these agents should be used early in the diabetes treatment algorithms. This early use will not take place unless the drugs become cheaper and safety outcome data are more secure after long-term therapy’, Dr Distiller noted.

The DPP-4 inhibitors, sitagliptin and vildagliptin,

are oral agents that target post-prandial glycaemia and do not cause hypoglycaemia. ‘They are weight neutral, unlike the GLP-1 analogues which cause weight loss’, Dr Distiller pointed out. ‘Data on the long-term use of these agents are also lacking and the continued safety profile needs to be established, Dr Distiller warned. ‘Other agents such as pramlintide, an amylin analogue and dapagliflozin, an inhibitor of renal glucose uptake are as yet untested agents, which, although offering physiological rationales for use, need further efficacy and safety testing’, he noted.

‘Perhaps we need to return to lifestyle change as a highly effective way of treating diabetes and truly adopt the motto “lifestyle change is the cornerstone of type 2 diabetes” in order to achieve better results’, Dr Distiller concluded.

**Megatrials on metformin: importance for Africa**

‘The numbers of people in Africa who will develop type 2 diabetes are set to increase dramatically as longevity improves in these countries, accompanied by rapid urbanisation. Egypt is likely to have 8.6 million diabetics by 2030, earning it an unenviable place in the list of top 10 countries contributing to the patient load worldwide.’

Presenting this view, Prof Fahmy

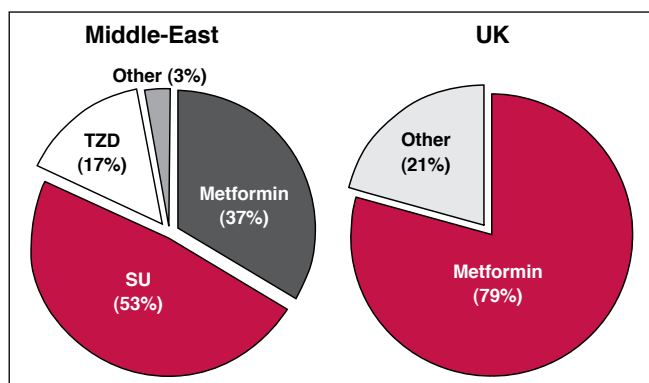


Fig. 5. Current use of metformin in the region.

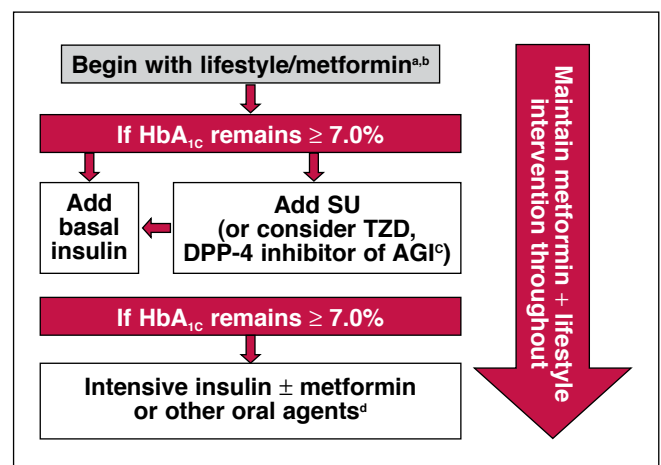


Fig. 6. Proposed algorithm for the management of type 2 diabetes in the Middle East. <sup>a</sup>Insulin may be required initially to stabilise patients presenting with severe hyperglycaemia. <sup>b</sup>A short trial of lifestyle intervention (e.g. one month) may be given before starting metformin (lifestyle intervention and metformin may be co-prescribed where additional clinic visits are problematic for the patient). <sup>c</sup>When appropriate for an individual patient. <sup>d</sup>Avoid combination of insulin with a thiazolidinediones (TZD) because of increased risk of oedema. Referral to a specialist will be appropriate for some patients.

Amara, emeritus professor, Alexandria University and president of the Egyptian Association of Endocrinology, Diabetes and Atherosclerosis, pointed out that the Diabetes Prevention Program (DPP) conducted in 2001 included a very large sample (45%) of patients with impaired glucose tolerance, representing ethnic minorities (African and Asian groups).

'This, together with the Indian DPP cohort of patients, led to the 2006 International Diabetes Federation consensus on type 2 diabetes management for both developed and developing countries, which focused on the value of lifestyle and metformin therapy. Metformin (850 mg twice daily) reduced the relative risk of progressing to type 2 diabetes by 31%, while intensive lifestyle counselling reduced the risk by 58%.

Recently, the 10-year follow up of the majority (88%) of the patients initially recruited into the DPP was completed. In this evaluation, the reduction of diabetes incidence was maintained but at a lower level; 18% in the metformin group and 34% in the lifestyle group.

Contrasting these results in IGT patients to the 10-year follow up of diag-

nosed type 2 diabetes patients recruited in the UKPDS study, Prof Amara noted that here also the effect of earlier metformin therapy was sustained. 'The legacy effect of metformin in type 2 diabetes, even when initiated early, is an excellent outcome for developing countries with limited health budgets, as metformin therapy is cheap, effective and has minimal side effects, Prof Amara concluded.

### Metformin's role in reducing cardiovascular and other conditions in IGT and non-diabetic patients

Metformin's action as an insulin sensitiser is key to its beneficial effects in reducing cardiovascular events along the continuum of dysglycaemia. 'The evidence of metformin's value in non-diabetics is limited, but there is some promising, if perhaps speculative evidence that it can be cardioprotective in non-diabetic high-risk patients', pointed out Dr Ian Campbell, St Andrews, United Kingdom.

Referring to an older, direct study in non-diabetics with dyslipidaemia, mainly hypertriglyceridaemia and heart disease, metformin therapy reduced angina and myocardial ischaemia in these patients by 70%.<sup>10</sup>

A more recent study of non-diabetic patients with angina and without coronary artery disease

(cardiac syndrome X) (Fig. 8) showed improved angina symptoms and increased forearm blood flow in those patients receiving metformin.<sup>11</sup>

'The mechanism of metformin vasodilation is perhaps the result of structural similarities between metformin and arginine, the potent precursor of nitric acid. Also metformin lowers CRP by 30 to 50%, which is indicative of a cardioprotective mechanism', Dr Campbell noted.

'If one turns to the circumstantial evidence, the UKPDS offers some tantalising views. After all, insulin and the sulphonylureas were equivalent to metformin in terms of controlling hyperglycaemia; but metformin was the only agent to show substantially greater cardiovascular benefits' (Table 2). 'This implies the involvement of other pharmacological actions of metformin', Dr Campbell pointed out.

Polycystic ovarian syndrome (PCOS), if regarded as a pre-type 2 diabetes condition with underlying insulin resistance, when treated with metformin during pregnancy, resulted in far fewer women developing gestational diabetes. Again, this indicates a cardioprotective role, as women with gestational diabetes experience increased cardiovascular events in later life, as evidenced from a Canadian study of extended follow up.<sup>12</sup>

'Metformin's role as an adjuvant in cancer therapy with some 55 ongoing trials could result in a further research lifespan of metformin beyond its current 52 years', Dr Campbell said. 'Its anti-cancer action in prostate, breast and bowel

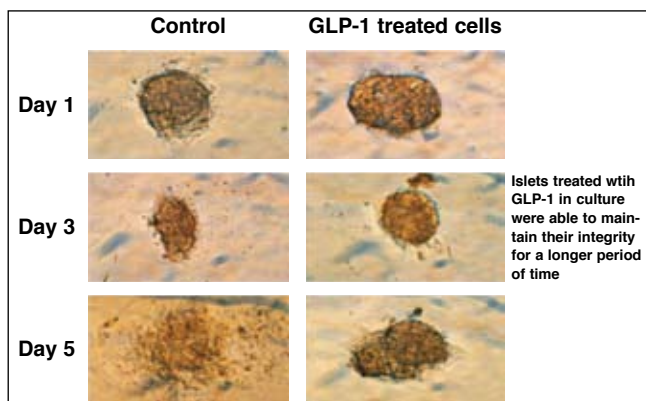
**TABLE 2. UKPDS: OUTCOMES OF INTENSIVE GLYCAEMIC THERAPY**

	<i>Metformin intensive</i>		<i>Sulphonylurea/insulin intensive</i>	
	<i>Change in risk*</i>	<i>p-value</i>	<i>Change in risk*</i>	<i>p-value</i>
Diabetes-related deaths	↓ 42%	0.017	↓ 20%	0.19
All-cause mortality	↓ 36%	0.011	↓ 8%	0.49
Any diabetes-related endpoint	↓ 32%	0.0023	↓ 7%	0.46
Myocardial infarction	↓ 39%	0.01	↓ 21%	0.11
Stroke	↓ 41%	0.13	↑ 14%	0.60

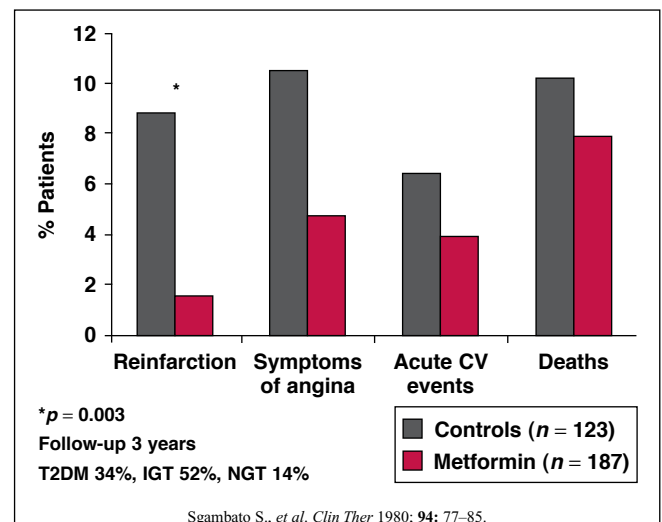
CV benefits substantially greater for metformin but all treatments were equivalent in controlling hyperglycaemia

\*Compared with conventional therapy (overweight group)

UK Prospective Diabetes study group. *Lancet* 1998; **352**(9131): 854–865.



**Fig. 7. GLP-1-preserved morphology of human islet cells in vitro.**



**Fig. 8. Three-year outcomes for post-MI patients treated with metformin.**

cancer is likely to be due to activation of LKB 1, an anti-tumour factor.’

Referring to the use of metformin in chronic congestive heart failure, Dr Campbell pointed out that if the patient is stable and ambulatory, he would use metformin at a left ventricular ejection fraction above 30%, based on the study results showing improved survival of diabetic patients with heart failure.<sup>13</sup>

In conclusion, Dr Campbell noted the excellent contributions from South African experts over many years, including the outstanding work by Profs WPU Jackson and EJ Coetzee on gestational diabetes.

### **Focus on thyroid dysfunction**

The second day of the symposium focused on thyroid dysfunction.

#### **Current aspects of thyroid hormone actions – a research view**

Prof Theo Visser of Rotterdam Erasmus University in the Netherlands gave an overview of the complex mechanisms involved in thyroid hormone transport into and out of cells. ‘For transport to take place, specific transporters are required to mediate the process. It does not simply take place by passive diffusion, as was once thought. There are two types: organic anion transporters and amino acid/monocarboxylate transporters.’

He spotlighted two of the latter type, MCT-8 and MCT-10, which are ‘particularly active’. ‘The expression of MCT-8 and MCT-10 stimulates the cellular uptake of T3 and T4’, he said. He also outlined a recent discovery in respect of thyroid dysfunction in Allan-Herndon-Dudley syndrome, a rare disorder that causes severe mental retardation.

A study by Prof Visser and his team found MCT-8 mutations in all 17 patients included in a study they undertook. This led them to conclude that the syndrome arises from thyroid hormone resistance, with the putative mechanism being impaired T3 uptake by the central nervous system as a result of the mutations in transporter MCT-8.

#### **Epidemiology and pathophysiology of thyroid dysfunctions**

Dr Gregory Hough, a specialist physician/endocrinologist in private practice in

Port Elizabeth, underscored that autoimmune hypothyroidism is more common in females than in males.

Focusing on Hashimoto’s thyroiditis, he noted that all the following mechanisms of injury potentially play a role: molecular mimicry, bystander activation, thyroid cell expression of HLA antigens and apoptosis. ‘Thyroid immunity is especially important, as immune tolerance is lost in autoimmune disease. The targets of autoimmunity are thyroglobulin, thyroid peroxidase and TSH receptors.’

In the case of thyroglobulin, the question is not why autoimmunity develops but how immune tolerance is maintained, given that thyroglobulin is exposed to many risk factors, including environmental ones. ‘An increasing number of pathogenic T-cell determinants are being discovered’, he said.

With regard to thyroid peroxidase, he observed that antibodies seem to develop as a result of antigens presented by thyrocytes and appear to play a more pathogenic role than was previously assumed. ‘TSH receptor antibodies can be either inhibitory or stimulatory; the former predominate in Hashimoto’s disease’, he said.

Turning to the genetics of thyroid disease, he noted, ‘Recent interest in chemokines has improved our understanding of their critical role in the initiation and maintenance of the immune response’.

#### **Autoimmune thyroiditis**

Prof John Lazarus of Cardiff University School of Medicine, Wales, UK reported on the aetiology/epidemiology, detection, treatment and control of autoimmune thyroiditis, also focusing mainly on Hashimoto’s thyroiditis. ‘Environmental and genetic factors combine to produce thyroid cell damage, causing an aberrant immune response and a Th1/Th2 imbalance. We’re also recognising the importance of a new player, Th17, in Hashimoto’s disease, and there is much to be discovered about this phenotype and its actions.’

Prof Lazarus underscored that the immunology of autoimmune thyroiditis is very complex and that while the basic mechanisms are understood, much of the detail is not.

Environmental factors play a role in the activation of the autoimmune

response. These include smoking, stress, drugs (notably lithium, amiodarone and interferon-alpha), irradiation, selenium/magnesium intake, infections, allergies and being pregnant/postpartum.

‘TPO antibodies are an important marker of autoimmune thyroiditis and TPO antibody abnormality leads to thyroid dysfunction that may be either overt or subclinical’, said Prof Lazarus.

Hashimoto’s disease affects mainly women over the age of 50, who can be either euthyroid or hypothyroid. It is associated with the presence of goitre, TPO antibodies with or without TgAB, hypoechogenicity, as well as the presence of other autoimmune diseases, notably rheumatoid arthritis, but also coeliac disease, Addison’s disease, pernicious anaemia, vitiligo and type 1 diabetes.

‘Thyroid failure is common in adults, especially women’, continued Prof Lazarus, ‘and it often goes unrecognised due to its protean and often non-specific symptomatology. The incidence increases with age and is associated with raised levels of both total and LDL cholesterol. All hyperlipidaemic patients should therefore undergo thyroid function tests to ascertain whether they might not also have subclinical hypothyroidism.’

‘Subclinical hypothyroidism is associated with a higher prevalence of both myocardial infarction and aortic atherosclerosis in elderly women, and it’s been shown to be as significant as other more well-known risk factors.’ Hypothyroidism is also characterised by psychiatric associations and there is a great deal of overlap between the condition and depression. The doctor’s clinical index of suspicion should therefore be high.

There is currently some controversy around screening for hypothyroidism in pregnancy. Guidelines advise that it be undertaken when there is a history of thyroid disease, goitre, suggestive symptoms, a family history of thyroid disease, type 1 diabetes and if the patient has undergone head/neck irradiation.

Levothyroxine is the treatment of choice. ‘It is commonly prescribed and reliable’, observed Prof Lazarus. ‘However, it has a very narrow therapeutic/toxic range that can have significant clinical consequences, including cardiovascular morbidity and mortality (when taken in excess) and raised LDL cholesterol levels and fatigue (when there is underdosing).’



Looking to the future, Prof Lazarus foresees a further dissection of the immune response as well as more insight into the long-term pathogenetic significance of antibodies. 'More auto-antigens might still be discovered and we will learn more about genetic predisposition and environmental factors.' He also anticipates the development of immune 'designer drugs'. 'But for now... T4 rules, OK?'

### Cardiovascular manifestations in hypothyroidism

From a clinical perspective, there are only three variations in the status of the thyroid – normal (in which case it requires no treatment), abnormal (where treatment is essential) and where subclinical disease is present. The latter area is where there is still lack of clarity and some controversy.

'Is subclinical hypothyroidism important to the clinician?' asked Prof James Ker (jun) of the University of Pretoria. Subclinical hypothyroidism affects five to 15% of the general population, is defined as an increased serum TSH level with normal free T4 levels and may be associated with increased morbidity from cardiovascular disease. Whether it should be viewed as a risk factor on a par with blood pressure and raised cholesterol remains controversial, however.

'Some, but not all, studies have shown a clear association between subclinical hypothyroidism and ischaemic heart disease', continued Prof Ker. 'There may be an age influence in that the incidence of IHD is higher in those under 65 years of age. Subclinical hypothyroidism might therefore be a more important risk factor in the young and may even be cardiovascular-protective in the elderly.' A reduced mortality risk has been observed in patients over the age of 85 with mild hypothyroidism.<sup>14</sup>

Overt hypothyroidism, on the other hand, is clearly associated with increased risk of atherosclerosis, increased CRP levels, endothelial dysfunction, increased arterial stiffness and altered coagulation parameters. All these measures have been shown to regress with levothyroxine administration. 'The cardiovascular benefits of replacement therapy in overt hypothyroidism are therefore unquestionable', said Prof Ker.

A broad meta-analysis of diverse patient groups, including African-American patients, published in the *International*

*Journal of Cardiology* in 2008<sup>15</sup> showed a clear and significant association between subclinical hypothyroidism and coronary heart disease at baseline. While subclinical hypothyroidism did not increase all-cause mortality, there was a significantly higher incidence of cardiovascular mortality at follow up.

Prof Ker observed that a single measurement of low serum TSH in individuals 60 years and older has been shown to be associated with increased mortality from all causes, particularly cardiovascular disease.<sup>15</sup> 'This suggests that subclinical hyper- and hypothyroidism might be equally bad for the heart.'

Because subclinical hypothyroidism is the result of a mix of aetiologies, treatment requires individualisation, especially in autoimmune contexts. A potential pathophysiological mechanism involves the autoimmunity often found in subclinical hypothyroidism.

The autoimmunity may cause local inflammation that induces coronary atherosclerosis – meaning that a single autoimmune process affects both the heart and thyroid. Other mechanisms include an atherogenic lipid profile induced by subclinical hypothyroidism. Thyroid hormones have also been shown to inhibit collagen-induced platelet aggregation *in vitro*. 'Platelet activity is a major culprit in IHD', said Prof Ker. 'The increased peripheral vascular resistance seen with subclinical hypothyroidism can also result in hypertension.'

When it comes to the relationship between subclinical hypothyroidism and type 2 diabetes, Prof Ker cited a 2007 study published in *Diabetic Medicine* that examined the relationship between subclinical hypothyroidism and the prevalence of retinopathy, nephropathy, cardiovascular disease and mortality in type 2 diabetics not taking thyroid replacement therapy.<sup>2</sup> 'The prevalence in these patients is high (in another study up to 17%).'

The study found a higher frequency of both nephropathy and cardiovascular events in those patients who had subclinical hypothyroidism, although the latter finding was non-significant after adjustment for microalbuminuria. It was the first report to show that subclinical hypothyroidism may be an independent risk factor for nephropathy, although not retinopathy in type 2 diabetics,' he said.

Brachial-ankle pulse-wave velocity is a parameter of arterial stiffening and

an independent predictor of cardiovascular events. Treating subclinical hypothyroidism with levothyroxine improves this parameter. This is likewise the case with impaired coronary flow and microvascular function.

Plasma viscosity, a cardiovascular risk factor, is also associated with subclinical hypothyroidism, and is usually accompanied by low HDL cholesterol levels in this context. Once again, patient profiles improve with thyroid treatment. 'Levothyroxine is therefore beneficial in restoring cardiac function abnormalities in the presence of subclinical hypothyroidism and has even shown benefit in patients with euthyroid autoimmune thyroiditis', said Prof Ker.

### Key conclusions

- Subclinical hypothyroidism is clearly associated with an increase in coronary heart disease, especially in those under 65 years old.
- It is accompanied by myocardial functional abnormalities, both systolic and diastolic, and these are evident even in euthyroid active thyroiditis.
- It has negative effects on coronary flow reserve and microvascular function, pulse-wave velocity and plasma viscosity.
- It raises the risk for nephropathy in type 2 diabetes.

Looking to the future, he speculated that in time, the upper limit of normal for TSH might be lowered to 3, or even 2.5.

### Subclinical hypothyroidism – where do we stand today?

Prof Said Khader of the Dr Suliaman Al Habib Centre in Riyadh, Saudi Arabia takes issue with the term 'subclinical hypothyroidism', preferring instead to call the condition 'mild thyroid failure' (MTF). He contends that there are almost always some symptoms associated with it, even though they may be mild enough not to be noticed by patients.

'It's a very scary condition', he said, 'and many patients have no obvious risk factors. Its clinical features are diverse and potentially affect virtually every part of the body. We know that cholesterol levels increase with rising TSH. This may explain the risk for coronary heart disease, which is more common in those with MTF than it is in diabetics. MTF



and depression are both common, and the overlap in symptoms often makes it difficult to differentiate between the two.'

Prof Khader defines MTF as an isolated elevated TSH level in the setting of normal T3 and T4 levels. Symptoms may be present or absent and various professional bodies differ when it comes to screening recommendations. Likewise, the TSH reference range for normal has been the focus of considerable debate, as this level is critical for diagnosing subclinical thyroid dysfunction. Like Prof Ker, he is of the opinion that the optimal level will be lowered in the future.

'The worldwide prevalence of MTF is one to 10%, and women over 60 are most affected. The risks include progression to overt thyroid disease, dyslipidaemia, cardiac dysfunction and atherosclerosis, neuropsychiatric symptoms, infertility and miscarriage risk and impaired foetal development. Consequently, many patients report symptoms that are easily confused with those of other conditions.'

The potential vascular complications include: elevated total cholesterol and LDL cholesterol levels, increased peripheral vascular resistance, alteration in endothelium-mediated vasodilation, increased C-reactive protein levels, and hypertension. Cardiac effects include corrected QT intervals that are significantly prolonged, and impaired ventricular systolic and diastolic function. MTF has also been identified as a potential cause of aortic atherosclerosis in women.

Prof Khader cited the findings of Canaris *et al.*<sup>17</sup> that the treatment of MTF may aid in the treatment of hyperlipidaemia and prevent associated cardiovascular morbidity. 'Quality of life is important', he said, 'and treatment with levothyroxine can help patients to feel better'.

Levothyroxine therapy can prevent progression to overt hypothyroidism, improve serum lipid profiles thus reducing cardiovascular risk, as well as address psychiatric symptoms. 'At the same time it's important to bear in mind factors that may reduce its effectiveness, such as malabsorption syndromes, intake of substances that reduce absorption (e.g. ferrous sulphate, espresso coffee) and concomitant use of drugs that reduce clearance, such as rifampicin and carbamazepine.'

Concluding, Prof Khader made the following points:

- Individuals with TSH levels between 5

and 10 should be treated selectively.

- Levothyroxine replacement therapy should be reserved for patients with goitre, women who are pregnant or planning to fall pregnant, and patients with depression or bipolar disorder.
- Patient preference, clinical circumstances, age, symptoms, presence of thyroid antibodies and progression of TSH over time should all be taken into account.
- Mayo clinic data show that individuals with TSH > 8 have a high likelihood of progressing to overt hypothyroidism in four years, so treatment is recommended.

### Pitfalls in treatment with levothyroxine

The number of pitfalls associated with levothyroxine therapy is significant, so patients need to consult qualified physicians. This is according to Prof Peter Laurberg of Aarhus University Hospital, Denmark.

Levothyroxine is contraindicated where there is known intolerance to the drug, and in patients who have untreated thyrotoxicosis, Addison's disease, acute myocardial infarction, acute myocarditis, acute pancreatitis or untreated pulmonary insufficiency/adrenal insufficiency. 'Also, watch out for low blood pressure, a pattern of low sodium/high potassium levels and don't simply administer in the presence of low T4 levels without appropriate TSH evaluation, as one needs to consider secondary hypothyroidism', he said.

There are also pharmacy pitfalls. Prof Laurberg cited an instance of a formulation processed by pharmacists in Brazil where patients ended up taking 10 times the normal dose. He underscored that patients and doctors need to be informed when reformulations enter the market. Not doing so is irresponsible and qualifies as patient neglect.

'The introduction of a reformulation of levothyroxine in New Zealand led to a 2 000-fold increase in reported adverse events. Something similar happened in Denmark. The possible cause is that a change in bioavailability led to an abnormal thyroid state, but because no-one had been told, no-one had checked.'

Overtreatment can have significant consequences. Prof Laurberg cited a 2002 study by Cooper and Ridgway to the

effect that iatrogenic hyperthyroidism as a result of insufficiently controlled levothyroxine therapy causes up to 17 000 cases of atrial fibrillation in the USA each year. 'The most common pitfall here is lack of control in dosing and adjustment. Doctors also make the mistake of believing that all patients are similar and that "normal" is always the same.'

Prof Laurberg maintains that there is ample room to adjust the dose within the reference range if patients are complaining. A pitfall to avoid here is evaluating the effect of this after only a week. 'You need to allow four to six weeks until a new steady-state concentration has been reached', he said.

Physicians need to bear in mind that when the thyroid state is changed, other parameters are potentially changed too. For example, when levothyroxine therapy is withdrawn from patients also taking lipid-lowering agents, their risk of myopathy increases. Levothyroxine can also interact with anticoagulants such as warfarin, to the detriment of the patient.

'We should be warning young women on levothyroxine that they need to be carefully controlled during pregnancy. Because pregnancy increases their levothyroxine requirement, the dose must be adjusted accordingly', he stated.

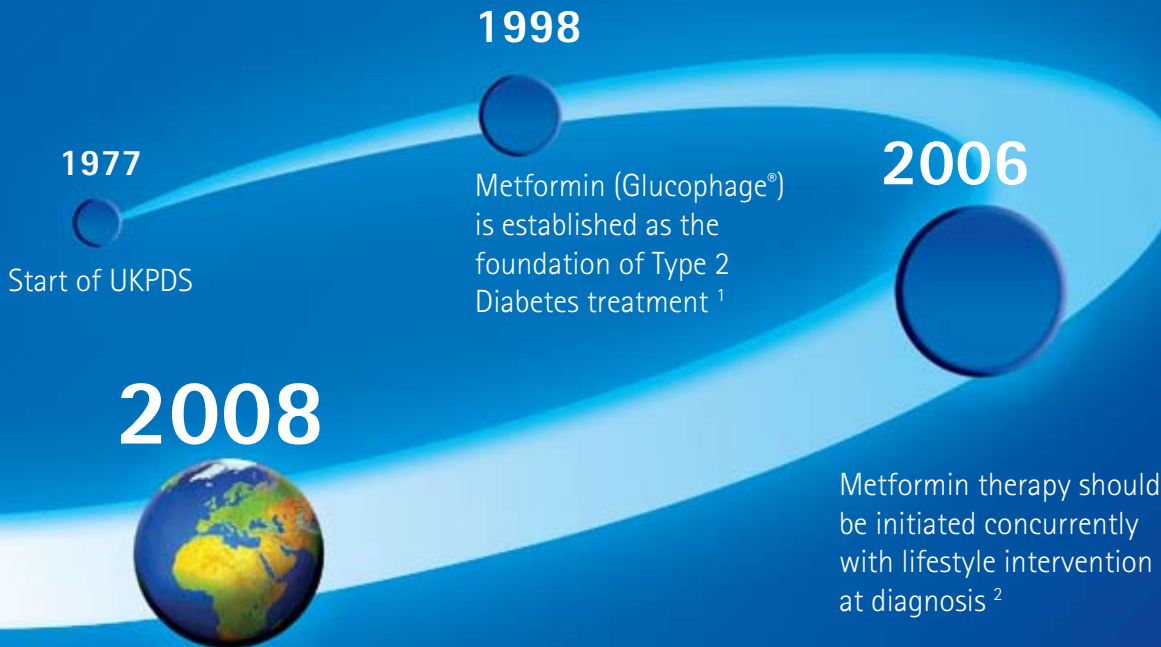
Prof Laurberg summarised the pitfalls as follows:

- Look for adrenal insufficiency and heart disease before introducing therapy.
- TSH is not a valid measure of function in secondary hypothyroidism.
- Bioactivity depends on the preparation.
- Patients' normal range is narrower than that in laboratory reference tests.
- Remember increased needs in pregnancy.
- Control needs to be checked regularly.
- In instances where findings are anomalous, consider whether the problem may not lie with the thyroid function tests being used and do additional testing using an alternative method.
- Absorption is partial only, and depends on many variable factors, including food, medicine and vitamin intake.

Report compiled by J Aalbers, Special Assignments Editor, and Peter Wagenaar, Gauteng correspondent.

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