**BEST PRACTICE**

**NEW APPROACHES TO TREATMENT OF THE METABOLIC SYNDROME IN SOUTHERN AFRICA**

South African experts on evidence-led treatments

**Introduction**

The metabolic syndrome is an extremely critical healthcare issue in South Africa as the ever-increasing incidence of obesity drives a dramatic increase in metabolic disease and related cardiovascular disease.

Initially, in the 1980s, the metabolic syndrome was described as an ‘insulin resistance syndrome’, recognising insulin resistance as the underlying mechanism of increased cardiovascular risk. Today, the cardiovascular risk of the metabolic syndrome is primarily believed to be the result of obesity, particularly due to the presence of central visceral fat causing insulin resistance.

The syndrome is defined by the presence of at least three out of five individual risk factors: elevated waist circumference, dyslipidaemia (elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol), elevated blood pressure and elevated fasting glucose (Table 1).

The long-term consequences of the metabolic syndrome include type 2 diabetes, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).³

### Table 1: Harmonised definition of the metabolic syndrome¹

<table>
<thead>
<tr>
<th>Measure</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>≥102cm in men – there is evidence of a lower level ≥82cm in African men⁴</td>
</tr>
<tr>
<td></td>
<td>&lt;90cm in south Asian and Chinese men</td>
</tr>
<tr>
<td></td>
<td>&lt;88cm in women, &lt;80cm in south Asian and Chinese women</td>
</tr>
<tr>
<td>Elevated triglycerides*</td>
<td>≥1.7mmol/l</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol*</td>
<td>&lt;1.0mmol/l in men</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2mmol/l in women</td>
</tr>
<tr>
<td>Elevated blood pressure*</td>
<td>≥130mmHg systolic</td>
</tr>
<tr>
<td></td>
<td>≥85mmHg diastolic</td>
</tr>
<tr>
<td>Elevated fasting glucose*</td>
<td>≥5.6mmol/l</td>
</tr>
</tbody>
</table>

Note: *Measure is also positive if on drug treatment targeting these individual criteria.

Pathobiology

The mechanism by which central obesity causes insulin resistance is still not fully understood. It is believed that as body fat increases, the rate of lipolysis also increases, mobilising free fatty acids (FFAs) from the adipose tissue to the bloodstream. This causes an increased influx of FFAs into the liver and muscles. As oxidation of FFAs in the muscles and liver increases, glucose utilisation in the muscle decreases and hepatic glucose production increases. Consequently, the FFAs released from the adipose tissue could contribute to the development of hyperglycaemia and impaired glucose tolerance.

As glucose levels start to rise, the insulin-producing β-cells of the pancreas will initially respond to the hyperglycaemia by releasing more insulin to maintain strict glucose control. Over time, the insulin-sensitive tissues of the body become less sensitive to the increased levels of circulating insulin, and insulin resistance develops. This also occurs at the level of the insulin receptors in the adipose tissue as well as those in the liver and muscle cells. When the β-cells of the pancreas are no longer able to produce enough insulin to ensure strict glucose control, glucose levels start to rise, leading to a pre-diabetes state and later to overt type 2 diabetes.

In the liver, the FFAs increase hepatic production of triglycerides from the liver, which are secreted as very low-density lipoproteins (VLDLs). These in turn are converted into small dense low-density lipoprotein (LDL) cholesterol. HDL particles are also reduced in size; hence HDL-cholesterol levels decrease.

Some interesting research on the metabolic syndrome in black South African women has shown that the presence of subcutaneous fat, a feature of obesity in these women, may protect against the metabolic syndrome by acting as a reservoir for systemic triglycerides, thus preventing their deposition in visceral adipose tissue, skeletal muscle or the liver, which then attenuates insulin resistance.

Therapeutic intervention in the metabolic syndrome

Weight loss

Achieving a relatively small reduction in overall body weight has been shown to have a significant beneficial effect on insulin-mediated glucose disposal. If weight loss of more than 5-7% can be achieved, plasma glucose levels, HbA1c and triglycerides are reduced, and HDL-cholesterol levels increase.

Pharmacotherapy

*Which risk factor to target first? Or should we target all five at once?*

Multiple pharmacological interventions are required to correct individual risk factors. Targeting a single risk factor without consideration of the other risk factors can lead to adverse effects of selected therapy on other co-existing risk factors. Targeted therapeutic intervention should therefore consider any potential detrimental effects on the non-targeted risk factors.
Dealing with atherogenic dyslipidaemia

**KEY MESSAGES**

- LDL-cholesterol is the primary target of statin lipid-lowering therapy as supported by large controlled clinical trials showing reduction in overall cardiovascular events and all-cause mortality\(^{12}\)
- The addition of a fibrate/another triglyceride-lowering drug can be considered if triglyceride levels remain >2mmol/l, but only after reaching the LDL-cholesterol target
- Consider referral to specialist level if triglycerides remain >5mmol/l on treatment.

The therapeutic target for LDL-cholesterol on statin therapy depends on an individual patient’s risk for cardiovascular disease; based on the risk stratification of the patient, less or more stringent LDL-targets should be considered.

**Is there a special case for rosuvastatin use in the metabolic syndrome?**

In a randomised clinical trial which compared rosuvastatin 10mg, atorvastatin 10mg and placebo in high-risk patients with the metabolic syndrome,\(^{13}\) LDL reductions of 49% and 42%, respectively, were reported. Reductions in triglycerides were similar for both statins, but only rosuvastatin increased HDL. However, the increase in HDL-cholesterol seen with statins is modest and studies with drugs that act mainly by increasing HDL-cholesterol levels have not been shown to reduce the incidence of cardiovascular disease. The main aim of therapy therefore remains the reduction of LDL-cholesterol. If triglyceride levels are very high, particularly if >10mmol/l there is a risk of pancreatitis and the addition of fibrate therapy should be considered.

**Treating hypertension in the metabolic syndrome**

According to the South African Hypertension Society 2014 guidelines,\(^{14}\) lifestyle management (weight reduction, smoking cessation, moderate alcohol intake and increased physical activity) is the cornerstone of the initial management of hypertension. The earlier guideline\(^{15}\) discussed the treatment of the metabolic syndrome within the overall therapeutic approach to hypertension (Figure 1).

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**Figure 1. Overview of approach to treatment.**

*BP >180/110mmHg*
Professor Brian Rayner pointed out that consensus is lacking in treatment decisions concerning hypertension with regard to newer risk factors such as obesity and the metabolic syndrome.

“The metabolic syndrome was not listed as a risk factor in the JNC 7 report, despite evidence of its link to cardiovascular risk and future diabetes.”

The syndrome, however, represents a combination of underlying and major risk factors. Where the metabolic syndrome is present, a systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥85mmHg requires treatment (weight loss and exercise followed by drug therapy, after an appropriate trial of lifestyle modification).”

Renin-angiotensin-aldosterone system inhibitors (ACE-inhibitors or ARBs) are generally recommended for patients with the metabolic syndrome and pre-diabetes. Potential enhancement of metabolic disturbances with thiazides (increase in prevalence of type 2 diabetes and increase in total cholesterol) should be considered in patients with the metabolic syndrome (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Indications for the use of ACE-inhibitors and ARBs</th>
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</thead>
<tbody>
<tr>
<td><strong>ACE-inhibitors</strong></td>
</tr>
<tr>
<td>• Heart failure</td>
</tr>
<tr>
<td>• Left ventricular dysfunction</td>
</tr>
<tr>
<td>• Post-myocardial infarction</td>
</tr>
<tr>
<td>• Non-diabetic nephropathy</td>
</tr>
<tr>
<td>• Type 1 diabetic nephropathy</td>
</tr>
<tr>
<td>• Prevention of diabetic microalbuminuria/proteinuria*</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
</tr>
<tr>
<td>• Type 2 diabetic nephropathy</td>
</tr>
<tr>
<td>• Type 2 diabetic microalbuminuria*</td>
</tr>
<tr>
<td>• Proteinuria</td>
</tr>
<tr>
<td>• Left ventricular hypertrophy</td>
</tr>
<tr>
<td>• ACE-inhibitor cough or intolerance</td>
</tr>
</tbody>
</table>

*Supportive of use in the metabolic syndrome with its pre-diabetes and higher risk of type 2 diabetes and its sequelae.

Source: 2014 South African Hypertension Guidelines

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Treating elevated fasting plasma glucose levels

The central obesity and insulin resistance of the metabolic syndrome can lead to hyperglycaemia, overt type 2 diabetes and NAFLD. It is important to note that elevated fasting plasma glucose levels, which are still below the threshold for overt type 2 diabetes, are included in the metabolic syndrome criteria. Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both reflect an intermediate dysglycaemic state between normal blood glucose levels and type 2 diabetes. This dysglycaemic state has been shown to be associated with both micro- as well as macrovascular complications. Microvascular disease may actually develop in the pre-diabetic stage.

The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2017 guidelines note that individuals with pre-diabetes and other criteria that meet the definition of the metabolic syndrome should be treated early. As many as 11% of people with pre-diabetes will progress to type 2 diabetes.

Recent results of the EMPA-REG OUTCOME trial of empagliflozin (a SGLT-2 inhibitor) and canagliflozin (also a SGLT-2 inhibitor) and three other trials of the GLP-1 RAs, liraglutide and semaglutide, have shown cardiovascular benefit in insulin-resistant patients.

Early intervention in patients with pre-diabetes (IFG and IGT) is currently attracting considerable interest. Current SEMDSA guidelines also reflect this approach and recommend the use of metformin in patients who have a very high risk of progression to type 2 diabetes. The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2017 guidelines note that individuals with pre-diabetes and other criteria that meet the definition of the metabolic syndrome should be treated early. As many as 11% of people with pre-diabetes will progress to type 2 diabetes.

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Metformin has also been shown to significantly reduce total as well as LDL-cholesterol levels independent of its glycaemic effects.26 While current SEMDSA guidelines do not make specific recommendations for treating the metabolic syndrome, the ACT NOW trial with pioglitazone, that did not make specific recommendations for treating the metabolic syndrome, showed clear benefits that were maintained years after conclusion of the trial. It is less clear whether similar interventions would improve the outcome in patients with pre-diabetes. Evidence has been shown in the ACT NOW trial with pioglitazone, that pioglitazone slows the progression of atherosclerosis in pre-diabetes, independent of changes in other cardiovascular risk factors.28 Pioglitazone use in pre-diabetes is supported by evidence.

The use of some SGLT-2 inhibitors (empagliflozin, dapagliflozin) and the GLP-1 RAs (lixisenatide and exemilapaglinide) have been shown to significantly reduce cardiovascular death as well as other outcomes such as combined MACE and heart failure.29 Their use in pre-diabetes has not, however, been tested to date.30, 31

Clinical use of SGLT-2 inhibitors, GLP-1 RAs and pioglitazone in the metabolic syndrome

“It has become clear from long-term interventional trials that early multifactorial risk factor control impacts on survival as well as complications in the patient with type 2 diabetes. The STENO-2 trial,32 with its extended follow-up of patients with intensive intervention, showed clear benefits that were maintained years after conclusion of the trial in patients with type 2 diabetes. It is less clear whether similar interventions would improve the outcome in patients with pre-diabetes. Evidence has been shown in the ACT NOW trial with pioglitazone, that

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5. Pi-Sunyer FX. The obesity epidemic: pathophysiology and pharmacological management of type 2 diabetes. The STENO-2 trial risk factor control impacts on survival as well as complications in the patient with type 2 diabetes. The STENO-2 trial, with its extended follow-up of patients with intensive intervention, showed clear benefits that were maintained years after conclusion of the trial. It is less clear whether similar interventions would improve the outcome in patients with pre-diabetes. Evidence has been shown in the ACT NOW trial with pioglitazone, that pioglitazone slows the progression of atherosclerosis in pre-diabetes, independent of changes in other cardiovascular risk factors. Pioglitazone use in pre-diabetes is supported by evidence.

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