

## The metabolic syndrome – What is the value of its identification?

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### Abstract

The identification of the metabolic syndrome (MS) has been under discussion and intense investigation since 1998. Only recently does it appear that consensus is being reached between different organisations regarding its identification. Nonetheless, the true value in identifying the MS remains under question, as does the debate around its existence. The real value in identifying the MS may simply be the ability to identify individuals at increased risk for developing cardiovascular disease (CVD) and diabetes. Further identification of abnormalities associated with the MS should encourage practitioners to investigate and search for other risk factors associated with CVD and diabetes. Part of the problem in identifying and treating the MS is that the cause of associated abnormalities remains unclear. However current research seems to indicate that oxidative stress and inflammation may play a pivotal role in the development of insulin resistance (IR) and the MS. Regardless of the usefulness of identifying the MS and its contributing causes, certain take home messages for practitioners remain the same, including emphasis on the importance of weight loss in overweight patients, the role of regular exercise and diet quality, with a new emphasis on the role of an adequate micronutrient intake and specifically nutrients with antioxidant properties..

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### The evolution of the concept of the metabolic syndrome

It was in the late 1980s and early 1990s that Gerald Reaven proposed that a clustering of abnormalities including increased plasma triglyceride (Tgs) levels, decreased high density lipoprotein-cholesterol (HDL-C) concentration and high blood pressure (BP) linked to decreased insulin mediated glucose uptake and impaired glucose tolerance (IGT) comprised a syndrome.<sup>1</sup> In 1998, the first formalised definition of the metabolic syndrome (MS) was proposed by a World Health Organization consultation group. The diagnosis of MS by the WHO criteria required evidence of insulin resistance (IR) for diagnosis.<sup>2</sup> It was subsequently pointed out by a position statement generated by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) task force, which was set up to provide guidance to clinicians on the identification and treatment of the MS, that the identification of IR in practice is not accurate due to the lack of standardised methods used to quantify plasma insulin concentrations in a laboratory setting. They stated that there is no evidence to support an individual being defined as insulin resistant, and at increased risk of developing any of the abnormalities of the MS, on the basis of plasma insulin concentrations alone. The AACE/ACE task force strongly cautioned practitioners against trying to identify individuals as IR, by making use of laboratory tests to identify fasting plasma insulin levels, in order to calculate a fasting insulin:glucose ratio (FIR) as a surrogate marker of IR.<sup>3</sup>

After the WHO criteria, other criteria came from the National Cholesterol Education Program Adult Treatment Panel III (ATP III) in 2001. ATP III did not require the identification of IR as part of the criteria for diagnosis of the MS. The ATP III criteria made

the presence of three of the following five features the basis for recognition of the MS: abdominal obesity (highly correlated with IR), elevated Tgs, reduced HDL-C, elevated BP, and elevated fasting glucose (impaired fasting glucose or type 2 diabetes mellitus).<sup>4</sup> MS is a predictor of CVD and diabetes. When CVD or diabetes develops, the MS is often present, and the number of components of the MS contributes to increased disease risk and disease progression.<sup>2</sup> In 2005, the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) attempted to address differences in the definitions of the MS.<sup>5,6</sup> However, differences remained with regard to separate recommendations relating to waist circumference cut off points. The IDF did not require the WHO criteria of insulin resistance for diagnosis, but made abdominal obesity necessary as one of five factors (Table I) required in the identification of MS, while highlighting waist circumference measurements as a useful screening tool; the remainder of the criteria were the same as those set by ATP III.<sup>2</sup> The AHA/NHLBI slightly adjusted the ATP III criteria but did not make waist circumference measurements and implied abdominal obesity a required criteria for diagnosis. The remaining four criteria were the same as defined by the IDF.<sup>6</sup> There was, however, no agreement on the cut points for waist circumference measurements and abdominal obesity between the IDF and AHA/NHLBI. The IDF recommended a threshold for waist circumference measurements to be defined for people of European origin (Europids) to be 94 cm for men and 80 cm for women; the AHA/NHLBI, recommended cut points of 102 and 88 cm, respectively.<sup>2</sup>

### Is it worthwhile identifying people with MS?

Much time and effort have gone into trying to establish uniform criteria for the identification of the MS. Yet controversy still exists around

the true value of identifying the MS. A recent scientific statement by the IDF, NHBLI, AHA, the World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity states that the MS is a complex of interrelated risk factors for CVD and diabetes, and that the MS is widespread and has an increasing incidence worldwide which relates mostly to the increased prevalence of obesity and sedentary living.<sup>2</sup> Further, a syndrome is merely a clustering of factors for which the cause is uncertain, and these factors occur simultaneously more often than by chance alone.<sup>2</sup> The MS does not determine absolute risk [it does not contain factors that determine entire risk such as other risk assessment tools, for example the Framingham 10 Year risk factor analysis for CVD, such as age, gender, smoking, total or low density lipoprotein cholesterol levels (LDL-C)]<sup>2,10</sup>. However, according to Alberti et al, patients with the MS have double the risk of developing CVD over five to ten years when compared with individuals who do not have the syndrome. The risk over a lifetime is most probably even greater.<sup>2</sup> In addition, the MS confers a fivefold increase in risk for type 2 diabetes.<sup>2</sup>

It appears therefore that the primary merit in identifying individuals with the MS is to identify risk for the development of CVD and diabetes<sup>2</sup> and that perhaps the other value of the syndrome as a concept is the obvious utility that the identification of one of the CVD risk factors in a patient should prompt search for other risk factors.<sup>7,10</sup>

It is also worthwhile noting that the criteria used for the identification of the MS is far from finite, there are many other signs and symptoms that are associated with IR and the MS, including, but not limited to, albuminuria, a prothrombotic and pro-inflammatory state [plasminogen activator inhibitor-1 and fibrinogen, elevated C-reactive protein (CRP), Tumour Necrosis Factor- (TNF ), Interleukin-6, decreased adiponectin levels, hyperuricaemia, elevated White Blood Cell (WBC) count, endothelial dysfunction, polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD) and others]<sup>2,3,7,9</sup> Furthermore even though an individual may or may not be identified as having the MS, it is strongly recommended that signs and symptoms associated with the MS should be treated individually and aggressively as each one will confer a degree of risk to the development of chronic disease and specifically CVD.<sup>8</sup>

**Table I: Criteria for clinical diagnosis of the metabolic syndrome<sup>2</sup>**

Measure Categorical Cut Points	
<i>The presence of 3 of 5 risk factors constitutes a diagnosis of the metabolic syndrome</i>	
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator <sup>†</sup> )	≤ 1.7 mmol/L
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator <sup>†</sup> )	≤ 1.0 mmol/L in males ≤ 1.3 mmol/L in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose <sup>‡</sup> (drug treatment of elevated glucose is an alternate indicator)	≤ 5,6 mmol/L

HDL-C indicates high-density lipoprotein cholesterol.

\* It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.

<sup>†</sup> The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose  $\Omega$ -3 fatty acids presumes high triglycerides.

<sup>‡</sup> Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

Apart from identification of an increased risk specifically for the development of CVD or diabetes, and using the identification of the MS as a indication for early medical intervention and prevention strategies, perhaps the most valuable lessons that are taught to us by the MS is confirmation that certainly obesity, poor dietary practices and reduced activity levels interacting with genetic and metabolic factors almost guarantee a complex metabolic derangement that in turn is associated with disease.<sup>10,11</sup>

### Can we connect the dots?

One of the primary reasons for identifying a disease process, as in this case the MS, would be to understand its cause and provide guidelines for prevention, if possible, appropriate treatment intervention and resolution of the disease state.<sup>7,8,10</sup> Unfortunately, the exact cause of the MS still appears to be elusive and as a result some controversy still exists about whether the MS is a true syndrome or a mixture of unrelated phenotypes.<sup>2</sup> A number of suggestions regarding the clustering of abnormalities and their precipitating cause(s) have been discussed and explored in the medical literature, and certainly there is no definitive answer at this time. Insulin resistance has, however, been identified as an underlying factor<sup>7</sup> and variability in insulin sensitivity has been largely attributed to differences in adiposity (25%), fitness (25%) and genetics (50%).<sup>8</sup> However, a hypothesis that seems to hold some further value, is the concept of oxidative stress as a pathogenic mechanism underlying insulin resistance, diabetes and cardiovascular disease.<sup>12</sup>

### Poor diet quality and a hypercaloric diet-link with oxidative stress and insulin resistance

Muscle and adipose tissue are primarily involved with the development of insulin resistance. When energy intake exceeds energy expenditure, there is a substrate-induced increase in the citric acid cycle, which in turn generates an excess of mitochondrial NADH (mNADH) and consequent reactive oxygen species (ROS). It has been proposed that muscle and adipose tissue cells protect themselves against harmful effects of ROS, by reducing the formation of ROS and/or enhancing the removal of ROS. Preventing a build-up of mNADH is achieved by inhibiting insulin-mediated glucose disposal and inhibiting the entrance of substrates (pyruvate, fatty acids) into the mitochondria, this in turn helps to attenuate the formation of ROS. It has been proposed that excessive NADH generation can be prevented through the inhibition of free fatty acid (FFA) oxidation. An increase in intracellular FFA in the cell cytoplasm, in turn, leads to reduced levels of insulin sensitive glucose transporter GLUT4 (C-GLUT4) translocation to the cell membrane, resulting in resistance to insulin mediated glucose disposal in muscle and adipose tissue. According to this hypothesis, IR can be considered a compensatory mechanism that develops to protect cells against further glucose and fatty acid uptake and therefore oxidative damage.<sup>12</sup>

Many studies support this hypothesis in that antioxidants have been shown to improve insulin sensitivity. Several clinical trials have demonstrated that treatment with vitamin E, vitamin C, or glutathione improves insulin sensitivity in insulin-resistant individuals. The recent finding that insulin resistance is associated with reduced intracellular antioxidant defence status in humans also support this hypothesis.<sup>12</sup>

### The link with $\beta$ -cell dysfunction and endothelial dysfunction – key features of the MS

It is rational to suggest that what occurs in muscle and fat cells may also take place in other cells, specifically in  $\beta$ -cells and endothelial

cells. What is more, these types of cells may be even more severely affected by a hypercaloric diet.  $\beta$ -cells and endothelial cells are not dependent on insulin for glucose disposal, which is achieved via facilitative diffusion.<sup>12</sup> When such cells are exposed to elevated levels of glucose or fatty acids, they are not able to down regulate the influx of nutrients through insulin resistance, and have to permit intracellular concentrations of these nutrients to increase. Ongoing exposure to high glucose and/or elevated FFA levels, or a combination of both, has been suggested by a number of research papers to be responsible for  $\beta$ -cell dysfunction and apoptosis.<sup>12</sup> It is also important to note that these cells are highly vulnerable to ROS, as antioxidant enzymes are in short supply in these cells. It has been shown that oxidative stress has the ability to damage mitochondria and in turn result in a markedly blunted insulin secretion by  $\beta$ -cells.<sup>12</sup>

It is well known that IR is associated with endothelial dysfunction, and there is evidence that indicates that oxidative stress is associated with endothelial dysfunction, which in turn contributes to CVD. Glucose and FFA overload can be expected to influence endothelial cells as they do  $\beta$ -cells via oxidative stress, and a number of studies confirmed such a relationship.<sup>12</sup> There is also convincing evidence that FFA may produce the same consequences and increase oxidative stress and induce endothelial dysfunction, which can be reversed by antioxidants.<sup>12</sup>

### Oxidative stress, Inflammation and Insulin resistance

The idea that oxidative stress is the common denominator underlying insulin resistance, CVD and type 2 diabetes, may explain the occurrence of inflammation in all these conditions. It is also well known that inflammation is one of the consequences of oxidative stress, and the mechanism that generates the mediators of inflammation include adhesion molecules and interleukins.<sup>12</sup> It is also worthwhile recognising that the subclinical pro-inflammatory state observed in many conditions including atherosclerosis, ageing and cancer, may well be associated with an over-production of free radicals by the mitochondria. This theory is supported by in vivo studies, showing that glucose and FFA cause inflammation through oxidative stress, and they have a cumulative and independent effect, and that antioxidants can, at least partially, ameliorate/reverse the occurrence.<sup>12</sup>

### The way forward

The abnormalities associated with the MS can be viewed in clusters or independently. What is known currently is that these abnormalities are indicative of a metabolic derangement associated with increased disease risk specifically for cardiovascular disease and diabetes. We do not know categorically at present what the exact causes of the syndrome's many abnormalities are, or, for that matter, why most abnormalities do not occur collectively in all individuals. What is clear though is that obesity, inactivity and diet quality play a pivotal role in preventing and treating the MS and/or its associated abnormalities and, by inference at this stage, chronic disease. Genetic predisposition is clearly an uncontrollable risk factor, but those predisposed to diabetes and CVD would be in need of more intensive intervention(s) and would need stricter adherence to the recommended dietary and lifestyle practices to prevent or treat abnormalities associated with the MS and end-stage disease. It appears therefore that practitioners should continue to advise patients on what they always have done regarding diet and lifestyle change, with some necessary adjustments toward improved diet quality and improved micronutrient intake, which current evidence

suggests may well play a key role in preventing oxidative stress, inflammation and IR.

Weight loss has been known to improve features of the MS and it has also been shown to reduce oxidative stress and to improve each component of the MS.<sup>3,10</sup> Practitioners should promote a low glycaemic load (GL) diet, as high GL diets have been linked with cardiovascular events and glucose spikes with endothelial dysfunction.<sup>10,14,16</sup>

Inflammation is an integral part of the MS that is worsened by the pro-inflammatory profile of the western diet. The available evidence is mostly supportive of benefits to be derived from diets rich in omega-3 fatty acids and other unsaturated fats, natural antioxidants in fruit and vegetables, and fibre in nuts and whole grains by patients with the MS.<sup>10,15</sup>

Supplementation with omega-3 fatty acids is an emerging treatment modality and should be strongly considered in patients unable to consume the required two fatty fish meals per week<sup>10,13</sup>. Additionally, one should encourage regular exercise – “a little is good and more is better”<sup>10</sup>, and finally, referral to a dietitian should be considered for long-term reinforcement and follow up.<sup>10</sup>

### Conclusion

The value of identifying the MS would appear to be a prudent approach for “quantifying” individual risk for CVD and diabetes and the presence of symptoms and signs of the syndrome should be accompanied by a search for other comorbidities. Risk factors for CVD, whether identified in clusters or separately should be treated appropriately, regardless of a diagnosis of the MS. Diet and lifestyle changes remain the cornerstone of treatment for the MS and associated abnormalities whether they present in clusters or individually. Greater emphasis needs to be placed on diet quality and intake of micro-nutrients, and, more specifically, nutrients with antioxidant properties.

### References

1. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med* 1993;44:121–31. (Abstract)
2. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WPT. Harmonizing the metabolic syndrome: a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society and International Association for the Study of Obesity. *Circulation*;120:1640–1645.
3. Einhorn D. ACE Position Statement. *Endocrine Practice* 2003;9(3):240–252.
4. Liao Y, Kwon S, Shaughnessy S, Wallace P, Hutto A, Jenkins AJ, Klein RL, Garvey WT. Critical evaluation of adult treatment panel III criteria in identifying insulin resistance with dyslipidemia. *Diabetes Care* 2004;27(4):978–983.
5. Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. *Lancet* 2005;366:1059–1062.
6. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–2752.
7. Kahn R. Is the metabolic syndrome a real syndrome? Metabolic syndrome: Is it a syndrome? Does it matter? *Circulation* 2007;115:1806–1811.
8. Reaven GM. The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr* 2006;83:1237–47.
9. Rizvi AA. Cytokine biomarkers, endothelial inflammation and atherosclerosis in the metabolic syndrome: emerging concepts. *Am J Med Sci* 2009;334:310–318.
10. Blaha MJ, Bansal S, Rouf R. A practical ABCDE approach to the metabolic syndrome. *Mayo Clin Proc* 2008;83:932–941.
11. Esposito K, Giugliano D. The metabolic syndrome and inflammation: association or causation? *Nutr Metab Cardiovascular Dis* 2004;14:228–232.
12. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 2004;24:816–823.
13. Lichtenstein AH, Appel LJ, Brands M, Daniels MCS, Franck HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: A Scientific Statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82–96.
14. Schleicher E, Friess U. Oxidative stress, AGE, and atherosclerosis. *Kidney International* 2007;72:S17–S26.
15. Bengmark S. Impact of nutrition on ageing and disease. *Current Opinion in Clinical Nutrition and Metabolic Care* 2006;9:2–7.
16. Bullo M, Casas-Agustench P, Amig-Correig P, Aranceta J, Salas-Salvado J. Inflammation, obesity and co-morbidities: the role of diet. *Public Health Nutrition* 2007;10(10A):1164–1172.