The metabolic syndrome

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Abstract

The metabolic syndrome is characterized by the cooccurrence of central obesity, dyslipidemia, altered glucose concentrations, and hypertension. Very recently, the International Diabetes Federation has published a consensus worldwide definition of the metabolic syndrome. However, as yet, no consensus exists for specific thresholds for establishing the diagnosis. The individual traits of the syndrome cluster together to a notably greater degree than expected by chance alone – a fact that lends substantial support to the idea of a common set of mechanisms with pleiotropic effects leading to the metabolic syndrome. Lifestyle modification is currently the preferred universal treatment option of the metabolic syndrome. In addition, treatment of modifiable risk factors of the syndrome should be addressed specifically.
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Introduction

The metabolic syndrome is characterized by the co-occurrence of central obesity, dyslipidemia (which is typically defined by high concentrations of triglycerides and low concentrations of high-density lipoprotein cholesterol, dysglycemia or hyperglycemia or both according to standard diabetes criteria), and hypertension [1–4].

The syndrome is a highly prevalent multifaceted clinical entity. Various prospective epidemiological studies across several populations have shown that the metabolic syndrome is a dynamic phenotype featuring a continuum of metabolic derangements. As yet, no consensus exists for specific thresholds for establishing the diagnosis of each of these traits as components of the syndrome.

The individual traits of the metabolic syndrome cluster together to a notably greater degree than expected by chance alone – a fact that also lends substantial support to the existence of a discrete disorder [5–9].

Current definition of the metabolic syndrome

Current definitions of the metabolic syndrome take into account two major outcomes, cardiovascular disease and type 2 diabetes, thereby perceiving the metabolic syndrome as 'prediabetes'. *Tables I–III* summarize the current definitions, including a very recent consensus statement provided by the International Diabetes Federation (IDF) [1–4].

Prevalence of the metabolic syndrome

Because of the lack of standardized criteria for recognizing the metabolic syndrome, a comparison of published prevalences for different populations is rather difficult. Nevertheless, despite differences in the criteria used, certain inferences can be made: prevalence of the metabolic syndrome is highly age-dependent (USA National Health and Nutrition Examination Survey [NHANES III]) [10]. The Framingham Offspring Study also revealed that the metabolic risk factors worsen continuously across the spectrum

Table I. National Cholesterol Education Program–Third Adult Treatment Panel III 2001 definition of the metabolic syndrome. (Adapted from [1]).

3 or more of the following 5 risk factors:		
Central obesity		Waist circumference:
	Men	> 102 cm (> 40 inches)
	Women	> 88 cm (> 35 inches)
Hypertriglyceridemia		Triglycerides: ≥ 1.7 mmol/L (≥ 150 mg/dL)
Low HDL cholesterol concentration	Men	< 1.0 mmol/L (< 40 mg/dL)
	Women	< 1.3 mmol/L (< 50 mg/dL)
Hypertension		Blood pressure: ≥ 130/85 mm Hg, *or* medication, *or* both
Fasting plasma glucose		≥ 6.1 mmol/L (> 110 mg/dL)

LDL, low-density lipoprotein.

of nondiabetic glucose tolerance, suggesting a continuous risk [11,12]. Using the Adult Treatment Panel III criteria, prevalence of the metabolic syndrome in Germany was also found to be age-dependent, and dependent on social status [13].

Treatment

Once a diagnosis of the metabolic syndrome is made, the management of the condition should be 'aggressive' in its aim to reduce the risk of both cardiovascular disease (CVD) and type 2 diabetes. Patients should undergo a full cardiovascular risk assessment that includes smoking status [3–5]. Lifestyle intervention includes a healthy diet – which means eating plenty of fruit and vegetables, lean cuts of white meat or fish rather than red meat, and avoidance of processed or deep-fried dinners. Items rich in dietary fiber, such as whole grains, beans, fruit and vegetables, which can decrease (pro)insulin concentrations, should also be used. Physical activity should be implemented with at least 30 min of moderately strenuous activity most days of the week. This intervention should be accompanied by regular checks of modifiable risks such as blood pressure, cholesterol and blood sugar concentrations. For primary intervention, the IDF recommends promotion of a healthy lifestyle, including moderate calorie restriction (to achieve a 5–10% loss of body weight in the first year), an increase in physical activity (5 × 30 min of moderate activity per week), and a change in dietary composition. Both a Finnish and an American (Diabetes Prevention Program) diabetes prevention study revealed that lifestyle modification will at least prevent the conversion to type 2 diabetes among high-risk individuals with glucose intolerance who were, generally, obese [14–16]. In addition, in people for whom lifestyle change is not enough and who are considered to be at high risk for CVD, secondary intervention with drug therapy may be suggested. However, pharmacotherapy that can modulate the underlying mechanisms of the metabolic syndrome as a whole and thereby reduce the impact of all the risk factors and the long-term metabolic and cardiovascular consequences is currently not available. Therefore, it is necessary to treat the individual components of the metabolic syndrome, in order that a reduction in the individual risk associated with each one will reduce the overall impact on CVD and diabetes risk [4].

Current controversies

The existing guidelines from the World Health Organization (WHO) and National Cholesterol Education

Table II. World Health Organization clinical criteria for the metabolic syndrome, 1999. (Adapted from [3]).

In order to make a diagnosis of the metabolic syndrome, a patient must present with glucose intolerance, impaired glucose tolerance or diabetes, or insulin resistance, or both, together with two or more of the following components:		
Obesity		BMI: > 30 kg/m^2 *or* Waist to hip ratio:
	Men	> 0.9
	Women	> 0.85
Dyslipidemia		Triglycerides: ≥ 1.7 mmol/L (≥ 150 mg/dL) *or* HDL cholesterol:
	Men	< 1.0 mmol/L(< 40 mg/dL)
	Women	< 1.3 mmol/L (< 50 mg/dL)
Hypertension		Blood pressure: > 140/90 mm Hg, *or* medication, *or* both
Microalbuminuria		Albumin excretion: ≥ 20 μg/min, *or* Albumin : creatinine ratio: ≥ 30 mg/g

BMI, body mass index; HDL, high-density lipoprotein.

Table III. The new International Diabetes Federation (IDF) definition, 2005. (Adapted from [4]).

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:		
Central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity-specific values* for other groups)		
Plus any two of the following four factors:		
Increased triglyceride concentration		≥ 150 mg/dL (1.7 mmol/L), *or* Specific treatment for this lipid abnormality
Reduced HDL cholesterol	Men	< 40 mg/dL (1.03 mmol/L†)
	Women	< 50 mg/dL (1.29 mmol/L†), *or* Specific treatment for this lipid abnormality
Increased blood pressure		SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, *or* Treatment of previously diagnosed hypertension
Increased FPG		≥ 100 mg/dL (5.6 mmol/L), *or* Previously diagnosed type 2 diabetes. If FPG is > 5.6 mmol/L or > 100 mg/dL, an OGTT is strongly recommended, but is not necessary to define presence of the syndrome

*Central obesity is most easily measured by waist circumference; values that are specific for sex and ethnic group (not country of residence) should be used. The IDF consensus group acknowledged that the following are pragmatic cutoff points taken from various different data sources and that better data will be needed to link them to risk:
Europids: ≥ 94 cm (men); ≥ 80 cm (women).
USA: The Adult Treatment Panel (ATP) III values are likely to continue to be used for clinical purposes: 102 cm (men); 88 cm (women).
South Asians, based on a Chinese, Malay and Asian-Indian population: ≥ 90 cm (men); ≥ 80 cm (women).
Chinese: ≥ 90 cm (men), ≥ 80 cm (women).
Japanese: ≥ 85 cm (men), ≥ 90 cm (women).
Ethnic South and Central Americans: Use South Asian recommendations until more specific data are available.
Sub-Saharan Africans: Use European data until more specific data are available.
Eastern Mediterranean and Middle East (Arab) populations: Use European data until more specific data are available.

†These values have been updated from those originally presented, to ensure consistency with ATP III cutoff points.
DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.

Program–Third Adult Treatment Panel (NCEP–ATP III) did not provide exact diagnostic criteria for identifying individuals with metabolic syndrome [1–3]. However, there is a strong need for a single, universally accepted diagnostic tool that may allow direct comparisons of the prevalences of the metabolic syndrome and may also make it possible to monitor the efficacy of any therapeutic intervention [4]. An additional difficulty is that no consensus exists for specific thresholds for establishing the diagnosis of each of these traits as components of the syndrome.

A unifying pathophysiological concept of the syndrome is also lacking. It has long been believed that insulin resistance may provide the unifying hypothesis, but current evidence has been questioned in a joint statement by the American Diabetes Association and the European Diabetes Association [17,18]. Even though most people who have the metabolic syndrome are insulin resistant, this is most probably attributable to the fact that almost all people with an increased blood glucose value are insulin resistant. Conversely, many studies have shown that only a minority of nondiabetic individuals with insulin resistance will suffer from the metabolic syndrome.

The value of including diabetes in the definition of the metabolic syndrome has been questioned in view of the lack of a clear rationale for including/excluding various CVD risk factors. Most importantly, the overall CVD risk value is variable and dependent on the specific individual risk factors present.

The syndrome is managed by treating each of its components. Provided that classical risk profiling has been performed, the medical value of diagnosing the syndrome is unclear.

Further points have been raised. (i) It remains unclear how the syndrome is best defined. (ii) Are all risk factors equally important, if combinations of risk factors portend greater CVD risk than others? (iii) A definition of the metabolic syndrome in which variables have defined lower and upper cutoff points or that uses continuous variables in a multivariate score system (eg, Framingham/UK Prospective Diabetes Study risk engine) requires more detailed study [17,19–21].

Perspective – the search for a unifying concept

The idea that a common set of factors with several diverse effects might influence obesity, type 2 diabetes, and related traits such as sensitivity to the effects of insulin, is not novel [5,7]. New data may provide further evidence of a common molecular link between insulin resistance, obesity, and type 2 diabetes. Very recently, the gene *ENPP1* (which encodes ectonucleotide pyrophosphatase/phosphodiesterase 1*, also known as plasma cell membrane glycoprotein PC-1) was shown to mediate some of the effects of the hormone insulin on glucose metabolism while simultaneously being associated with obesity and type 2

diabetes. This observation supports the idea that a common molecular mechanism underlies features of the body's response to the effects of the hormone insulin, in addition to the predisposition to develop obesity and type 2 diabetes [22]. These findings also suggest that several variants of *ENPP1* may have a primary role in mediating insulin resistance and in the development of both obesity and type 2 diabetes, implying that an underlying molecular mechanism is common to both conditions.

The AMP-activated protein kinase (AMPK) pathway* is an evolutionarily conserved sensor of cellular energy status that plays a critical role in systemic energy balance. Complex signaling networks suggested that AMPK may prevent insulin resistance, in part by inhibiting pathways that antagonize insulin signaling. Through signaling, metabolic, and gene expression effects, AMPK enhances insulin sensitivity and fosters a metabolic milieu that may reduce the risk for obesity and type 2 diabetes [23]. It was recently shown that metformin, one of the drugs most widely prescribed for type 2 diabetes therapy, requires leukotriene B_1* and subsequent AMPK activation in the liver in order to decrease blood glucose concentrations [24].

Conclusion

The metabolic syndrome is a multifaceted clinical entity resulting from the interaction of genetic, hormonal, and lifestyle factors. Over the past two decades, the number of people diagnosed with the syndrome has steadily increased. A better understanding of the underlying molecular pathophysiology should lead to novel preventive strategies. A research agenda to identify the underlying cause(s) is recommended [4,13,19,25].

Universally speaking, the metabolic syndrome is a huge clinical problem and is one that is growing at an alarming rate. The new IDF criteria provide a robust framework for making the diagnosis of the syndrome and for implementing lifestyle changes, at least, in the individuals diagnosed. The opportunity should not be missed, in view of this worldwide epidemic. ■

* See glossary for definition of these terms.

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