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Features of the metabolic syndrome and the risk of cardiovascular disease

BENOÎT LAMARCHE & ANNIE C. ST-PIERRE

Institute on Nutraceuticals and Functional Foods, Laval University, Québec, Canada

Abstract
The metabolic syndrome is being increasingly recognized as an important risk factor for cardiovascular disease (CVD). While several clinical definitions have been proposed to identify patients with this syndrome, additional metabolic markers may be considered to improve one's ability to assess and predict the risk of CVD in this population. The objective of this short review is to provide an overview of the risk of CVD associated with specific features of the metabolic syndrome. The extent to which these markers may be used one day in clinical practice in primary prevention is also briefly discussed.

Keywords: *Metabolic syndrome, dyslipidemia, LDL size, waist girth, obesity*

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Introduction

The metabolic syndrome is a concept that emerged in 1988 at the Banting Lecture of the American Diabetes Association, which was given by Dr Gerald Reaven, when he suggested that insulin resistance was the cornerstone of a series of metabolic alterations that included compensatory hyperinsulinaemia, hypertension, hypertriglyceridaemia and reduced HDL-cholesterol levels (Reaven 1988a). It was also suggested that the metabolic syndrome, which was then referred to as syndrome X, characterized a significant proportion of the non-diabetic population and would lead to significant elevations in the risk of cardiovascular disease (CVD). On a historical note, the metabolic syndrome was a concept that appeared much before in the literature. Kylin (1923) was probably the first to describe a clustering of risk factors that comprises hypertension, hyperglycaemia and gout. The metabolic syndrome is now being thoroughly and seriously investigated by many groups around the world. More than 15 years after Reaven's landmark hypothesis, it is now well recognized that the metabolic syndrome comprises several other risk factors for CVD such as small dense LDL particles, hyperapoB, impaired post-prandial lipoprotein metabolism, impaired fibrinolytic activity, inflammation, as well as abdominal obesity (Despres 2003, Reaven 2003).

Correspondence: Benoît Lamarche, PhD, Institute on Nutraceuticals and Functional Foods, 2440 Hochelaga Boulevard, Laval University, G1K 7P4, Ste-Foy, Québec, Canada. Tel: 418-656-3527. Fax: 418-656-5877. Email: benoit.lamarche@inaf.ulaval.ca

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Clinical definitions of the metabolic syndrome

Several organizations have now recognized the metabolic syndrome as an important entity that should be clinically diagnosed for a more adequate prevention of CVD. In 2001, the National Cholesterol Education Program–Adult Treatment Panel III (NCEP ATPIII) has proposed a clinical definition of the metabolic syndrome based on the presence of three of the following five features: (1) abdominal obesity (waist girth >102 cm or >88 cm in men and women, respectively), moderate hypertriglyceridaemia (plasma TG levels >1.7 mmol l^{-1}), reduced plasma HDL cholesterol levels (<1.0 and <1.3 mmol l^{-1} in men and women, respectively), hypertension ($>130/85$ mmHg) and moderate hyperglycaemia (>110 mg dl^{-1}) (NCEP ATPIII 2001). The World Health Organization (WHO 1999) has also proposed a definition of the metabolic syndrome. This definition is based on the presence of insulin resistance (hyperinsulinaemia in normal glucose tolerance subjects corresponding to the upper quartile of plasma insulin levels or impaired glucose tolerance or type II diabetes) and of at least two of the following four risk factors: (1) obesity defined by an elevated waist-to-hip ratio (>0.85 and >0.90 in women and men, respectively) or by a body mass index (BMI) >30 kg m^{-2}, (2) dyslipidaemia (plasma TG >1.7 mmol l^{-1} and/or plasma HDL-cholesterol levels <0.9 mmol l^{-1} in men and <1.0 mmol l^{-1} in women), (3) hypertension ($>160/90$ mmHg), (4) micro-albuminuria (≥ 20 ug ml^{-1}) (WHO 1999).

The metabolic syndrome and the risk of cardiovascular disease

Several studies have recently shown, using various definitions, that the metabolic syndrome was associated with a 2–5-fold increase in the risk of CVD. This is true in both men and women (Wilson et al. 1999, Hu et al. 2004). These numbers are important since it was also shown that the prevalence of the metabolic syndrome was quite high in the general population. For example, Ford et al. (2002) have shown using data from NHANES III that $\sim$25% of the American population had the metabolic syndrome according to the NCEP ATPIII criteria. They also showed that the prevalence increased with age, reaching almost 50% in individuals older than 60 years. The prevalence of the metabolic syndrome based on the WHO definition is usually lower. For example, Isomaa et al. (2001) have shown that 15% of men and 10% of women in the Finnish population had the metabolic syndrome according to the WHO definition. Thus, data clearly indicate that the metabolic syndrome is quite prevalent, particularly in ageing populations, and that its associated CVD risk is significantly increased, thus emphasizing the importance of identifying as accurately and adequately as possible these high-risk subjects.

This raises the question on the most appropriate approach to identify individuals with the metabolic syndrome. Recent data have suggested that the WHO definition will identify patients who are at greater risk for developing Type II diabetes while the NCEP ATPIII definition has been more closely related to the risk of CVD (Hanley et al. 2003). More data in that regard will be required before one definition or the other can be privileged in identifying patients with a metabolic syndrome (Hunt et al. 2004). The following paragraphs describe how some of the numerous features that have been associated with the metabolic syndrome are associated with an increased risk of CVD.

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Specific features of the metabolic syndrome and the risk of cardiovascular disease

The clinical features associated with insulin resistance and the metabolic syndrome can be essentially divided into four sub-groups, namely the core features related to insulin resistance, features related to dyslipidaemia, features related to anthropometry and features related to impaired fibrinolytic activity and inflammation. Only the first three will be discussed in this short review.

The core

Insulin resistance, compensatory hyperinsulinaemia and hyperglycaemia have been considered by many as the core of the metabolic syndrome (Reaven 1988b). Insulin resistance is measured in humans using the euglycemic hyperinsulinaemic clamp technique. Insulin resistance can also be evaluated using other techniques such as intravenous glucose tolerance test or oral glucose tolerance test with frequent sampling (Best et al. 1990). These techniques are time-consuming and not appropriate as biomarkers for CVD risk prediction in the context of a large population application. Fasting plasma insulin levels have been suggested to be a relatively accurate surrogate of insulin resistance in non-diabetic populations (Ascaso et al. 2001). A meta-analysis of publications on this topic has resulted in an estimated summary relative risk of 1.18 (95% confidence intervals 1.08–1.29) for differences in insulin levels (4^{th} vs 1^{st} quartile) (Ruige et al. 1998). Using prospective data from the Québec Cardiovascular Study, one has shown that elevated fasting plasma insulin levels in a non-diabetic population of men was a strong risk factor for ischemic heart disease and that the association between the plasma insulin levels and the risk of future events was independent of several other risk factors associated with the metabolic syndrome such as increased plasma triglyceride or apolipoprotein B concentrations as well as reduced HDL cholesterol levels (Despres et al. 1996). Recent data from the Veteran Affair HDL Intervention Trial (VA-HIT) have shown that most of the benefit attributable to fibrate therapy was ascribed to the sub-group of secondary prevention patients in the highest quartile of fasting plasma insulin levels (Robins et al. 2003). Although these data show promises in terms of the potential usefulness of plasma fasting insulin levels as a powerful risk factor, several issues must still be addressed before a measure of fasting insulin concentrations can be considered as part of the tools currently used in clinical practice in primary or secondary prevention of CVD. First, the extent to which pro insulin contributes to the risk associated with hyperinsulinaemia needs to be resolved. Standardization of the assays is an issue that needs to be addressed as well. Finally, the meta-analysis published by Ruige et al. (1998) showed significant heterogeneity in the relationship between elevated fasting plasma insulin and risk of future coronary events according to ethnicity and type of assay used. Thus, the extent to which fasting insulin levels may be a powerful risk predictor in various populations still needs to be thoroughly investigated.

Dyslipidemia

Perhaps one of the most central features of the dyslipidaemia associated with the metabolic syndrome is moderate hypertriglyceridaemia (HyperTG). HyperTG has been related to reductions in plasma HDL cholesterol levels, to impaired

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post-prandial lipoprotein metabolism and to an increased prevalence of small dense LDL particles, all of which are important risk factors for cardiovascular disease (Austin et al. 2000). The meta-analysis published by Hokanson and Austin (1996) has also provided strong support to the concept that plasma triglyceride levels should be considered as an important and even independent risk factor for CVD. It has recently been shown that dichotomizing men of the Québec Cardiovascular Study on the basis of plasma triglyceride levels below or above the median value of the population (1.6 mmol l^{-1}) identified very distinct sub-groups of low and high risk subjects. Thus, non-diabetic individuals with plasma TG levels >1.6 mmol l^{-1} had a higher BMI (7%), lower HDL cholesterol levels (-13%), a higher total/HDL-C ratio (34%), increased apolipoprotein B (26%) and higher plasma fasting insulin concentrations (11%) compared to individuals with plasma TG levels <1.6 mmol l^{-1}. The risk of ischemic heart disease in the moderately hyperTG men was increased by $\sim$3-fold (Lamarche et al. 1999). Individuals with elevated plasma TG levels also generally show smaller and denser LDL particles (Tchernof et al. 1996) and small dense LDL particles *per se* have been associated with an increased risk of CVD. It has been shown that individuals who preferentially accumulated small LDL particles had an increased risk of CVD that was 3–6-fold higher than individuals who accumulated large LDL particles (Lamarche et al. 2001, St-Pierre et al. 2001). This association between small dense LDL particles and incident CVD in the Québec Cardiovascular Study was independent of any other features related to the metabolic syndrome including elevated plasma triglyceride levels and reduced HDL cholesterol concentrations (Lamarche et al. 2001, St-Pierre et al. 2001). A clinical measure of LDL particle size has yet to be made available to general practitioners. LDL size characterization by nuclear magnetic resonance (NMR) may be promising, but more data are required before this measure can be used in clinic.

While small dense LDL particles are being increasingly recognized as a risk factor for CVD, LDL particle number is also an important feature of the dyslipidaemias associated with the metabolic syndrome. Several studies have shown that plasma apolipoprotein B levels, a surrogate of particle number in the circulation, are associated with an increased risk of CVD (Schaefer et al. 1994, Lamarche et al. 1996, Westerveld et al. 1998). The largest two studies that have provided strong evidence supporting this concept are the AMORIS Study and the InterHeart Study (Walldius et al. 2001, Yusuf et al. 2004). In both cases, apolipoprotein B levels taken individually or as a ratio in combination with apolipoprotein AI levels were independent predictors of the risk of future events. These data suggest that adding apolipoprotein B to the series of clinical tool available for the prevention of CVD should be considered. In addition, results of several of the major statin clinical trials demonstrated that apolipoprotein B may be a more adequate index of the adequacy of statin therapy than any of the cholesterol indices (Sniderman 2004). The NCEP ATPIII has suggested that the non-HDL cholesterol be used as a surrogate for apolipoprotein B levels. While non-HDL cholesterol and apolipoprotein B are strongly correlated, it has recently been shown that they do not provide fully concordant risk information in a significant proportion of the population. It has also been shown that individuals with apolipoprotein B levels that are higher than what would be predicted based on their non-HDL cholesterol levels still had a 3.4-fold increase in the risk of ischemic heart disease in the Quebec Cardiovascular Study (Sniderman et al. 2003). Taken together, these data provide solid evidence for the clinical utility of

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apolipoprotein B as a primary prevention tool, particularly in the context of evaluating the risk in patients with the metabolic syndrome.

Anthropometry

Obesity is an important feature of the metabolic syndrome. However, it is not clear that the body mass index (BMI) is the most appropriate measure to predict the risk of CVD associated with obesity. Several groups have suggested that the waist circumference may be more appropriate to characterize the risk of CVD attributable to obesity and the metabolic syndrome (Carey et al. 1996). In that regard, the NCEP ATPIII has recommended using the waist circumference, not the BMI, to assess the degree of obesity in their definition of the metabolic syndrome (NCEP ATPIII 2001). It has also been suggested that variations in waist circumference, in combination with plasma TG levels, were very powerful in predicting individuals who are characterized as having the metabolic triad, namely elevated plasma insulin and apolipoprotein B levels as well as small dense LDL particles (Lemieux et al. 2000). It has been shown that this triad was associated with an 18-fold increase in the risk of ischemic heart disease in men of the Quebec Cardiovascular Study (Lamarche et al. 1998). Thus, one has proposed that assessment of plasma TG levels along with waist girth should be part of all preventive screening strategies aimed at identifying high risk individuals, most likely those with the metabolic syndrome.

Conclusion

The metabolic syndrome is being increasingly recognized as an important risk factor for CVD. Several definitions have been suggested and it is yet not clear which one should be used in clinic to best predict the risk of future CVD events. Several features of the metabolic syndrome have been associated with variations in the risk of CVD. It is, therefore, relevant to consider some of these risk factors for inclusion into the array of variables currently used in clinical practice in order to improve one's ability to adequately predict the risk of CVD in patients with and without the metabolic syndrome. Future research should be dedicated to the identification of the most powerful and sensitive markers through epidemiological and clinical studies.

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