The Quest for the Optimal Assessment of Global Cardiovascular Risk: Are Traditional Risk Factors and Metabolic Syndrome Partners in Crime?

Benoit J. Arsenault, Philippe Pibarot, Jean-Pierre Després

Departments of Anatomy and Physiology and Medicine, and Division of Kinesiology, Faculty of Medicine, Université Laval, and Québec Heart Institute, Hôpital Laval Research Centre, Québec, Qué., Canada

Key Words
Abdominal obesity · Cardiovascular disease risk · Metabolic syndrome

Abstract
Global risk calculators such as the Framingham risk score generally take into account traditional risk factors such as age, sex, blood pressure, smoking status, total cholesterol and high-density lipoprotein cholesterol levels, and the presence of diabetes which are recommended to be used in clinical practice to estimate patients’ cardiovascular disease (CVD) risk. Over the last decades, the prevalence of obesity has dramatically increased all over the world. The deleterious form of obesity, visceral obesity, is the most prevalent form of the so-called metabolic syndrome, a constellation of risk factors associated with perturbations of the lipoprotein-lipid profile and of the plasma glucose-insulin homeostasis also likely to be associated with increased blood pressure and a proinflammatory and prothrombotic state. To this date, metabolic syndrome is still in need of a place in global CVD risk prediction. As the metabolic syndrome is not likely to replace currently used global risk scoring algorithms, both traditional risk factors and emerging metabolic markers associated with the metabolic syndrome should be incorporated in future risk scoring systems to be developed in order to adapt CVD risk prediction tools to the epidemic of obesity which has direct consequences on the daily life of health professionals.

Introduction

A recent report from the National Heart, Lung, and Blood Institute on morbidity and mortality has revealed that age-adjusted cardiovascular disease (CVD) death rates in the United States have declined by more than 58% between 1972 and 2004 [1]. This remarkable fall in CVD mortality is likely to be associated with our global understanding of the pathophysiology of CVD that has been brought to another level by several investigations such as the Framingham Heart Study which has contributed to the identification of most of the key risk factors for CVD that are still taken into consideration in today’s clinical practice. Along with our increased understanding of the pathophysiology of CVD, treatment of CVD has been greatly improved over the past decades, especially with the development of lipid-lowering drugs such as statins that were even thought to potentially eradicate heart at-
tacks by the end of the past century [2]. Although this overly optimistic prediction did not materialize, the continuously improving pharmacological arsenal designed to target total and low-density lipoprotein (LDL) cholesterol levels has contributed to lower (or at least maintain) blood cholesterol levels over the last 40 years [3, 4]. However, as encouraging as these observations may seem, the death rate attributable to CVD was 289.5 per 100,000 individuals in 2004, putting CVD at the very top of the list of 2004′s mortality causes in the United States. This conclusion can be reached in most of the Westernized societies. A recent investigation from the Centers for Disease Control confirmed the fact that age-adjusted CVD mortality rates have decreased steadily between 1980 and 2002 in men and women [5]. However, age-stratification of the data from this investigation by Ford and Capewell [5] resulted in a striking and somewhat alarming finding: the CVD mortality rates among young adults have leveled off since the beginning of the present century. The decline in mortality rates among women aged 35–44 years has not only slowed, but a reversal of this trend has been reported with an increase on average of 1.3% per year since 1997. In the same timeframe, an obesity pandemic has struck the developed world [6, 7]. As a consequence, this rise in obesity prevalence, particularly of abdominal obesity, has been associated with a considerable deterioration in known risk factors such as diabetes and hypertension but has also brought in a plethora of new emerging cardiometabolic risk factors, despite few noticeable changes in blood cholesterol levels [8, 9].

To identify individuals carrying a constellation of metabolic abnormalities often referred to as the metabolic syndrome, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) suggested that if an individual had at least 3 out of 5 features of the following criteria, he/she should be diagnosed as having the metabolic syndrome: an elevated waist circumference, i.e. ≥102 cm in men and ≥88 cm in women (≥90 cm in Asian men and ≥80 cm in Asian women), elevated triglyceride levels (≥1.7 mmol/l), low high-density lipoprotein (HDL) cholesterol levels (<1.05 mmol/l in men and <1.29 mmol/l in women), elevated blood pressure (≥130/≥85 mmHg) and fasting glucose (≥5.60 mmol/l) [10]. This review will focus on the impact of the burden of abdominal obesity on classical CVD risk factors and emerging metabolic markers associated with the metabolic syndrome that are involved in the pathogenesis of either diabetes or CVD. How this emerging concept would transform our approach towards CVD prevention/management will also be discussed.

**What We Have Learned from the Framingham Heart and the Prospective Cardiovascular Münster Studies**

During the first half of the 20th century, CVD was thought to be a male disease that was an inevitable part of aging [11]. At this time, the notion of modifiable CVD risk factors was nonexistent and very little was known about the pathophysiology of CVD until the first results of the Framingham Heart Study were published during the early sixties. Throughout this period, results of the Framingham Heart Study showed that cigarette smoking, blood cholesterol levels, physical inactivity and obesity represented key CVD risk factors [12–15]. The most important CVD risk factors have been incorporated into a coronary heart disease (CHD) risk prediction engine that took into account age, total or LDL cholesterol, HDL cholesterol, blood pressure, diabetes and smoking status [16]. The Framingham risk score grades these risk factors and provides an estimate of absolute CHD risk over the next 10 years. It is now recognized as an essential and somewhat effective tool used in primary prevention providing risk estimates by categorizing patients, on the basis of the severity of the risk factors that they carry for selection of appropriate interventions. Since the Framingham risk score was based on participants of a relatively homogeneous population of European origin and limited to a specific geographical area, it might not be totally optimal to use this risk engine for estimating CHD risk in other populations of the world. In this regard, the Prospective Cardiovascular Münster (PROCAM) study was initiated in 1979 to address the use of risk assessment in a Northern European population. On top of all ‘Framingham-based’ risk factors, PROCAM added triglycerides and family history of premature myocardial infarction (MI) to its algorithm [17]. Among the key findings of PROCAM, the identification of the total cholesterol/HDL cholesterol ratio as one of the best predictors of CHD risk certainly represented an important step in the field of preventive cardiology [18]. Additional risk estimation systems such as the Systematic Coronary Risk Evaluation [19] and the United Kingdom Prospective Diabetes Study risk engine (to be used in patients with diabetes) have been developed to quickly identify high-risk individuals based on risk factor classification [20]. Altogether, these studies have had a strong clinical impact first by introducing the notion of ‘risk factors’, but more importantly, by showing that most of these risk factors might be modifiable. These concepts are still an integral part of modern clinical practice, and much evidence now suggests that the decline in age-ad-
justed CVD death rates is attributable to the improvement in risk factors that have been put on the map by the Framingham team and other pioneer groups. However, the obesity epidemic that is currently striking almost every region of the world will have serious public health impacts and will definitely change many concepts in preventive cardiology [9, 21]. Obesity, and particularly its most deleterious form, visceral obesity, is the most frequently observed underlying cause of the metabolic syndrome. Visceral obesity and metabolic syndrome have been described 15 years ago as a ‘civilization syndrome’ [8]. Today, the prevalence of this syndrome has unfortunately reached unprecedented proportions. As the increasing prevalence of the metabolic syndrome comes along a plethora of new modifiable risk factors for acute coronary syndrome, atherosclerotic vascular disease, hypertension and diabetes, several lines of evidence suggest that the metabolic syndrome is likely to contribute to the pathophysiology of CVD. Increasing evidence also supports the notion that the relationship between the metabolic syndrome and CVD incidence could be independent from traditional CVD risk factors.

**Beyond Body Weight: Abdominal Obesity Is an Underdiagnosed Risk Factor for CVD and Diabetes**

It is well known that the worldwide obesity epidemic goes hand in hand with the simultaneous increase in the prevalence of type 2 diabetes [22]. As diabetes is considered an important risk factor for CVD [23], the underlying causes of diabetes-related cardiometabolic complications need to be better understood in order to optimize treatment and care for obese patients with insulin resistance carrying several CVD risk factors. Measuring waist circumference as an approximation of abdominal adiposity is certainly an important step towards that aim. Although the relationship between abdominal obesity and CVD risk has been initially described more than 60 years ago by Vague [24], the importance of considering abdominal obesity in CVD risk prevention was further emphasized by the INTERHEART study in 2005 [25]. In this large MI case-control study, the relationship between body mass index (BMI), waist-to-hip ratio and personal MI history was assessed among 27,098 participants (12,461 cases and 14,637 controls) in 52 countries representing several major ethnic groups (fig. 1). As expected, an increased BMI was associated with MI, as the odds
ratio for MI in participants of the top BMI quintile was 1.44 (95% CI 1.32–1.57). However, after adjustment for waist-to-hip ratio, this relationship barely reached statistical significance. On the other hand, participants in the top waist-to-hip ratio quintile showed a considerably increased risk of MI compared with participants classified on the basis of the BMI (OR = 2.52, 95% CI 2.31–2.74). Unlike the relationship between BMI and MI that was considerably affected after adjustment for waist-to-hip ratio, the association of waist-to-hip ratio and MI was hardly altered by control for variation in BMI. Within each category of the BMI, a further increase in waist-to-hip ratio was associated with an increased risk of MI. In order to extend the finding of INTERHEART, another cross-sectional study, the International Day for the Evaluation of Abdominal Obesity study, was performed [26].

In that study, the relationship between BMI, waist circumference and the risk of diabetes was evaluated in 168,159 primary care patients on 2 prespecified half-days in 63 countries. It was reported that an elevated waist circumference was highly associated with previously diagnosed CVD and diabetes and that each additional centimeter of waist circumference increased the risk, even after controlling for BMI (fig. 2). Overall and in most regions of the world, associations of waist circumference to comorbidities were stronger than those found with the BMI and more closely associated with diabetes than CVD even in ‘lean’ individuals (BMI <25 kg/m²). Recently published data from the European Prospective Investigation into Cancer and Nutrition-Norfolk confirmed these observations in a large prospective study of 24,508 British men and women [27]. During a mean follow-up of 9.1

![Fig. 2. Percentage of men (a) and women (b) with CVD and of men (c) and women (d) with diabetes classified on the basis of waist circumference tertiles and BMI categories in the International Day for the Evaluation of Abdominal Obesity study. Reproduced with permission.](image-url)
In the INTERHEART study, 44,636 women were followed for an average of 16 years, and 751 cardiovascular deaths and 1,748 cancer deaths were reported. Compared with women with a waist circumference of less than 28 inches and after adjustment for potential confounders including BMI, women with a waist circumference greater than or equal to 35 inches had a 70% increased risk of mortality. The same model, compared with women with a hip circumference less than or equal to 36 inches, women with a hip circumference greater than or equal to 45 inches had a 30% reduced risk of mortality. Altogether, these recent studies clearly support the notion that the waist circumference should be measured on top of the BMI in primary care settings in order to capture the risk associated with excess body weight and especially body fat distribution.

Adipocyte Hypertrophy and Macrophage Infiltration: A Potential Link between the Expanded Insulin-Resistant Visceral Adipose Tissue and the Metabolic Syndrome

Over the past 15 years, many investigations have addressed the topic of adipose tissue as an endocrine organ which certainly represents a key pathophysiological link between visceral adipose tissue mass and CVD. However, there is a considerable debate in the medical and scientific community regarding the underlying pathophysiology behind the clinical manifestations of the metabolic syndrome. Two potential common denominators of the metabolic syndrome have been identified: visceral obesity and insulin resistance. No matter what the underlying cause of the metabolic syndrome is, an increased accumulation of visceral adipose tissue is almost always associated with insulin resistance and vice versa, as insulin resistance can also be directly measured in the enlarged visceral adipose tissue. As opposed to subcutaneous adipose tissue which primarily acts as a metabolic reservoir of storing energy excess, energy requirements of visceral adipocytes are extremely high, as these fat cells have considerably increased metabolic requirements to maintain cytoplasmic volume and glycolytic enzyme activities. Therefore, several lines of evidence suggest that the visceral adipocytes of subjects with a low visceral adipose tissue accumulation are characterized by a somewhat elevated insulin-mediated glucose uptake. As local insulin sensitivity within the adipocytes of the visceral depot is extremely high in these individuals, Virtanen et al. [30] have shown that increasing visceral adipose tissue mass is negatively and reciprocally associated with a decrease in insulin sensitivity within this atherogenic fat depot. With increasing visceral adipose tissue mass, insulin action becomes progressively impaired in visceral adipocytes. This local insulin resistance state has severe metabolic consequences, and some of these consequences directly imply the nuclear receptor peroxisome-proliferator activated receptor-γ (PPAR-γ). Under homeostatic conditions, PPAR-γ is mainly expressed in adipose tissue and regulates diverse functions such as the development of fat cells (adipogenesis) and their capacity to store lipids. A recent study has also shown that activating PPAR-γ contributes to expanding subcutaneous adipose tissue, which in turn, promotes lipid uptake and esterification in a competent subcutaneous metabolic reservoir. Moreover, lipid uptake was modestly changed and energy expenditure greatly increased in visceral adipose tissue, with consequent reduction in visceral fat accumulation upon PPAR-γ activation. As PPAR-γ fails to be activated by its natural ligands in insulin-resistant visceral adipocytes, adipogenesis is altered, and as the demand for triglyceride storage remains elevated in individuals with a daily positive energy balance, adipocytes become large, lipid-laden cells that are considerably more insulin resistant than small, metabolically active adipocytes. This hypertrophy of visceral adipocytes is another consequence of insulin resistance in visceral adipose tissue, which creates a vicious circle between insulin resistance and hypertrophy of fat cells. The impaired insulin action in visceral adipocytes also influences the catabolism of triglyceride-rich lipoproteins. The metabolic alterations...
associated with increased lipolysis of visceral adipose tissue will be discussed later. The pathophysiological consequences of an increased visceral adipose tissue accumulation and associated hypertrophied adipocytes are summarized in Figure 3.

Increasing evidence also suggests that several hormones secreted by visceral adipocytes, also called 'adipokines', such as leptin and monocyte chemoattractant protein-1 (MCP-1) make possible the infiltration of leukocytes, mostly macrophages, in visceral adipose tissue. A few studies have also suggested that the state of chronic inflammation that is associated with visceral adipose tissue accumulation is more likely to be attributable to infiltrated macrophages than to the endocrine function of visceral adipocytes per se [32]. To illustrate this concept, Cancello et al. [33] have shown that bariatric surgery considerably reduced macrophage infiltration in adipose tissue and associated inflammatory markers such as MCP-1, C-reactive protein (CRP) and hypoxia inducible factor-1α. This study also underlined the role of hypoxia in recruiting macrophages within adipose tissue. A recent investigation performed by Öhman and colleagues [34] has provided novel mechanisms linking adipose tissue distribution, inflammation and the progression of atherosclerosis in apolipoprotein E-deficient \( apoE^{-/-} \) mice. In that study, \( apoE^{-/-} \) mice were transplanted with either visceral or subcutaneous adipose tissue and were compared with sham-operated \( apoE^{-/-} \) mice. Although macrophage infiltration was comparable between all fat-transplanted depots, visceral adipose tissue-transplanted \( apoE^{-/-} \) mice showed increased circulating levels of leptin, resistin and MCP-1 in comparison with subcutaneous adipose tissue-transplanted \( apoE^{-/-} \) mice and sham-operated \( apoE^{-/-} \) mice. As a consequence, they were characterized by the highest progression of atherosclerosis. Despite a similar inflammatory response, transplantation of subcutaneous adipose tissue had no effect on atherosclerosis which suggests that the deleterious effects of metabolic syndrome-associated inflammation on the development of atherosclerosis might be the result of macrophage-visceral adipocyte interactions rather than of macrophage infiltration of adipose tissue alone. Of particular interest, treatment of visceral adipose tissue-transplanted \( apoE^{-/-} \) mice with the PPAR-γ agonist pioglitazone resulted in decreased levels of MCP-1, fat inflammation and atherosclerosis. These observations provided further evidence that the activation of the nuclear receptor PPAR-γ might decrease atherosclerosis via other pathways than its effect on blood glucose levels, even in the absence of diabetes. The relationships between the hypoxia-dependent macrophage infiltration of adipose tissue, the vascularity of adipose tissue and an altered pattern of cytokine production (increased secretion of leptin, resistin, MCP-1 and low adiponectin) have also been recently described in an investigation by Rausch et al. [35] in the C57BL/6J mouse.

**Table 1.** Pathophysiological role of large, hypertrophied and insulin-resistant adipocytes of the visceral depots in comparison with small and insulin-sensitive adipocytes. AT = Adipose tissue; HSL = hormone-sensitive lipase; ASP = acylation-stimulating protein.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Small adipocytes</th>
<th>Large adipocytes</th>
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<tr>
<td>Subcutaneous AT</td>
<td>Low</td>
<td>Visceral AT</td>
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<tr>
<td>Insulin sensitivity</td>
<td>High</td>
<td>Normal</td>
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<tr>
<td>Lipolysis/HSL activity</td>
<td>Normal</td>
<td>High</td>
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<tr>
<td>Triglycerides/glucose storage</td>
<td>Normal</td>
<td>Impaired</td>
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<td>LPL activity</td>
<td>Normal</td>
<td>Low</td>
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<tr>
<td>ASP activity</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>Leukocyte infiltration</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Adiponectin expression</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Local hypoxia</td>
<td>No</td>
<td>Yes</td>
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<td>Association with metabolic syndrome</td>
<td>No</td>
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**Figure 3.** Pathophysiological role of large, hypertrophied and insulin-resistant adipocytes of the visceral depots in comparison with small and insulin-sensitive adipocytes. AT = Adipose tissue; HSL = hormone-sensitive lipase; ASP = acylation-stimulating protein.
What Are the Clinical Manifestations of the Metabolic Syndrome?

The Atherogenic Dyslipidemia of the Metabolic Syndrome

The complex interplay between the pivotal organs involved in the pathogenesis of the metabolic syndrome is depicted in figure 4. A typical dyslipidemia, often called 'metabolic or diabetic dyslipidemia', accompanies the state of insulin resistance and is characterized by increased plasma triglyceride levels and low plasma levels of HDL cholesterol. Elevated apoB levels and small LDL particles are also frequently observed along this metabolic dyslipidemia, as these risk markers are all interrelated [36]. In the context of the metabolic syndrome, this dyslipidemia might have several origins. As mentioned above, the impaired insulin action of visceral adipocytes has a considerable impact on the lipoprotein-lipid metabolism. First, lipoprotein lipase (LPL), which is the key regulator of triglyceride-rich lipoprotein catabolism, requires the presence of insulin to achieve its catabolic properties [37]. Therefore, by reducing LPL activity, an important consequence of the impaired insulin action within visceral adipose tissue is the increased plasma levels of triglycerides and non-HDL cholesterol. As LPL and the hormone-sensitive lipase have reciprocal activities, lipolysis is enhanced in individuals with insulin resistance. This process through which adipose tissue releases nonesterified fatty acids, a direct consequence of the impaired insulin action on hormone-sensitive lipase inhibition, contributes to triglyceride enrichment of the liver. This phenomenon, also known as the portal vein nonesterified fatty acid theory, represents an important pathway that links visceral adipose tissue accumulation, liver fat accumulation (or ectopic fat deposition) and its associated atherogenic dyslipidemia.

Although the metabolic syndrome is not necessarily associated with elevated plasma LDL cholesterol concentrations, it nonetheless influences LDL particles by aiming at LDL quality rather than LDL quantity, creating small and dense LDL particles with an increased plasma half-life. The role of small, dense LDL particles on CVD has recently been reviewed [38]. An increased free fatty acid delivery to the liver is associated with an increased triglyceride-rich VLDL production, and the catabolism of these particles is also decreased in the metabolic syndrome [39]. This observation has several consequences on the lipoprotein-lipid metabolism as it is associated with an increase in remnant-like particles and with an increased activity of the cholesteryl ester transfer protein which promotes the transfer of triglycerides from apoB-containing lipoproteins to HDL particles in exchange of cholesteryl.
ers [40, 41]. As a consequence, LDL particles become triglyceride-enriched and, as a result, turn into smaller and denser particles. These modified LDL particles are more likely to be oxidized by circulating reactive oxygen species which are also present in abdominally obese individuals [42]. The increased cholesteryl ester transfer protein activity is also likely to reduce HDL cholesterol concentration and to promote the formation of small HDL particles with a decreased capacity of promoting reverse cholesterol transport and its other antiatherogenic properties such as its anti-inflammatory, antioxidative and antiapoptotic actions [43]. To evaluate the cardiovascular risk resulting from the metabolic abnormalities associated with the lipoprotein-lipid profile, many screening tools or lipid ratios have been suggested. One of the most recognized lipid ratios for the assessment of CVD is the total cholesterol/HDL cholesterol ratio that measures the risk associated with high LDL and VLDL cholesterol and low HDL cholesterol levels [44]. Recently, the triglyceride/HDL cholesterol ratio has also been shown to be associated with insulin resistance and associated CVD risk [45]. However, these results of the Framingham Offspring Study have shown that the triglyceride/HDL cholesterol ratio predicted CHD risk to a similar extent as the total cholesterol/HDL cholesterol ratio. Finally, it has been suggested more than 30 years ago that the apoB/apoA-1 ratio might outperform these traditional lipid ratios in terms of CVD risk prediction [46]. Although almost every study performed on the topic has shown that the apoB/apoA-1 ratio is associated with an increased CVD risk, many studies have shown conflicting results regarding the ability of the apoB/apoA-1 ratio to predict CVD risk after adjustment for other lipid (or cholesterol) ratios [47–50]. From a practical standpoint, as each LDL particle carries one apoB particle, apoB clearly represents a good estimate of both LDL quality and quantity. On the other hand, there is increasing evidence suggesting that the antiatherogenic properties might be more attributable to apoA-1 rather than to HDL cholesterol levels per se. Van der Steeg et al. [51] have recently brought epidemiological evidence to support this notion by showing that, after adjustment for the apoB/apoA-1 ratio, HDL cholesterol levels were not associated with CVD risk in 2 independent studies. On the other hand, apoA-1 was still associated with a decreased CVD risk after adjustment for apoB and HDL cholesterol levels.

**The Proinflammatory and Prothrombotic State**

It has been documented more than 50 years ago that one of the first steps of atherosclerosis is the infiltration of lipids in the arterial wall that once infiltrated become toxic and induce an inflammatory process [52]. As this phenomenon is still valid today, a considerable body of research data has confirmed the importance of low-grade inflammation in the progression of atherosclerosis [53]. One of the first steps in atheroclerosis is the penetration of the arterial wall by chemically altered LDL particles (small, dense and/or oxidized). Once they have reached the arterial wall, these lipoproteins stimulate the recruitment of several leukocytes such as macrophages and Th2 lymphocytes [54, 55]. The binding and influx of such inflammatory cells is also dependent upon monocyte recruitment mediators such as P-selectin, E-selectin, vascular cell adhesion molecule-1 and intracellular cell adhesion molecule-1, of which the expression is made possible by circulating cytokines such as tumor necrosis factor-α (TNF-α), CRP and interleukin (IL)-1β [56, 57]. Oxidized LDL particles have also been shown to induce an inflammatory response, independently of leukocyte penetration. This chronic inflammatory state is also important to consider later in the development of atherosclerosis as it is involved in the rupture of the atheroma.

The contribution of visceral adipose tissue accumulation and associated macrophage infiltration plays a key role in predicting circulating levels of several inflammatory markers. For instance, it has been shown that total adiposity and especially visceral adiposity are closely associated with circulating levels of CRP, a liver-derived acute-phase protein that is thought to reflect this low-grade inflammatory state that promotes and enhances atherosclerosis [58, 59]. IL-6, a visceral adipose tissue-derived hormone, also upregulates hepatic CRP production [60, 61]. A recent study by Cartier et al. [62] has shown that obesity is associated with elevated circulating levels of TNF-α and IL-6 with a specific contribution to visceral adipose tissue in predicting IL-6 levels. In that study, subjects with the highest plasma IL-6 and TNF-α levels were found to have increased features of insulin resistance. Another investigation performed in the same group of men has shown that the plasma levels of adiponectin, an anti-diabetic adipokine, were only decreased in subjects with the highest plasma IL-6 and TNF-α levels in the presence of visceral obesity, as overweight/obese men with a low visceral adipose tissue accumulation have comparable adiponectin levels with lean men [63]. On top of its well-recognized anti-diabetic properties, adiponectin also exerts several antiatherogenic and anti-inflammatory actions. It has been show in vasculature that adiponectin suppresses monocyte adhesion to endothelial cells, by suppressing the expression of vascular cell adhesion molecule-1, intracellular cell adhesion molecule-1
and E-selectin [64]. This observation might be attributable to the inhibitory effect of adiponectin on the TNF-\(\alpha\)-dependent expression of monocyte adhesion proteins. In macrophages, adiponectin has been shown to reduce the intracellular cholesterol content by suppressing the expression of specific scavenger receptors and might improve plaque stabilization via the increased expression of the anti-inflammatory cytokine IL-10 [65–67]. Adiponectin also slows the proliferation and migration of vascular smooth muscle cells, another pathway potentially linking adiponectin and plaque stabilization [68]. As endothelial dysfunction is another clinical feature of the metabolic syndrome [69], maintaining angiogenesis and an elevated vasodilatory activity is crucial to prevent coronary events associated with the metabolic syndrome. In this context, increased nitric oxide (NO) production might help avoid these complications. It has been suggested that adiponectin increased NO production via the activation of endothelial NO synthase and also by reducing oxidized LDL-induced endothelial NO synthase suppression [70, 71].

On the other hand, visceral obesity and ectopic fat deposition are closely associated with several markers of altered hemostatic and fibrinolytic systems such as increased levels of the plasminogen activator inhibitor-1 and fibrinogen [72, 73]. Therefore, this proinflammatory and prothrombotic milieu enhances the progression of atherosclerosis by several mechanisms that have recently been reviewed [74].

Although a plethora of circulating inflammatory markers is associated with CVD risk, their role in overall CVD risk prediction remains to be determined. Most of the studies that have sought to provide epidemiological evidence for a role of inflammation in CVD incidence have either used CRP or white blood cell count as the inflammatory risk marker of interest [75–77]. Over the last decade, CRP has evolved to be the most recognized inflammatory marker as it shows linear associations with CVD risk and is relatively easy and inexpensive to measure [77–79]. Although many studies have shown that the association between CRP and CVD risk was independent from traditional risk, the role of CRP in global cardiovascular risk prediction needs to be further investigated. As it is well established that CRP is closely associated with features of the metabolic syndrome, especially waist circumference, the ability of CRP to predict CVD risk on top of metabolic syndrome components and traditional CVD risk factors is yet to be established [80]. Given the close association between visceral adiposity, the metabolic syndrome and CRP, it is reasonable to believe that CRP might represent a marker of this atherogenic/diabetogenic phenotype rather than being a critical causal actor in the pathogenesis of CVD [81]. Further studies are needed to sort out the extent to which CRP predicts CVD risk, once the components of the metabolic syndrome have been controlled for.

**Beyond Hyperglycemia, What Is the Impact of the Metabolic Syndrome on the Glucose-Insulin Homeostasis?**

The rising prevalence of an expanded waistline that is seen across several populations will eventually increase the risk of diabetes-driven CVD. Ten years ago, it has been shown that the CVD risk associated with diabetes was similar to the CVD risk attributable to the presence of a previous MI [23]. Although hyperglycemia is considered one of the components of the metabolic syndrome, the consequences of an expanded waistline on the glucose-insulin homeostasis can be witnessed even in the presence of normal glucose levels. As a consequence of the portal vein theory, the increased nonesterified fatty acid flux is strongly correlated with hepatic fat, a phenomenon also known as ectopic fat deposition [82]. Kotronen and Yki-Järvinen [83] have recently reviewed the role of the fatty liver in the pathophysiology of the metabolic syndrome. In this context, the ability of insulin to inhibit glucose production by the liver is impaired, resulting in increased blood glucose levels which in turn stimulate insulin production to create a vicious circle [84]. Under these pathophysiological conditions, the ability of adiponectin to stimulate glucose utilization and hepatic \(\beta\)-oxidation of fatty acids is also impaired [85]. Increasing evidence supports the notion that the fatty liver is pivotal in the relationship between visceral adiposity, insulin resistance and associated CVD/diabetes risk [86, 87]. On top of its benefits for hepatic fatty acid metabolism and the vascular endothelium, adiponectin, which is thought to be the most abundant adipose tissue-derived hormone, has also been shown to be decreased in visceral obese men [63, 88], an observation that is likely to be attributable to the repression of the adiponectin gene by the local action of TNF-\(\alpha\) and/or IL-6 [89, 90]. On the other hand, activation of PPAR-\(\gamma\) within the adipose tissue is associated with adipocyte hyperplasia and increased expression, and more importantly, circulating levels of adiponectin [91–93]. A recent investigation has shown that adiponectin is not only highly expressed by fat cells of the omental adipose tissue, but also by the non-fat cells of the human adipose tissue [94]. In that study, it has been shown that adiponectin secretion was stimu-
In order to estimate low-grade inflammation, an inflammation score based on plasma levels of CRP, adiponectin, IL-6 and TNF-α was developed. One point was attributed to men each time an inflammatory marker was in the top 50th percentile (≥1.22 mg/l for CRP, ≥1.57 pg/ml for IL-6, and ≥2.68 pg/ml for TNF-α) or in the bottom 50th percentile for adiponectin (≤8.65 μg/ml). Men with a low inflammatory score had 0, 1 or 2 points, and men with low-grade inflammation scored 3 or 4 on the inflammation score. In this figure, the percentage of men with an elevated inflammation score is shown in each category (n = 188).

Fig. 5. Percentage of subjects characterized by low-grade inflammation in healthy, middle-aged men classified on the basis of the BMI and visceral adipose tissue (AT) accumulation. In order to estimate low-grade inflammation, an inflammation score based on plasma levels of CRP, adiponectin, IL-6 and TNF-α was developed. One point was attributed to men each time an inflammatory marker was in the top 50th percentile (≥1.22 mg/l for CRP, ≥1.57 pg/ml for IL-6, and ≥2.68 pg/ml for TNF-α) or in the bottom 50th percentile for adiponectin (≤8.65 μg/ml). Men with a low inflammatory score had 0, 1 or 2 points, and men with low-grade inflammation scored 3 or 4 on the inflammation score. In this figure, the percentage of men with an elevated inflammation score is shown in each category (n = 188).

Increased Blood Pressure: Another Obesity-Driven Cardiovascular Risk Factor?

It is now well-recognized that the prevalence of hypertension is higher in obese individuals compared with normal weight individuals [95, 96]. Nevertheless, not all obese patients are hypertensive, and hypertension is often found in patients with an apparently healthy body weight, suggesting that the relationship between obesity and increased blood pressure may depend, at least partly, upon the presence of an inadequate body fat distribution. Based on the fact that insulin resistance is another risk factor for hypertension [97], investigators of the Quebec Health Survey have examined the relationship between insulin resistance, crudely estimated by fasting insulin levels, hypertension and body fat distribution in 907 men and 937 women [98]. It was found that independently from BMI categories, having a waist circumference ≥88 cm (74 cm in women) was associated with a significant increase in systolic and diastolic blood pressure. Similar findings were observed when participants were classified on the basis of fasting insulin levels. For every fasting insulin tertile considered, a further increase in waist circumference was associated with increased systolic and diastolic blood pressure. However, inside each waist circumference tertile, a further increase in fasting insulin levels was not associated with concomitant increases in systolic and diastolic blood pressure, which suggests that abdominal obesity largely explains the relationship between insulin resistance and blood pressure.

Meanwhile, obesity is also associated with increased renal tubular sodium reabsorption, which is associated with glomerular and overall hypertension. As glomerular hypertension causes glomerulosclerosis, renal damage or chronic kidney disease, increased renal tubular sodium reabsorption might represent another important pathway that links metabolic syndrome and CVD risk [99]. Increasing evidence also suggests that the endocrine function of adipose tissue is a potential link between obesity and hypertension. Indeed, recent studies have shown that several enzymes of the renin-angiotensin system are partly derived from adipose tissue. In this regard, Masiera et al. [100] have shown that transgenic mice exclusively overexpressing angiotensinogen in adipose tissue had a higher blood pressure than wild-type littermates. Interestingly, these mice were also characterized by adipocyte hypertrophy, an observation likely to alter the adipokine secretion pattern. Increasing evidence suggests that obesity, and particularly visceral obesity, is associated with increased levels of mineralocorticoids such as aldosterone and angiotensinogen II, which in turn could act as growth factors for adipocytes by stimulating lipogenesis and preadipocyte differentiation [101, 102]. The role of body fat distribution and the renin-angiotensin system and the cardiac natriuretic peptide system has recently been reviewed elsewhere [103]. In a recent study, the relationship between insulin resistance and hypertension was also highlighted as adiponectin levels and insulin sensitivity were considerably increased in patients with hypertension treated with either an angiotensin-
converting enzyme inhibitor or an angiotensin II receptor blocker [104]. Altogether, these observations could explain, at least to a certain extent, the role of drugs affecting the renin-angiotensin system in preventing type 2 diabetes [105].

**Is There a Role for Metabolic Syndrome in CVD Risk Prediction?**

The American Diabetes Association and the European Association for the Study of Diabetes have simultaneously and jointly criticized the utility of the concept of the metabolic syndrome in primary care settings for many reasons including the fact that CVD risk associated with the metabolic syndrome does not appear to be greater than the sum of its parts, i.e. abdominal obesity, abnormal lipids, increased blood pressure and insulin resistance. As a consequence, treatment of the metabolic syndrome does not appear to be different from treating each of its individual components. On the other hand, 2 meta-analyses have recently shown that metabolic syndrome is associated with a 1.5- to 2-fold increase in CVD risk [106, 107]. However, very few studies have sought to determine whether metabolic syndrome provides additional information regarding CVD incidence after adjustment for the Framingham risk score, which is globally accepted as an estimate of the 10-year cardiovascular risk. Wanamethee et al. [108] have investigated the predictive ability of the Framingham risk score and metabolic syndrome as evaluated by the criteria of the NCEP-ATP III in 5,128 British men who were followed for 20 years. Overall, they found that the Framingham risk score was more closely associated with incident CHD whereas metabolic syndrome was a better predictor of incident diabetes. Similarly, in the San Antonio Heart Study, Stern et al. [109] have followed 2,570 participants for 7.5 years and reported that the NCEP-ATP III criteria for the metabolic syndrome did not predict CVD on top of the Framingham risk score. However, it is important to note that these previous studies used statistical analyses that were based on the area under the receiver-operating characteristic curve (AUC under the ROC, the c-statistic), a method that has been described as very conservative when it comes to testing the predictive ability of a certain phenotype and/or biomarker. Cook [110] has shown in the Women’s Health study that adding deep-rooted cardiovascular risk factors such as HDL cholesterol, total cholesterol or LDL cholesterol individually to age, systolic blood pressure and smoking status did not have much of an impact on the c-statistic, which suggests that relying on the c-statistic alone has a clear limitation for the identification of novel phenotypes, biomarkers or algorithms such as the metabolic syndrome. Further research is clearly warranted in this area. Because of the rising prevalence of abdominal obesity, insulin resistance and metabolic syndrome, primary care physicians and health professionals now face patients who are likely to have signs of insulin resistance and CVD even if they show few CVD classical risk factors. In this regard, figure 6 shows how traditional and emerging CVD risk factors associated with the metabolic syndrome should be incorporated into new, more adapted CVD risk prediction algorithms.

![Fig. 6. Hypothetical model of the interplay between traditional CVD risk factors and some emerging risk factors associated with the metabolic syndrome. As the traditional CVD risk markers, that are often referred to as the Framingham risk score, enhance CVD risk prediction, risk factors associated with the metabolic syndrome should be incorporated into new, more adapted CVD risk prediction algorithms.](image-url)
needs to be weighed up to provide a better estimate of patients’ diabetes or CVD risk. Such an exercise has been performed by Macchia et al. [111] who have shown that a metabolic syndrome score based on a Cox proportional hazard including components of the metabolic syndrome was highly associated with diabetes incidence compared with NCEP-ATP III criteria. The score had an AUC under the ROC of 0.650, and the AUC under the ROC for NCEP-ATP III criteria was 0.587. The prediction of CVD risk associated with the metabolic syndrome would benefit from such an approach. However, it is important to keep in mind that the metabolic syndrome only represents one piece of the complex puzzle of CVD risk prediction and that the markers associated with the metabolic syndrome should be incorporated in currently available CVD risk prediction algorithms to better estimate and manage CVD risk in primary care settings.

Conclusion

Over the past decades, the industrialization and computerization of our society have been in constant progression. Although these socioeconomic changes have brought many advantages to societies of the developed world, we have engineered our world so that a large segment of our population spends very little time performing physical activity and/or exercise training. Countering the rising prevalence of obesity that comes along with societies’ modernization represents a huge and important challenge which is beyond the skills of the medical community. Throughout the world, it is of critical importance that health professionals emphasize the importance of being physically active and of adopting healthy nutritional habits in order to prevent visceral fat accumulation and its deleterious effects on CVD mortality and morbidity. As there are many genetic and other CVD risk factors that are not modifiable, the good news with the rise in emerging risk markers is that they can be modified with the adoption of healthy lifestyle habits. The time has now come to promote physical activity and healthy lifestyle habits through aggressive and global health policies.

Acknowledgements

Benoit J. Arsenault is recipient of a training scholarship from Hôpital Laval Research Centre. Philippe Pibarot holds the Canada Research Chair in Valvular Heart Disease awarded by the Canadian Institutes of Health Research, and Jean-Pierre Després is the Scientific Director of the International Chair on Cardiometabolic Risk which is supported by an unrestricted grant awarded to Université Laval by Sanofi Aventis.

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