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Scientific Update™

The Obesity Epidemic: A Focus on Global Cardiometabolic Risk

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Obesity has reached epidemic proportions globally. The metabolic syndrome represents a culmination of obesity-driven risk factors for atherosclerotic cardiovascular disease (CVD) and type-2 diabetes. Definitions of the syndrome may vary but, in general, they agree closely in identifying subjects. The relationships between the metabolic syndrome and atherosclerotic CVD and diabetes also vary, with relative risks of approximately 1.5-3.0 and 3.0-5.0, respectively. Insulin resistance appears to account for much of the pathophysiology of the syndrome. Adipose tissue is the body's largest repository of energy and plays an important role in total energy homeostasis. This issue of *Cardiology Scientific Update* discusses the mechanisms of components of the metabolic syndrome that predispose to diabetes and atherosclerotic CVD, as well as strategies to better quantify the risk for diabetes and CVD.

Obesity and the heart: function and metabolism

Obesity, insulin resistance, and their frequent complications in type-2 diabetes are risk factors for left ventricular diastolic dysfunction, systolic dysfunction, and clinical heart failure.[1] Although obesity, insulin resistance, and diabetes are risk factors for coronary artery disease and, therefore, ischemic cardiomyopathy-related heart failure, there is increasing evidence that these risk factors are also implicated in the development of cardiac dysfunction that is not related to epicardial coronary disease.[1] There are several mechanisms by which this triad may cause cardiac dysfunction, including alterations in hemodynamics, neurohormonal mechanisms, and myocardial metabolism that may initially be adaptive, but evolve into maladaptive responses over time.[2,3]

Alterations in myocardial metabolism may be particularly important mechanisms mediating the impairment of cardiac performance in obese subjects, especially obese women. To test the hypothesis that myocardial fatty acid metabolism and efficiency are abnormal in obese women, 31 young women with a body mass index (BMI) of 19 to 52 kg/m^2 were studied.[2] Myocardial oxygen consumption (MVO_2) and fatty acid uptake (MFAUp), utilization (MFAU), and oxidation (MFAO) were quantified by positron emission tomography. As shown in Figure 1, the BMI in these subjects correlated with MVO_2, MFAUp, and efficiency.

Insulin resistance, quantified by the glucose area under the curve (AUC) during an oral glucose tolerance test, correlated with MFAUp, MFAU, and MFAO. Multivariate stepwise regression analysis revealed that BMI was the only independent predictor of MVO_2 and efficiency. Glucose AUC was the only independent predictor of MFAUp, MFAU, and MFAO. Therefore, in young women, obesity is a significant predictor of increased MVO_2 and decreased efficiency, and insulin resistance is a robust predictor of MFAUp, MFAU, and MFAO. This increase in fatty acid metabolism and decrease in efficiency may play a role in the pathogenesis of decreased cardiac performance in obese women. Further advances in the understanding of these mechanisms may aid the development of novel therapies, including metabolic manipulations, that could prevent and treat cardiac dysfunction in patients with obesity, insulin resistance, and diabetes.

Obesity is a heterogeneous condition and not every obese patient is at increased risk of CVD.[4] It is now well-established that the regional distribution of body fat is a critical correlate of the metabolic complications of obesity. Studies that have assessed adipose tissue distribution by imaging techniques (eg, computed tomography [CT] scans) have demonstrated the importance of the abdominal (visceral) fat depot as a marker of a cluster of metabolic abnormalities, including glucose intolerance, insulin resistance, hyperinsulinemia, hypertriglyceridemia, an elevated number of apo B-carrying lipoproteins, as well as hypoalphalipoproteinemia. Although the associations between visceral obesity and metabolic complications are well-established, it has been suggested that they may not necessarily represent a causal relationship.

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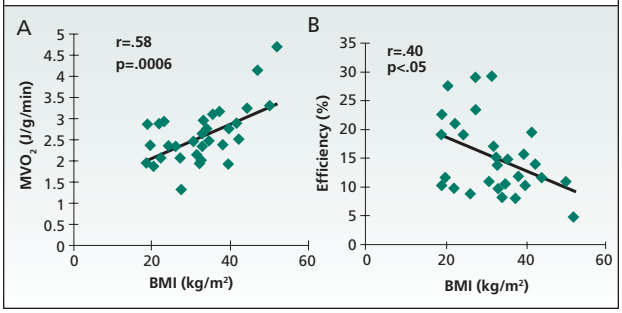
Figure 1: Relationship between A) MVO_2 and BMI, and B) cardiac efficiency and BMI in young, otherwise healthy women[2]



MVO_2 = myocardial oxygen consumption, BMI = body mass index
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Obesity and global cardiometabolic risk

The presence of the metabolic syndrome is associated with an increased risk for the development of type 2 diabetes and CVD.[5-8] Although there is ongoing debate on metabolic syndrome as a distinct scientific concept,[9] most authorities generally recognize it as a key risk factor for CVD.[10,11] The 5 variables proposed to screen for metabolic syndrome include waist circumference, circulating levels of triacylglycerols and of high-density lipoprotein (HDL)-cholesterol, fasting glycemia, and blood pressure.[10] The existence of metabolic syndrome signifies a conceptual shift from a pathophysiological construct based on metabolic abnormalities resulting from an insulin-resistant state to an epidemiological construct based on abdominal obesity and rather crude correlates of the features of insulin resistance. The recommendation by the National Cholesterol Education Program – Adult Treatment Panel III (NCEP–ATP III) to measure waist circumference, rather than BMI, indicates a recognition of the important role played by abdominal obesity in metabolic syndrome.[12]

Even though obesity is a risk factor for the development of insulin resistance, diabetes, and a significant risk factor for CVD, not every obese patient is necessarily insulin-resistant or at high-risk of diabetes and CVD.[4] This explains why obesity has been an ill-defined and modifiable CVD risk factor compared with other risk factors; eg, hypertension, smoking, and cholesterol (high low-density lipoprotein [LDL] and low HDL). But, for any given amount of total body fat, the subgroup of individuals with a selective excess of intra-abdominal or visceral adipose tissue may be at higher risk of being characterized by insulin resistance and by features of metabolic syndrome.[13]

The pathophysiology of visceral obesity

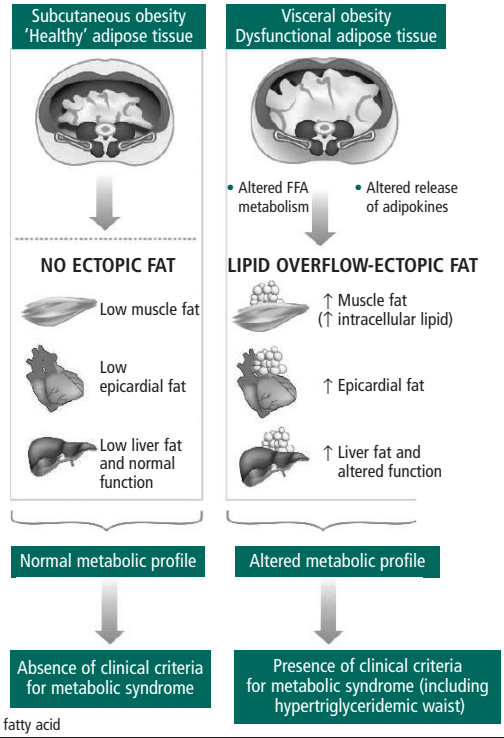
An important question has been whether visceral obesity is a causal factor or, rather simply, a marker of a dysmetabolic profile. An impairment in the metabolism of nonesterified free fatty acid (NEFFA) may be an important mechanism mediating insulin resistance in individuals with abdominal obesity.[12] Hypertrophied intra-abdominal adipocytes are characterized by a hyperlipolytic state that is resistant to the anti-lipolytic effect of insulin. For example, the canine omental adipose bed represents a highly insulin-resistant depot that drains directly into the portal vein. Increased FFA flux to the liver may account for hepatic insulin resistance in the moderately obese state.[14] The resulting NEFFA flux to the liver may impair liver metabolism, leading to increased hepatic glucose production. Hepatic insulin resistance is associated with decreased apolipoprotein B degradation and increased production of triacylglycerol-rich lipoproteins. In humans, there is evidence to suggest that adipose tissue is not only specialized in the storage and mobilization of lipids, but also an endocrine organ that releases cytokines, including the proinflammatory molecules interleukin (IL)-6 and tumour necrosis factor-alpha (TNF-α). In obesity, there have been observations of macrophage infiltration in adipose tissue,[15] which could, therefore, contribute to the development of the inflammatory profile reported in abdominally obese patients.[16] Plasma levels of C-reactive protein (CRP) are also known to be increased in patients with visceral obesity.[17]

The protein adiponectin circulates in blood and is specifically derived from adipose tissue.[18] Contrary to the proinflammatory adipokines, adiponectin levels are reduced in obese individuals, especially among patients with excess visceral adiposity.[19] Adiponectin possesses many *in vitro* effects that are compatible with improved insulin signaling and potential protection against atherosclerosis.[20] The reduced adiponectin levels observed in abdominally obese patients may be one of the factors responsible for their atherogenic and diabetogenic metabolic risk factor profile. Indeed, abdominally-obese patients with excess visceral adipose tissue have elevated plasma CRP concentrations, accompanied by elevated IL-6 and TNF-α levels and reduced adiponectin concentrations.[19] However, even though low adiponectin levels are associated with visceral obesity, whether this adipokine actually plays a central role in the altered metabolic risk profile of patients with visceral obesity remains unclear. Nevertheless, overall, these results are consistent with an important endocrine function of the expanded visceral adipose depot, not only leading to altered NEFFA metabolism, but also a proinflammatory profile that may contribute to insulin resistance and altered glucose homeostasis.

Both the altered NEFFA metabolism and endocrine function hypotheses imply that visceral adipose tissue is causally involved in the pathophysiology of the metabolic syndrome.[12] The lipid outflow-ectopic fat model offers an additional pathophysiologic mechanism for abdominal obesity (Figure 2).[12] According to this model, excess visceral fat accumulation is causally-related to features of insulin resistance, but may also be indicative of dysfunctional adipose tissue that is unable to appropriately store excess energy. Thus, the body's ability to cope with surplus calories – the result of excess caloric consumption and/or physical inactivity – might ultimately determine an individual's susceptibility to developing the metabolic syndrome. Interestingly, evidence suggests that if the extra energy is channeled into insulin-sensitive subcutaneous adipose tissue, the individual, in spite of having a positive energy balance, is protected against the development of the metabolic syndrome. However, in cases where adipose tissue is absent, deficient, or insulin-resistant and, therefore, where there is a limited ability to store excess energy, the triacylglycerol surplus will be deposited at undesirable sites (ie, the liver, heart, skeletal muscle, and visceral adipose tissue). This phenomenon is described as ectopic fat deposition.

Factors associated with a preferential accumulation of visceral fat and features of insulin resistance include, among others, smoking, the well-documented genetic susceptibility to visceral obesity,[21] and a neurohormonal profile characteristic of a maladaptive response to stress.[22] The metabolic consequences of this 'defect'

Figure 2: The lipid outflow-ectopic model for abdominal obesity[12]



FFA = free fatty acid

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in energy partitioning include visceral obesity, insulin resistance, atherogenic dyslipidemia, and a pro-thrombotic, inflammatory profile, ie, features of the metabolic syndrome. This constellation of abnormalities can be detected by considering the clinical criteria for metabolic syndrome, the 2 simplest being the simultaneous presence of increased waist girth and fasting triacylglycerol levels, a condition that has been described as the "hypertriglyceridemic waist."[12,23]

Clinical criteria of metabolic syndrome

The 5 criteria and cut-off values proposed by the NCEP–ATP III panel[10,11] and endorsed by the International Diabetes Federation (IDF)[24] to diagnose the likely presence of metabolic syndrome were reached mainly through expert consensus and interpretation of the literature. They have not been validated for their ability to discriminate optimally for individuals with both metabolic syndrome and a related increase in CVD risk. This is especially important for the assessment of CVD risk associated with excess visceral adiposity in non-Caucasian populations. Despite this limitation, prospective observational studies have generally shown that individuals who meet the clinical criteria for metabolic syndrome are at increased risk of CVD events and diabetes compared with individuals without the syndrome.[25] Using different cut-offs or metabolic syndrome markers for different outcomes might improve identification of patients at increased risk. Since the publication of the consensus, the conceptual definition of metabolic syndrome has often been confused with the 5 proposed clinical criteria. These criteria should be regarded as surrogate variables to help identify a subgroup of high-risk individuals likely to be characterized by key features of the metabolic syndrome: abdominal obesity, insulin resistance, high triacylglycerol–apolipoprotein B, low HDL-cholesterol, small, dense LDL dyslipidemia, a pro-thrombotic state, and an inflammatory profile. These clustering features are the most prevalent form of the metabolic syndrome as defined by NCEP–ATP III.[5] This constellation of abnormalities might be accompanied by hypertension and/or diabetes, depending on the individual's genetic susceptibility. However, it remains uncertain whether all possible combinations of 3 of the 5 NCEP-ATP III criteria similarly increase CVD risk.

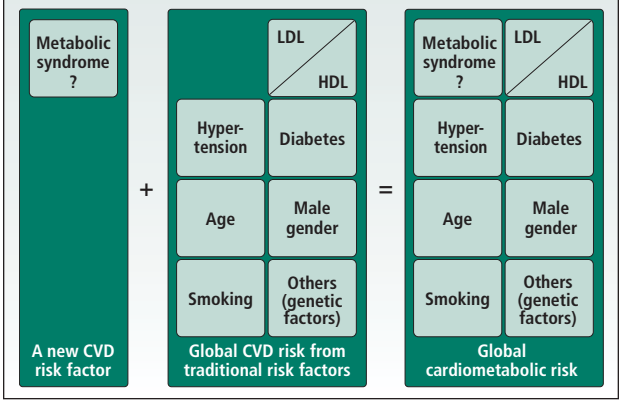
Although the presence of the metabolic syndrome can lead to an approximate 2-fold increase in relative CVD risk,[25] when assessing a patient, it should not replace the determination of overall CV risk, taking into account conventional CVD risk factors such as age, gender, smoking, blood pressure, cholesterol, and diabetes. The Framingham Heart Study calculator, for instance, considers some elements of the metabolic syndrome, such as blood pressure and HDL-cholesterol levels. Although the presence of clinical criteria for metabolic syndrome is predictive of an increased relative risk of CVD, the absolute risk is mainly determined by the presence or absence of traditional risk factors. Therefore, meeting the clinical criteria for metabolic syndrome does not necessarily equal a very high absolute risk of CVD.[12] When assessing the absolute CVD risk for patients who meet the clinical criteria for metabolic syndrome, it is necessary to first pay attention to conventional risk factors. Debate continues as to whether the metabolic syndrome enhances the understanding of global coronary heart disease risk as assessed by available algorithms such as the Framingham risk calculator.[26]

To date, conflicting and mostly neutral results have been reported.[27,28] There exists, however, preliminary evidence to suggest that when sophisticated markers of the metabolic syndrome, such as fasting insulin and apolipoprotein B levels and LDL size, are measured, their presence increases CVD risk beyond that which would be calculated using traditional CVD risk algorithms.[29] A diagnosis of the metabolic syndrome, therefore, identifies an individual with dysfunctional metabolism who needs to change his or her lifestyle and lose weight, particularly abdominal fat. Thus, a diagnosis of metabolic syndrome does not automatically identify a candidate for pharmacotherapy, nor should it detract from the importance of pharmacological management of traditional risk factors in accordance with current guidelines.

Global cardiometabolic risk assessment

From the previous discussions, it is apparent that more precise global risk-assessment algorithms are needed to quantify diabetes and CVD risk resulting from the presence of classical risk factors and the presence of abdominal obesity or insulin resistance-related metabolic markers. The term 'cardiometabolic risk' has been coined by organizations such as the American Diabetes Association and the American Heart Association[30] to describe the overall risk of developing diabetes and CVD,[12] and this idea can potentially reconcile both the protagonists, as well as the antagonists, of the metabolic syndrome concept. As depicted in Figure 3, cardiometabolic risk encompasses the global risk of CVD and type-2 diabetes associated with traditional risk factors, while also taking into consideration the potential additional contribution of abdominal obesity and/or insulin resistance and related metabolic markers of global CVD risk.

Figure 3: Factors contributing to global cardiometabolic risk
Cardiometabolic risk is the overall risk of CVD resulting from the presence of metabolic syndrome, as well as traditional risk factors and other unknown risk factors, including genetic factors that cannot be assessed in clinical practice. According to this model, metabolic syndrome does not replace the need to assess global CVD risk, but eventually has to be considered.[12]



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To date, there is insufficient evidence to support a proposal that the presence of clinical criteria for metabolic syndrome adds to global CVD risk. Additional prospective studies that consider measurements of sophisticated metabolic markers and abdominal visceral and subcutaneous adiposity have the potential to answer this important question. Once the results of these studies are available, the key questions, ie, what constitutes a high-risk abdominal obesity phenotype among various regions of the world, as well as what are the main determinants of risk in different populations, can be better addressed. However, a clear distinction must be made between metabolic syndrome as a "concept," and the criteria used in clinical practice to identify individuals with features of the metabolic syndrome.

Conclusion

Although insulin resistance is a key component of a constellation of metabolic abnormalities that increase the risk of type-2 diabetes and CVD, the most prevalent form of insulin resistance is associated with abdominal obesity and "dysfunctional" adipose tissue that cannot properly handle the energy surplus.[31] Initial indicators of high-risk abdominal obesity are an increased waist circumference, along with raised fasting plasma triacylglycerol concentrations.[23] To properly evaluate cardiovascular risk, physicians must first consider traditional CVD risk factors. Whether the presence of the clinical criteria for the metabolic syndrome increases the risk of CVD beyond that of traditional risk factors is not clear at this point in time and resolving this issue is crucial to the optimal assessment of global CVD risk.

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