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Jean-Pierre Després, Isabelle Lemieux, Jean Bergeron, Philippe Pibarot, Patrick Mathieu, Eric Larose, Josep Rodés-Cabau, Olivier F. Bertrand and Paul Poirier

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Metabolic Syndrome and Atherosclerosis

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Abdominal Obesity and the Metabolic Syndrome: Contribution to Global Cardiometabolic Risk

Jean-Pierre Després, Isabelle Lemieux, Jean Bergeron, Philippe Pibarot, Patrick Mathieu, Eric Larose, Josep Rodés-Cabau, Olivier F. Bertrand, Paul Poirier

Abstract—There is currently substantial confusion between the conceptual definition of the metabolic syndrome and the clinical screening parameters and cut-off values proposed by various organizations (NCEP-ATP III, IDF, WHO, etc) to identify individuals with the metabolic syndrome. Although it is clear that in vivo insulin resistance is a key abnormality associated with an atherogenic, prothrombotic, and inflammatory profile which has been named by some the “metabolic syndrome” or by others “syndrome X” or “insulin resistance syndrome”, it is more and more recognized that the most prevalent form of this constellation of metabolic abnormalities linked to insulin resistance is found in patients with abdominal obesity, especially with an excess of intra-abdominal or visceral adipose tissue. We have previously proposed that visceral obesity may represent a clinical intermediate phenotype reflecting the relative inability of subcutaneous adipose tissue to act as a protective metabolic sink for the clearance and storage of the extra energy derived from dietary triglycerides, leading to ectopic fat deposition in visceral adipose depots, skeletal muscle, liver, heart, etc. Thus, visceral obesity may partly be a marker of a dysmetabolic state and partly a cause of the metabolic syndrome. Although waist circumference is a better marker of abdominal fat accumulation than the body mass index, an elevated waistline alone is not sufficient to diagnose visceral obesity and we have proposed that an elevated fasting triglyceride concentration could represent, when waist circumference is increased, a simple clinical marker of excess visceral/ectopic fat. Finally, a clinical diagnosis of visceral obesity, insulin resistance, or of the metabolic syndrome is not sufficient to assess global risk of cardiovascular disease. To achieve this goal, physicians should first pay attention to the classical risk factors while also considering the additional risk resulting from the presence of abdominal obesity and the metabolic syndrome, such global risk being defined as cardiometabolic risk. (*Arterioscler Thromb Vasc Biol* 2008;28:1039-1049)

Key Words: global cardiometabolic risk ■ insulin resistance ■ metabolic syndrome ■ visceral obesity
■ waist circumference

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The Pioneer

In his seminal 1988 Banting award lecture, Reaven¹ proposed that insulin resistance was a fundamental “disorder” associated with a set of metabolic abnormalities which not only increased the risk of type 2 diabetes but also contributed to the development of cardiovascular disease (CVD) before the appearance of hyperglycemia. Reaven coined the term “syndrome X” to describe the clustering abnormalities associated with insulin resistance but since another syndrome X had been documented in cardiology,² the term insulin resistance syndrome became more frequently used to describe what should have been legitimately called the Reaven syndrome. It is also relevant to mention that as Reaven found insulin resistant individuals who were not obese, he did not include obesity as a feature of the insulin resistance syndrome.

Since the introduction of the syndrome X concept, a plethora of studies³⁻⁷ have shown that insulin resistance assessed by various methods is indeed a key factor associated with clustering atherogenic abnormalities which include a typical atherogenic dyslipidemic state (high triglyceride and apolipoprotein B concentrations, an increased proportion of small dense LDL particles and a reduced concentration of HDL-cholesterol, HDL particles also being smaller in size), a prothrombotic profile, and a state of inflammation (Figure 1). Furthermore, insulin resistance could also contribute to an elevated blood pressure⁸⁻¹¹ and to dysglycemia,^{6,12-14} eventually leading, among genetically susceptible individuals, to systemic hypertension and type 2 diabetes.

It is not the scope of this short review to deal with the question of whether or not it is insulin resistance or visceral obesity/ectopic fat which is the key primary culprit for the metabolic syndrome. Rather, the present article will propose that it is the mismanagement of energy under conditions of positive energy balance which leads to visceral/ectopic fat-insulin resistance and to features of the metabolic syndrome.

From Pathophysiology to Clinical Assessment

As most physicians cannot measure indices of insulin sensitivity in the context of their clinical practice, some organizations such as the World Health Organization (WHO),¹⁵ the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III),^{16,17} the European Group for the study of Insulin Resistance (EGIR),¹⁸ the American Association of Clinical Endocrinologists (AACE),¹⁹ and more recently the International Diabetes Federation (IDF)²⁰ have proposed to use simple clinical parameters with cut-off values to find individuals who would probably be insulin resistant and who would also show the atherogenic and diabetogenic abnormalities related to an impaired insulin action: the “metabolic syndrome” was born. However, it should be pointed out that there is no direct marker of insulin resistance in the NCEP-ATP III or IDF clinical criteria to diagnose the metabolic syndrome. Although patients diagnosed with the metabolic syndrome are likely to be more insulin resistant, there may be some discrepancies in the prevalence of insulin resistance depending on the metabolic syndrome clinical criteria used.

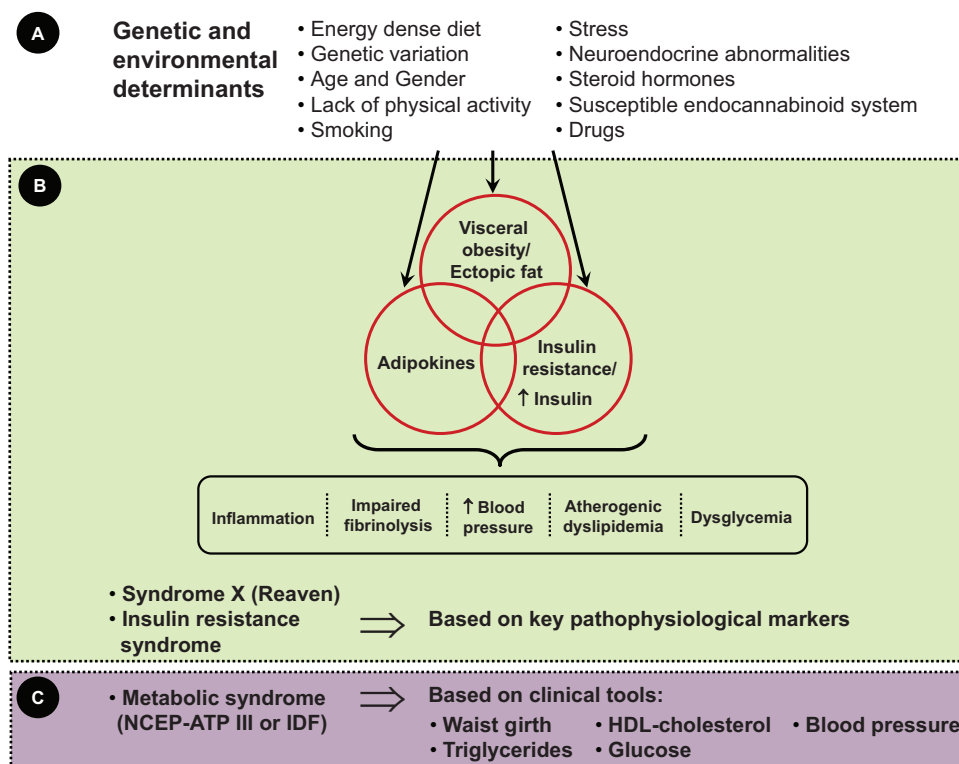


Figure 1. Simplified model illustrating the possible correlates (A) of insulin resistance often found among individuals with excess visceral/ectopic fat. Panel B emphasizes the notion that the syndrome X/insulin resistance syndrome concept was based on pathophysiological considerations, whereas panel C highlights the fact that National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) and International Diabetes Federation (IDF) metabolic syndrome is an entity identified in clinical practice by the presence of simple screening tools.

With the use of these simple criteria, investigators found that a clinical diagnosis of the metabolic syndrome (either by NCEP-ATP III or IDF criteria) was associated with an increased *relative* risk of CVD.^{21–31} However, the fact that the 5 variables proposed in NCEP-ATP III and IDF are not used as continuous variables in a proper risk calculator but rather counted as “present” or “absent” likely makes these screening tools less than perfect for the optimal diagnosis of the metabolic syndrome (“presence” or “absence” of an abnormality may be too crude to assess an individual risk profile or response to therapy). Furthermore, there is a mosaic of combinations of 3 of the 5 criteria which makes it very unlikely that all these subgroups are similar entities from a pathophysiological standpoint and clinical prognosis.³² One classic example of this problem is the case of type 2 diabetic patients who are hyperglycemic (by definition as they have diabetes) and who are also most often obese and hypertensive. Because they have 3 criteria, these patients with type 2 diabetes are diagnosed as having the metabolic syndrome. However, these patients with diabetes are likely to be metabolically quite distinct from nondiabetic but high triglyceride, low HDL-cholesterol dyslipidemic abdominally obese patients.³³ Under the current metabolic syndrome diagnosis tools, they are considered as a homogeneous entity, which is very unlikely. For instance, it is clear that an elevated fasting blood glucose concentration, which is often referred to as a “prediabetic” state, is more useful to predict type 2 diabetes risk than the other markers of the metabolic syndrome.^{28,34,35} Additional work is needed to clarify this issue and a global metabolic syndrome calculator with variables treated as continuous variables would help address this problem. Investigators have therefore raised the issue that better tools are needed to assess the clustering abnormalities of the metabolic syndrome and the severity of this condition and that only new metabolic syndrome calculators providing a continuous score will be able to address this question.³⁶

Metabolic Syndrome: Putting Abdominal Obesity on the Front Line

One key conceptual advance made, however, with the introduction of the metabolic syndrome as a clinically measurable (although imperfect) entity was the recognition of abdominal obesity as its most prevalent form,^{16,20,37,38} a notion still debated by Reaven nowadays.^{39,40} For instance, NCEP-ATP III made an index of abdominal adiposity (assessed by waist circumference) and not obesity (assessed by the body mass index [BMI]) as 1 of 5 criteria on which clinicians could diagnose the syndrome, the presence of 3 of the 5 criteria being required. However, the relationship of waist circumference to abdominal adiposity, especially visceral or intra-abdominal (the terms can be used interchangeably) obesity, is age- and gender- as well as ethnicity-dependent,^{41–44} and these issues were not properly addressed in the initial NCEP-ATP III guidelines. For instance, waist circumferences of 102 cm and 88 cm were average values corresponding to a BMI of 30 kg/m² in men and women, respectively.⁴⁵ There is clearly a continuous relationship between waist circumference and clinical outcomes, and these cut-off values are currently difficult to justify, especially if we consider that

women have, on average, more subcutaneous fat and less visceral fat than men.^{46,47} However, menopause is associated with a selective deposition of visceral fat, a phenomenon which again makes the single 88-cm value questionable.^{48–50} Regarding ethnicity, the IDF has recognized this problem and proposed to lower the waist circumference (which is a mandatory criterion in IDF) cut-offs for some ethnic groups.²⁰ However, the ethnic-specific waist cut-off values that they proposed were not always validated against direct imaging data of visceral fat and clinical outcomes, and further work is needed to define what is high-risk abdominal obesity in various populations of the world.

Abdominal Obesity and the Metabolic Syndrome: Too Much Visceral Adipose Tissue or a Marker of Ectopic Fat?

There is substantial evidence supporting the notion that too much abdominal fat is predictive of insulin resistance and of the presence of related metabolic abnormalities commonly referred to as the metabolic syndrome.^{51–63} Despite the fact that abdominal obesity is a highly prevalent feature of the metabolic syndrome, the mechanisms by which abdominal obesity is causally related to the metabolic syndrome are not fully understood. Imaging studies using measurements of abdominal adiposity (MRI and computed tomography) have generally reached the conclusion that it is the excess of intraabdominal or visceral adipose tissue and not the amount of subcutaneous abdominal fat which is the key correlate of the metabolic abnormalities observed in overweight/obese patients.^{3,51,54,56,57,64–68} For instance, individuals perfectly matched for subcutaneous abdominal adiposity but with either a low versus a high accumulation of visceral adipose tissue have been shown to be markedly different in their levels of insulin resistance and glucose tolerance.^{51,54,56,57,69} However, after being matched for visceral adiposity, individuals with low or high levels of subcutaneous fat were not found to differ in insulin sensitivity.^{56,57} This finding provides evidence that despite the fact that numerous studies have shown that weight, BMI, subcutaneous fat, and visceral fat are all well correlated with insulin resistance and with alterations in indices of plasma glucose-insulin homeostasis, it is the subgroup of overweight/obese patients with an excess of visceral fat that shows the most severe insulin resistant state. However, we have to keep in mind that subcutaneous fat is not neutral although it may represent a “metabolic sink”. Evidence suggests that if hyperplasia goes on in expanding adipose tissue, patients may not develop features of the metabolic syndrome, whereas, if it becomes hypertrophic in response to positive energy balance with a limited ability to expand, then it may become insulin resistant and also contribute to the dysmetabolic state.^{70–73}

However, these findings do not provide experimental evidence that visceral adiposity is causally related to insulin resistance. In a review article from our group³⁷ 3 scenarios have been proposed to explain the relation of visceral adiposity to the metabolic syndrome (Figure 2): (1) The hyperlipolytic state of the omental adipose tissue, which shows resistance to the action of insulin, contributes to expose (through the portal circulation) the liver to high

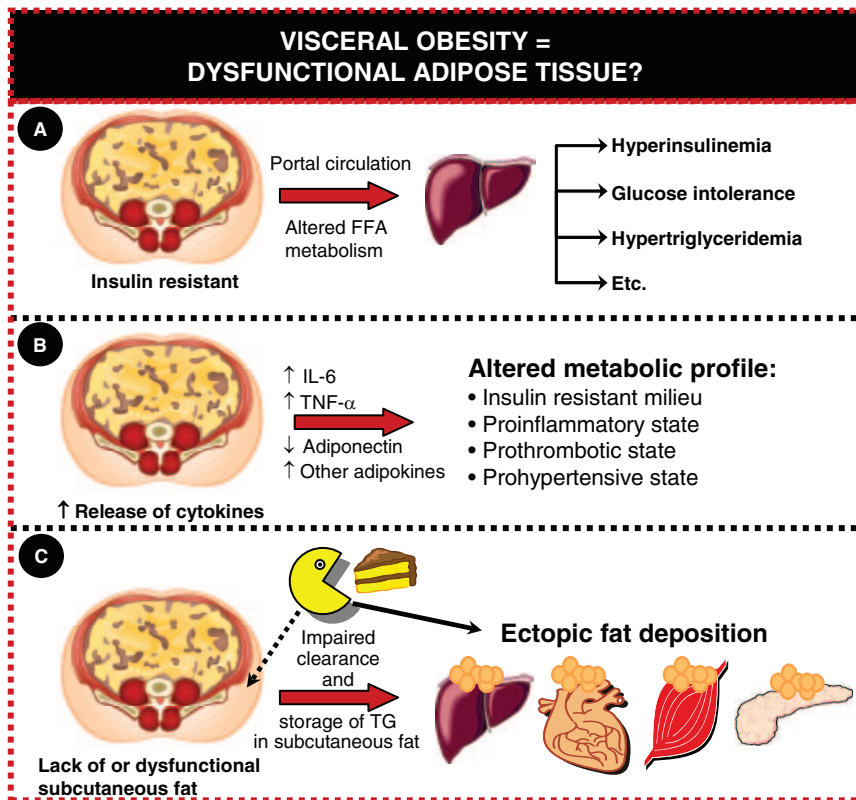


Figure 2. Proposed mechanisms by which visceral obesity, as the most dangerous form of obesity, could be linked to the athero-thrombotic-inflammatory abnormalities of insulin resistance. See text for further details. Apo indicates apolipoprotein; FFA, free fatty acids; IL-6, interleukin-6; TG, triglycerides; TNF- α , tumor necrosis factor- α .

concentrations of free fatty acids, impairing several hepatic metabolic processes leading to hyperinsulinemia (decreased insulin clearance), glucose intolerance (increased hepatic glucose production), and hypertriglyceridemia (increased VLDL-apolipoprotein B secretion); (2) The adipose tissue is a remarkable endocrine organ which is a source of adipokines like adiponectin and inflammatory cytokines such as interleukin (IL)-6 (IL-6) and tumor necrosis factor (TNF)- α (to only name a few) which contribute to the insulin resistant, proinflammatory, -thrombotic, and -hypertensive state of visceral obesity; (3) Excess visceral adiposity is only (or partly) a marker of the relative inability of subcutaneous adipose tissue to act as a protective metabolic sink because of its inability to expand (lipodystrophy) or because it has become hypertrophied, dysfunctional and insulin resistant. Under this third scenario, sedentary individuals who cannot store their energy surplus in the subcutaneous adipose tissue would be characterized by accumulation of fat at undesired sites such as the liver, the heart, the skeletal muscle, and the pancreas.

However, a more plausible explanation for the metabolic abnormalities of abdominal obesity is that all the above mechanisms are involved. An additional possibility is that a more primary neuroendocrine profile may channel excess energy both preferentially in the visceral depot and at undesired sites leading to visceral obesity, ectopic fat deposition, insulin resistance, and metabolic abnormalities.⁷⁴ In this regard, the remarkable change in both body fat distribution and metabolic profile of transsexual patients on hormonal therapy^{75,76} provides spectacular evidence that a certain neuroendocrine profile may represent a primary

abnormality leading to the development of ectopic fat and the metabolic syndrome.

Metabolic Syndrome Does Not Assess Global CVD Risk: The Notion of Cardiometabolic Risk

One key criticism addressed to the metabolic syndrome is that although numerous studies have shown that its presence is associated with an approximately 2-fold increase in CVD risk,^{21,22} such an increase in *relative* risk cannot evaluate *absolute* risk. Furthermore, reported relative CVD risks associated with the metabolic syndrome have not always taken into account confounding variables which makes the study comparisons rather difficult. For that purpose, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as well as the International Chair on Cardiometabolic Risk have emphasized the critical importance of first using global risk calculators such as the Framingham risk score, the PROCAM algorithm or the European SCORE.^{37,77,78} Once such global risk is estimated, one key question remains: does the diagnosis of the metabolic syndrome have an impact on coronary heart disease (CHD) risk once attention has been paid to the presence/absence of "traditional" risk factors? To provide a framework on which further discussions/debates could be conducted, the concept of global cardiometabolic risk has been proposed³⁷ (Figure 3). Under this model, cardiometabolic risk is the global risk of CVD resulting from the presence of traditional risk factors combined with the possible additional contribution of the metabolic syndrome. Under this working model, the metabolic syndrome cannot be used

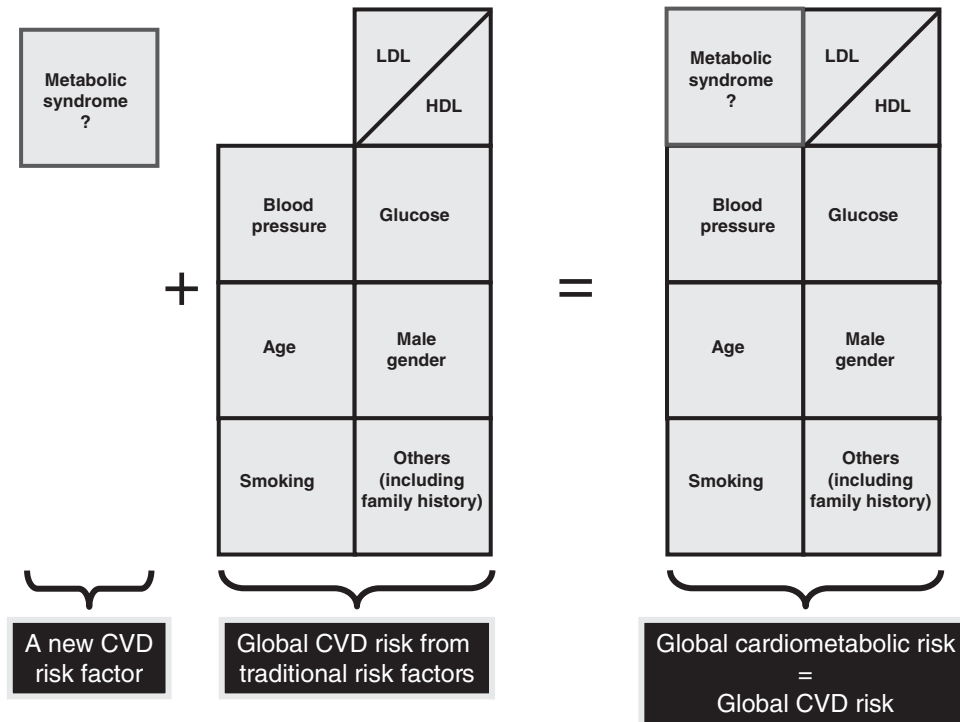


Figure 3. The “building blocks” of global cardiometabolic risk. Cardiometabolic risk is the overall risk of cardiovascular disease (CVD) resulting from the presence of the metabolic syndrome but also of traditional risk factors such as lipids (LDL and HDL), blood pressure, glucose, age, male gender, smoking, and other unknown risk factors (including genetic factors that cannot be assessed in clinical practice most of the time). Under this model, the metabolic syndrome does not replace the need to assess global CVD risk but may eventually have to be considered in global risk assessment. Whether the metabolic syndrome is an independent “building block” which significantly adds to global CVD risk assessed by traditional risk factors is uncertain and is highlighted by the question mark. Only additional prospective studies which will consider the measurement of sophisticated metabolic markers and of abdominal visceral and subcutaneous adiposity have the potential to answer this important question. Adapted from reference.³⁷

to assess global CVD risk but is at best one more modifiable CVD risk factor. It is important to point out that the Framingham risk score cannot equate to global cardiometabolic risk unless all the risk of the metabolic syndrome was captured by the Framingham algorithm, which is unlikely to be the case. Rather, Framingham captures the risk associated with traditional CVD risk factors such as type 2 diabetes, smoking, or LDL-cholesterol but it only takes into account some elements of the metabolic syndrome such as blood pressure and HDL-cholesterol. Thus, although it is very useful and important to use in clinical practice, we have proposed that the Framingham algorithm is not sufficient to adequately capture the additional risk related to the metabolic syndrome. In addition, the Framingham risk score does not properly assess lifetime risk particularly among young adults with abdominal obesity and the metabolic syndrome.⁷⁹ Thus, until we get answers on the importance of considering the metabolic syndrome in global CVD risk assessment, we should especially pay attention to young individuals with the metabolic syndrome who may not be considered at elevated risk of CVD because of their young age. Figure 3 also highlights a problem frequently flagged with the current clinical diagnosis of the metabolic syndrome because 3 of the 5 metabolic syndrome criteria are already considered by global risk assessment algorithms (HDL-cholesterol, blood pressure, and glucose). As the most prevalent form of the metabolic syndrome is observed among patients with excess

visceral adiposity/ectopic fat, and as we have proposed that the combination of elevated waist circumference and triglycerides was enough to screen for patients with an excess of visceral/ectopic fat and insulin resistance,⁸⁰ we believe that further attention should be given to add “hypertriglyceridemic waist” to the list of variables considered in global risk assessment algorithms.^{80,81} The importance of this simple clinical phenotype will be further addressed in later sections of this review.

Why Measuring Waist Circumference in Addition to the BMI?

It is well-documented that obesity is associated with insulin resistance.^{82–88} However, obesity is remarkably heterogeneous as some obese patients are insulin sensitive whereas others are insulin resistant.^{89–91} Even some massively obese patients show a normal plasma lipoprotein-lipid profile despite their very significant excess of body fat.^{92,93} It is with this heterogeneity in mind that measuring an index of abdominal adiposity such as the waist circumference is clinically relevant, as it allows the identification of subgroups of abdominally obese patients who are more likely to be insulin resistant. Nevertheless, some investigators have argued that because BMI and waist circumference are strongly correlated (Figure 4), measuring waist circumference provides little additional information over BMI.^{94–96} To fully address this question, however, it is important to keep in mind

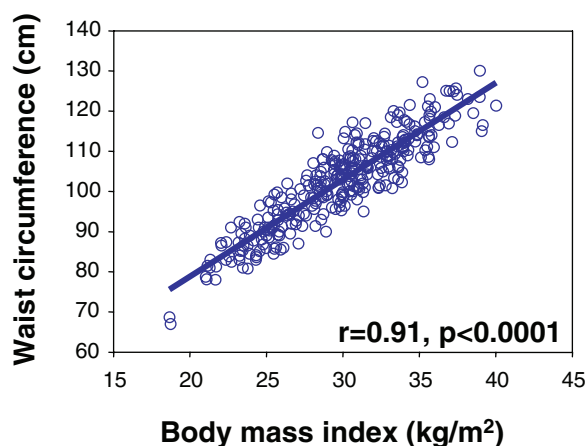


Figure 4. Relationship between waist circumference and the body mass index in men. The high correlation coefficient is explained by the fact that the sample includes lean to obese individuals. At any given body mass index, substantial individual variation in waist girth can be noted. Adapted from reference.¹²²

that when heterogeneous samples of lean to obese individuals are studied, correlation coefficients between BMI and waist girth will most often be above $r=0.80$. Such a strong correlation is no surprise: as we get bigger our waistline increases, otherwise very unusual body shapes will be noticed. Rather, the critically important question is whether or not, for any given BMI, variation in waist circumference affects whichever marker or correlate of insulin sensitivity. Investigators who have specifically examined this question, i.e. the impact of variation in waist girth for a given BMI, have generally reported that individuals with similar BMI values but with different waistlines had different metabolic risk profiles and showed differences in their risk of diabetes and CVD.^{97–100} In the landmark cross-sectional epidemiological study, INTERHEART, which compared myocardial infarction cases with asymptomatic controls, it was reported that an increased waist-to-hip circumference ratio, as a marker of the *relative* amount of abdominal fat, was associated with a significant increased risk of myocardial infarction.⁹⁷ More recently, investigators of the EPIC-Norfolk study reported the respective relationships of waist and hip circumferences to incidence of CHD over a follow-up of 9.1 years.¹⁰⁰ The authors reported that an increased waist circumference was associated with an elevated CHD risk, whereas a large hip girth appeared to protect against CHD after adjusting for confounding variables which included BMI.

Despite the importance given to waist circumference, it is relevant to point out that an elevated BMI is not a trivial phenotype with no risk. Rather, it should be made clear that an increased BMI is predictive of an increased probability of finding metabolic abnormalities. However, for any given BMI, assessing the location of excess body fat further refines the evaluation of the risk associated with overweight/obesity.¹⁰¹ Measuring waist circumference is therefore another step in refining the assessment of the patient's risk.¹⁰¹ However, as the relationship of waist girth to risk is linear,⁹⁹ there is no scientific or clinical rationale to propose a cut-off value to define abdominal obesity.

Without Measuring Waist Circumference, Can We Find Abdominally Obese, Insulin Resistant Patients With Features of the Metabolic Syndrome?

Despite these findings, skeptical clinicians may nevertheless prefer to pay attention to triglyceride and HDL-cholesterol levels to find obese patients with abdominal obesity. Thus, a question remains, why bother measuring waist girth if BMI and the high triglyceride, low HDL-cholesterol dyslipidemia allow us to find abdominally obese and insulin resistant patients? Because of the relationship between waist circumference and the BMI and as patients classified as obese from a BMI standpoint and who would also be characterized by the features of the metabolic syndrome are probably insulin resistant because they are abdominally obese, the presence of the high triglyceride, low HDL-cholesterol dyslipidemia in a patient with an elevated BMI could likely be the consequence of abdominal obesity. This situation is illustrated by analyses performed on the Québec Health Survey which studied a representative sample from Québec, Canada, aged from 18 to 74 years of age.¹⁰² Figure 5 shows that in both men and women, equally obese (from a BMI standpoint) individuals with or without high-triglyceride, low HDL-cholesterol levels were markedly different in their average waist circumference despite similar BMI values. These results derived from a population-based study clearly show the limitation of the BMI and the added values of measuring waist circumference to identify abdominally obese patients with the atherogenic dyslipidemia of the metabolic syndrome.

An Increased Waistline Does Not Always Mean High-Risk Abdominal Obesity

It is also important to mention that waist girth is not only a crude marker of abdominal adiposity, it is also largely influenced by the patient's total adiposity.¹⁰³ Thus, as mentioned above, the higher the BMI, the higher will generally be the waistline. However, although waist circumference is a fairly good correlate of the amount of total abdominal fat, it cannot distinguish visceral adiposity, an important correlate of metabolic abnormalities, from the amount of subcutaneous abdominal fat. Many studies have shown that subcutaneous obesity is causing less prejudice to the patient's metabolic profile whereas patients with an excess of visceral fat are characterized by the worst metabolic profile.^{3,51,54,56,57,64–68} Thus, the measurement of waist circumference alone cannot distinguish between subcutaneous and visceral obesity.

Hypertriglyceridemic Waist: Bringing Back Triglycerides to the Table of Risk Markers

The relevance of plasma triglyceride levels as a CHD risk marker has been debated for decades,^{104–107} although some recent studies have suggested that nonfasting triglyceride concentrations may be a useful marker of risk.^{108,109} As a simple initial screening approach to distinguish visceroally obese from subcutaneously obese patients, we have previously proposed that the simultaneous presence of fasting hypertriglyceridemia and of an increased waist circumference (hypertriglyceridemic waist) could represent a simple clinical

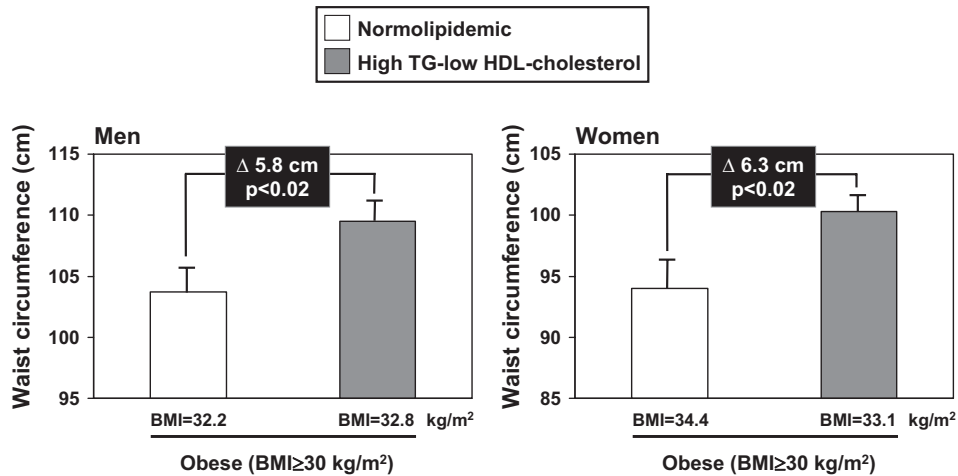


Figure 5. Differences in waist circumference values in obese women and men of the Québec Health Survey who had either a normal lipid profile (triglycerides (TG) <1.69 mmol/L and HDL-cholesterol \geq 1.03 mmol/L in men and \geq 1.29 mmol/L in women) or an atherogenic dyslipidemia (TG \geq 1.69 mmol/L and HDL-cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women). The average body mass index (BMI) for each obese group is also provided.

phenotype to identify patients with an excess of visceral adipose tissue, with ectopic fat and with the related features of the metabolic syndrome.⁸⁰ Cut-offs of 90 cm and 2.0 mmol/L in men⁸⁰ and of 85 cm and 1.5 mmol/L in women¹¹⁰ were proposed for the diagnosis of visceral obesity and metabolic syndrome in Europeans, and these cut-offs will have to be validated for other ethnic populations, in both genders and across different age groups. Later on, we proposed a mechanism by which plasma triglyceride levels could be a useful marker of visceral adiposity in the presence of a given waist circumference.¹¹¹ For instance, we have shown that obese women with a large accumulation of subcutaneous fat were characterized by a normal postprandial lipemia attributable to the fact that their subcutaneous fat depot could act as a protective metabolic sink storing with great efficiency the excess energy derived from dietary triglycerides.¹¹² However, we found that men with more visceral fat and less subcutaneous fat were characterized by marked postprandial hypertriglyceridemia and by a substantially delayed clearance of dietary triglycerides, visceraally obese men still being severely hypertriglyceridemic 8 hours after an oral fat load.¹¹² Thus, this retarded clearance of dietary triglycerides and the resulting hypertriglyceridemic state provide indirect evidence that the subcutaneous adipose tissue of visceraally obese individuals has a limited energy storage capacity which cannot handle the energy surplus, leading to the accumulation of fat at undesired sites such as the liver, the heart, the skeletal muscle, etc, a phenomenon referred to as ectopic fat deposition. Reviewing this evidence is beyond the scope of this brief review, but numerous studies have related insulin resistance and the features of the metabolic syndrome to excess liver fat, epicardial fat, and to an increased skeletal muscle content.^{113–116} Some investigators have even proposed that the metabolic abnormalities of visceral obesity may be largely explained by liver fat deposition.¹¹⁶ Under this model, we have proposed that there may be little causal relationship between excess visceral adiposity and metabolic abnormalities, visceral adiposity being simply a marker of ectopic fat.³⁷ There is, however, compelling evidence also linking excess visceral

adiposity to the features of the metabolic syndrome^{117,118} which led us to propose that visceral obesity is partly a cause of the dysmetabolic state of insulin resistance but also partly a good reliable feature of the clustering abnormalities of insulin resistance and the metabolic syndrome.

The Tale of the Tape: Is “Waist” Loss a Better Therapeutic Target?

As mentioned in the NCEP-ATP III guidelines,¹⁶ the concept of the metabolic syndrome was introduced mainly to emphasize the need for these patients to reshape their lifestyle, to eat better, and to be more physically active to lose weight. However, for the abdominally obese patient, available evidence suggests that weight loss may not always be able to detect favorable changes in the patient’s body composition in response to a physical activity/exercise program.¹¹⁹ For instance, patients losing a substantial amount of visceral fat (i.e. about 30% loss) but gaining some muscle mass because they have adopted a physically active lifestyle could be disappointed by trivial changes in their body weight. Such lack of substantial change in body weight could leave both the patient and the physician perplexed as the metabolic risk profile may nevertheless substantially improve. In this regard, in our lifestyle modification program conducted at the Québec Heart Institute, we have found cases of patients reducing their waist circumference by 5 to 6 cm despite little changes in body weight (Figure 6). Despite the lack of change in body weight, the metabolic profile of these patients was improved as they had lost a substantial amount of visceral fat. For that reason, there is a clear advantage of following-up changes in waist circumference in addition to weight loss in response to a lifestyle modification program. Thus, reducing waist circumference may represent a more useful and clinically relevant therapeutic target than weight loss.

Syndrome X, Insulin Resistance or the Metabolic Syndrome? From Confusion to Concerted Action

From the plethora of epidemiological, metabolic, and clinical studies published over more than 2 decades, it is clear that

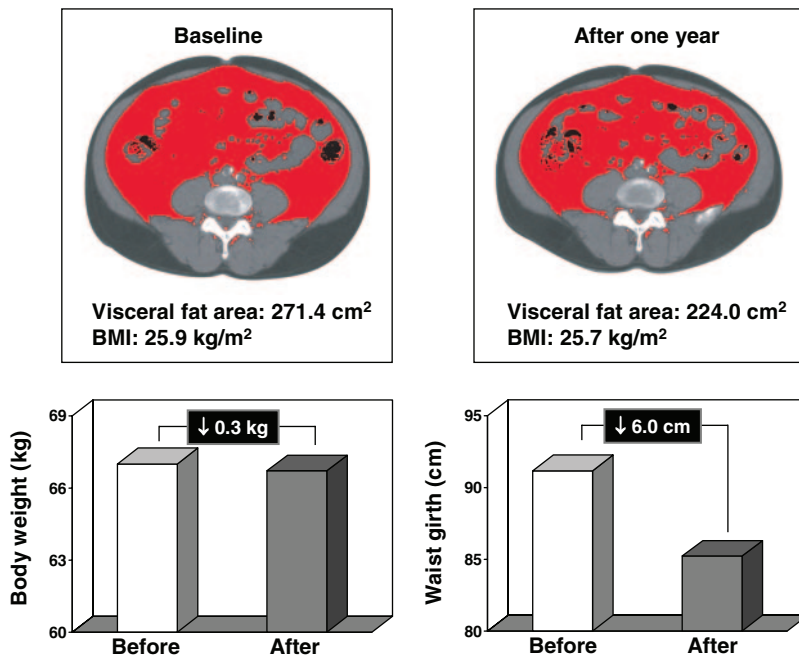


Figure 6. Illustration of the response of a viscerally obese man involved in a 1-year lifestyle modification program at the Québec Heart Institute. Despite the fact that this patient has apparently lost only 0.3 kg, he has reduced his waist girth by 6 cm, such reduction being accompanied by a substantial loss of visceral adipose tissue (17.5%). These findings emphasize the critical importance of assessing changes in waist circumference in addition to body weight.

investigators who have used measurements of insulin resistance or crude screening approaches for the clinical diagnosis of the so-called “metabolic syndrome” such as those proposed by NCEP-ATP III, IDF or the simple “hypertriglyceridemic waist” phenotype have all been able to identify subgroups of patients at greater risk of type 2 diabetes and at increased *relative* risk of CHD. However, none of these approaches can properly assess global CVD risk. As already mentioned by other investigators, populations identified by these different criteria largely overlap¹⁷ but also include subgroups of individuals who are partly distinct from each other depending on the assessment approach used. For instance, unpublished data from our research group revealed that a large proportion of men with the hypertriglyceridemic waist phenotype also met NCEP-ATP III (82.7%) or IDF criteria (89.2%). Investigators actively pursue their quest for a better understanding of primary factors leading to insulin resistance, visceral obesity/ectopic fat, and the development of a constellation of atherothrombotic and inflammatory metabolic abnormalities. Should this constellation be called syndrome X, the Reaven syndrome, the insulin resistance syndrome, the metabolic syndrome, or simply visceral obesity/ectopic fat? Ultimately, what do we need to measure in clinical practice to capture the additional risk associated with insulin resistance? Do we need to obtain an index of insulin resistance in clinical practice? How will it be integrated into our current CHD risk algorithm? Will it be better than our crude assessment of the metabolic syndrome which does not use sophisticated metabolic markers? Do we need to develop new risk calculators that will use risk markers/factors as continuous variables? If so, which markers will be ready for prime time: insulin, apolipoprotein B, LDL size, C-reactive protein, adiponectin, to only name a few of them? Will these calculators be user friendly and simple enough to allow their widespread use in clinical practice? Will they incorporate consideration for “normal” versus “abnormal” values so that

physicians can identify clinically relevant therapeutic targets? Will it be possible to adapt our algorithms developed in the adult population to better screen younger individuals including children? What about the increasing subgroup of elderly patients? We have evidence that abdominal obesity remains a significant risk factor in this population as well.^{120,121} However, is the impact of abdominal obesity attenuated in the geriatric population because of the survival bias? Can we develop proper risk calculators for older adults as well?

Therefore, many issues remain to be addressed. Meanwhile, the introduction of the concept of insulin resistance (based on pathophysiology) and of the metabolic syndrome (based on diagnosis tools; Figure 1) should be considered as attempts to put a greater focus on new emerging causes of premature CHD: a sedentary lifestyle and consumption of an energy dense diet leading to insulin resistance, its most prevalent form being visceral obesity/ectopic fat. Thus, whether patients are diagnosed as being insulin resistant, with a “metabolic syndrome” or “viscerally obese” depend on the tools that are used to assess their condition. A clinical diagnosis of insulin resistance, metabolic syndrome, or of visceral obesity should spur some action and clear recommendations to the patient. He/she needs to recalibrate his/her physical activity and nutritional habits to lose weight (especially some abdominal fat) and improve his/her insulin sensitivity, which will be the cornerstone of therapy. This is certainly the greatest merit of these concepts. Although debating about semantics is relevant in academic circles, physicians and their patients should no longer be confused. It is time for diabetologists, cardiologists, internists, “obesologists”, lipidologists, nephrologists, hypertension experts, nutritionists, exercise physiologists, and other relevant health care professionals to join forces in our fight against the “toxic” environment of our patients. We have gone a long way with the pharmacological management of systemic hypertension, dyslipidemia, and diabetes, but the residual risk

of treated patients remains elevated if we do not deal with the additional features of what was initially called syndrome X and now often referred to as the metabolic syndrome. While we continue to work on improving our assessment and management of global CVD risk, let's all agree that it is time for less confusion and more concerted action.

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Correction

In the article “Abdominal Obesity and the Metabolic Syndrome: Contribution to Global Cardiometabolic Risk” by Després et al, which appeared in the June 2008 issue of the journal (*Arterioscler Thromb Vasc Biol.* 2008;28:1039–1049), Figure 1 needs a correction:

There should be a blue bar in Figure 1A. Please see the revised figure below.

The publisher regrets this error.

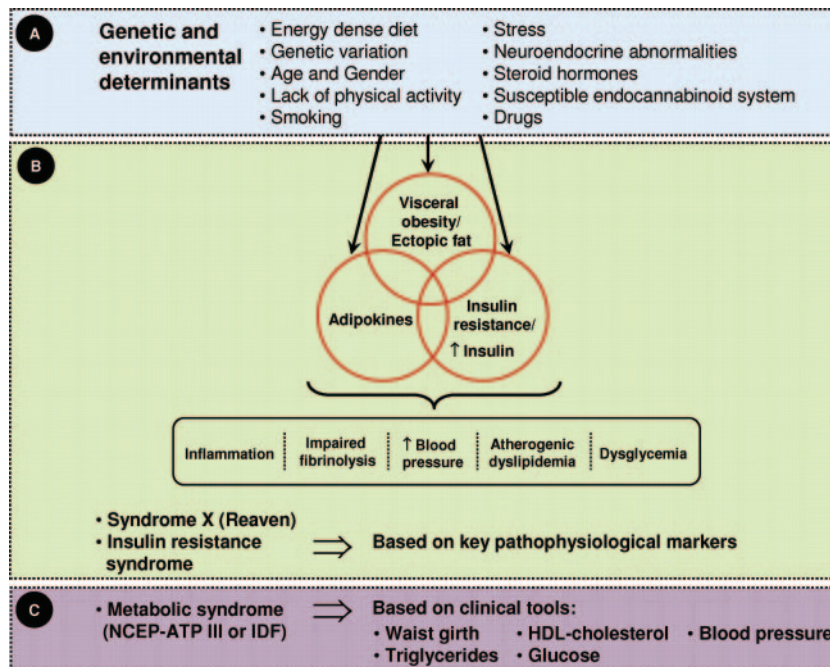


Figure 1.