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

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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

The Pioneer

In his seminal 1988 Banting award lecture, Reaven[1] 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 studies[3–7] 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 pressure[8–11] 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.
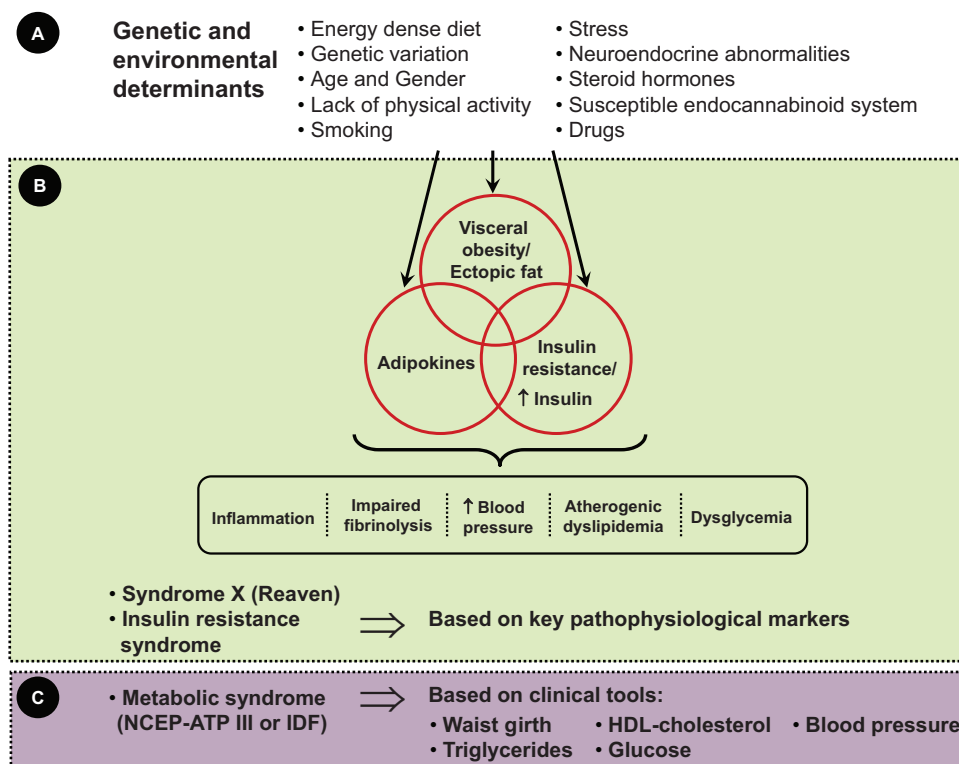
Figure 1. Simplified model illustrating the possible correlates (A) of insulin resistance often found among individuals with excess visceral/ectopic fat. Panel B emphasizes the notion that the syndrome X/insulin resistance syndrome concept was based on pathophysiological considerations, whereas panel C highlights the fact that National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) and Arteriosclerosis 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 intraabdominal (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/m^2 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 group[37] 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
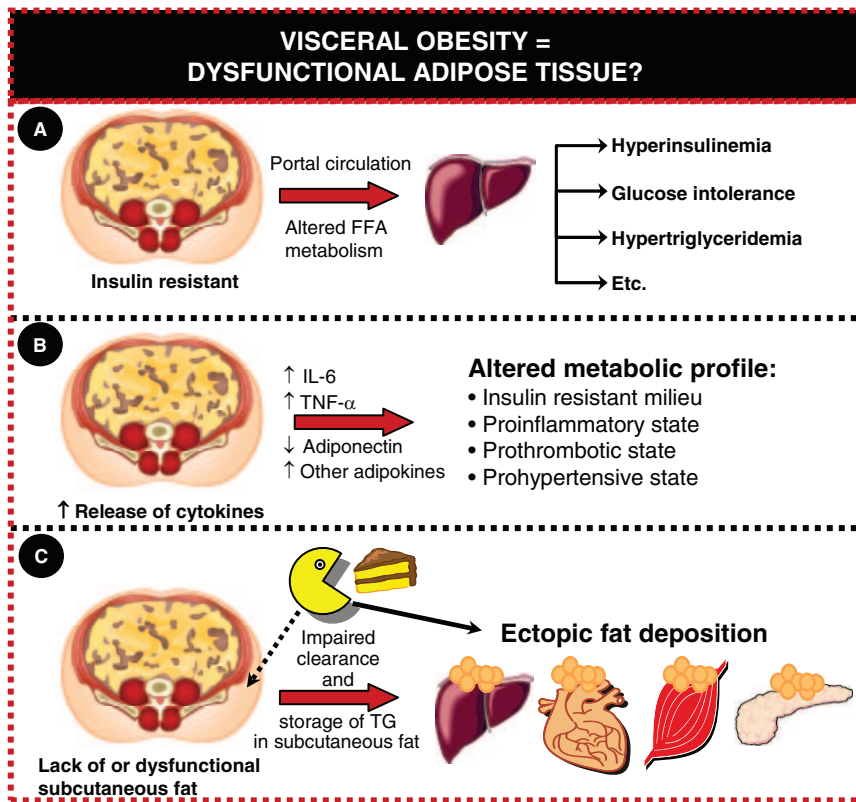
Figure 2. Proposed mechanisms by which visceral obesity, as the most dangerous form of obesity, could be linked to the athero-thrombotic-inflammatory abnormalities of insulin resistance. See text for further details. Apo indicates apolipoprotein; FFA, free fatty acids; IL-6, interleukin-6; TG, triglycerides; 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 proposed[37] (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
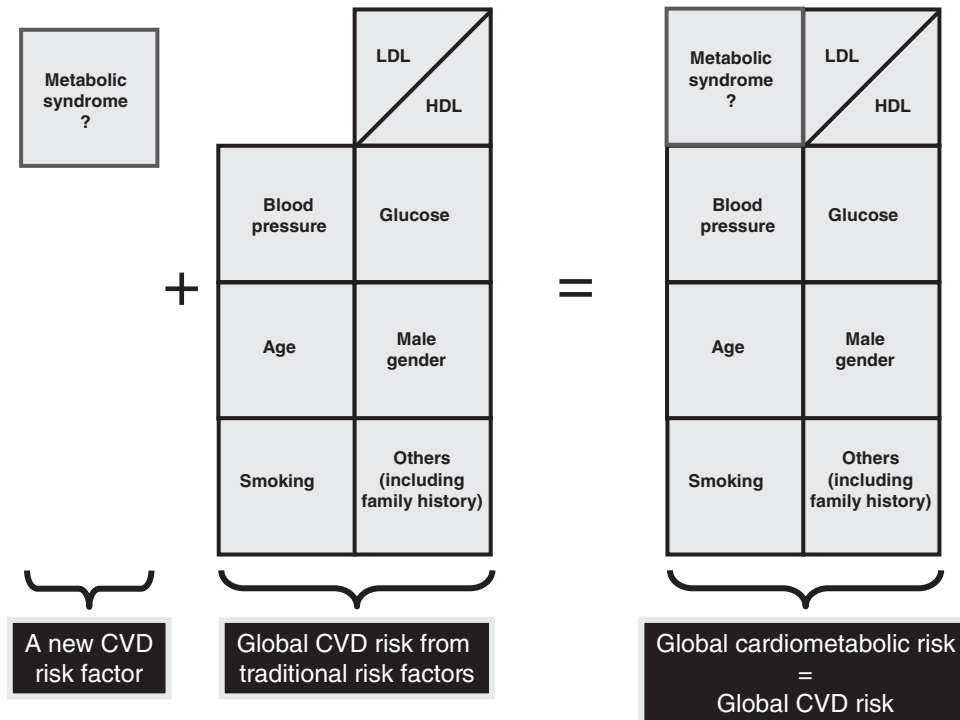
Figure 3. The "building blocks" of global cardiometabolic risk. Cardiometabolic risk is the overall risk of cardiovascular disease (CVD) resulting from the presence of the metabolic syndrome but also of traditional risk factors such as lipids (LDL and HDL), blood pressure, glucose, age, male gender, 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
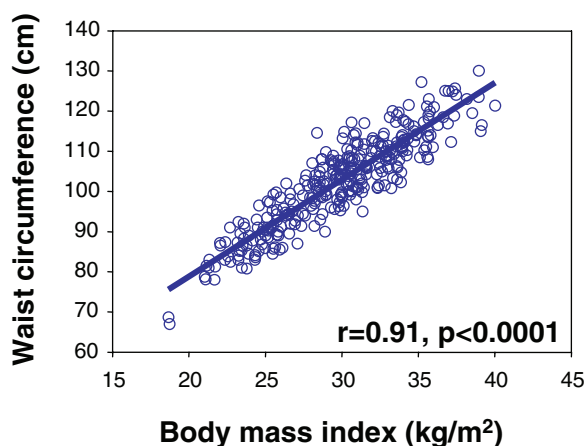
Figure 4. Relationship between waist circumference and the body mass index in men. The high correlation coefficient is explained by the fact that the sample includes lean to obese individuals. At any given body mass index, substantial individual variation in waist girth can be noted. Adapted from reference.[122]

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 viscerally 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
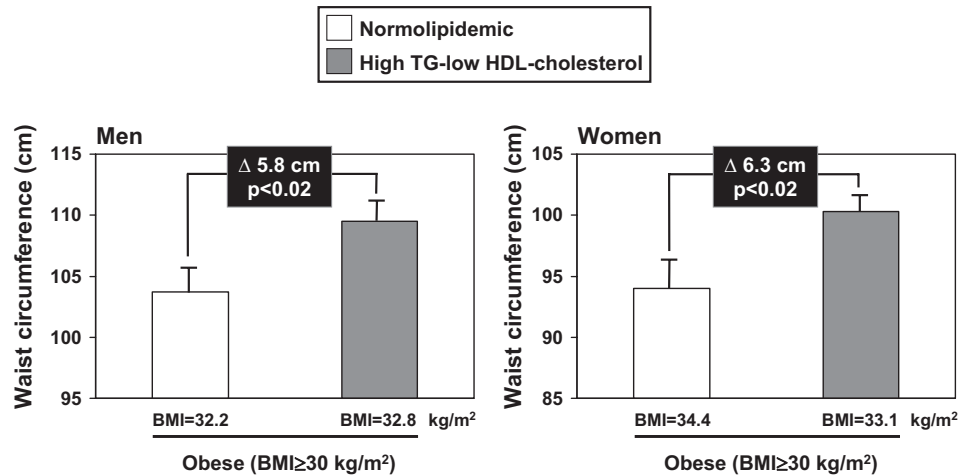
Figure 5. Differences in waist circumference values in obese women and men of the Québec Health Survey who had either a normal lipid profile (triglycerides (TG) <1.69 mmol/L and HDL-cholesterol ≥1.03 mmol/L in men and ≥1.29 mmol/L in women) or an atherogenic dyslipidemia (TG ≥1.69 mmol/L and HDL-cholesterol <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 men[80] and of 85 cm and 1.5 mmol/L in women[110] were proposed for the diagnosis of visceral obesity and metabolic syndrome in Europids, 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, viscerally 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 viscerally 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
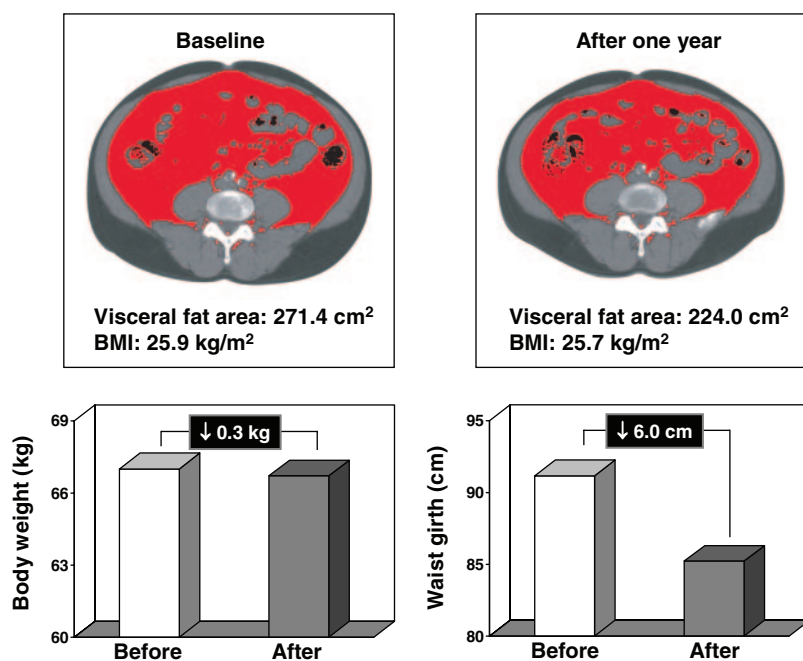
Figure 6. Illustration of the response of a viscerally obese man involved in a 1-year lifestyle modification program at the Québec Heart Institute. Despite the fact that this patient has apparently lost only 0.3 kg, he has reduced his waist girth by 6 cm, such reduction being accompanied by a substantial 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 overlap[17] 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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Disclosures

References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
2. Cheng TO. Cardiac syndrome X versus metabolic syndrome X. *Int J Cardiol*. 2007;119:137–138.
3. Després JP. Is visceral obesity the cause of the metabolic syndrome? *Ann Med*. 2006;38:52–63.
4. Zimmet P, Boyko EJ, Collier GR, de Courten M. Etiology of the metabolic syndrome: potential role of insulin resistance, leptin resistance, and other players. *Ann N Y Acad Sci*. 1999;892:25–44.
5. Grundy SM. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol*. 1999;83:25F–29F.
6. DeFronzo RA, Ferrannini E. Insulin resistance: A multifaced syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173–194.
7. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S. Insulin resistance in essential hypertension. *N Engl J Med*. 1987;317:350–357.
8. Welborn TA, Breckenridge A, Rubinstein AH, Dollery CT, Fraser TR. Serum-insulin in essential hypertension and in peripheral vascular disease. *Lancet*. 1966;1:1336–1337.
9. Saad MF, Rewers M, Selby J, Howard G, Jinagouda S, Fahmi S, Zaccaro D, Bergman RN, Savage PJ, Haffner SM. Insulin resistance and hypertension: the Insulin Resistance Atherosclerosis study. *Hypertension*. 2004; 43:1324–1331.
10. Lin MW, Hwu CM, Huang YH, Sheu WH, Shih KC, Chiang FT, Olshen R, Chen YD, Curb JD, Rodriguez B, Ho LT. Directly measured insulin resistance and the assessment of clustered cardiovascular risks in hypertension. *Am J Hypertens*. 2006;19:1118–1124.
11. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities–the role of insulin resistance and the sympathoadrenal system. *N Engl J Med*. 1996;334:374–381.
12. Belfiore F, Iannello S, Camuto M, Fagone S, Cavaleri A. Insulin sensitivity of blood glucose versus insulin sensitivity of blood free fatty acids in normal, obese, and obese-diabetic subjects. *Metabolism*. 2001; 50:573–582.
13. Reaven GM. Pathophysiology of insulin resistance in human disease. *Physiol Rev*. 1995;75:473–486.
14. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia*. 2003;46:3–19.
15. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
16. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
17. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–2752.
18. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med*. 1999;16:442–443.
19. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9:237–252.
20. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome–a new worldwide definition. *Lancet*. 2005;366:1059–1062.
21. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med*. 2006;119:812–819.
22. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403–414.
23. Girman CJ, Rhodes T, Mercuri M, Pyorala K, Kjekshus J, Pedersen TR, Beere PA, Gotto AM, Clearfield M. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol*. 2004;93:136–141.
24. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation*. 2004;110:1251–1257.
25. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. *Arch Intern Med*. 2004;164: 1092–1097.
26. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
27. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reillly DS, Haffner SM, Isles C, Macfarlan PW, Packard CJ, Cobbe SM, Shepherd J. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003;108:414–419.
28. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112:3066–3072.
29. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683–689.
30. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288: 2709–2716.
31. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Bonadonna RC, Muggeo M. Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: prospective data from the Bruneck study. *Diabetes Care*. 2003;26:1251–1257.
32. Marquis K, Maltais F, Duguay V, Bezeau AM, LeBlanc P, Jobin J, Poirier P. The metabolic syndrome in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil*. 25:226–232, 2005; discussion 233–234.
33. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52:1210–1214.
34. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in beaver dam. *Diabetes Care*. 2002;25:1790–1794.
35. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the met-

abolic syndrome in a prospective cohort study. *Am J Epidemiol*. 2002;156:1070–1077.

36. Sattar N. The metabolic syndrome: should current criteria influence clinical practice? *Curr Opin Lipidol*. 2006;17:404–411.

37. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444:881–887.

38. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109:433–438.

39. Reaven GM. The individual components of the metabolic syndrome: is there a raison d'etre? *J Am Coll Nutr*. 2007;26:191–195.

40. Reaven GM. The metabolic syndrome: requiescat in pace. *Clin Chem*. 2005;51:931–938.

41. Han TS, McNeill G, Seidell JC, Lean ME. Predicting intra-abdominal fatness from anthropometric measures: the influence of stature. *Int J Obes Relat Metab Disord*. 1997;21:587–593.

42. Lemieux S, Prud'homme D, Nadeau A, Tremblay A, Bouchard C, Després JP. Seven-year changes in body fat and visceral adipose tissue in women. Association with indexes of plasma glucose-insulin homeostasis. *Diabetes Care*. 1996;19:983–991.

43. Després JP, Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. *Arterioscler Thromb Vasc Biol*. 2000;20:1932–1938.

44. Misra A, Wasir JS, Vikram NK. Waist circumference criteria for the diagnosis of abdominal obesity are not applicable uniformly to all populations and ethnic groups. *Nutrition*. 2005;21:969–976.

45. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ*. 1995;311:158–161.

46. Kvist H, Sjöström L, Tylen U. Adipose tissue volume determinations in women by computed tomography: technical considerations. *Int J Obes*. 1986;10:53–67.

47. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Després JP. Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr*. 1993;58:463–467.

48. Kotani K, Tokunaga K, Fujioka S, Kobatake T, Keno Y, Yoshida S, Shimomura I, Tarui S, Matsuzawa Y. Sexual dimorphism of age-related changes in whole-body fat distribution in the obese. *Int J Obes Relat Metab Disord*. 1994;18:207–212.

49. Zamboni M, Armellini F, Milani MP, De Marchi M, Todesco T, Robbi R, Bergamo-Andreis IA, Bosello O. Body fat distribution in pre- and post-menopausal women: metabolic and anthropometric variables and their inter-relationships. *Int J Obes Relat Metab Disord*. 1992;16:495–504.

50. Toth MJ, Sites CK, Eltabbakh GH, Poehlman ET. Effect of menopausal status on insulin-stimulated glucose disposal: comparison of middle-aged premenopausal and early postmenopausal women. *Diabetes Care*. 2000;23:801–806.

51. Després JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis*. 1990;10:497–511.

52. Lemieux I, Pascot A, Prud'homme D, Alméras N, Bogaty P, Nadeau A, Bergeron J, Després JP. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol*. 2001;21:961–967.

53. Pascot A, Lemieux I, Prud'homme D, Tremblay A, Nadeau A, Couillard C, Bergeron J, Lamarche B, Després JP. Reduced HDL particle size as an additional feature of the atherogenic dyslipidemia of abdominal obesity. *J Lipid Res*. 2001;42:2007–2014.

54. Pouliot MC, Després JP, Nadeau A, Moorjani S, Prud'homme D, Lupien PJ, Tremblay A, Bouchard C. Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. *Diabetes*. 1992;41:826–834.

55. Tchernof A, Lamarche B, Prud'homme D, Nadeau A, Moorjani S, Labrie F, Lupien PJ, Després JP. The dense LDL phenotype. Association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. *Diabetes Care*. 1996;19:629–637.

56. Ross R, Aru J, Freeman J, Hudson R, Janssen I. Abdominal adiposity and insulin resistance in obese men. *Am J Physiol Endocrinol Metab*. 2002;282:E657–E663.

57. Ross R, Freeman J, Hudson R, Janssen I. Abdominal obesity, muscle composition, and insulin resistance in premenopausal women. *J Clin Endocrinol Metab*. 2002;87:5044–5051.

58. Mertens I, Van der Planken M, Corthouts B, Van Gaal LF. Is visceral adipose tissue a determinant of von Willebrand factor in overweight and obese premenopausal women? *Metabolism*. 2006;55:650–655.

59. Brunzell JD, Hokanson JE. Dyslipidemia of central obesity and insulin resistance. *Diabetes Care*. 1999;22 Suppl 3:C10–C13.

60. Nieves DJ, Cnop M, Retzlaff B, Walden CE, Brunzell JD, Knopp RH, Kahn SE. The atherogenic lipoprotein profile associated with obesity and insulin resistance is largely attributable to intra-abdominal fat. *Diabetes*. 2003;52:172–179.

61. Boyko EJ, Leonetti DL, Bergstrom RW, Newell-Morris L, Fujimoto WY. Visceral adiposity, fasting plasma insulin, and lipid and lipoprotein levels in Japanese Americans. *Int J Obes Relat Metab Disord*. 1996;20:801–808.

62. Lebovitz HE, Banerji MA. Point: visceral adiposity is causally related to insulin resistance. *Diabetes Care*. 2005;28:2322–2325.

63. Björntorp P. Visceral obesity:a "civilization syndrome". *Obes Res*. 1993;1:206–222.

64. Björntorp P. Metabolic implications of body fat distribution. *Diabetes Care*. 1991;14:1132–1143.

65. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB, Schwartz AV, Kritchevsky S, Newman AB. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care*. 2003;26:372–379.

66. Kissebah AH, Krakower GR. Regional adiposity and morbidity. *Physiol Rev*. 1994;74:761–811.

67. Matsuzawa Y, Shimomura I, Nakamura T, Keno Y, Kotani K, Tokunaga K. Pathophysiology and pathogenesis of visceral fat obesity. *Obes Res*. 1995;3 Suppl 2:187S–194S.

68. Nielsen S, Jensen MD. Obesity and cardiovascular disease: is body structure a factor? *Curr Opin Lipidol*. 1997;8:200–204.

69. Bacha F, Saad R, Gungor N, Janosky J, Arslanian SA. Obesity, regional fat distribution, and syndrome X in obese black versus white adolescents: race differential in diabetogenic and atherogenic risk factors. *J Clin Endocrinol Metab*. 2003;88:2534–2540.

70. Björntorp P, Bengtsson C, Blohme G, Jonsson A, Sjostrom L, Tibblin E, Tibblin G, Wilhelmsen L. Adipose tissue fat cell size and number in relation to metabolism in randomly selected middle-aged men and women. *Metabolism*. 1971;20:927–935.

71. Krotkiewski M, Björntorp P, Sjöström L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest*. 1983;72:1150–1162.

72. Tchoukalova YD, Koutsari C, Karpyak MV, Votruba SB, Wendland E, Jensen MD. Subcutaneous adipocyte size and body fat distribution. *Am J Clin Nutr*. 2008;87:56–63.

73. Adams M, Montague CT, Prins JB, Holder JC, Smith SA, Sanders L, Digby JE, Sewter CP, Lazar MA, Chatterjee VK, O'Rahilly S. Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. *J Clin Invest*. 1997;100:3149–3153.

74. Björntorp P. Visceral fat accumulation: the missing link between psychosocial factors and cardiovascular disease? *J Intern Med*. 1991;230:195–201.

75. Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, Gooren LJ. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. *Clin Endocrinol (Oxf)*. 2003;58:562–571.

76. Elbers JM, Asscheman H, Seidell JC, Gooren LJ. Effects of sex steroid hormones on regional fat depots as assessed by magnetic resonance imaging in transsexuals. *Am J Physiol*. 1999;276:E317–E325.

77. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2005;28:2289–2304.

78. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.

79. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *J Clin Endocrinol Metab*. 2007;92:399–404.

80. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Alméras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Després JP. Hypertriglyceridemic waist. A marker of the atherogenic metabolic

triad (hyperinsulinemia, hyperapolipoprotein B, small, dense LDL) in men? *Circulation*. 2000;102:179–184.

81. Lemieux I, Poirier P, Bergeron J, Alméras N, Lamarche B, Cantin B, Dagenais GR, Després JP. Hypertriglyceridemic waist: A useful screening phenotype in preventive cardiology? *Can J Cardiol*. 2007;23: 23B–31B.

82. O'Rahilly S. Human obesity and insulin resistance: lessons from experiments of nature. *Biochem Soc Trans*. 2007;35:33–36.

83. Abate N, Garg A, Peshock RM, Stray Gundersen J, Adams Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes*. 1996;45:1684–1693.

84. Berglund G, Ljungman S, Hartford M, Wilhelmsen L, Bjorntorp P. Type of obesity and blood pressure. *Hypertension*. 1982;4:692–696.

85. DeFronzo RA. The effect of insulin on renal sodium metabolism. A review with clinical implications. *Diabetologia*. 1981;21:165–171.

86. Bonadonna RC, Groop L, Kraemer N, Ferrannini E, Del Prato S, DeFronzo RA. Obesity and insulin resistance in humans: a dose-response study. *Metabolism*. 1990;39:452–459.

87. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol*. 1985;248:E286–E291.

88. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). *J Clin Invest*. 1997;100: 1166–1173.

89. Abbasi F, Brown BW Jr, Lamendola C, McLaughlin T, Reaven GM. Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol*. 2002;40:937–943.

90. Reaven G, Abbasi F, McLaughlin T. Obesity, insulin resistance, and cardiovascular disease. *Recent Prog Horm Res*. 2004;59:207–223.

91. Reaven GM. The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr*. 2006;83:1237–1247.

92. Drapeau V, Lemieux I, Richard D, Bergeron J, Tremblay A, Biron S, Marceau P, Mauriège P. Metabolic profile in severely obese women is less deteriorated than expected when compared to moderately obese women. *Obes Surg*. 2006;16:501–509.

93. Lemieux I, Drapeau V, Richard D, Bergeron J, Marceau P, Biron S, Mauriège P. Waist girth does not predict metabolic complications in severely obese men. *Diabetes Care*. 2006;29:1417–1419.

94. Bouchard C. BMI, fat mass, abdominal adiposity and visceral fat: where is the 'beef'? *Int J Obes (Lond)*. 2007;31:1552–1553.

95. Farin HM, Abbasi F, Reaven GM. Body mass index and waist circumference correlate to the same degree with insulin-mediated glucose uptake. *Metabolism*. 2005;54:1323–1328.

96. Kiernan M, Winkleby MA. Identifying patients for weight-loss treatment: an empirical evaluation of the NHLBI obesity education initiative expert panel treatment recommendations. *Arch Intern Med*. 2000;160:2169–2176.

97. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 2005;366:1640–1649.

98. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE. Abdominal adiposity and coronary heart disease in women. *JAMA*. 1998;280:1843–1848.

99. Balkau B, Deanfield JE, Després JP, Bassand JP, Fox KA, Smith SC Jr, Barter P, Tan CE, Van Gaal L, Wittchen HU, Massien C, Haffner SM. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation*. 2007;116:1942–1951.

100. Canoy D, Boekholdt SM, Wareham N, Luben R, Welch A, Bingham S, Buchan I, Day N, Khaw KT. Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk cohort: a population-based prospective study. *Circulation*. 2007;116:2933–2943.

101. Poirier P. Adiposity and cardiovascular disease: are we using the right definition of obesity? *Eur Heart J*. 2007;28:2047–2048.

102. Lemieux I, Alméras N, Mauriège P, Blanchet C, Dewailly E, Bergeron J, Després JP. Prevalence of "hypertriglyceridemic waist" in men who participated in the Quebec Health Survey: association with atherogenic and diabetogenic metabolic risk factors. *Can J Cardiol*. 2002;18: 725–732.

103. Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol*. 1994;73:460–468.

104. Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decision: the association between triglyceride and coronary heart disease. *N Engl J Med*. 1980;302:1383–1389.

105. Brunzell JD. Clinical practice. Hypertriglyceridemia. *N Engl J Med*. 2007;357:1009–1017.

106. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb Vasc Biol*. 1991;11:2–14.

107. Criqui MH, Heiss G, Cohn R, Cowan LD, al. e. Plasma triglyceride level and mortality from coronary heart disease. *N Engl J Med*. 1993;328: 1220–1225.

108. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309–316.

109. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308.

110. Blackburn P, Lemieux I, Lamarche B, Bergeron J, Perron P, Tremblay G, Gaudet D, Després JP. Type 2 diabetes without the atherogenic metabolic triad does not predict angiographically assessed coronary artery disease in women. *Diabetes Care*. 2008;31:170–172.

111. Lemieux I. Energy partitioning in gluteal-femoral fat: does the metabolic fate of triglycerides affect coronary heart disease risk? *Arterioscler Thromb Vasc Biol*. 2004;24:795–797.

112. Couillard C, Bergeron N, Prud'homme D, Bergeron J, Tremblay A, Bouchard C, Mauriège P, Després JP. Gender difference in postprandial lipemia: importance of visceral adipose tissue accumulation. *Arterioscler Thromb Vasc Biol*. 1999;19:2448–2455.

113. Ravussin E, Smith SR. Increased fat intake, impaired fat oxidation, and failure of fat cell proliferation result in ectopic fat storage, insulin resistance, and type 2 diabetes mellitus. *Ann N Y Acad Sci*. 2002;967: 363–378.

114. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med*. 2005;2:536–543.

115. Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. *Int J Obes Relat Metab Disord*. 2004;28 Suppl 4:S58–S65.

116. Kotronen A, Yki-Jarvinen H. Fatty liver: a novel component of the metabolic syndrome. *Arterioscler Thromb Vasc Biol*. 2008;28:27–38.

117. Bergman RN. Orchestration of glucose homeostasis: from a small acorn to the California oak. *Diabetes*. 2007;56:1489–1501.

118. Tchernof A. Visceral adipocytes and the metabolic syndrome. *Nutr Rev*. 2007;65:S24–S29.

119. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. *Ann Intern Med*. 2000;133:92–103.

120. Ostlund RE Jr, Staten M, Kohrt WM, Schultz J, Malley M. The ratio of waist-to-hip circumference, plasma insulin level, and glucose intolerance as independent predictors of the HDL2 cholesterol level in older adults. *N Engl J Med*. 1990;322:229–234.

121. Janssen I, Katzmarzyk PT, Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. *J Am Geriatr Soc*. 2005;53:2112–2118.

122. Després JP, Lemieux I, Alméras N. Abdominal obesity and the metabolic syndrome. In: Bray GA, Ryan DH, eds. *Overweight and the Metabolic Syndrome: From Bench to Bedside.* New York: Springer Science+Business Media Inc.; 2006.

Arteriosclerosis, Thrombosis, and Vascular Biology

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

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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.
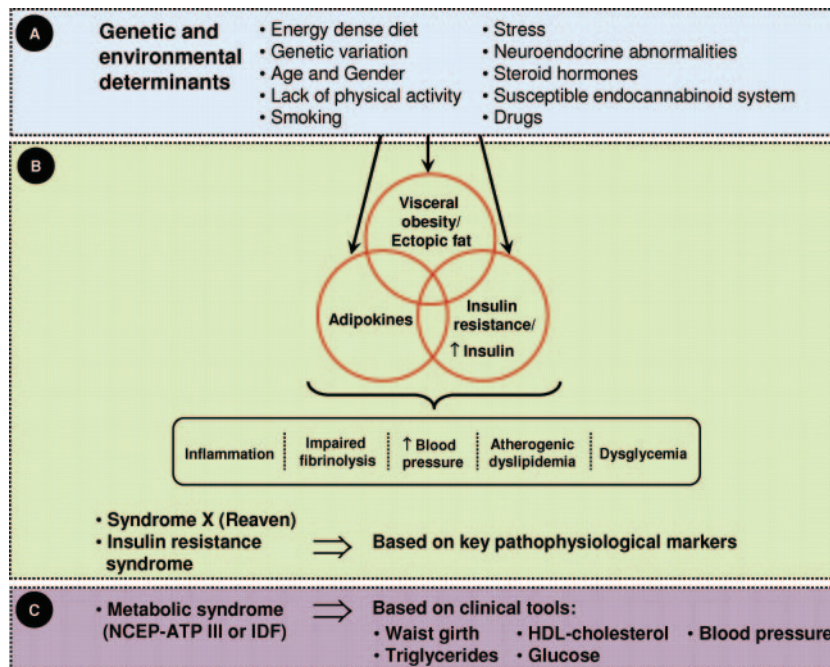
The publisher regrets this error.

Figure 1.