Chapter 8

Abdominal Obesity and the Metabolic Syndrome

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1. INTRODUCTION

Despite the fact that the obesity epidemic has received intense media coverage, many physicians still fail to recognize that the rapidly growing prevalence of type 2 diabetes in their practice is the result of our "toxic" sedentary and affluent lifestyle that promotes weight gain, obesity, a positive energy balance, and the progressive development of a dysmetabolic state [1], potentially leading to glucose intolerance and—eventually—outright hyperglycemia. Citing obesity's key role in the etiology of type 2 diabetes, Zimmet foresaw a rapid increase in the prevalence of type 2 diabetes worldwide [2, 3]. Unfortunately, the progression of obesity has been so brisk that the worldwide prevalence of type 2 diabetes continues to grow at an alarming rate. This phenomenon should be of great concern to health care providers, as type 2 diabetes has been clearly linked to major health care expenses [4]. Indeed, it is a major cause of retinopathy causing blindness, of nephropathy leading to end-stage renal disease and dialysis, as well as of neuropathic complications, which are the leading cause of amputations [5]. In addition to the microcirculatory damage it causes, type 2 diabetes also plays a key role in atherosclerotic macrovascular disease. For instance, the majority of type 2 diabetic patients will die from cardiovascular disease [6–8]. It is therefore crucial to diagnose type 2 diabetic patients early with a view to optimal management of their condition, given that some 10% of the North American population has this metabolic disease [9]. Further, its prevalence is largely underestimated, as it has been found to be even more prevalent in some populations worldwide [2, 3].

Although it has been shown that better glycemic control can reduce the complications of diabetes related to microcirculatory damage, the benefits of glycemic control for prevention of coronary heart disease (CHD) in diabetic patients are modest at best [10, 11]. Although, as a group, type 2 diabetic patients are clearly at higher risk of CHD than the nondiabetic population, recent

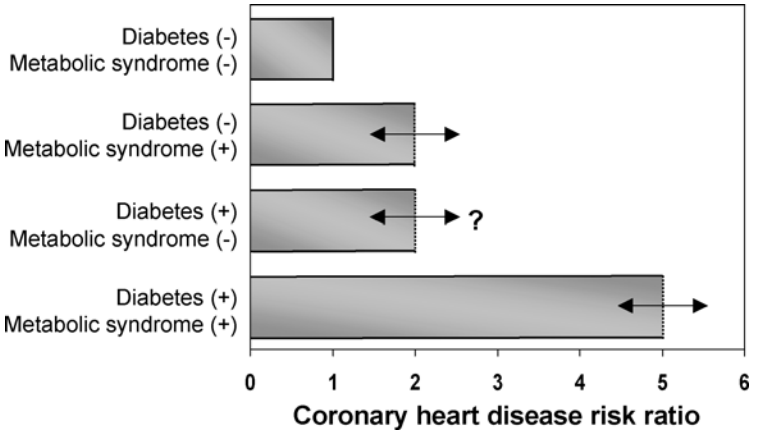

Figure 1. Heterogeneity of coronary heart disease (CHD) risk is associated with the metabolic syndrome and type 2 diabetes. There is considerable evidence that metabolic syndrome features increase CHD risk, even in nondiabetic individuals. Further, studies have shown that CHD risk is heterogeneous in type 2 diabetes. Clearly, type 2 diabetic patients with features of the metabolic syndrome are at the highest risk of CHD. However, debate is currently ongoing as to whether diabetes *per se* (in the absence of the metabolic syndrome) significantly increases CHD risk. These results emphasize the need to watch for factors other than glycemic control in optimally managing CHD risk in type 2 diabetic patients.

studies have shown that type 2 diabetes is a heterogeneous entity: the more abdominally obese type 2 diabetic patients are, the greater is their likelihood of being characterized by the features of the metabolic syndrome [12] and the higher their corresponding CHD risk will be (Figure 1).

The features of the metabolic syndrome may therefore be more important than glycemic control in predicting CHD risk in patients with type 2 diabetes. This finding is consistent with results in nondiabetic subjects indicating that even in the absence of hyperglycemia, nondiabetic, overweight/obese individuals with features of the metabolic syndrome are also characterized by an increased risk for CHD [13–16]. Reaven introduced the concept of an insulin resistance-linked syndrome of abnormalities in 1988 [17] and was the first to suggest that impaired *in vivo* insulin action was central to a cluster of metabolic abnormalities that did not necessarily include classical risk factors such as raised low-density lipoprotein (LDL)-cholesterol, but which was instead characterized by hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol, fasting hyperinsulinemia, and elevated blood pressure. At the time, Reaven argued that he could find insulin-resistant subjects among nonobese individuals and therefore did not include obesity as a necessary component of "his" syndrome X (or insulin resistance syndrome [17]). More than two decades before Reaven's landmark conceptual contribution, Crepaldi and

colleagues had reported that obesity was often accompanied by hyperinsulinemia, hypertriglyceridemia, and hypertension [18]. In the mid-forties, Jean Vague had suggested that regional body fat distribution—but not obesity *per se*—was the culprit, and he coined the term "android obesity" to describe a form of upper body adiposity most often associated with diabetes and cardiovascular disease [19]. Another pioneer in the history of abdominal obesity was Jeremy Morris, who reported in the mid-1950s that sedentary London bus drivers were at greater risk of CHD compared to more active conductors who had to walk and climb the bus stairs during their shifts [20]. Interestingly, he also reported that higher risk, sedentary bus drivers were substantially more likely to have abdominal obesity (as revealed by the size of their trousers) than lower risk, active bus conductors [21]. This early report is one of the key early findings to link a sedentary lifestyle and abdominal obesity to CHD risk [21]. Later, in the early 1980s, two groups reported almost simultaneously that a high proportion of abdominal fat, expressed as an elevated waist-to-hip ratio, was tied to glucose intolerance, hyperinsulinemia, and hypertriglyceridemia [22, 23]. Investigators in the Gothenburg prospective study published evidence that an elevated waist-to-hip ratio was predictive of an increased risk of ischemic heart disease, independent of body mass index (BMI) [24, 25]. In studying the risk of developing diabetes [26], they also found over the 13 ½ years of study follow-up that an elevated BMI *per se* was not associated with an increased risk of developing the disease. However, being overweight or obese and also having a greater proportion of abdominal fat (as crudely estimated by an elevated waist-to-hip ratio) entailed a 30-fold increase in the risk of developing diabetes [26]. The scientific community studying obesity received these findings with considerable interest. At about the same time, imaging techniques such as computed tomography (CT) began to be used in the field of body composition not only to accurately measure abdominal fat but also to distinguish intraabdominal (visceral) from subcutaneous fat [27, 28]. Since then, numerous studies over the last two decades have clearly indicated that abdominal fat accumulation along with an excess of intraabdominal (or visceral) adipose tissue are predictive of the metabolic syndrome [27, 29–38]. It has also been shown that even individuals of apparently normal weight may nonetheless have excess visceral adipose tissue, placing them at greater risk of a disturbed metabolic profile [37, 39–41].

The metabolic complications associated with obesity and overweight have been extensively studied in the last 20 years. The use of high-precision technologies to measure total body fat and abdominal fat accumulation (e.g., dual-energy x-ray absorptiometry [DEXA], computed tomography, and magnetic resonance imaging) has allowed investigators to conclusively demonstrate that, irrespective of the absence/presence of clinical obesity (BMI above 30 kg/m^2),

individuals with a selective excess of intraabdominal or visceral adipose tissue are at a substantially increased risk of developing the cluster of metabolic abnormalities originally described by Reaven [17] as well as being characterized by the features subsequently added to the metabolic syndrome's expanded dysmetabolic profile (hypertriglyceridemia, low HDL-cholesterol, fasting hyperinsulinemia, insulin resistance, elevated apolipoprotein B, small dense LDL, prothrombotic profile, and elevated inflammatory markers) [42].

2. METABOLIC SYNDROME WITHOUT HYPERGLYCEMIA PREDICTS AN INCREASED CHD RISK

We now have evidence that features of the metabolic syndrome commonly found in abdominally obese patients with excess visceral adipose tissue increase CHD risk, even when hyperglycemia is not present. The Québec Cardiovascular Study, a prospective study of middle-aged men in the Québec City Metropolitan Area, has shown that the simultaneous presence of certain metabolic syndrome features—namely fasting hyperinsulinemia (a marker of insulin resistance in nondiabetic individuals), increased apolipoprotein B levels (a marker of atherogenic lipoprotein concentration), and the presence of small LDL particles—substantially increases CHD risk, even in the absence of classical risk factors such as diabetes, raised LDL-cholesterol, hypertension, and smoking [15]. A substantial amount of additional evidence would be required to gauge whether measuring additional metabolic syndrome markers (such as C-reactive protein levels) would further refine our understanding of CHD risk. In this respect, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria are a conceptual leap forward as they include not only aspects of the insulin resistance syndrome (such as triglycerides, HDL-cholesterol, elevated blood pressure, and elevated fasting glucose [as a crude marker of an altered glucose homeostasis likely resulting from an insulin-resistant state]), but also waist circumference as an index of abdominal obesity [43]. The NCEP-ATP III criteria therefore recognize abdominal obesity as a driving force behind the metabolic syndrome's rise to epidemic proportions, a notion that can never be emphasized enough in clinical practice. Studies have consistently shown that individuals meeting the NCEP-ATP III criteria for the metabolic syndrome are at increased relative risk of developing cardiovascular disease [13, 44, 45]. However, this increased relative risk does not necessarily imply a substantial increase in absolute risk, which must be estimated via a global risk algorithm such as the Framingham risk score [46].

3. WHY MEASURE WAIST CIRCUMFERENCE AS WELL AND NOT JUST BMI?

As shown in Figure 2A, population studies have established a fairly strong correlation between BMI and waist girth. The question, then, is why waist cir-

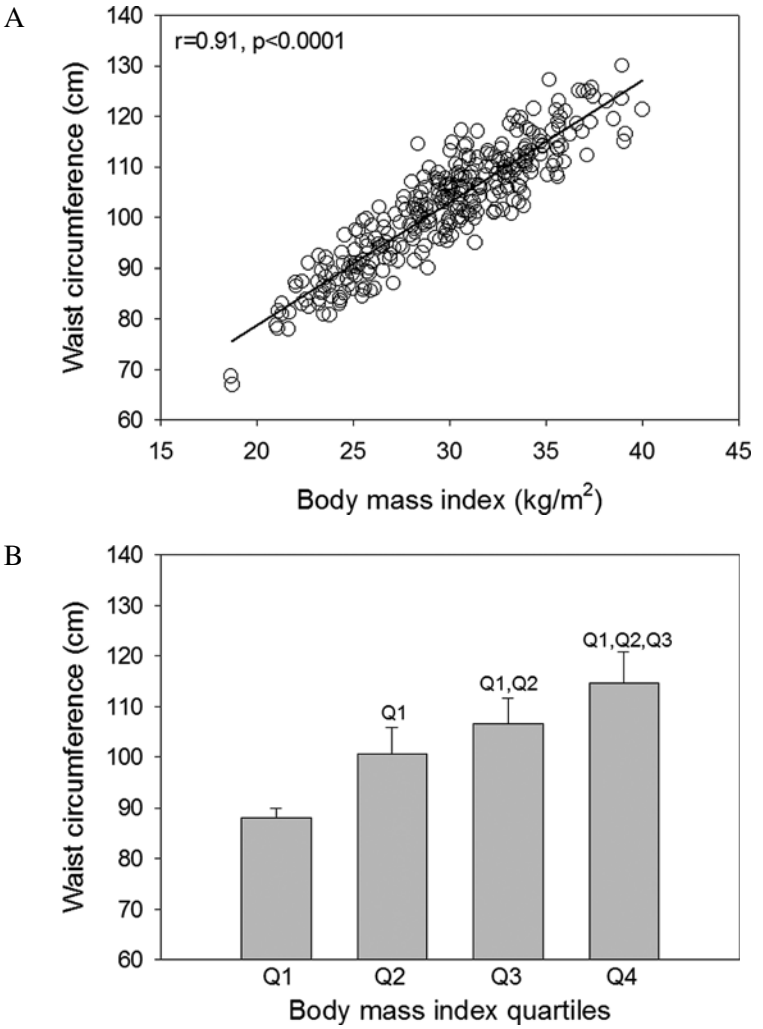

Figure 2. Although there is a highly significant correlation between body mass index (BMI) and waist circumference (upper panel), this correlation is explained by the large variation in BMI values in the samples studied. For instance, standard deviation values for given BMI quartiles (lower panel) clearly show that waist circumference varies substantially per BMI quartile. Waist circumference and BMI are therefore not equivalent in clinical practice. Q1, Q2, Q3: different from the corresponding quartile; $p < 0.0001$. Quartile cutoffs: 25th: 26.62 kg/m^2; 50th: 30.04 kg/m^2; 75th: 32.99 kg/m^2.

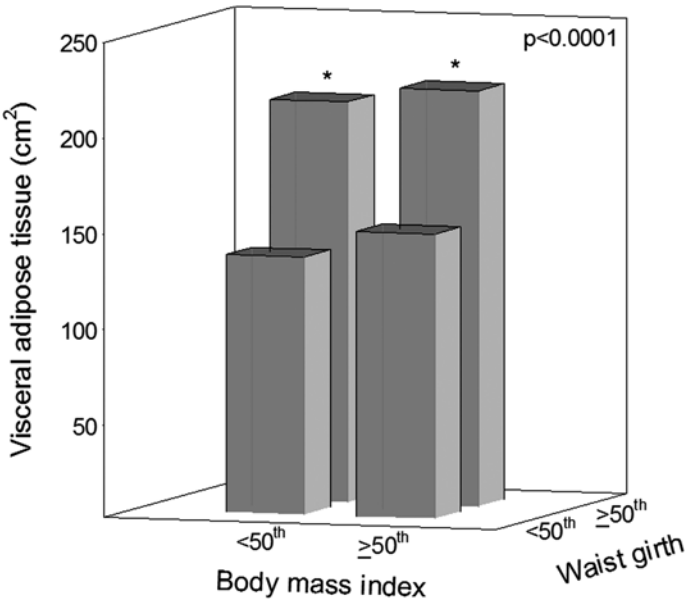

Figure 3. Average cross-sectional areas of visceral adipose tissue measured by computed tomography (expressed in cm^2) among groups of men stratified according to median body mass index and waist circumference values. For any given BMI subgroup, subjects with a higher waist circumference have a much greater accumulation of visceral adipose tissue than men with lower waist girth values. Body mass index cutoff: 50th: 30.04 kg/m^2; waist circumference cutoff: 50th: 103.5 cm. *Significantly different from individuals with low waist circumference, regardless of BMI.

cumference is preferable to BMI, which is an internationally accepted index of adiposity. Looking further at Figure 2A, the strength of the correlation depends largely on the sample's weight heterogeneity (BMI). Figure 2B shows waist circumference variations for various BMI quartiles, demonstrating that circumference varies considerably for any given BMI quartile. Thus, if waist circumference and BMI do not equally predict the metabolic syndrome, BMI cannot be considered a surrogate for waist girth. This is further supported by Figure 3, which clearly indicates that for any BMI subgroup, subjects with an elevated waist circumference have a much greater accumulation of visceral adipose tissue, a key factor underpinning the dysmetabolic profile associated with abdominal obesity [30–35]. Therefore, waist girth and BMI are not comparable markers of abdominal obesity and do not similarly predict the presence of metabolic complications. In addition, recent findings of the INTERHEART myocardial infarction case-control study have revealed that increased abdominal fat is a key predictor of myocardial infarction, even among individuals with presumably "normal" BMI values [47].

4. ABDOMINAL OBESITY: THE DRIVING FORCE BEHIND THE METABOLIC SYNDROME?

Although rare forms of insulin resistance not accompanied by overweight or obesity can be found in clinical practice [48], clinicians must recognize the pivotal role of abdominal obesity in elevating the metabolic syndrome to the status of an epidemic. Unpublished data from the Québec Health Survey cohort revealed that waist circumference values were markedly elevated among all combinations of NCEP-ATP III criteria that did not include waist circumference (Lemieux I et al., unpublished data). These results clearly indicate that an expanded waistline is the most prevalent form of the metabolic syndrome. Thus, measuring waist circumference is a key step toward identifying individuals likely to have features of the metabolic syndrome.

5. THE METABOLIC SYNDROME: IS WAIST GIRTH SUFFICIENT?

Although we have repeatedly stressed the importance of measuring waist girth, its ability to predict visceral fat accumulation and the presence of the metabolic syndrome is limited. The high waist circumference values often found in very obese premenopausal women provide a telling example of how this measurement can mislead in clinical practice. Though these women may have a substantial accumulation of subcutaneous abdominal fat, they may also have little atherogenic visceral adipose tissue as compared to men [49–51]. To solve this dilemma, we have worked to identify a simple and inexpensive blood marker that could help physicians identify individuals likely to have the atherogenic features of the insulin resistance syndrome. Such a blood marker appears to be fasting plasma triglyceridemia. For example, we have found that middle-aged Caucasian men with both elevated triglyceride concentrations (above 2 mmol/L) and a waist circumference of 90 cm were far more likely (greater than 80% probability) to be characterized by visceral obesity and the metabolic syndrome [52]. Conversely, men with a waist circumference smaller than 90 cm and triglyceride levels under 2 mmol/L were much less likely (about 10% probability) to display features of the metabolic syndrome [52]. We have validated this screening approach in several studies [52–55]. We therefore submit that an elevated waist circumference (as a marker of abdominal obesity) and hypertriglyceridemia (as a crude marker of the dysmetabolic, dyslipidemic profile accompanying abdominal obesity) are the two key variables that should be included in a simple and inexpensive initial screening for individuals at high risk of developing the metabolic syndrome.

6. ARE NCEP-ATP III CRITERIA VALID IN ALL POPULATIONS?

As a concept, NCEP-ATP III recognizes that some simple clinical markers (including waist circumference) can be used to identify individuals likely to have the metabolic syndrome [43]. Further, studies have shown that individuals who meet these criteria have an increased prevalence or incidence of CHD [13, 44, 45]. However, we do not know whether the NCEP-ATP III cutoffs proposed provide optimal discrimination of CHD risk. Further data must be generated through various cutoffs to verify which values provide optimal sensitivity and specificity in discriminating for clinical events. In addition, it has been shown that susceptibility to visceral fat deposition and the likelihood of developing complications for any given level of abdominal visceral fat can vary by population [56–59]. For instance, African Americans are less likely to accumulate visceral adipose tissue than Caucasians for any given level of total body fat or waist circumference. We had previously reported that the lower susceptibility of African Americans to visceral obesity accounted for their lower triglyceride and apolipoprotein B levels compared to Caucasians [56]. Further proof of the need to develop population-specific cutoffs comes from the Asian population, which develops type 2 diabetes at much lower BMI (and therefore lower waist circumference) values than the Caucasian population [60].

NCEP-ATP III is a remarkable advance in that it provides clinicians with simple syndrome markers whose relationship to CHD risk has been established. However, further study of population differences is clearly warranted to refine NCEP-ATP III criteria and cutoff values for optimal assessment of metabolic syndrome-related risk. This was the rationale underlying the recent International Diabetes Federation (IDF) recommendations on identifying individuals with the metabolic syndrome [61]. In light of evidence that the most prevalent form of the metabolic syndrome is found in patients with abdominal obesity, elevated waist circumference was included as a mandatory criterion in IDF recommendations. Population-specific waist cutoffs for abdominal obesity have also been proposed to reflect population differences in susceptibility to visceral adiposity for a given BMI. However, such criteria should be considered a work in progress, and additional scientific evidence will be necessary to refine screening approaches to optimally discriminate for the metabolic syndrome and the related risk of diabetes and cardiovascular disease in various populations worldwide. Key considerations regarding this process are listed in Table 1.

Table 1. Metabolic syndrome vs. CHD risk: issues

• Impact on heterogeneity of CHD risk in type 2 diabetes
• Impact on CHD risk in the nondiabetic population
• Critical markers (and cutoff values) for identifying and quantifying related CHD risk
• Susceptibility to metabolic syndrome in various populations
• Population differences in susceptibility to visceral adipose tissue deposition
• Population differences in susceptibility to developing complications (type 2 diabetes, CHD) for any given excess of visceral adipose tissue

7. MANAGING CHD RISK IN PATIENTS WITH THE METABOLIC SYNDROME: WHAT SHOULD BE OUR GOAL?

It is clear that features of the metabolic syndrome increase the risk of CHD, whether classical risk factors are present or not [16]. This means that the metabolic syndrome further increases the CHD risk already posed by traditional risk factors such as hypertension, diabetes, elevated LDL-cholesterol, and smoking. These factors must of course be managed in patients with the metabolic syndrome. However, treating them is unlikely to eliminate the risk resulting from the presence of the metabolic syndrome. The findings of the Heart Protection Study (HPS) in diabetic patients provide a simple illustration of this problem. For example, although all diabetic patients benefited from simvastatin therapy in HPS, patients with low HDL-cholesterol levels (presumably resulting from the presence of abdominal obesity and hypertriglyceridemia, the most common form of low HDL-cholesterol in our population) remained at higher risk of CHD events and related mortality than type 2 diabetic patients with normal HDL-cholesterol levels (presumably less abdominally obese and likely to have lower triglyceride levels) [62]. Thus, although it may provide significant clinical benefit, statin therapy in type 2 diabetic patients with low HDL-cholesterol (and presumably the metabolic syndrome) may not normalize their CHD risk if they are abdominally obese and also have features of the metabolic syndrome. It may therefore be necessary to manage other dysmetabolic abnormalities to optimally reduce CHD risk in these high-risk patients. Further study is required to identify which features of the metabolic syndrome should be targeted. This will be a key focus of future studies. Evidence from fibrate trials has suggested that patients with obesity, hypertriglyceridemia, and low HDL-cholesterol (with either hyperinsulinemia or type 2 diabetes) may benefit from fibrate therapy [63–66]. However, recently published results of the long-awaited FIELD trial have failed to confirm this. Further, statin-fibrate combination therapy in very high-risk patients with

type 2 diabetes, CHD, and the metabolic syndrome has yet to be tested in large trials for safety and clinical benefits.

It is crucial that physicians stress the importance of weight loss, especially given the spectacular results of Finnish and US diabetes prevention studies demonstrating that small weight loss could afford substantial clinical benefit by preventing or at least delaying by several years the conversion to type 2 diabetes among high-risk obese individuals with glucose intolerance [67, 68]. Whether this finding will prove useful for managing the other features of the metabolic syndrome will likewise have to be tested in clinical trials.

If lifestyle modification cannot successfully spur weight loss and the mobilization of abdominal fat, pharmacotherapy should be considered for high-risk patients with high-risk visceral obesity. The two available weight loss agents approved in clinical practice—sibutramine and orlistat—have both been shown to induce significantly greater weight loss than placebos [69, 70]. With the exception of the XENDOS study [71], which included a subgroup of patients with impaired glucose tolerance, these agents have mostly been tested in low-risk obese women. Trials involving high-risk abdominally obese patients with clinically meaningful outcomes are needed.

Lastly, recent studies have identified the endocannabinoid system as a target for inducing abdominal fat loss and mitigating features of the metabolic syndrome [72, 73]. Blocking CB_1 receptors may therefore be an additional, complementary way to address the root cause of the clustering atherothrombotic–inflammatory and diabetogenic abnormalities of the metabolic syndrome: abdominal obesity. Further trials with hard end points are needed to quantify the clinical benefits of the metabolic improvements observed with this new therapeutic approach.

8. SUMMARY

Recognition of the metabolic syndrome as a major and prevalent cause of CHD in the NCEP-ATP III guidelines represents a remarkable contribution to preventive medicine by stressing the importance of assessing abdominal obesity in clinical practice. The NCEP-ATP III panel has proposed simple variables to identify individuals who are likely to have features of the metabolic syndrome and who are at increased relative risk of type 2 diabetes and cardiovascular disease. Among the five criteria (waist circumference, triglycerides, HDL-cholesterol, fasting glycemia, blood pressure) proposed to identify metabolic syndrome carriers, the recommendation to measure waist circumference rather than BMI has been a giant conceptual leap forward, as it recognizes abdominal obesity as the most important component of the metabolic syndrome in our affluent, sedentary population. The NCEP-ATP III guidelines have also recognized the value of elevated triglyceride and

reduced HDL-cholesterol levels as lipid markers for the presence of an atherogenic "dysmetabolic" profile that adds to the impact of raised plasma LDL-cholesterol levels on the risk of CHD.

Unfortunately, since the publication of the NCEP-ATP III guidelines, clinicians have often confused the conceptual definition of the metabolic syndrome with the above five criteria, which are intended for use in clinical practice as simple surrogate variables to identify high-risk individuals likely to be characterized by abdominal obesity, insulin resistance, and atherogenic dyslipidemia, as well as by a prothrombotic, inflammatory profile that may or may not coexist with hyperglycemia and/or hypertension (Figure 4). More recently, the recommendations of an IDF working group placed further emphasis on abdominal obesity as the most prevalent component of the metabolic syndrome and consequently on the need to first have an elevated waist circumference before being considered at risk of having the metabolic syndrome (Figure 4). Further, in light of compelling evidence that the waist circumference cutoff values proposed by NCEP-ATP III was too high, recent IDF recommendations have reduced the waist girth value to 94 cm in men and 80 cm in women, adding that factors such as ethnicity and age affect the relationship of waist circumference to abdominal visceral fat deposition and related metabolic ab-

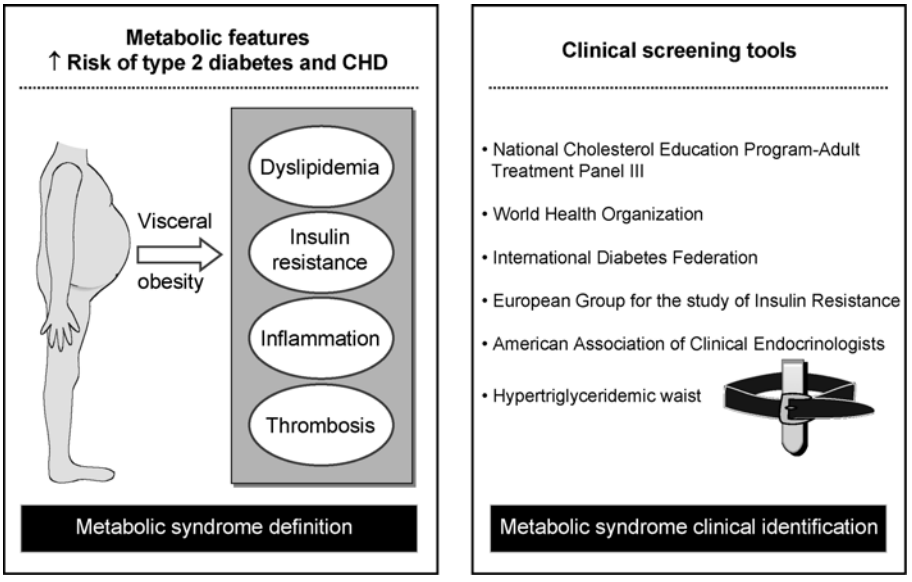

Figure 4. A distinction should be drawn between the metabolic syndrome as a concept and the clinical tools proposed by various organizations/groups to identify patients likely to have the clustering abnormalities of the metabolic syndrome. Careful attention should be paid to this issue so as not to confuse the metabolic syndrome definition with the criteria used for its identification in clinical practice.

normalities. Thus, the mandatory inclusion in the IDF guidelines of elevated waist girth as the initial criterion used to denote likely metabolic syndrome patients marks another step toward developing a simplified approach to identifying these patients in clinical practice. Based on additional work performed by several groups, there is now evidence that the simultaneous presence of elevated waist circumference and fasting triglyceride levels (a condition termed the "hypertriglyceridemic waist") may be initially useful in identifying a subgroup of individuals at high risk of being carriers of the metabolic syndrome (Figure 4). The syndrome features could then be confirmed through additional and more sophisticated metabolic risk marker measurements.

However, given the knowledge gaps in recent IDF recommendations, these new waist circumference criteria should be considered a work in progress. Accordingly, their ability to optimally discriminate for subgroups at high risk of type 2 diabetes or CHD because of the presence of metabolic syndrome features will have to be validated. Finally, based on evidence that both abdominal obesity and related metabolic syndrome features affect the absolute residual CHD risk of patients treated for traditional risk factors, new therapeutic approaches that either modify the visceral obesity phenotype or target abdominal obesity and related metabolic abnormalities may hold out great promise to optimally reduce CHD risk in abdominally obese patients with features of the metabolic syndrome.

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