CONTROVERSIAS EN TORNO AL SÍNDROME METABÓLICO

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HOSPITAL CLÍNICO UNIVERSITARIO SANTIAGO

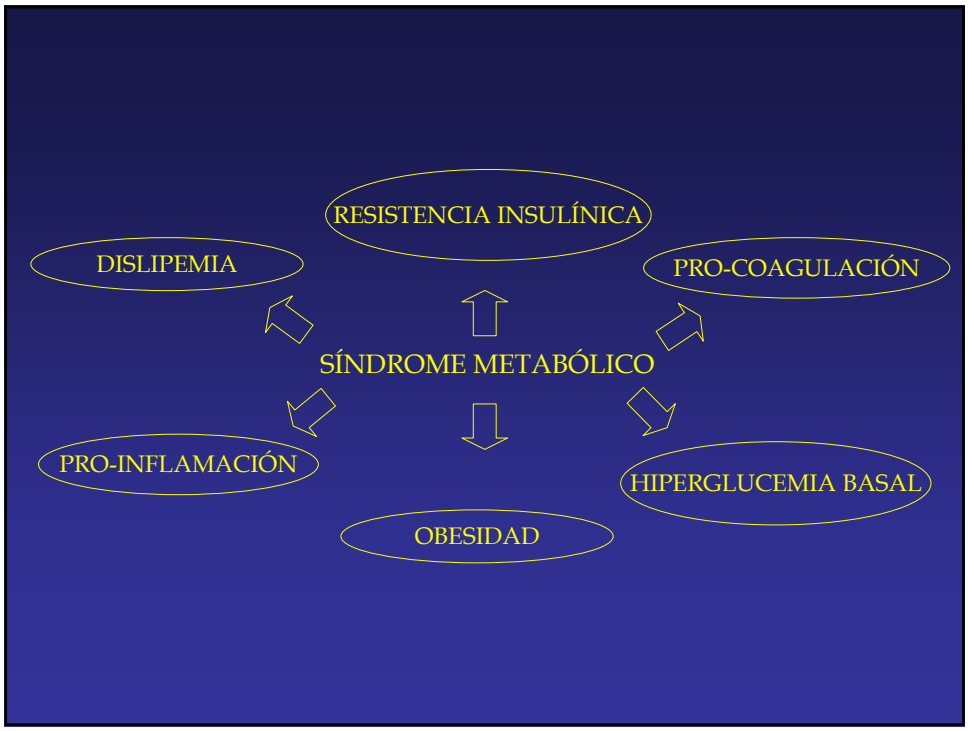
Banting lecture 1988. Role of insulin resistance in human disease.

Reaven GM.

Department of Medicine, Stanford University Medical Center, California.

Resistance to insulin -stimulated glucose uptake is present in the majority of patients with impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM) and in approximately 25% of nonobese individuals with normal oral glucose tolerance. In these conditions, deterioration of glucose tolerance can only be prevented if the beta-cell is able to increase its insulin secretory response and maintain a state of chronic hyperinsulinemia. When this goal cannot be achieved, gross decompensation of glucose homeostasis occurs. The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma free-fatty acid (FFA) concentration. Patients with NIDDM are also resistant to insulin suppression of plasma FFA concentration, but plasma FFA concentrations can be reduced by relatively small increments in insulin concentration. Consequently, elevations of circulating plasma FFA concentration can be prevented if large amounts of insulin can be secreted. If hyperinsulinemia cannot be maintained, plasma FFA concentration will not be suppressed normally, and the resulting increase in plasma FFA concentration will lead to increased hepatic glucose production. Because these events take place in individuals who are quite resistant to insulin-stimulated glucose uptake, it is apparent that even small increases in hepatic glucose production are likely to lead to significant fasting hyperglycemia under these conditions. Although hyperinsulinemia may prevent frank decompensation of glucose homeostasis in insulin-resistant individuals, this compensatory response of the endocrine pancreas is not without its price. Patients with hypertension, treated or untreated, are insulin resistant, hyperglycemic, and hyperinsulinemic. In addition, a direct relationship between plasma insulin concentration and blood pressure has been noted. Hypertension can also be produced in normal rats when they are fed a fructose-enriched diet, an intervention that also leads to the development of insulin resistance and hyperinsulinemia. The development of hypertension in normal rats by an experimental manipulation known to induce insulin resistance and hyperinsulinemia provides further support for the view that the relationship between the three variables may be a causal one

Diabetes. 1988 Dec;37(12):1595-607.



SÍNDROME METABÓLICO (OMS 99)

RESISTENCIA INSULÍNICA (DM II/IGT/IFG)
+
(≥ 2 factores de riesgo)

Obesidad visceral

Índice cintura/cadera > 0.85 mujer (>0,9 hombre)

ó IMC > 30 kg/m^2

Dislipemia

Triglicéridos ≥ 150 mg/dl

ó HDL < 39 mg/dl mujer (< 35 mg/dl hombre)

TAS/TAD

≥ 140/90

Microalbuminuria

VEA ≥ 20 µgrs/min

ó cociente albúmina/creatinina ≥ 30 mgrs/g

SÍNDROME METABÓLICO (ATP III 02)

El diagnóstico precisa ≥ 3 factores de riesgo

Circunferencia cintura	
Hombre	> 102 cms
Mujer	> 98 cms
Triglicéridos	
≥ 150 mg/dl	
Colesterol HDL	
Hombre	< 40 mg/dl
Mujer	< 50 mg/dl
TAS/TAD	
≥ 130/85 mmHg	
Glucemia ayunas	
≥ 110 (≥100)mg/dl	

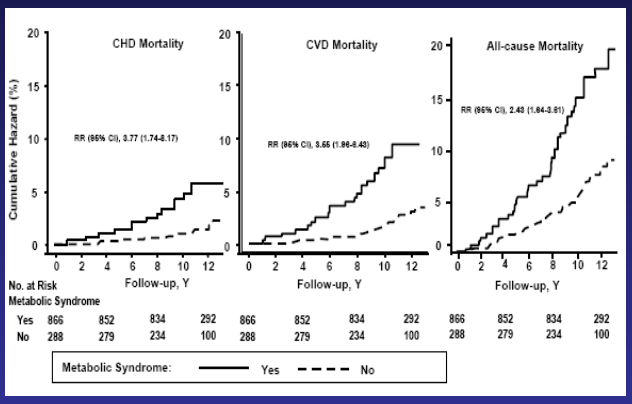
SÍNDROME METABÓLICO (AACE 03)

1 FACTOR DE RIESGO:

- IMC≥25 ó circunferencia cintura>102 cms(H);>88cms (M)
- 40 años
- Sedentarismo
- No caucasico
- Antecedentes familiares de DM ó enf. C-V
- Antecedentes personales de intolerancia a la glucosa ó diabetes gestacional
- Acantosis nigricans
- Síndrome de ovario poliquístico
- Hígado graso no alcohólico

2 PARÁMETROS:

- Triglicéridos > 150 mgrs/dl
- Colesterol-HDL: <40 (H);< 50(M)
- TAS/TAD≥130/85
- Glucemia en ayunas: 110-125 mgrs/dl
- Test sobrecarga oral glucosa: >140 mgrs/dl (2 horas)



Lakka HM, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA. 2002; 288: 2709-2716.

Definition of Metabolic Syndrome

Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition

Scott M. Grundy, MD, PhD; H. Bryan Brewer, Jr, MD; James I. Cleeman, MD; Sidney C. Smith, Jr, MD; Claude Lenfant, MD; for the Conference Participants*

Metabolic Syndrome as a Predictor of Diabetes

When the risk for new-onset diabetes was examined for the Framingham cohort, in both men and women, the presence of metabolic syndrome was highly predictive of new-onset diabetes. Almost half of the population-attributable risk for diabetes could be explained by the presence of ATP III metabolic syndrome.

European Heart Journal (2004) 25, 342–348

ELSEVIER

EUROPEAN SOCIETY OF CARDIOLOGY

Clinical research

The Metabolic Syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm

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Original Research

The metabolic syndrome: a cause of sexual dysfunction in women

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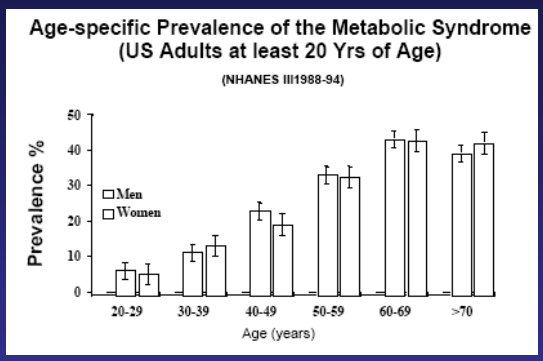
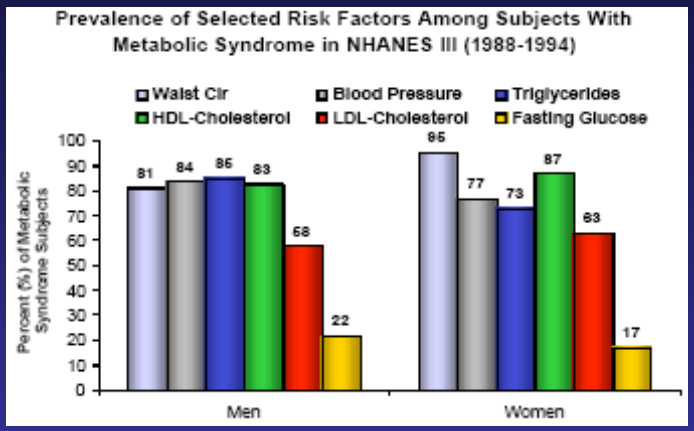
[2]*Department of Gynecology, Obstetrics and Reproduction, Second University of Naples, Naples, Italy*

Female sexual dysfunction (FSD) is a significant public health problem. We assessed the prevalence of FSD in premenopausal women with the metabolic syndrome as compared to the general female population. Compared with the control group ($N=80$), women with the metabolic syndrome ($N=120$) had reduced mean full Female Sexual Function Index (FSFI) score (23.2 ± 5.4 *vs* 30.1 ± 4.7, $P<0.001$), reduced satisfaction rate (3.5 ± 1.1 *vs* 4.7 ± 1.2, $P<0.01$), and higher circulating levels of C-reactive protein (CRP: 2.2 (0.6/4.9) *vs* 0.8 (0.2/2.9) mg/l, median (interquartile range), $P=0.01$). There was an inverse relation between CRP levels and FSFI score ($r=-0.32$, $P=0.02$). Investigation of female sexuality is suggested for patients with the metabolic syndrome.
International Journal of Impotence Research advance online publication, 17 February 2005; doi:10.1038/sj.ijir.3901310

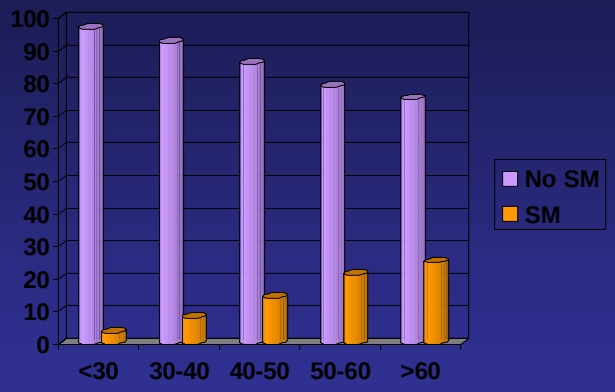


Ford E. et al. JAMA 2002 (287): 356-9.



Wong et al. Am J Cardiol. 2003; 91: 1421-26.

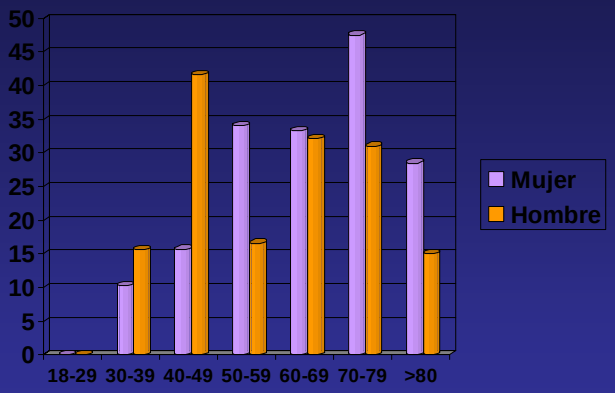
PREVALENCIA SÍNDROME METABÓLICO EN ESPAÑA



N: 176314

Síndrome metabólico en población laboral. Plan de Prevención del Riesgo Cardiovascular IBERMUTUAMUR

PREVALENCIA SÍNDROME METABÓLICO EN ESPAÑA



N: 470/18350

SÍNDROME METABÓLICO: ETIOLOGÍA

➢RESISTENCIA INSULÍNICA

Stress oxidativo → Disfunción endotelial → Ateromatosis

López-Candales et al. J. Med. 2001;32:283-300.

➢HIPERCORTISOLEMIA

Stress crónico → Lipogénesis → Resistencia insulínica

Bjorntorp P. et al. Scand. Cardiovasc. J. 2001; 35:172-7.

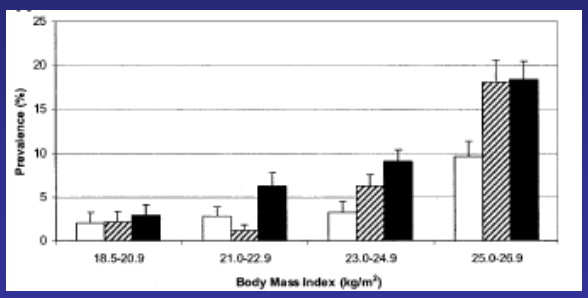
SÍNDROME METABÓLICO: ETIOLOGÍA (II)

➢OBESIDAD

ILK-6; PCR; NEFA; PAI-1

⇩

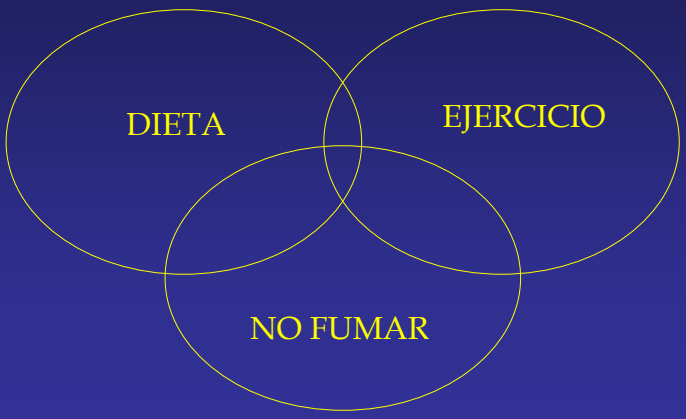
Pro-inflamación/trombosis/resistencia insulínica

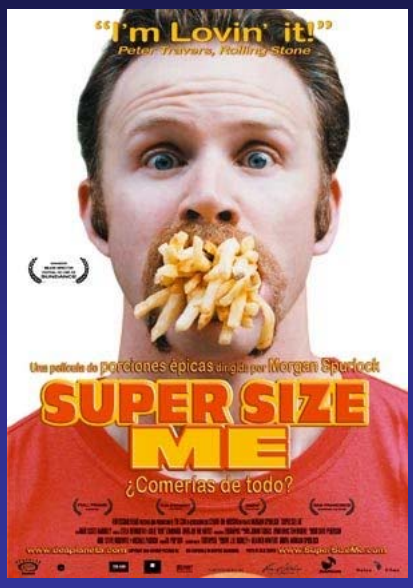


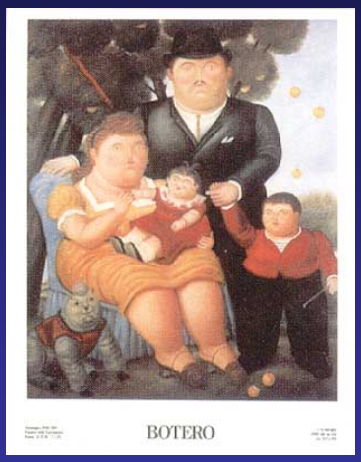
St-Onge M-P et al. Diabetes Care 2004; 27: 2222-28.

SÍNDROME METABÓLICO: TRATAMIENTO

1_ MODIFICAR ESTILO VIDA







Duncan et al. Diabetes care 2003;26:557-62

Katzmorzyk PT et al. Heritage study. Med Sci Sport 2003; 35:1703-09.

SÍNDROME METABÓLICO: TRATAMIENTO

2_ RESISTENCIA INSULÍNICA

Definition of Metabolic Syndrome

Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition

Scott M. Grundy, MD, PhD; H. Bryan Brewer, Jr, MD; James I. Cleeman, MD; Sidney C. Smith, Jr, MD; Claude Lenfant, MD; for the Conference Participants*

Insulin Resistance as Target of Therapy

If insulin resistance, whether primary or secondary to obesity, is in the chain of causation of metabolic syndrome, it would be an attractive target. Certainly, weight reduction and increased physical activity will reduce insulin resistance. Insulin resistance as a target has caught the imagination of the pharmaceutical industry, and drug discovery is underway. Two classes of drugs are currently available that reduce insulin resistance. These are metformin and insulin sensitizers such as thiazolidinediones (TZDs).

Metformin has long been used for treatment of type 2 diabetes. In UKPDS, metformin apparently reduced new-onset CHD in obese patients with diabetes. In the Diabetes Prevention Program, metformin therapy prevented (or delayed) onset of type 2 diabetes in persons with IGT. There are, however, no CVD end-point studies on metformin-treated patients with metabolic syndrome. Thus, at present, metformin cannot be recommended for the express purpose of reducing risk for CVD in persons with the metabolic syndrome.

TZDs currently are approved for treatment of type 2 diabetes. They reduce insulin resistance, favorably modify several metabolic risk factors, and reverse abnormal arterial responses. Nonetheless, no clinical trial data yet exist to document benefit in CVD risk reduction. Thus, in spite of promise, TZDs cannot be recommended at present for preventing CVD in patients with either metabolic syndrome or diabetes.

SÍNDROME METABÓLICO: TRATAMIENTO

3_ DISLIPEMIA

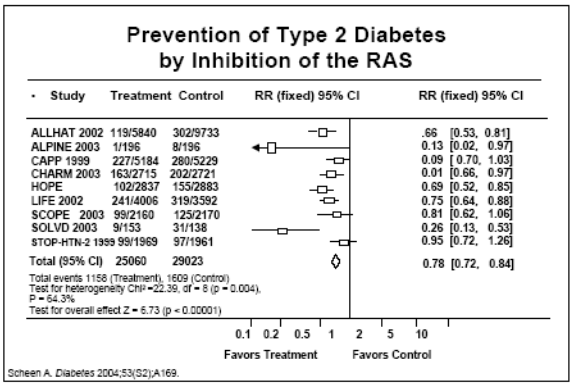
CATEGORÍA RIESGO	OBJETIVO LDL (MG/DL)
MUY ALTO RIESGO: Coronariopatía y/o equivalente de riesgo (diabetes)	< 100 (opcional <70)
ALTO RIESGO: ≥ 2 factores riesgo*	< 130 (opcional <100)
BAJO RIESGO: 0-1 factores riesgo	< 160

* Tabaquismo, HTA≥ 140/90, HDL<40,AF Coronariopatía precoz (<55 varon;< 65 mujer),edad (>45 varón;>55mujer)

Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.

SÍNDROME METABÓLICO: TRATAMIENTO

4_ HIPERTENSIÓN



SÍNDROME METABÓLICO: TRATAMIENTO

4_ ANTIAGREGACIÓN

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Prothrombotic State

No drugs are available that target PAI-1 and fibrinogen. An alternative approach to the prothrombotic state is antiplatelet therapy. For example, low-dose aspirin reduces CVD events in both secondary and primary prevention. Thus, use of aspirin for primary prevention in patients with metabolic syndrome is promising. According to current recommendations, low-dose aspirin therapy has a favorable efficacy/side effect ratio when 10-year risk for CHD is ≥10%.

Papers in Press. First published March 3, 2005 as doi:10.1373/clinchem.2005.048611

Clinical Chemistry 51:6
000–000 (2005)

Review

The Metabolic Syndrome: Requiescat in Pace

GERALD M. REAVEN

Values for insulin-mediated glucose disposal vary continuously throughout a population of apparently healthy individuals, with at least a sixfold variation between the most insulin sensitive and most insulin resistant of these individuals. The more insulin resistant a person, the more insulin must be secreted to prevent decompensation of glucose tolerance. Insulin resistance is not a disease, but a description of a physiologic state, and approximately one third of an apparently healthy population is sufficiently insulin resistant to be at increased risk to develop a cluster of abnormalities and related clinical syndromes. The primary value of the concept of insulin resistance is that it provides a conceptual framework with which to place a substantial number of apparently unrelated biological events into a pathophysiological construct. In contrast, the metabolic syndrome was introduced as a diagnostic category to identify individuals that satisfy three of five arbitrarily arbitrarily chosen criteria to initiate lifestyle changes with the goal of decreasing risk of cardiovascular disease. Consequently, the value of the notion of the metabolic syndrome must be considered not in pathophysiologic terms, but as a pragmatic approach to obtain a better clinical outcome. In this review an effort is made to critically evaluate the concept of the metabolic syndrome, the criteria chosen to identify individuals with the syndrome, and the clinical utility of making, or not making, a diagnosis of the metabolic syndrome.

In 2001, the Adult Treatment Panel III (ATP III)[1] of the National Cholesterol Education Program proposed criteria for diagnosing what they designated the metabolic syndrome (*1*). Since the original report by Ford et al. (*2*) in 2002 describing the prevalence of the metabolic syndrome in the United States, multiple papers have been published addressing the same issue. As an example of this phenomenon, I cite 14 articles (*3–16*) that represent a small sample of those published on this topic in 2004; they were based primarily on retrospective analyses of population-based studies, conducted in several countries, with experimental data gathered for a variety of different reasons, in groups differing in terms of age, sex, and ethnicity. Although this burst of creative activity has led to an enormous amount of published data, it is not clear that it has led to the delivery of any new information of significant utility to the practicing clinician. In fact, as will be discussed subsequently, if taken at face value, there is a real possibility that use of the ATP III criteria could do more harm than good. As the basis, it might be useful to take a somewhat skeptical look at the clinical implications of implementing the diagnostic criteria proposed by the ATP III, and the effort to address this issue is the justification for this presentation.

Definition of the Metabolic Syndrome

The establishment of criteria for diagnosing what the ATP III report termed the metabolic syndrome (*1*) represented an effort to acknowledge the importance of resistance to insulin action, and its consequences, as increasing the risk of cardiovascular disease (CVD). The ATP III recognized (*1*) the importance as CVD risk factors of what they called a "constellation of lipid and non-lipid risk factors of metabolic origin," designated this cluster as the metabolic syndrome, and stated that "this syndrome is closely related to insulin resistance." Table 1 lists the five criteria selected by the ATP to identify individuals with the metabolic syndrome [abdominal obesity, impaired fasting glucose, high triglyceride (TG) and low HDL-cholesterol (HDL-C) concentrations, and increased blood pressure], and reflects their view that insulin resistance is at the root of the problem. The primary goals of the ATP III in establishing criteria for making the diagnosis of the metabolic syndrome were to identify individuals at increased

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[1] Nonstandard abbreviations: ATP III, Adult Treatment Panel III; CVD, cardiovascular disease; TG, triglyceride; HDL-C, HDL-cholesterol; WC, waist circumference; BMI, body mass index; ADA, American Diabetes Association; IFG, impaired fasting glucose; and IGT impaired glucose tolerance.

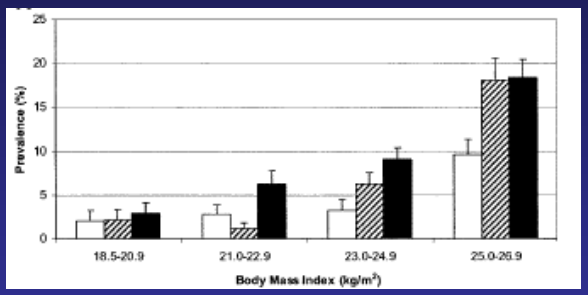
Height and weight are routinely measured in most healthcare facilities in a reasonably simple fashion, and the BMI is easily calculated by referring to simple tables. In contrast, the following paragraph contains the directions for measuring WC according to the NHANES protocol.

The subject stands and the examiner, positioned at the right of the subject, palpates the hip bone to locate the iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at normal minimal inspiration.

To the best of my knowledge, data as to the reproducibility of measurements of WC at any given clinical site, let alone from site to site, when following this precise protocol, are not available. It also seems reasonable to express skepticism concerning the likelihood that measurements of WC will be performed with this same degree of seriousness, and in a uniform manner, in health centers throughout the United States.

Furthermore, as pointed out in a recent report *(32)*, it appears that studies demonstrating the relationship between increased abdominal obesity and adverse clinical consequences have relied on at least 14 different methods to quantify WC, and even the 4 most commonly used approaches yielded quite different absolute values for WC. This issue is further confounded by a recent report from the WHO expressing concern that because the untoward effects of obesity will vary as a function of ethnicity, it will be necessary to develop ethnicity-specific values to identify overweight/obese individuals at greatest risk *(33)*

The fact that obesity is not a consequence of insulin resistance/hyperinsulinemia should not obscure the fact that the more overweight/obese an individual, the more likely it is that the individual will be sufficiently insulin resistant to be at increased risk to develop one or more of the adverse clinical consequences associated with the defect in insulin action. This is clearly of great clinical significance in light of the current worldwide epidemic of obesity. On the other hand, although being overweight/obese increases the chances of an individual being significantly insulin resistant, by no means are all overweight/obese individuals insulin resistant, and, of greater clinical relevance, weight loss in overweight/individuals who are not insulin resistant does not lead to substantial clinical benefit *(26–30)*. Therefore, being overweight/obese is a finding that should alert the healthcare provider to the possibility that an individual is insulin resistant and at increased risk to develop the clinical syndromes listed in Table 2. As such, the question then becomes one of the most effective way to identify these individuals.



St-Onge M-P et al. Diabetes Care 2004; 27: 2222-28.

In the most general sense, the higher the fasting plasma glucose concentration, the more likely an individual is to be insulin resistant and at increased risk for developing the clinical syndromes listed in Table 2. Determining the fasting plasma glucose concentration is clearly of importance for identifying patients with type 2 diabetes and subsequently leading to the initiation of appropriate glycemic control. On the other hand, knowledge of the fasting plasma glucose concentration does not provide a particularly useful surrogate estimate of insulin resistance, accounting for only ~5–15% of the variance (depending on degree of adiposity) in insulin-mediated glucose disposal in the population at large *(44)*. If the plasma glucose concentration is to be used for identifying insulin-resistant individuals with increased risk to develop CVD, it seems that measurements made after an oral glucose challenge offer the most clinical utility *(38, 39, 42, 43)*. In the absence of obtaining this information, neither cut point for identifying patients with the metabolic syndrome proposed by the ATP III seems to be particularly useful.

The evidence summarized above provides substantial support for the view that the CVD risk associated with increases in blood pressure is significantly increased when the hemodynamic abnormality is present in insulin-resistant individuals. Consequently, it may be more important from a clinical standpoint to focus on whether an increase in blood pressure is associated with the dyslipidemic manifestations of insulin resistance, rather than questioning if the patient in question meets the diagnostic criteria for the metabolic syndrome.

Despite the potential limitations of the criteria that have been proposed to diagnose the metabolic syndrome, the most fundamental question relates to the clinical utility of using them to decide whether an individual does, or does not, deserve that sobriquet. In that context, imagine two men, both of whom have blood pressures and plasma TG concentrations high enough to satisfy the ATP III criteria to merit the diagnosis of the metabolic syndrome, but neither had a large enough waist or a high enough fasting plasma glucose to qualify for that diagnosis. In fact, the only apparent difference between them was that the HDL-C concentration was 380 mg/L in one of them, whereas the other one had a value of 420 mg/L. By definition, one man has the metabolic syndrome; the other does not. Are these individuals fundamentally different? Would the treatment options differ in any substantive way? Does knowing that a patient has an increased blood pressure, as well as a high plasma TG concentration, not merit appropriate clinical intervention? Does it matter that the patient does not have the metabolic syndrome, because his WC, fasting plasma glucose concentration, and HDL-C concentration do not meet the arbitrary criteria established by the ATP III?

In conclusion, it appears that making the diagnosis of the metabolic syndrome does not bring with it much in the way of pathophysiologic understanding or clinical utility, and deciding that individuals do not have it because they fail to satisfy three of five arbitrarily chosen criteria may withhold relevant therapeutic intervention. Does the APP III concept of the metabolic syndrome have any redeeming virtues? That is a question that only the reader can answer.