

Full Length Research Paper

Hypoadiponectinemia: A link between visceral obesity and metabolic syndrome

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Metabolic syndrome (MetS) represents a combination of cardio-metabolic risk factors, including visceral obesity, glucose intolerance or type 2 diabetes, elevated triglycerides, reduced HDL cholesterol, and hypertension. MetS is rapidly increasing and prevalent worldwide as a consequence of the “epidemic” obesity, with a considerable impact on the global incidence of cardiovascular disease and type 2 diabetes. At present, some authors are disappointed on the role of insulin resistance as unifying factor in the occurrence of all the MetS components, whereas the role of visceral obesity is increasing. This review summarizes and critically evaluates the clinical and scientific evidence supporting the existence of MetS as a “fatal consequence of visceral obesity”. In view of this, the effects of some adipocytokines and other proinflammatory factors produced by fat accumulation on the occurrence of the MetS have been also emphasized. Accordingly, the “hypoadiponectinemia” has been proposed as the most interesting new hypothesis to explain the pathophysiology of MetS.

Key words: Metabolic syndrome, visceral obesity, adipocytokines, adiponectin, cardiovascular disease.

INTRODUCTION

The combination of cardio-metabolic risk factors known as “Metabolic syndrome (MetS)” was described in the past 70 years by several authors (Avogaro and Crepaldi, 1965; Reaven, 1988). Reaven used the term “Syndrome X”, to attribute to the clustering (arterial hypertension and metabolic risk factors) role of a clinical entity related to insulin-resistance calling this condition “Insulin-Resistance Syndrome”.

More recently Harold Bays (Bays et al., 2005) coined the term “adiposopathy”, pointing to a particular alteration of the function of the adipose tissue, promoted and exacerbated by fat accumulation and by physical inactivity, which might represent the beginning of the appearance of the components of MetS and therefore of atherosclerosis (Figure 1).

This hypothesis has been promoted by ourselves since 1996 (Licata et al., 1996), and recent data seem attractive to confirm it, indicating that visceral obesity may

be considered a unifying factor in the occurrence of MetS, promoting new definition criteria and a reevaluation of its pathogenesis. In fact, it is abundantly demonstrated that some measurements both of obesity degree, such as BMI, and of fat distribution, such as waist/hip ratio or waist circumference, correlate with all the components of MetS (Bruce et al., 2009) (Figure 2).

It also has to be emphasized that obesity and in particular visceral obesity have to be actually considered an independent cardiovascular risk factor. In fact, the results from extensive epidemiological studies suggest that obesity, especially when characterized by visceral fat distribution, is associated with higher prevalence or incidence of cardiovascular diseases and overall mortality (Licata et al., 1996; Calle et al., 1999; Kaplan et al., 2002).

All these data suggest that there is an increase in the risk of chronic disease associated with a progressive increase in total adiposity. This hypothesis is supported by several studies following the discovery of Leptin in 1994, indicating that the adipose tissue cannot be considered merely as an organ that passively stores excess energy but as an endocrine organ, directly

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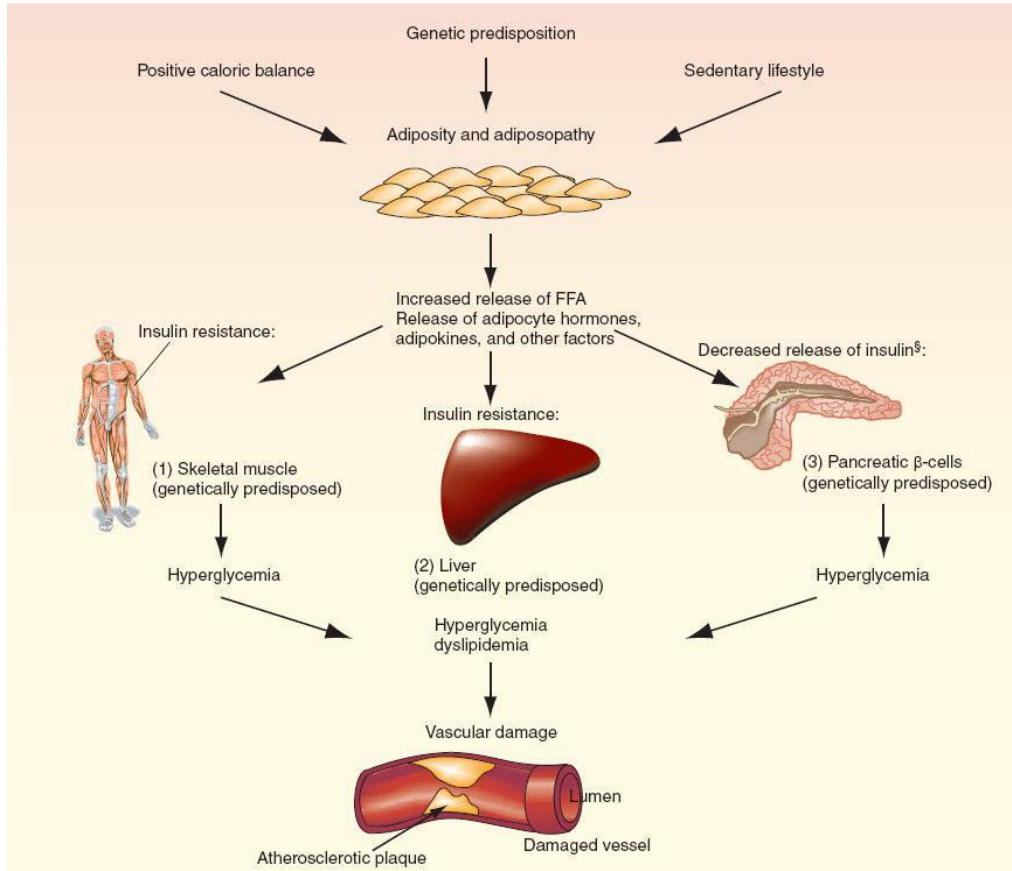


Figure 1. Relationship between adiposopathy, metabolic syndrome and atherosclerosis (*).
 (*) From Bays et al. (2005) modified.

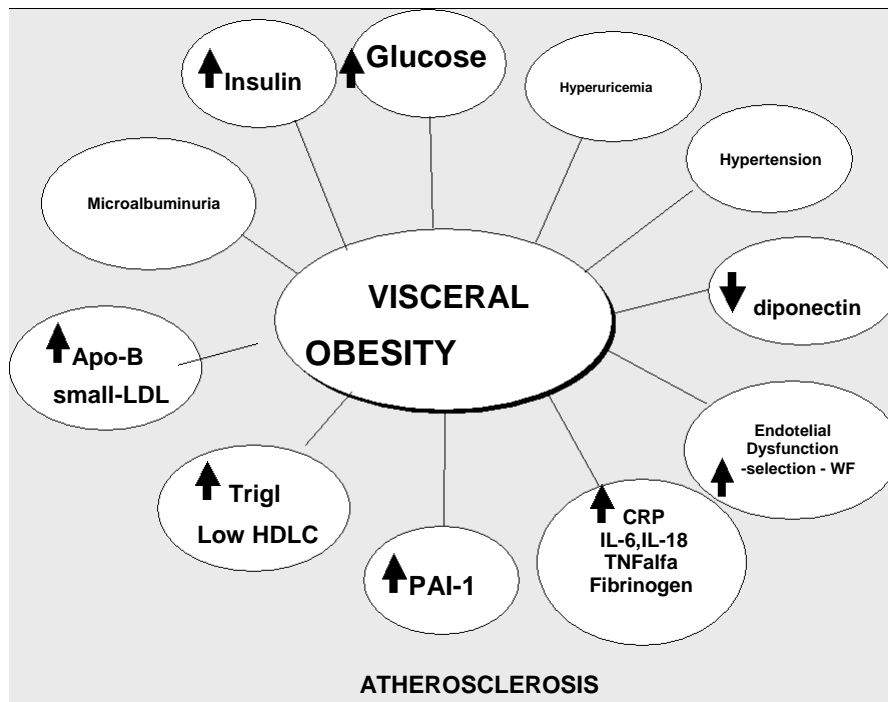


Figure 2. Relationship between visceral obesity and atherosclerosis.

Table 1. Principal metabolic syndrome definitions.

	WHO (1999)	EGIR (1999)	NCEP ATP III (2001)
Fasting plasma glucose	Glucose intolerance, IGT or Insulin resistance (defined as diabetes and/or insulin resistance hyperinsulinemia – top 25 % or fasting together with two or more of the insulin values among the non-diabetic following:	population). Plus two of the following: 6.1 mmol/l (110 mg/dl) but non-diabetic	Three or more of the following five factors: Skd 5.6 mmol/l (100 mg/dl)
Blood pressure	> 140/90 mmHg	140/90 mmHg or treatment	130/ 85 mmHg
Triglycerides	Raised plasma triglycerides 1.7 mmol/l (150 mg/dl) and/or	> 2.0 mmol/l (178 mg/dl) or treatment and/or	1.7 mmol/l (150 mg/dl)
HDL-cholesterol	Men: < 0.9 mmol/l (35 mg/dl) Women: < 1.0 mmol/l (39 mg/dl)	< 1.0 mmol/l (39 mg/dl) or treatment	Men: < 1.03 mmol/l (40 mg/dl) Women: < 1.29 mmol/l (50 mg/dl)
Obesity	Men: waist-hip ratio > 0.90 Women: waist-hip ratio > 0.85 and/or BMI > 30 Kg/ ²	Men: waist circumference 94 cm Women: waist circumference 80 cm	Men: waist circumference > 102 cm Women waist circumference > 88 cm
Microalbuminuria	Urinary albumin excretion rate 20 g/min or albumin: creatinine ratio 30 mg/g		

involved in the pathophysiology of the MetS and obesity-related cardiovascular disease (Bergman et al., 2007). In this area particular importance has been attributed to the role of adiponectin (Weyer et al., 2001).

In this review we have reported some recent findings on the diagnostic criteria, pathophysiology and management of MetS, suitable for supporting a possible new hypothesis indicating that this syndrome may be considered “a fatal consequence of visceral obesity” and related to hypoadiponectinemia.

DIAGNOSTIC CRITERIA OF METS

Although the concept of the MetS is now accepted (Bruce et al., 2009), in the last years several controversies have involved the definition, pathogenesis and therapy of MetS (Reaven, 2005).

In an attempt to provide a tool for clinicians and researchers, WHO proposed a set of criteria (WHO / NCD / NCS, 1999). Subsequently, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP3 2001) and the European group for the study of insulin resistance (Balkau and Charles, 1999) have formulated definitions in agreement with the core components of the MetS (glucose intolerance, obesity,

hypertension and dyslipidaemia). However, they provide differential criteria to identify such as a cluster (Table 1). In 2005 the American Heart Association proposed that any 3 of 5 criteria constitute diagnosis of MetS: elevated blood pressure, elevated waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated fasting glucose (Grundy, 2005). In the same year, international diabetes federation (IDF) convened a workshop, including worldwide experts, as well as from WHO and NCEP/ATP III, to establish a new definition of the MetS, suitable for use in clinical practice worldwide. After this workshop, a consensus statement was produced, reviewed and approved by all the participants. According to the definition of IDF (Alberti et al., 2006), for subjects to be defined as having the MetS, they must have visceral obesity plus any two of four additional factors (Table 2). A major issue for the IDF consensus consultation was the fact that criteria used for obesity in Asian and other populations could be different from those used in the West. The amount of obesity associated with increased risk differs between populations (Table 3). Accordingly, this is the first recommendation that includes visceral obesity as an obligatory component of the MetS.

The existing definitions are based on different expert opinions, but few longitudinal epidemiological studies have shown the impact of all these classifications on

Table 2. International Diabetes Federation metabolic syndrome world-wide definition.

Central obesity	Waist circumference – ethnicity specific plus any two of the following
Raised triglycerides	1.7 mmol/l (150 mg/dl) or specific treatment
Reduced HDL-Cholesterol	< 1.03 mmol/l (40 mg/dl in males) < 1.29 mmol/l (50 mg/dl) in females or specific treatment
Raised blood pressure	Systolic 130 mmHg or Diastolic 85 mmHg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	Fasting plasma glucose 5.6 mmol/l (100 mg/dl) or previously diagnosed Type 2 diabetes. If > 5.6 mmol/l or 100 mg/dl, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome.

Table 3. Values of waist circumference according to ethnicity.

Europids	- Male >94 cm - Female >80 cm
South Asians	- Male >90 cm - Female >80 cm
Chinese	- Male >90 cm - Female >80 cm
Japanese	- Male >85 cm - Female >90 cm
South and Central Americans	Use South Asian recommendations
South Saharian Africans	Use European data
Eastern Mediterranean and Middle East	Use European data

mortality. The required presence of three out of the five MetS components in order to establish a diagnosis of MetS is the common feature of three more followed classifications. The heterogeneity of the MetS and cluster of risk factors was clearly pointed out in a recent study (Strazzullo et al., 2008) indicating the need to reach a consensus around a univocal definition of the diagnostic criteria if the recognition of MetS has to be implemented in the clinical practice.

VISCERAL OBESITY AS A LINK BETWEEN MetS COMPONENTS

Insulin resistance has been long considered to have a central role in the pathophysiology of MetS. However the

metabolic disorders of MetS, except for hyperglycemia, cannot be interpreted by insulin resistance. An important question is, then: why does visceral fat accumulation cause common disorders? More importantly, why is this syndrome so atherogenic? To answer these questions, we have reported some data indicating the importance of visceral obesity in the development of MetS. We have also analyzed the crucial role of adipocytokines to support the hypothesis that MetS may represent a fatal consequence of visceral obesity.

The adipocytokines

To elucidate the molecular mechanism of visceral fat-related disease, several studies have investigated the

biological characteristics of both visceral and subcutaneous adipose tissue by analysis of the gene-expression profile. Of the gene group classified by function and localization, approximately 20% of all genes in the subcutaneous adipose tissue encode secretory proteins and about 30% in the visceral adipose tissue. These bioactive substances are classified as "adipocytokines", and are subdivided into adipocytokines adipose tissue specific bioactive substances (that is, leptin and adiponectin), and adipocytokines abundantly secreted from adipose tissue which is nonspecific for adipose tissue (that is, PAI-1, tumor necrosis factor, interleukines, etc) (Matsuzawa, 2006). Adipocytokines have a role both in the regulation of the glucose and lipid metabolism, in the control of oxidative stress and in the maintenance of the vascular wall integrity. For example TNF-, IL-6, and leptin are able to induce insulin-resistance, whereas adiponectin improves insulin-sensitivity. Several studies suggest that leptin may be considered an important link between central obesity, hypertension and MetS. Results from an Italian prospective study emphasize that higher circulating plasma leptin levels are a significant predictor of the risk of MetS and, in particular, for higher blood pressure and IFG components (Galletti, 2007).

The TNF- has a paracrine and autocrine action; it is able to increase lipolysis and FFA circulating and muscular levels which will then interfere with the insulin signal. In addition, it has a direct role in the pathogenesis of endothelial dysfunction and atherosclerosis, promoting circulating monocytes adhesion and migration in the arterial wall and their conversion into macrophages. IL-6 is secreted by the visceral deposits in the portal system and is able to alter the insulin signal at the liver level, so will stimulate the production and secretion of triglycerides by the liver, and gluconeogenesis with compensatory hyperinsulinemia. IL-6 reduces nitric oxide production and determines intravascular recruitment of the leukocytes. It increases liver synthesis of C reactive protein and promotes the development of the pro-atherogenic inflammatory pattern (Matsuzawa, 2006).

HYPOADIPONECTINEMIA: A LINK BETWEEN VISCERAL OBESITY AND MetS

Adiponectin was discovered during gene-expression profiling of human adipose tissue conducted by the human cDNA project. Located on chromosome 3q27, a locus for diabetes susceptibility (Sarzani et al., 2008), adiponectin encodes a secretory protein expressed exclusively in adipose tissue. Adiponectin contains 244 amino acids, a signal peptide, a collagen-like domain at its N-terminus and a globular domain at its C-terminus, which shares sequence similarities with collagens X and VIII as well as complement factor C1q. Despite the absence of primary sequence similarity, the crystal

structure of the C-terminal globular domain resembles that of TNF- α . During the same period, two other groups identified ACRP30 and AdipoQ as mouse homologs of adiponectin. Adiponectin has anti-inflammatory and anti-atherogenic properties (Matsuzawa, 2006). The adiponectin receptors (adipoR1 and adipoR2) have been cloned. AdipoR1 is expressed ubiquitously, whereas adipoR2 is predominantly expressed in the liver, and are both correlated positively with insulin sensitivity. The plasma range of adiponectin in humans is 3 - 30 g/ml, accounting for 0.01% of total plasma protein (Kadowaki and Yamauchi, 2005). Adiponectin exists in a wide range of multimer complexes in plasma and combines via its collagen domain to create three major oligomeric forms: trimers, hexamers and a high-molecular-mass form. A smaller form of adiponectin that includes the globular domain cleaves proteolytically from full-length adiponectin and exists in plasma, although in very small amounts (Kadowaki and Yamauchi, 2005; Takahashi et al., 2000).

Biological effects of adiponectin in experimental models

Data from animal models demonstrate the biological effects of adiponectin. In particular it is able to influence insulin sensitivity, glucose and lipid metabolism (Matsuzawa, 2006; Kadowaki and Yamauchi, 2005) and to modulate blood pressure regulation and hypertensive target organ disease (Ouchi et al., 2003)

In addition, cell biological studies demonstrate multiple antiatherogenic functions for adiponectin. When the endothelial barrier is injured by attacking factors (oxidized LDL, chemical substances and mechanical stress), adiponectin accumulates in the subendothelial space of vascular walls by binding to subendothelial collagen, at which point antiatherogenic properties of adiponectin become apparent (Ouchi et al., 2003). Adiponectin also attenuates growth factor induced proliferation of visceral smooth muscle cells by the inhibition of mitogen activated protein-kinase. It suppresses foam-cell formation by the inhibition of the expression of scavenger receptors (Matsuzawa, 2006) and protects plaque from rupture by inhibition of matrix metalloproteinase function through the induction of interleukin-10 dependent production of tissue inhibitor metalloproteinase. In addition, adiponectin-deficient mice show enhanced left ventricular hypertrophy and increased mortality under pressure overload. On the contrary, adenovirus mediated adiponectin supplementation attenuates cardiac hypertrophy in response to pressure overload (Shibata et al., 2004).

Biological effects of adiponectin in humans

The first indication that adiponectin might have a role in

human obesity, is derived from the report of Hu, indicating that the expression of adiponectin using Northern blots is reduced in the adipose tissue of obese mice and humans (Tarquini et al., 2007; Hu et al., 1996). However, data on adiponectin in humans are increased by the introduction of an adiponectin immunoassay (Arita et al., 1999). Accordingly, plasma adiponectin levels are found higher in women than in men and in non-obese than in obese subjects (Weyer et al., 2001).

Therefore, adiponectin is the only fat protein that has down-regulation in relation to weight gain, and it is possible that an accumulation of visceral fat might produce inhibiting factors for adiponectin synthesis or secretion, such as TNF alpha (Halleux et al., 2001; Maeda et al., 2001).

Lower plasma levels of adiponectin are also predictive of type 2 DM and are found in diabetic subjects, and in patients with hypertriglyceridemia, low HDL-cholesterol and hypertension (Matsuzawa, 2006; Kadowaki and Yamauchi, 2005; Ouchi et al., 2003; Diez et al., 2003). Human subjects with more cardiovascular risk factors, or with MetS, would be expected to have lower plasma adiponectin levels (Shargorodsky et al., 2009).

In this area of interest, conflicting evidences have emerged about the prognostic role of adiponectin on CVD. In fact antiatherogenic effects of adiponectin have also demonstrated in some clinical studies, indicating that higher adiponectin levels are associated with a reduced risk of acute myocardial infarction in men (Pischon et al., 2004). Subjects with hypoadiponectinemia (plasma levels < 4 g/ml) have an increased risk of coronary heart disease and multiple metabolic risk factors (Kumada et al., 2003). Subjects with renal insufficiency with higher adiponectin levels are free from cardiovascular death for a longer period than those with renal insufficiency and low adiponectin levels (Zoccali et al., 2002). These data are also confirmed by the results of some large epidemiological studies (Koenig et al., 2006; Frystyk et al., 2007).

On the contrary, other prospective studies (Sattar et al., 2006; Lawlor et al., 2005) do not report a significant cardioprotective effect of adiponectin. These conflicting results raise the possibility that adiponectin may have different prognostic implications in population at different risk of vascular disease.

In addition to the studies linking plasma adiponectin levels to various human diseases, human genetic studies provide evidence of an association between lower adiponectin levels and obesity, DM, dyslipidemia, hypertension, MetS, insulin resistance and CAD (Matsuzawa, 2006; Ouchi et al., 2003). Interestingly, the association of the adiponectin genetic variation with obesity, MetS, and DM has been recently reported in a Taiwanese elderly population, suggesting the genetic effects of adiponectin inherited at birth could be extended all the way to this later stage of life (Vozarova et al., 2002). These data suggest that in addition to

hypoadiponectinemia associated with visceral fat accumulation, genetic hypoadiponectinemia may exhibit a clinical phenotype of MetS.

Relationship among adiponectin, obesity, and insulin resistance

Adiponectin may be considered the molecular link between obesity and insulin resistance. Is hypoadiponectinemia the cause or the result of obesity and adipose tissue-specific insulin resistance in humans?

Animal experiments using injection of recombinant adiponectin proteins and the adiponectin KO mice clearly demonstrate that adiponectin produces effects on both body weight and insulin sensitivity in the liver and muscle (Ouchi et al., 2003). However, the severity of obesity observed in adiponectin deficiency is totally out-weighted by that in leptin-deficient mice (*ob/ob*), suggesting that leptin is the master hormone of long-term weight regulation in animals. Therefore, hypoadiponectinemia is not likely the main cause of obesity and adipose tissue-specific insulin resistance. Low adiponectin expression, on the other hand, is found in many animal models of obesity (Vozarova et al., 2002).

The metabolic effects of adiponectin, including lowering glucose, enhancing fatty acid -oxidation, and improving insulin sensitivity, appear to be convincing and significant. Therefore, it is reasonable to propose that hypoadiponectinemia is the result of obesity and adipose tissue-specific insulin resistance, but it is the mediator from obesity to the insulin resistance in the other peripheral tissues (such as liver and muscle) and associated metabolic outcomes. Human genetic studies clearly demonstrate that adiponectin gene variants are one of the causes of obesity and insulin resistance, usually with an odds ratio of less than 2, which is as expected for a polygenic disorder. Hypoadiponectinemia also does not predict obesity in a human prospective study while it is shown to predict the development of type 2 DM. Interestingly, significant body weight reduction in humans was shown to raise plasma adiponectin levels accompanied with improved insulin sensitivity (Duncan et al., 2004).

The next question then is what causes low adiponectin expression in obesity, and how does this happen. It is possible to hypothesize that the expression of adiponectin in the adipose tissue is inhibited by the mechanisms related to obesity-induced insulin resistance, such as inflammation. This inhibition could be reversed by weight reduction, which improves adipose tissue-specific insulin sensitivity. In human subjects treated with PPAR 2 agonist, the insulin sensitizer that mainly acts in the adipose tissue increases plasma adiponectin, by approximately two fold in spite of a significant body weight gain, which is almost routinely seen in this kind of treatment (Yang et al., 2002). These

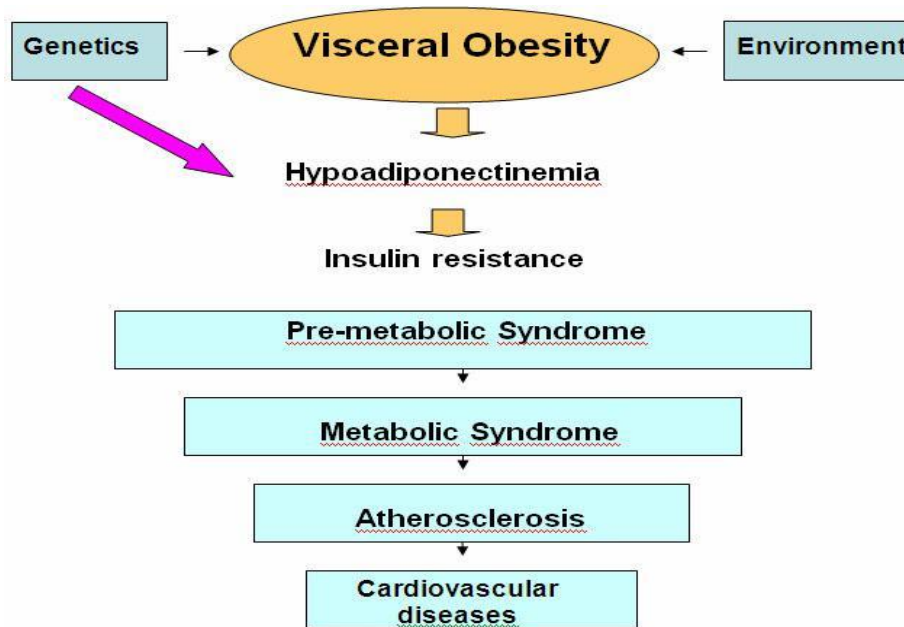


Figure 3. Role of visceral obesity on the pathogenesis of the metabolic syndrome.

findings indicated that improving adipose-specific insulin sensitivity increase adiponectin gene expression irrespective of the changes in adiposity.

Therefore, adipose tissue-specific insulin sensitivity rather than general adiposity itself determines the adiponectin expression in adipose tissues. Secondary to the increased plasma adiponectin, the whole body insulin sensitivity would be expected to improve.

We may be able to elucidate the molecular mechanisms of obesity-induced adipose tissue-specific insulin resistance by studying the molecular regulation of adiponectin gene expression.

Conclusions

The existence of multiple definitions for MetS has inevitably led to confusion and to the publication of many studies comparing the merits of each definition. There is thus a strong need for one simple definition/diagnostic tool for clinical practice that might be used easily in any country and by any physician. This should facilitate a better understanding of MetS and targeting the best care to people who would benefit from cardiovascular risk reduction.

In our opinion, data reported in this review may indicate that MetS may be considered “a fatal consequence of visceral obesity”. This hypothesis may be further supported by the recommendations of all International societies that include weight loss as the first line preventive and therapeutic strategy of MetS. In fact, the recommendation of NCEP-ATP III and IDF identify the

treatment of obesity and the principal therapeutic target in the management of the MetS, since it is known that weight loss improves all of the associated risk factors (WHO/NCD/NCS, 1999; NCEP/ATP3, 2001; Balkau and Charles, 1999; Grundy, 2005; Alberti et al., 2006).

Accordingly, adiponectin may be considered an important modulator of the adipovascular axis that affects the cardiovascular risk profile, from the premetabolic syndrome, through the metabolic syndrome to overt atherosclerosis. However, hypoadiponectinemia alone may represent an early phenomenon that long precedes the occurrence of all components for overt MetS (Figure 3).

Even in humans, the protective role of adiponectin seems to be confirmed by the finding that thiazolidinediones (Yang et al., 2002), ACE-I and ARBs (Furuhashi et al., 2003) are associated with an increase in adiponectin levels and with an improvement in insulin sensitivity and endothelial dysfunction. The early identification of patients at cardiovascular risk means in current practice, a search for such indices of metabolic alterations and proinflammatory status as adiponectin.

Adipocytes secrete several adipocytokines to control the function of other organs and cells. Lifestyle factors, such as overeating or physical inactivity induce visceral fat accumulation that results in the dysfunction of adipocytes. Oversecretion of offensive adipocytokines (PAI-1, TNF alfa, interleukins etc.) and hyposecretion of defensive adipocytokines, such as adiponectin, might be the major mechanism of life style-related disorders (diabetes, hypertension, hyperlipidemia).

In conclusion, with aging and increasing obesity, all

components of MetS appear and worsen. Many obese subjects develop type 2 diabetes, hyperdyslipidemia, and hypertension. As the visceral obesity and MetS advance, risk for cardiovascular disease increase.

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