Obesity and Cardiovascular Disease: Pathogenetic Role of the Metabolic Syndrome and Therapeutic Implications

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Interests:
1. Etiopathogenesis of insulin resistance and pathophysiology of the metabolic syndrome.

2. Management of dyslipidemia, diabetes and obesity.

3. Prevention of cardiovascular disease.

Introduction:

Both primary and secondary prevention strategies for cardiovascular disease (CVD) currently revolve around the concept that a concerted management of major risk factors, conditions that have been associated with increased risk for CVD in population studies, will reduce morbidity and mortality from CVD. Some of the major risk factors management, such as plasma lipids control, blood pressure lowering, life-style modifications and diabetes have been shown to induce CVD risk reduction in clinical trials. Based on the data from clinical trials we now recommend our patients following "healthy" life style modifications, by discontinuing smoking, decreasing fat and cholesterol content in the diet and exercise regularly. We also recommend keeping lipids levels within the goals set by the ATP II (1), blood pressure below 140/90 mm Hg (2) and glycemic control with HbA1c below 7% (3). Population surveys indicate that these strategies for CVD prevention have a significant positive impact and there is a secular trend towards a reduction in CVD mortality (4). However, despite a favorable trend, CVD remains the # 1 cause of morbidity and mortality in US (5). Many factors may account for the lack of a more significant impact of current CVD prevention strategies on the prevalence of CVD morbidity and mortality. One of these factors is the growing epidemic of obesity (6), which may, in the near future, significantly offset our efforts in both primary and secondary prevention of CVD. Obesity is a major modifiable risk factor for CVD and certainly increases the risk of developing conditions, such as type 2 diabetes, dyslipidemia and hypertension that, in turn, increase CVD risk. Reduced physical activity is often associated with obesity and seems to have an independent role on CVD risk. Despite the continuous emphasis of public health officials and investigators on the importance of obesity and physical inactivity on CVD, little attention to these problems is generally given in the routine management of our patients. Perhaps the paucity of effective intervention tools for weight management and life-style modifications and the incomplete knowledge of the mechanisms leading from obesity and reduced physical activity to CVD, are discouraging facts that invite physicians to often avoid an appropriate evaluation of obesity and obesity-related metabolic abnormalities of their patients.

This grand round will focus on the metabolic syndrome as a major mechanistic link between obesity and CVD. We will discuss the pathophysiologic mechanisms relating obesity, lack of adequate physical activity, the metabolic syndrome and CVD. We will then discuss therapeutic options to reduce CVD risk in the obese patients. The recent advances in the knowledge of pathophysiology and treatment of the metabolic syndrome should encourage physicians to pay more attention to the evaluation of the obesity status and level of physical activity of their patients. **An increased awareness of obesity and CVD, the use of all available tools to control the complex metabolic abnormalities of obese patients are necessary steps to achieve a more positive impact of current preventive strategies for CVD in our population.**

Obesity, lack of physical activity and cardiovascular disease: general considerations.

Definition: Obesity is defined by the presence of excessive total body fat. Since total body fat content is difficult to measure directly and since it correlates with total body mass divided by height^2 (Body Mass Index=BMI), overweight and obesity are commonly evaluated with simple measurement of height and weight and are defined as BMI between 25 and 29.9 kg/m2, and BMI above 30 kg/m2, respectively (Table 1) (7). Another important component for the definition of obesity includes the pattern of fat distribution. A waist circumference above 104 cm (or 40 in) for men and above 88 cm (35 in) for women indicates abdominal obesity (also called truncal, upper body, male-type, android, or visceral

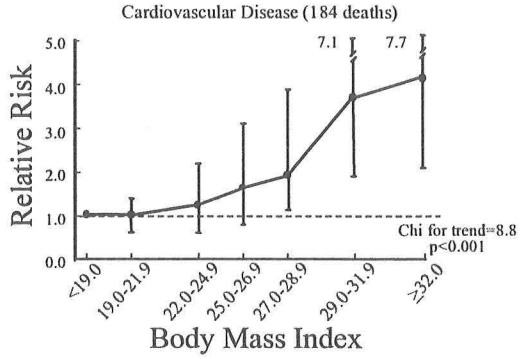
obesity). A waist circumference below or equal 104 cm for men and below or equal 88cm for women, indicates lower body obesity (also called female-type or gynoid obesity), in which the excess weight accumulates in the femoral and gluteal regions. BMI and fat distribution are independently associated with increased risk of obesity-related morbidity and mortality, including CVD (8-15).

Table 1: Classification of obesity (Ref. 7)

			Disease Risk Relative to Normal weight and Waist Circumference	
	BMI kg/m²	Obesity Class	Men ≤102 cm (≤40 in) Women ≤88 cm (≤35 in)	>102 cm (>40 in) >88cm (>35 in)
Underweight	<18.5			
Normal	18.5-24.9			
Overweight	25.0-29.9		Increased	High
Obesity	30.0-34.9	I	High	Very High
	35.0-39.9	II	Very High	Very High
Extreme Obesity	> 40	III	Extremely High	Extremely High

Epidemiology: The morbidity and mortality associated with being overweight or obese have been known to the medical profession for more than 2000 years. Hippocrates was the first to note a relationship between obesity and sudden death (8). More recently, actuarial data from the life insurance industry and epidemiological studies have proved that obesity plays a major role in the development of various conditions, such as cardiovascular disease (CVD) and increases the risk of death. The Nurses' Health Study (9), for example, examined the association between the BMI and mortality in a cohort of 115,195 women. These women were 30 to 55 years of age and had no known cardiovascular disease at study entry in 1976. During 16 years of follow-up, 881 women died from cardiovascular disease. Relative risk rose progressively in women with a BMI above 29 kg/m2 (Figure 1). Among women with a BMI at or above 32.0 kg/m2 who had never smoked, the relative risks of death from cardiovascular disease was 4.1, compared with women with a BMI below 19.0. The mortality rate was lowest among women who weighed at least 15 percent less than the United States average for women of similar age and among those whose weight had been stable since early adulthood.

Fig. 1: Relationship between obesity and CVD (Ref. 9)



These results are consistent with a study of 8800 Seventh Day Adventist men who were followed for 26 years (10). Men with a BMI greater than 27.5 kg/m2 had a twofold risk of death from all causes and a 3.3-fold risk of death from coronary heart disease (CHD) compared with those with a BMI <22.3 kg/m2. The mean age at death of men with a BMI <22.3 kg/m2 and >27.5 kg/m2 was 80.5 and 75.8 years, respectively.

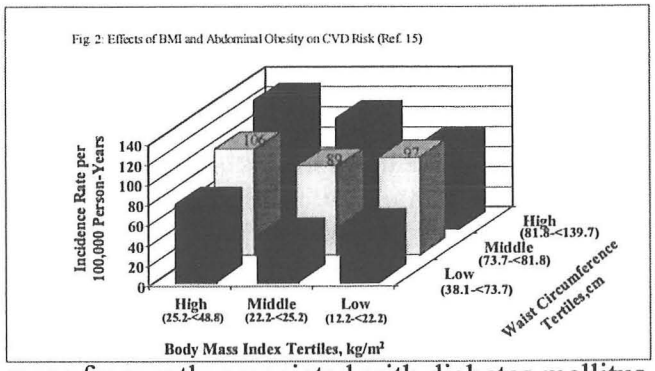
Table 2: Features of obesity that modify CVD risk

• Body Fat Distribution	• Gender
• Physical Activity	• Ethnicity
• Co-morbidities	• Weight Gain
	• Weight Cycling
	• Age

The relationship between obesity and cardiovascular risk may be influenced by several features of obesity (Table 2). The main risk-modifying features of obesity are listed in table 2 and include degree of weight gain, age, weight cycling, body fat distribution, gender, ethnicity, cardiovascular fitness, the presence of co-morbidities. The mortality risk associated with greater body weight may vary depending upon patient age. In one study, over 62,000 men and 262,000 women were followed for twelve years (11). Greater BMI was associated with higher mortality from all causes and from cardiovascular disease in men and women up to 75 years of age. Nevertheless, the

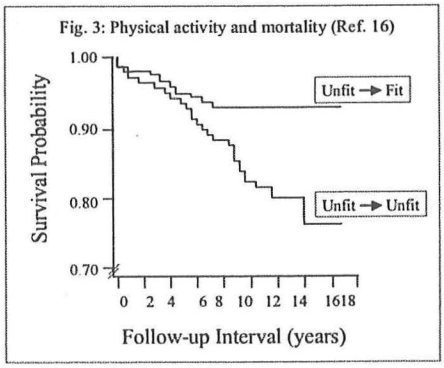
relative risk associated with greater BMI declined with age. As an example, the relative risk of cardiovascular death associated with a one-point increase in BMI was 1.10 for 30 to 44 year-old men and 1.08 for women of the same age. For 65 to 74-year-old men and women, these numbers declined to 1.03 and 1.02, respectively. Age of onset of overweight and obesity, as well as duration and degree of weight gain are other important factors that modify the relationship between obesity and CVD morbidity and mortality (12).

Among the various risk-modifying features of obesity, body fat distribution and level of physical activity deserve special attention.



Body fat distribution – The pattern of regional fat distribution plays a major role in the excess death associated with obesity. The importance of abdominal obesity was suggested by life insurance data at the beginning of the 20th century and confirmed later by epidemiological and clinical studies. However, the first systematic evaluation of the role of fat distribution on risk for obesity-related morbidity was first introduced by Vague (13), who in 1956 coined the term "android" and "gynoid" obesity. In that study, android obesity was found to be more frequently associated with diabetes mellitus, coronary artery disease than gynoid obesity. Since that original observation longitudinal studies have confirmed that android, or upper body, obesity strongly predicts CVD, independently of overall excess of fat. In a population study of 1462 Swedish women ages 38 to 60, for example, mortality and the risk of myocardial infarction was increased when a high WHR was used as an index of central fatness (13). As illustrated in figure 2, the Nurse's Health study (15) revealed that women with waist-to-hip circumference ratio of 0.88 or higher have higher relative risk for CVD (RR=3.25) than women with waist-to-hip ratio less than 0.72. The increased relative risk in the women with abdominal obesity was found independent of BMI in that particular study.

Sedentary lifestyle – According to the "Physical activity and health" report by the Surgeon General (1996), low levels of physical activity, resulting in fewer calories used than consumed, contribute to the high prevalence of obesity in US. While reduced physical activity definitely contributes to the development of obesity, it has also a direct effect in predisposing to CVD. Low levels of physical fitness are associated with an increased risk of CVD, with age-adjusted relative risks of CVD up to eightfold greater for the unfit groups than their fit counterparts. A longitudinal study conducted by Blair et al. (16) on 9777 men aged 20 to 82 years, followed for 19 years, revealed that men who maintained or improved adequate physical fitness were less likely to die from CVD during follow-up than persistently unfit men (Fig. 3). Another study conducted in a Dutch elderly population (mean age 71.4 years) revealed that mortality risk from CVD decreased with increasing physical activity with adjusted relative risk of 0.70 in the highest tertile of total physical activity (17).



The observation that obesity and sedentary life-style have a major impact on CVD morbidity and mortality, together with the significant increase in the prevalence of these conditions, has induced the American Heart Association (AHA) to recently classify obesity as a major, modifiable risk factor for CVD (18). This position is an encouragement to focus researchers' and physicians' attention on this growing health problem for Americans. NHANES study reveal that the prevalence of obesity has progressively increased during the last 20 years and has now estimated to affect over 50% of the U.S. population (6). This condition has the potential to significantly affect the status of overall cardiovascular health in our population. A better knowledge of the exact nature of the relationships between obesity and CVD would allow the evaluation of better strategies at both population and patient level to reduce the burden of CVD in US.

Pathophysiology: Obesity, particularly of the abdominal type, and sedentary life style may induce excessive CVD morbidity and mortality through several mechanisms. First, obesity promotes the development of multiple morbid conditions that are independent risk factors for CVD, including type 2 diabetes, hypertension, dyslipidemia. Second, obesity promotes the clustering of these risk factors, thus increasing the risk exponentially. Third, obesity has an effect on the cardiovascular system that appears to be independent of diabetes, hypertension and dyslipidemia. These "independent" effects of obesity on CVD could be related to sub-clinical conditions that the recent technological advances have allowed detecting in obese patients. Table 3 is a summary of the possible clinical and sub-clinical abnormalities that could play a role in mediating the effects of obesity on cardiovascular system. One sub-clinical factor that seems to have a major pathophysiologic role is **"insulin resistance"**, a condition characterized by defective biological activity of insulin, which is often seen in obese patients and in patients with sedentary life-style, and that has been associated with most of the other clinical and subclinical abnormalities found in obesity. Obesity-related insulin resistance has also been considered as the major mechanism leading to the typical clustering of various morbid conditions, such as diabetes, dyslipidemia and hypertension, seen in obesity. If insulin resistance is the common pathohysiologic denominator that promotes cardiovascular events in the obese and sedentary population, the first question to answer is: **what are the mechanisms that relate obesity and sedentary life-style to insulin resistance?** In the next section the known mechanisms of interaction will be discussed.

Table 3: Mechanism playing a role in the excessive CVD of patients with obesity and sedentary life-style

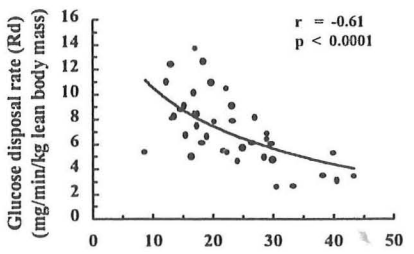
Clinical	Sub-clinical
• Dyslipidemia	• Insulin Resistance
• Type 2 Diabetes	• Cardiac Hypertrophy
• Hypertension	• Increased Vascular Thickness
	• Pro-coagulant state
	• Endothelial dysfunction

Obesity, lack of physical activity and insulin resistance: the result of a complex interaction between genes and environment.

Studies performed in various ethnic groups and in both genders have shown that increasing body fat content is linearly and inversely related to insulin-mediated peripheral glucose disposal, an important and quantifiable biological action of insulin (19-22). The inverse relationship persists up to a body fat content of about 28% of total body weight (Fig. 4). When total body fatness exceeds 28%, the linearity

of the relationship is lost and peripheral glucose disposal is uniformly suppressed with little inter-individual variability. On the other hand, in lean subjects a significant variability of insulin sensitivity has been uniformly observed. Therefore, some individuals may be significantly insulin resistant despite minimal accumulation of body fat.

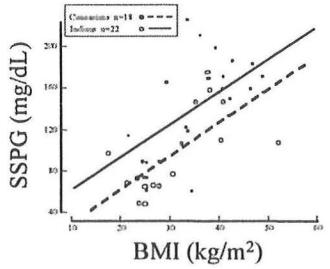
Fig. 4: Relationship between obesity and insulin resistance (Ref. 22)



In a study of Rosenthal et al. (22) sedentary life-style was associated with insulin resistance independent of generalized obesity and age in non-diabetic individuals. Therefore, it is possible that lean individuals who do not exercise are insulin resistant despite the absence of obesity. The reverse has also been observed with insulin resistance reduced by exercise in obese individuals. Level of physical activity may influence the relationship between obesity and insulin resistance and may explain at least in part the variability of insulin resistance in the general population.

Another important factor in determining the variability of insulin resistance in subjects with different degree of body fat content is the way fat is distributed. Several studies have demonstrated that when fat is distributed preferentially in the abdominal area, insulin-mediated glucose disposal is reduced, independent of overall degree of adiposity (19,22-24). Therefore, it is conceivable that even in the absence of significant accumulation of total body fat, even a minimal deposition of fat in the abdominal area may induce insulin resistance. Thus, total body fat, body fat distribution and level of physical activity influence significantly the variability of insulin sensitivity in the general population. The role of these variables in modulating the obesity and insulin resistance is evident in population studies that include various ethnic groups. For example, American life-style has an impact on Pima Indians living in Arizona who are significantly more obese and insulin resistant than genetically related Native-Americans living in Mexico (26). Also, Hispanics who live in Mexico have lower incidence of obesity and abdominal obesity than Hispanics living in US (27). Furthermore, US-born Hispanics have more obesity, particularly central obesity at younger age than the first generation Hispanic-Americans and the Non-Hispanic Whites (28). Similarly, Japanese who live in Japan have low prevalence of obesity and type 2 diabetes compared to White-Americans (29). However, Japanese-American migrated to Hawaii have higher prevalence of abdominal obesity and type 2 diabetes that become even more prevalent in Japanese-Americans living in Continental US (29,30). Similar data are available for other Asian groups migrated to western Countries (31,32) and support the notion that environmental conditions, such as hypercaloric diet and sedentary life-style play a major role in the development of insulin resistance and its related morbidity. This is modulated by the tendency of a particular group of people to develop abdominal obesity. So, ethnic groups, such as the Hispanics and the Asians that are more prone to develop abdominal obesity have more insulin resistance than those, like the African-Americans or White-Americans, who develop less abdominal obesity for similar degree of generalized adiposity. Ethnic differences in fat distribution could, at least in part, explain the observed differences in the relationship between obesity and insulin resistance in various ethnic groups. In figure 5 the relationship between BMI and insulin sensitivity is compared in Pima Indians and Caucasians. This study

Fig. 5: Differences in the relationship between BMI and insulin resistance in Caucasians and Asian Indians (Ref. 33)



(33) clearly shows that for any degree of obesity, Pima Indians have more insulin resistance than Caucasians. Similar data are available for Mexican-Americans compared to White-Americans (34). In the IRAS study (35), African-American subjects have been shown to be more insulin resistant than non-Hispanic whites for a similar degree of obesity. McKeigue et al. (32) have reported that Asian Indians living in U.K. are more insulin resistant than weight-matched Caucasians. Therefore, although there is no doubt that obesity, abdominal fat distribution and sedentary life-style are determinant for the development of insulin resistance, it seems that other factors may modulate this relationship. This is evident from a recent study (36) we have conducted in Asian Indians, a population characterized by unusually excessive insulin resistance and type 2 diabetes. Even minimal accumulation of total body fat (Figure 6-A) or abdominal fat (Figure 6-B) are associated with excessive insulin resistance in this ethnic group as compared to Caucasians.

Therefore, although observational and epidemiological studies in different ethnic groups suggest that obesity, fat distribution and level of physical activity contribute significantly to the variability of insulin resistance in humans, other factors, such as a genetic predisposition plays a major modulating role. Therefore, the evaluation of the molecular mechanisms relating obesity, exercise and genetic predisposition should provide important insights in the pathogenesis of insulin resistance. The recent advances in the understanding of insulin action provide an essential step for the elucidation of these mechanisms.

Fig. 6-A: Relationship between generalized obesity and insulin resistance (Ref. 36)

Fig. 6-B: Relationship between abdominal obesity and insulin resistance (Ref. 36)

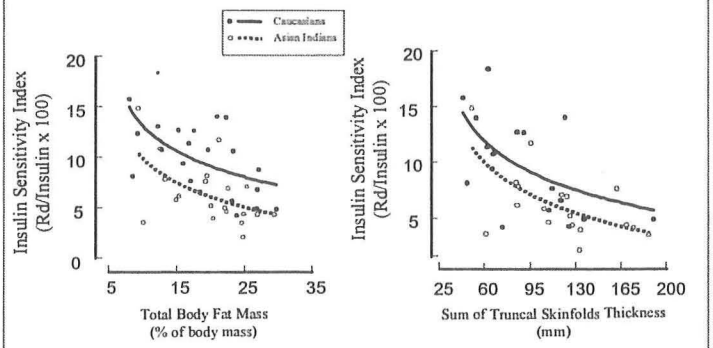
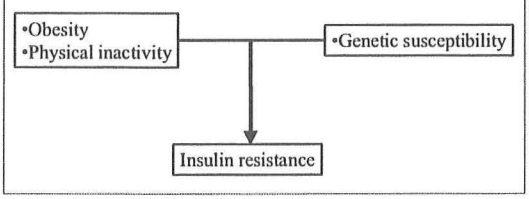


Fig. 7: Pathogenesis of insulin resistance

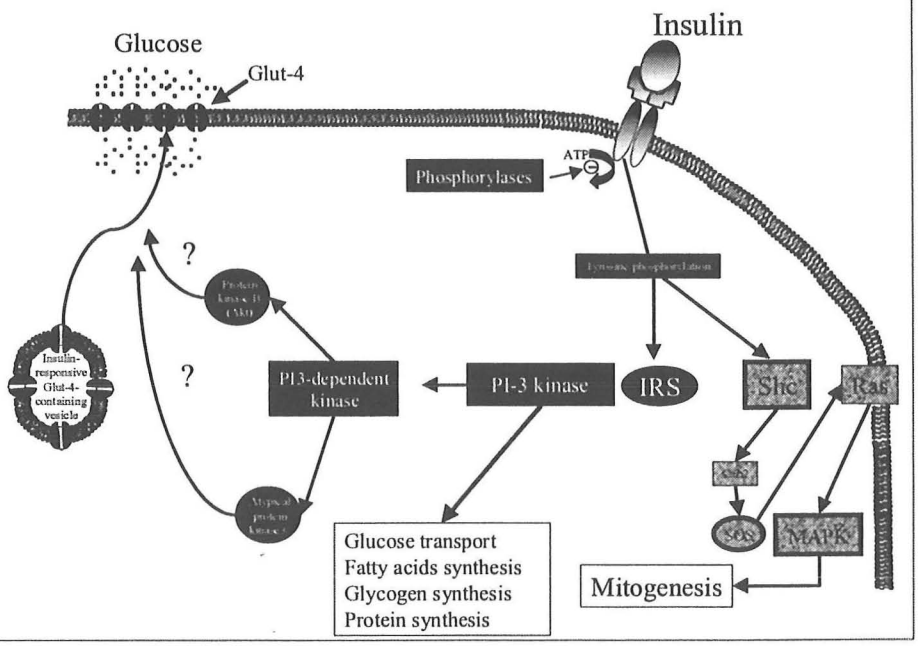


Molecular mechanisms of insulin action.

The biological action of insulin is initiated by the interaction between the hormone and its receptor (Fig. 8). The insulin receptor is a large trans-membrane glycoprotein consisting of two alpha and two beta subunits, which forms a heterotetramer (37). The beta sub-units possess tyrosine kinase activity (38). Following insulin binding, the receptor is phosphorylated in one beta sub-unit. This reaction is catalyzed by a specific domain in the other beta sub-unit. The authophosphorylation of the insulin receptor renders the kinase activity of the same receptor more effective allowing accelerated transfer of phosphate to other tyrosine sites within the same receptor as well as exogenous substrates (39). Phosphorylation of some residues of the receptor results in a reduced activity of the receptor itself (40). De-phosphorylation is mediated by phosphorylases (41). Both mechanisms, phosphorylation of inactivating residues and de-phosphorylation of activating residues, represent regulatory feedback mechanisms. Besides the receptor itself, several other proteins are rapidly phosphorylated on tyrosine residues in response to insulin binding. Some of these proteins are known as insulin receptor substrates (IRS-1, 2, 3 and 4) (42-46). Shc, Gab-1 and p62 dok are other proteins that are phosphorylated by ligand bound insulin receptors that do not have enzymatic activity but interact with other intracellular proteins that mediate the effects of insulin (47-49). From the functional point of view, all proteins in this family bind to the

autophosphorylated insulin receptor only transiently and then dissociate, after which they can be recognized by SH-2 domains of several other proteins. They are also indicated as "docking proteins". The two best-studied docking proteins are IRS-1 and Shc. These proteins interact with other proteins, the "adaptor proteins" that transmit the signal downstream through interaction with other non-enzymatic proteins. One of the adaptor proteins is Grb-2 that mediates the mitogenic and growth effects of insulin. IRS and Shc dock to Grb-2 and activate the Ras signaling pathway that eventually leads to activation of MAP kinase, MAP kinase kinase and pp90 S6 kinase. This cascade mediates the mitogenic and growth promoting effects of insulin. The signaling transduction for insulin effects on metabolism proceeds via different pathways that are less defined. It may involve other docking proteins, such as the regulatory subunits of the enzyme phosphatidylinositide-3 kinase (PI-3 kinase) that mediates the metabolic effects of insulin-activated IRSs. There are at least 8 different isoforms of regulatory subunits of PI-3 kinase. These include p85-alpha, AS53, p50-alpha, p85-beta and p55 PIK. Each of these regulatory subunits associates with IRS proteins in response to insulin and transduces to signal from IRS proteins to PI3-kinase activation. PI3-kinase activation mediates insulin-stimulated glucose uptake by stimulating translocation of Glut-4 vesicle to the plasma membrane. PI3-kinase activation also mediates other biological activities of insulin, including activation of fatty acids synthesis, acetyl-CoA-carboxylase, glycogen synthase, stimulation of protein and DNA synthesis.

Fig. 8: Schematic representation of insulin action



Exercise activates Glut-4 containing vesicles independent of PI-3-kinase activation and therefore independently of insulin. Exercise and insulin have a synergistic effects on Glut-4 vesicles mobilization (50).

Genetic mechanisms that may predispose to insulin resistance.

The recent advances in the understanding of the molecular basis of insulin signaling have elucidated some genetic mechanisms that could be responsible for development of insulin resistance. It appears that the genetic alterations responsible for the occurrence of complex diseases, such as insulin resistance, may more likely involve multiple point mutations that, accumulated over the course of thousands of years, may have developed as a genetic advantage (51,52). According to the thrifty genotype hypothesis (53), a predisposition to insulin resistance may have protected individuals during periods of food deprivation by reducing muscle utilization of glucose and favoring glucose utilization in organs, such as

the brain that operate through an insulin-independent mechanism. The recent occurrence of excessive food availability and reduced physical activity constitute a rapid environmental change that interacts with the genetic predisposition to insulin resistance inducing a pathological decrease in glucose utilization. A genetic advantage has therefore become a genetic disadvantage and cause of disease. Multiple mutations of genes that individually are associated with a small change in insulin sensitivity, when combined may induce a significant reduction in insulin sensitivity. Therefore, the identification of individual mutations contributing to reduced biological effects of insulin will likely provide the key to the understanding of the genetic basis of insulin resistance. The following is a summary of the known effects of genetic mutations affecting the function of specific proteins involved in the various steps of the insulin-signaling pathway.

1) **Insulin receptor:** Several mutations of the insulin receptor that can cause insulin resistance have been described (54). However, these mutations occur infrequently in the general population and thus account only for a small portion of the genetic causes of insulin resistance.

2) **Phosphotyrosin Phosphatase (PTPase):** PTPase is responsible for dephosphorylation of the insulin receptor and its substrates, and hence, for the turnings off of the insulin signal. Total membrane-bound phosphatase activity is increased in skeletal muscle of type 2 diabetic patients (55). Immunodepletion experiments in muscles from these diabetic patients and obese individuals suggest that especially two phosphatases, protein- tyrosine phosphatase lB (PTP-1B) and leukocyte antigen-related (LAR) phosphatase, are responsible for this increase (55). Plasma cell differentiation factor-l (PC-l) is a membrane glycoprotein with ectonucleotide pyrophosphatase activity that seems to act as an intrinsic inhibitor of insulin receptor tyrosine kinase activity (56). In healthy subjects with no clinically significant defects in glucose metabolism, PC-l expression in muscle negatively correlates with insulin sensitivity in intravenous insulin tolerance test and in vitro stimulation of muscle insulin receptor tyrosine kinase activity (57). Theoretically, polymorphisms of PTP-1B, LAR, PC-1 could impair insulin-signaling cascade and contribute to insulin resistance. However, no polymorphism of PTPase is described at this time.

3) **IRS-l:** IRS-1 was the first insulin-receptor substrate identified and the first to be found to have multiple natural polymorphisms (58-63). Polymorphisms of IRS-1 are significantly more common in type 2 diabetic patients than in controls and include the G972R (glycine 972arginine), S892G, G819R, R1221C, and A513P variants (58,59,63). Of these, the G972R polymorphism is the most common and has been studied most extensively. This polymorphism is found in Caucasian populations, with a prevalence of 5.8% in normal and 10.7% in type 2 diabetic patients, respectively. In Caucasian populations, obese carriers of this polymorphism show decreased insulin sensitivity during an oral glucose tolerance test, and an individual homozygous for the codon 972 mutation had a diabetic response to dexamethasone challenge. The polymorphism G972R does not occur in Pima Indians (64). Diabetic Asian Indians do not seem to have increased prevalence of G972R variant as compared to diabetic Caucasians (65). However, no studies are available on the prevalence of this polymorphism in non-diabetic Asian Indians. In Japanese type 2 diabetic patients, several additional polymorphisms have been described, including P190R, M209T, and S809F polymorphisms, and silent nucleotide variants Ll42 and G625 A804 (60). While the prevalence of each of these polymorphisms alone is not different between patients and healthy controls, the combined prevalence of these polymorphisms, along with the G972R polymorphism, is threefold greater compared with healthy controls (29.5 vs. 8.5%; $p < 0.05$). In a euglycemic, hyperinsulinemic clamp, the insulin sensitivity in the carriers versus noncarriers of these polymorphism is decreased 29.5% in type 2 diabetics and 22% in healthy subjects. Recently, two polymorphisms in IRS-2 have been described in the Caucasian population: a substitution of G1057D and

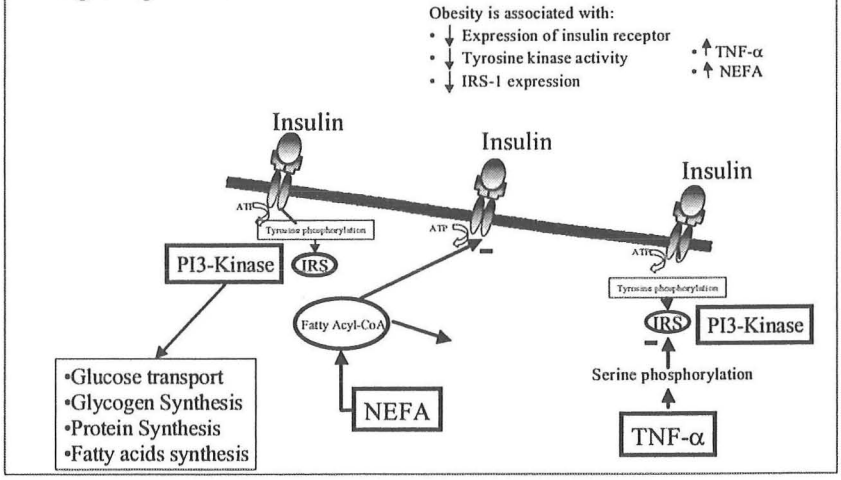
G879S (66). Amino acid polymorphisms of IRS-4 are also common in the Caucasian population. However, neither of these identified polymorphisms is associated with type 2 diabetes or insulin resistance (66,67).

4) **PI3-kinase:** A common polymorphism of the p85 subunit of PI3-kinase changes methionine in position 326 to isoleucine. In one study, 31% of Caucasians carried the mutation in its heterozygous form and 2% in its homozygous form. This polymorphism occurs in a region between the SH3 domain and the first SH2 domain, but the functional effects have not been studied in vitro. Although the frequency is not increased in diabetes, homozygous individuals do exhibit a 32% reduction in insulin sensitivity compared with wild type and heterozygous carriers in an intravenous glucose tolerance test (68).

Other genetic variants associated with insulin resistance involve the Rad gene – Ras associated with diabetes) (69-71).

*Mechanisms whereby obesity and sedentary life-style may **induce** insulin resistance.*

Fig. 9: Schematic representation of obesity-related insulin signaling abnormalities



Although the details of the mechanisms involved in the development of insulin resistance are still incompletely understood, an increasing body of scientific data is being accumulated on the effects of obesity and sedentary life-style on specific molecular mechanisms related to cellular insulin-signaling (Fig. 9). Obese human subjects have decreased insulin receptor expression and decreased tyrosine kinase activity in skeletal muscle cells (72) and adipocytes (73). Insulin receptor expression is regulated by the rates of synthesis, internalization and degradation. Insulin receptor's tyrosine kinase activity is regulated by post-translational modifications of the insulin receptor, namely autophosphorylation of the receptor. Both insulin receptor expression and its tyrosine kinase activities are restored by weight loss, which also improves insulin sensitivity. In animal models of both acquired and genetic obesity, insulin receptor number in the liver is decreased and can be corrected by ameliorating hyperinsulinemia (74). Together these data suggest that downregulation of insulin receptor expression and its tyrosine kinase activity may be secondary to obesity, or more likely, hyperinsulinemia, which accompanies it.

Insulin receptor's tyrosine kinase activity may also be impaired in obesity through a different mechanism involving TNF-alpha. This is a protein that is over-expressed in adipocytes of obese patients (75) and appears to have a paracrine function. In the same adipocytes or surrounding skeletal muscle cells, TNF-alpha may increase serine phosphorylation of IRS-1 (76) and possibly other proteins. Serine-phosphorylated IRS-1 has been shown to inhibit insulin receptor tyrosine kinase activity, which leads to impaired downstream insulin-signaling (77).

Obese patients have also been found to have a reduced expression of IRS-1 in the skeletal muscle. In severely obese patients, with BMI above 50%, IRS-1 expression in skeletal muscle is decreased 54% of that of non-obese patients (78). In addition, obese patients also have decreased phosphorylation of IRS-1 and PI3-kinase activation in skeletal muscle (78).

The effects of obesity on IRS-associated PI3-kinase activity may be mediated by NEFA. Obese patients frequently have excessive concentrations of plasma NEFA (79) and this condition has been shown to induce insulin resistance to muscle glucose disposal concomitantly with reduced IRS-1 phosphorylation and PI3-kinase activity (80). Exogenous administration of NEFA, inducing elevation of plasma concentration, leads to reduced mobilization of Glut-4 to the plasma membrane and to consequent impaired glucose penetration and phosphorylation in the muscle cell. NEFAs also stimulate insulin secretion in the pancreatic beta-cell (81). The resulting hyperinsulinemia may contribute to the down-regulation of the insulin receptor and its tyrosine kinase activity observed in obesity.

Recent studies have shown that exercise has a facilitating effect on mobilization of Glut-4 to the plasma membrane, independent of insulin (82). Exercise has been shown to modulate post-receptor insulin signaling and glucose transport in muscle-specific insulin receptor knockout mice (50). This would suggest that insulin receptor is not needed for exercise-mediated increase in glucose uptake in vivo. Insulin and exercise seem to have synergistic effects on glucose uptake.

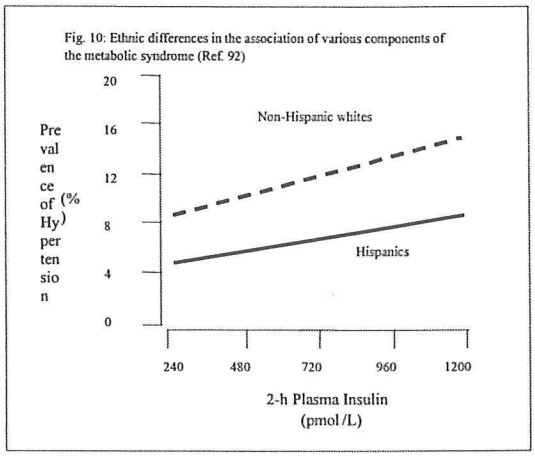
Obesity and the frequently associated sedentary life-style may therefore independently affect peripheral glucose disposal by reducing Glut-4 mobilization through separated mechanism. A better understanding of the exact mechanisms involved will probably provide more insights on the nature of the interaction between genetic polymorphisms, causing predisposition to insulin resistance, and specific biochemical pathway affected by the obese and sedentary status.

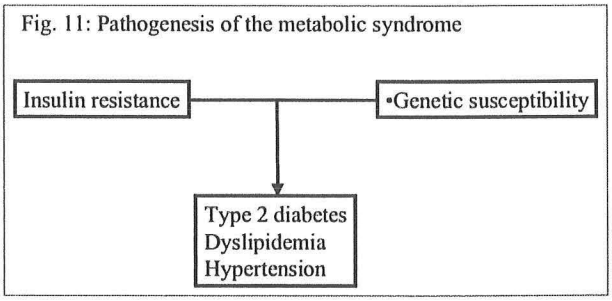
At this point the question is: **how can insulin resistance develop into the metabolic syndrome?**

Insulin resistance and the metabolic syndrome:

Several epidemiological and cross-sectional studies have revealed that patients with various components of the metabolic syndrome often have a defect in insulin-mediated glucose metabolism. These observations have led to the notion that insulin resistance should be viewed as the common denominator for the various components of the metabolic syndrome and that therefore insulin resistance has a major pathogenic role in obesity-related CVD. However, whereas it is true that obese patients with the metabolic syndrome are almost uniformly severely insulin resistant, not all individuals with obesity and insulin resistance develops the metabolic syndrome or, if they do, the phenotypic combinations can be variable. In fact, studies in different ethnic groups have revealed inconsistency in the relationship between obesity, insulin resistance, hypertension, dyslipidemia and type 2 diabetes. For example, Pima Indians, a population with an extremely high prevalence of obesity and insulin resistance, is frequently found to have type 2 diabetes (87). However, the same population does not have higher prevalence of dyslipidemia (88) and hypertension (89). Similarly, in other ethnic groups, such as the Pacific islanders, a population at high incidence of obesity and diabetes, hypertension was found to have no significant relationship with insulin resistance (90). Insulin resistance and hypertension is also unrelated in African-Americans (91). Similarly, for any degree of insulin resistance, Mexican-Americans have less prevalence of hypertension than Caucasians (Fig. 10) (92). These epidemiological observations would

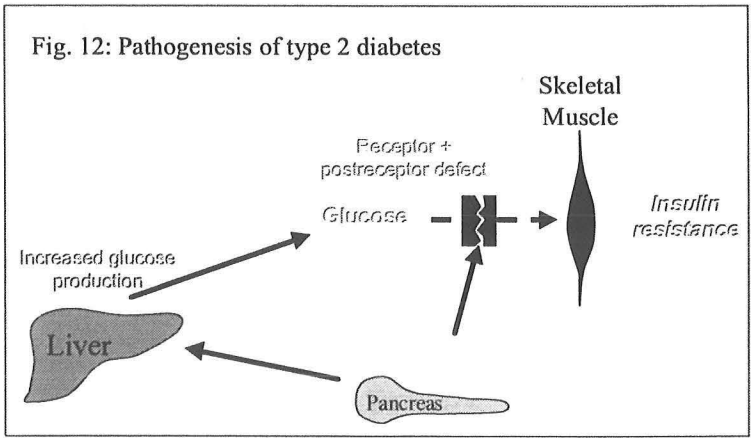
suggest that other factors, such as a genetic background or another pathophysiologic mechanism must be present for the insulin resistance to translate into a phenotype such as type 2 diabetes, dyslipidemia or hypertension. This notion is supported by a new epidemiological analysis conducted in different populations with insulin resistance. This analysis, called "factor analysis" is useful to investigate the possible presence of a factor that is responsible for a specific clustering of various components of the metabolic syndrome. This statistical method is utilized to investigate relationships among several variables by identifying presumed underlying "factors". All the known interrelated variables of the metabolic syndrome, including hyperinsulinemia, plasma glucose concentration elevations, body mass, waist circumference, plasma triglycerides, HDL-C and small-dense LDL, systolic and diastolic blood pressure, have been mathematically reduced to 3 main "factors" that are independent from each other (93-96). The 3 main identified "factors" of the metabolic syndrome are: 1) Glucose/obesity factor; 2) blood pressure factor; 3) dyslipidemia factor. The glucose/obesity, blood pressure and dyslipidemia factors explain 70 to 80% of the total variability of the included data in different populations examined. Edwards et al. (96) have also shown that these factors are heritable, thus giving support to the notion that a genetic predisposition may have a major role in determining the different clustering of various components of the metabolic syndrome in the presence of insulin resistance in various individuals and ethnic groups (Fig. 11). We will now discuss known metabolic consequences of insulin resistance that contribute to mechanistically mediate the onset of various components of the metabolic syndrome in obese patients.





Insulin resistance and type 2 diabetes mellitus.

Insulin resistance has a major pathogenic role in the development of type 2 diabetes mellitus (97). Other abnormalities associated with type 2 diabetes are increased hepatic glucose production and impaired insulin secretion from the pancreatic β-cell (Fig. 12). Insulin resistance has been found to precede and predict the development of type 2 diabetes in several ethnic groups, including Pima Indians (98), Hispanics (99), Pacific islanders (100), Japanese (101) and individuals of European origin (102). In addition, nondiabetic relatives of diabetic patients have been reported to be insulin resistant at a time when their glucose tolerance was still normal (103-105). First degree relatives of patients with type 2 diabetes have been found to have impaired insulin action upon skeletal muscle

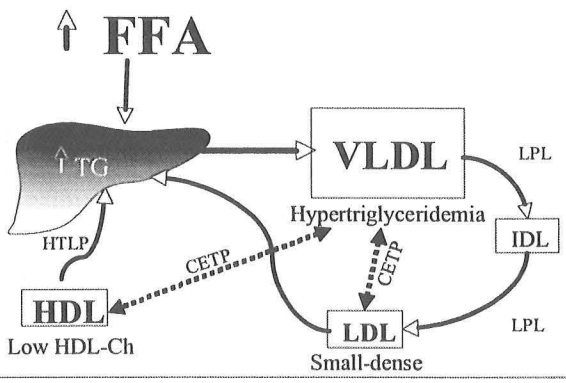


glycogen synthesis due to both decreased stimulation of tyrosine kinase activity of the insulin receptor and reduced glycogen synthase activity (106,107). These observations support the "insulin-resistance/pancreatic exhaustion" hypothesis of type 2 diabetes. This hypothesis holds that as a result of chronic insulin resistance, compensatory hyperinsulinemia develops to maintain glucose homeostasis, and that diabetes eventually develops when pancreatic hypersecretion of insulin fails (97). Since over 85% of the population of type 2 diabetic patients are overweight, excessive adiposity may play an important role in the pathogenesis of this disease. A recent study we have conducted in newly diagnosed mild type 2 diabetic patients revealed that for any degree of obesity and abdominal fat distribution, type 2 diabetic patients are more insulin resistant than matched non-diabetic subjects (108). This observation suggest that obesity has a contributing factor but other variables, such as genetic predisposition, play a significant role in the development of the severe insulin resistance of diabetic patients. Excessive insulin resistance even with mild accumulation of body fat may increase the risk of β-cell dysfunction, an essential component for the onset of clinical diabetes. Genetic predisposition may also be involved in the development of β-cell dysfunction in type 2 diabetes.

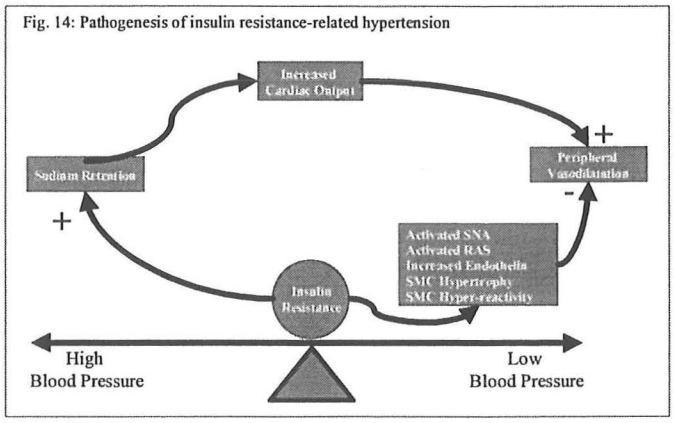
Insulin resistance and lipid metabolism.

There are three major components of the dyslipidemia that occurs in the metabolic syndrome: 1. Increased plasma triglycerides concentrations; 2. decreased plasma concentrations of HDL-C; and 3. Compositional changes of LDL (small-dense LDL) (109-111). These abnormalities appear to be caused by characteristics of the insulin-resistant state itself rather than by elevated insulin concentrations or obesity. Cross-sectional studies with hyperinsulinemic clamps have shown an association between insulin resistance and dyslipidemia independent of body fat and abdominal obesity (112). As represented in Figure13, one of the features of insulin resistance is excessive plasma concentration of free fatty acids (FFA). FFA may induce liver accumulation of triglycerides and increased production of triglycerides-enriched VLDL particles. In addition, insulin resistance impairs lipoprotein lipase (LPL) activity. The excessive liver output of TG-enriched VLDL particles and the reduced LPL activity will therefore result in elevated plasma triglycerides concentrations. Additionally, the excess of circulating plasma TG induces accelerated exchange of TG for cholesterol esters with other lipoproteins such as LDL and HDL. This process is mediated by cholesterol ester transfer proteins (CETP) and results in an accumulation of TG and loss of cholesterol esters content in both LDL and HDL fractions. These qualitative changes explain both the lowering of HDL-C levels and the qualitative changes of the LDL particles towards small-dense LDL. Lower plasma concentrations of HDL-C are also promoted by activation of hepatic lipoprotein lipase associated with insulin resistance. This enzymes contributes to accelerate HDL-C catabolism. Other mechanisms, such as reduced liver production of Apolipoprotein AI and reduced hepatic secretion of nascent HDL may have additional role in the pathogenesis of insulin resistance-related low-HDL-C.

Fig. 13: Insulin resistance and dyslipidemia

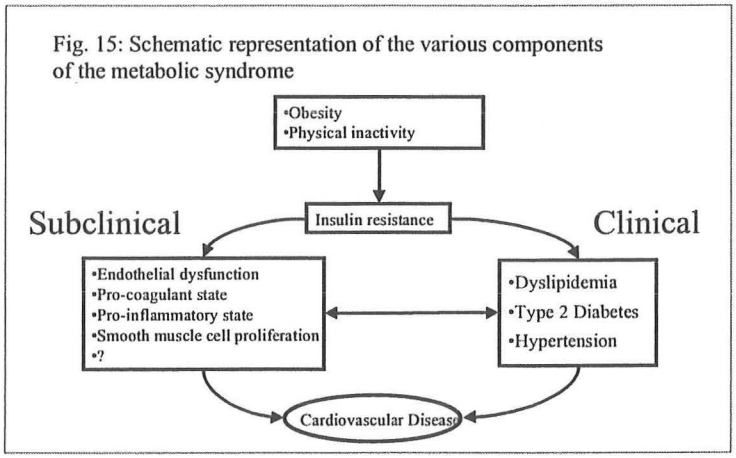


Insulin resistance and blood pressure control.



As illustrated in Fig. 14, insulin resistance can stimulate renal sodium re-absorption leading to volume expansion (113-114). Sodium retention is responsible for increased cardiac output that is normally met by peripheral vasodilatation to maintain normal blood pressure. However, in the presence of insulin resistance, peripheral vasodilatation is impaired. Several mechanisms may be responsible for this effect of insulin resistance. Insulin resistance has been shown to enhance sympathetic adrenergic activity (117), and to up-regulate Angiotensin II type 1 receptors by post-translational mechanisms (118). Sodium retention associated with impaired vasodilatation predispose to blood pressure elevation in insulin resistant states.

Type 2 diabetes, dyslipidemia and hypertension are the most common clinical entities associated with obesity in the "metabolic syndrome". However, recent evidence support the presence of various sub-clinical abnormalities associated with insulin resistance that should be considered part of the metabolic syndrome. Sub-clinical abnormalities that are present in insulin resistant conditions and may have a major role in predisposing obese patients to CVD include pro-thrombotic state, endothelial dysfunction, pro-inflammatory state (Fig. 15). These abnormalities and their relationship with insulin resistance are now discussed.



Insulin resistance and coagulation physiology.

Hyperinsulinemia has been shown to stimulate liver production of fibrinogen and PAI-1 (119,120). The exact mechanisms leading to these changes in the presence of insulin resistance have not been completely elucidated. Since MAPK pathway mediates PAI-1 expression, it is possible that Ras activation has a role in the pro-thrombotic state of insulin resistant conditions, including obesity. Pro-thrombotic state predisposes to atherosclerotic plaque complication and cardiovascular event.

Insulin resistance, endothelial function and plaque formation.

Insulin has been shown to induce vasodilatation. The effect of insulin on vascular reactivity is mediated by nitric oxide (NO) production (121). Activation of PI3-kinase by insulin interaction with its receptor has the effect of stimulating NO synthesis in the endothelial cells. The exact mechanisms involved are not completely understood, at this time. However, conditions associated with insulin resistance, such as obesity and diabetes have been shown to manifest impaired NO production in association with reduced PI3-kinase activity. Steinberg et al. (122) also demonstrated that elevated concentrations of plasma FFA

may mediate the effect of insulin resistant on NO production. Probably the same mechanism that leads to reduced PI3-kinase activation is responsible for impaired Glut-4 mobilization in skeletal muscle cells and for impaired NO synthesis in endothelial cells in obese patients with insulin resistance. Defective NO production and endothelial dysfunction promote atherosclerosis. In fact, physiologically, NO attenuates the inflammatory reaction that promotes atherogenesis and plaque complication in atherosclerosis. NO also has the important function of inhibiting the expression of adhesion molecules such as vascular cell adhesion molecule-1, E-selectin, and intra-cellular adhesion molecule. It also inhibits the activity of inflammatory cytokines, such as TNF-alpha and the production of chemokines, such as monocyte chemo-attractant protein-1. Therefore, NO attenuates the binding of inflammatory cells such as monocytes and macrophages to the vascular wall. **By reducing NO production, insulin resistance promotes endothelial dysfunction and inflammation in the vessel wall.** This condition may promote atherosclerosis and plaque complication.

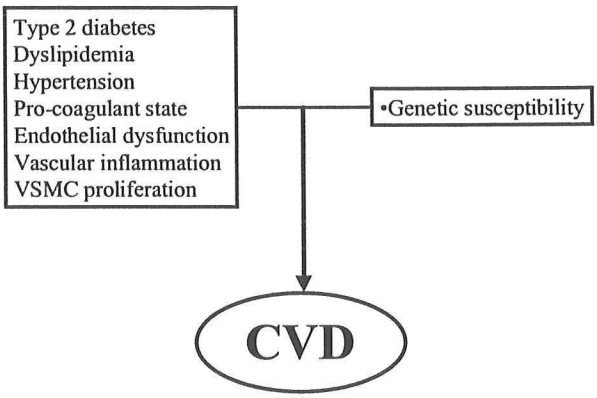
Another action of insulin in vessels is stimulation of smooth muscle cells growth and migration. These effects are mediated by Ras-related activation of MAPK and are independent of the IRS and PI3-kinase mediated pathway (123). It appears that insulin resistant conditions may be associated with defective PI3-kinase related insulin function but with intact MAPK related insulin functions. Therefore, the hyperinsulinemia of insulin resistance may promote smooth muscle cells proliferation and migration to the forming plaque.

The Metabolic syndrome and CVD:

Many of the various conditions found in patients with the metabolic syndrome, i.e. type 2 diabetes, low plasma levels of HDL-cholesterol, high plasma concentrations of triglycerides, small-dense LDL and hypertension, are major and independent risk factors for CVD. Each of these abnormalities directly promotes atherosclerosis. Therefore, since the metabolic syndrome is characterized by the "clustering" of these independent CVD risk factors, the likelihood that patients with the metabolic syndrome develop premature CVD is significantly increased. In addition, the sub-clinical abnormalities induced by insulin resistance may be responsible for additional atherogenic mechanisms in patients with the metabolic syndrome. Several epidemiological studies support an "independent" effect of insulin resistance on CVD risk (124-127). The "independent" effect of insulin resistance on atherogenesis and development of CVD may be, at least in part explained by the most recent findings on the effects of insulin resistance on vascular reactivity, endothelial function, VSMC proliferation and pro-thrombotic state. These mechanisms have not been taken into account in the various epidemiological studies performed. Other factors not yet identified may also play a role in mediating CVD in patients with the metabolic syndrome. For example, studies conducted in various ethnic groups support the notion that genetic susceptibility has a major impact on whether an individual with various components of the metabolic syndrome will develop CVD. This has been shown in studies such as the "Insulin Resistance Atherosclerosis Study (IRAS)" (128) which examined the relation between insulin resistance and atherosclerosis of the carotid artery (by B-mode ultrasound) in a large, multiethnic population (398 African-Americans, 457 Hispanics, and 542 non-Hispanic European-Americans). There was a positive association between insulin resistance and intimal medial thickness of the carotid artery in Hispanics and non-Hispanics European-Americans. The effect was decreased but not completely explained by adjustment for traditional risk factors as well as glucose tolerance, adiposity, and fasting insulin levels. However, there was no significant association between insulin resistance and intimal medial thickness in African-Americans. Similarly, in both Hispanics and Pima Indians, population at high prevalence of

type 2 diabetes and obesity, CVD prevalence is lower than Caucasians. The are no clear explanations for these findings, but again a "genetic susceptibility" to develop cardiovascular disease may modulate the effect of various components of the metabolic syndrome (Fig. 16).

Fig. 16: Metabolic syndrome and CVD



Certainly, the increasing prevalence of obesity and sedentary life-style in US population is a factor that may promote increasing prevalence of insulin resistant-related conditions. The changing ethnic composition of this population could also have an important role. The US population now includes a growing percentage of ethnic groups that are particularly predisposed to develop insulin resistance, such as the Hispanics and Asians. These ethnic groups are predicted to represent 50% of the entire US population within the next 50 years (129). Likely as a consequence we are already witnessing a significant increase in the prevalence of Type 2 diabetes, now about 5 times more prevalent than 15 year ago (130). These changes may have significant public health impact and stop or even reverse the current trend toward decreasing prevalence of CVD mortality. Public awareness, screening and early identification of risk is needed at population levels. From the individual patient perspectives, the presence of obesity, insulin resistance and the metabolic syndrome implies a high risk status that requires a comprehensive evaluation and treatment strategy for CVD prevention. The therapeutic approaches to consider for the patient with the metabolic syndrome will be discussed in the next paragraph.

Therapy:

Cardiovascular risk reduction in the obese patients should include at least three level of intervention: A. Control of obesity and lack of physical activity; B. Control of insulin resistance; and C. Control of the individual components of the metabolic syndrome.

A. Control of obesity and lack of exercise: patient education on healthy life style is essential. Collective classes and individual discussions on risk of cardiovascular disease and possible management strategies are necessary to involve the patient in a life-long modification of acquired habits, such as excessive caloric intake and lack of regular exercise. If this approach fails, control of obesity can be approached pharmacologically or surgically. The initial goal of weight loss therapy is to reduce body weight to approximately 10 percent from baseline. If this goal is achieved, further weight loss can be attempted, if indicated through further evaluation. For patients unable to achieve significant weight loss, prevention of further weight gain is an important goal; such patients may also need to participate in a weight management program.

Fig. 17: Treatment of obesity and physical inactivity

- Lifestyle modification
  - Diet
  - Regular exercise
- Pharmacotherapy
- Surgery

Dietary therapy: a diet should create a deficit of 500 to 1,000 Kcal/day. Depending on the patient's risk status, the low calorie diet should be consistent with Step I or Step II diet of the National Cholesterol Education Program (1). Besides decreasing saturated fat, total fat should be 30% or less of total calories. Reducing percentage of fat alone will not produce weight loss unless total calories are also decreased.
Recently, diet rich in fats have become very popular to lose weight. Promoting excessive saturated fats intake, among other problems, may worsen glucose metabolism and increase risk for CVD despite the much advertised apparent, although transitory, effect of these diets in weight loss.
A more gradual weight loss with caloric restrictions and a diet containing adequate amounts of unsaturated fats, as included in the AHA diet, may induce a more balanced weight control with positive effects on metabolism, including the various components of the metabolic syndrome. A weight loss of about 15-20% is associated with metabolic benefits and is a reasonable goal for most of our patients.

Physical activity: an increase in physical activity is an important component of weight loss therapy, although acting alone, physical activity usually will not produce significant weight loss in obese patients. Most weight loss occurs because of decreased caloric intake. Sustained physical activity is, however, helpful for maintaining a lower weight. In addition, regular exercise reduces cardiovascular and diabetes risks beyond that produced by weight reduction alone.

Behavior therapy: strategies based on learning principles such as reinforcement, helps to overcome barriers to compliance with dietary therapy and/or increased physical activity. Specific strategies include self-monitoring of both eating habits and physical activity, stress management, stimulus control, problem solving, cognitive restructuring and social support.

A combined intervention of behavioral therapy, low-calorie diet and increased physical activity offers the most effective therapy for achieving weight loss and weight maintenance. This type of intervention should be maintained for at least 6 months before considering pharmacotherapy. In carefully selected patients, weight loss drugs can augment weight loss from a low calorie diet, increased physical activity and behavior therapy. Weight loss drugs that have been approved by FDA for long-term use may be useful for some patients with a BMI>30 with no concomitant risk factors or diseases. The risk factors (or co-morbidities) that warrant consideration of weight-loss drugs at a BMI of 27 to 29.9 kg/m2 are hypertension, dyslipidemia, type 2 diabetes, sleep apnea and clinical cardiovascular disease. One approved weight-loss drug is sibutramine. It can induce moderate weight loss and can help facilitate weight maintenance at lower weight. Monitoring is required for side effects, particularly increases in blood pressure and heart rate. Sibutramine should not be used in patients with, CHD, CHF, arrhythmias or history of stroke; the presence of hypertension also is a relative contraindication.
Another weight-loss drug approved for treatment of obesity in US is orlistat. Orlistat is a pancreatic lipase inhibitor that blocks digestion and absorption of dietary fat (131). It causes increased fecal fat loss in patients eating diets with more than 30% of fat. It can induce moderate weight loss and can facilitate weight maintenance (132). Orlistat gives frequent gastrointestinal side effects (133).

Weight loss surgery is one option for weight reduction in a limited number of patients with clinically severe obesity, i.e. BMI$\geq$40 kg/m2 or $\geq$35 kg/m2 with co-morbid conditions (134). Weight loss surgery should be reserved for patients in whom efforts at medical therapy have failed and who are suffering from the complications of extreme obesity. Gastrointestinal surgery is an intervention of weight loss option for motivated subjects with acceptable operative risks. Gastrointestinal surgery for weight loss includes gastric restriction procedures (vertical or horizontal banded gastroplasty, vertical ring

gastroplasty), adjustable silicone gastric banding, gastric bypass, bilio-pancreatic bypass. The vertically banded gastroplasty and Roux-en-Y gastric bypass have now become the standard procedures used in most obese patients. Although the operative mortality is below 1%, these procedures are associated with a variety of side effects and complications. Intra- or post-operative complications such as anastomotic leakage and infection are more common with the Roux-en-Y procedure. This procedure may also cause vitamin B12 deficiency, anemia and neuropathy. Rapid weight loss generally follows any of these procedures and often result in increased incidence of gallstones. Requirement of revision is also a frequent complication of weight loss surgery.

B. Control of insulin resistance: insulin resistance can be a consequence of obesity and lack of physical activity. Therefore, the control of obesity and lack of physical activity, as discussed above, will have an impact on insulin sensitivity. In fact, diet composition and physical activity may have an effect on insulin resistance that is independent of the effects of weight loss.

Fig. 18: Treatment of insulin resistance

- Weight loss
- Exercise
- PPR-Gamma Activators
- Metformin

Diet: High fat diets have been implicated in the etiology of insulin resistance and glucose intolerance. Clinical studies have revealed adverse effects of experimental high fat, low-carbohydrate diets on glucose and insulin metabolism in some (135,136) but not in all (137) instances. Insulin resistance can be induced in laboratory animals by diets high in fat, fructose or sucrose, although physical activity or n-3 fatty acid supplementation can attenuate this effect. In addition, high fats diet may promote obesity (138) and insulin resistance may ensue as a mechanism to limit further weight gain. Habitual intake of dietary fat has been positively related to insulin concentration (as a surrogate of insulin resistance) in several studies of free-living, non-diabetic individuals. In the Keiser Permanente Women Twins Study (139), obesity accounted for 30% of the positive relation of total dietary fat intake to fasting insulin concentration in 542 nondiabetic women. Saturated fat, oleic acid, and linoleic acid were each positively related to fasting insulin concentrations, and these associations were strongest among relatively sedentary women. Using estimates of insulin sensitivity based on homeostatic modeling, Fesken et al. (140) reported significant adverse associations of total dietary fat, saturated fat, and monounsaturated fat intakes with insulin sensitivity independent of body mass index, although no significant association was observed for polyunsaturated fats. Lovejoy and DiGirolamo (141) showed habitual, high fat diets to be related to worsened insulin sensitivity as measured by an intravenous glucose tolerance test in 45 lean and obese subjects, but this association was no longer significant after adjustment for obesity. The Insulin resistance atherosclerosis study (IRAS) measured insulin sensitivity directly by frequently sampled intravenous glucose tolerance test and included 1625 men and women of non-Hispanic white, African-American, and Hispanic ethnicity (142). Total fat intake was inversely related to insulin sensitivity, but this association was not significant after adjustment for BMI and WHR. These findings were consistent on all ethnic groups studied. Some other studies have suggested that indeed high carbohydrate intake reduces insulin sensitivity in humans. Beyond the issue of dietary fat vs. carbohydrate on insulin resistance, the possibility exists that diet composition directly affects the risk factors of the metabolic syndrome. There is evidence both in populations using high monounsaturated fat diets, such as the mediterranean populations, and in experimental studies, that diet rich in mono-unsaturated fats reduces LDL-C, Apo-B, triglycerides, increases HDL-C and improves carbohydrate

metabolism. Population with traditionally high mono-unsaturated diets have less incidence of both CVD and type 2 diabetes. Perhaps the mechanism is to be found in the effects of mono-unsaturated fats on insulin sensitivity.

Exercise: Regular exercise increases the number of capillaries surrounding muscle fibers and also increases the skeletal muscle fiber composition that favors insulin-mediated glucose disposal (143). Bouts of exercise stimulate translocation of GLUT-4 to the plasma membrane and increase glucose transport in skeletal muscle (144). The signal that mediate exercise-induced GLUT-4 recruitment differ from those that mediate insulin-induced recruitment, in that insulin receptor expression and PI-3-kinase activity is not required for the exercise effect (145,146). Instead, activation of the 5-AMP-activated kinase may have a role (147). Exercise-induced production of NO and subsequent production of cyclic GMP may be involved in the regulation of glucose transport in muscle, independently of the effects of NO on vasodilatation (148). Bradikinin may also play a role in exercise-induced glucose transport, since it is released from muscle during exercise and, in cells expressing bradikinin receptors, it stimulates GLUT-4 translocation (149). Muscle has high levels of bradikinin receptors, and as with the glucose uptake stimulated by exercise, bradikinin-stimulated glucose uptake is not blocked by inhibitors of PI-3 kinase (149). The beneficial effects of exercise on insulin activity has recently been confirmed in the IRAS study (150). When diet and exercise are not enough to control insulin resistance in a patient, pharmacological intervention may be used. Biguanides and Thiazolidinediones are the most widely used medications to control insulin resistance but are only approved by the FDA for use in patients who have type 2 diabetes.

Biguanides: Although the liver is the primary site of action of the biguanide drugs such as metformin, in vivo studies indicate that metformin also increases glucose uptake into peripheral tissues (151). Metformin improves glycemic control in monotherapy and in combination with other hypoglycemic agents. In addition, the use of metformin in diabetic patients with obesity was associated with decreased weight gain and decreased incidence of CVD in UKPDS (152). However, the beneficial effects of metformin on CVD still awaits confirmation from clinical trials specifically designed to answer this important question.

Thiazolidinediones: Thiazolidinediones are a new class of insulin-sensitizing drugs that increase the disposal of glucose in peripheral tissues in animals and humans with insulin resistance, including subjects with type 2 diabetes (151). How these agents increase insulin-mediated glucose uptake is unclear. They appear to act as a ligand for a nuclear receptor, the peroxisomal proliferator-activated receptor gamma (PPAR-γ), augmenting the insulin action by enhancing insulin signaling at a post-receptor step (153). The effects of these agents in skeletal muscle may be direct or indirect. Treatment of insulin resistant rodents with thiazolidinediones restores the expression and translocation of GLUT-4 in adipocytes (154). Thiazolidinediones also overcome the TNF-alpha-induced inhibition of insulin-stimulated glucose transport in adipocytes (155). In insulin resistant rats given high fat diets and insulin-deficient rats with streptozocin-induced diabetes, thiazolidinedione treatment increases insulin-stimulated glucose uptake in muscle (154). Thiazolidinediones do not increase the expression of GLUT-4 in rodent muscle or human muscle cells, although they do induce expression of GLUT-1 (156). Furthermore, thiazolidinediones do not restore defective insulin-stimulated GLUT-4 translocation in muscle in insulin-resistant Zucker rats (157). Thus, the cellular mechanism by which thiazolidinediones increase glucose uptake in muscle in vivo is uncertain. Besides the effects on glucose utilization, these agents also have profound direct vascular effects. Troglitazone has been shown to inhibit VSMC

migration (158). The latter was demonstrated in a rat model with balloon-injured aorta. The injury resulted in substantial intimal hyperplasia, reflecting VSMC growth and migration. When the rats were treated with troglitazone, the neo-intimal medial area was markedly decreased 14 days after injury. The mechanism whereby troglitazone reduces proliferation and migration of VSMC is still unclear. However, Hsuet et al. (159) have recently proposed that thiazolidinediones inhibit ETS-1 expression, which regulates matrix metalloprotease activity. Inhibition of metalloprotease activity may be able to inhibit the invasion aspect of migration. Inhibition of metalloprotease may also stabilize atherosclerotic plaque.

PPAR-γ reduces monocytes secretion of IL-1β, and IL-6 and TNF-α (160). These effects may be therapeutic on atherogenesis and could be obtained by PPAR-γ pharmacological ligands, such as the thiazolidinediones. PPAR-γ activation with troglitazone also stimulates collagen production and stabilization of atherosclerotic plaque. Minamikawa et al (161) have recently shown that troglitazone induces inhibition of carotid arterial wall thickness in patients with type 2 diabetes. In addition, a recent study by Shiomi et al (162) revealed that troglitazone can suppress atherosclerosis and xanthomata.

Enhanced expression of PPAR-γ could also lead to negative effects. In fact, PPR-γ is activated by oxidized lipid components derived from LDL and colony-stimulating factors in human atheroma monocyte-macrophage and is expressed at high levels in the foam cells of the atherosclerotic lesions (163). Enhanced PPAR-γ expression also induces transcription of a scavenger receptor in monocyte/macrophages so that these cells acquire the ability to bind and internalize oxidized LDL, an undesirable effect in cardiovascular terms.

There is no evidence that treatment with a thiazolendinedione reduces cardiovascular events. However, it improves cardiovascular risk profile. Because of potentially serious side effects, such as LFTs abnormalities and liver failure, troglitazone and other thiazolidenedines should be used with caution in patients with type 2 diabetes.

B. Control of the individual components of the metabolic syndrome: a number of safe pharmacological agents are available to control the main components of the metabolic syndrome, such as type 2 diabetes, hypertension and dyslipidemia. A large body of data also supports goals of therapy summarized in guidelines from the ADA (164), JNC-6 (2), NCEP (1). A coordinated management of all these factors is required to effectively reduce cardiovascular risk in our patients. As recently stated by the AHA "compelling scientific evidence demonstrate that comprehensive risk factor interventions; -extend overall survival, improve quality of life, -decrease need for interventional procedures, -reduces the incidence of subsequent myocardial infarction" (165). Clinical trial data that support these recommendations derive from studies of myocardial infarction survivors and other patients with diagnosed coronary artery disease (166-168) but can be extrapolated to all patients with CVD and possibly to high risk patients. Primary prevention trials (169,170) also support the importance of treating high risk patients without clinical evidence of CVD with LDL-C lowering

Fig. 19: Priorities in lipids management of obese patients

- Reduce high LDL-cholesterol
- Increase low HDL-cholesterol
- Reduce high triglycerides

therapy. The management of lipids in patients with the metabolic syndrome should emphasize the importance of including treatment for LDL-C lowering but also for HDL-C raising and triglycerides lowering (Fig.19). The statin trial performed in the last 10 years have demonstrated that lowering LDL-C is effective in decreasing morbidity and mortality in patients with CVD. More recently, evidence has been accumulated that besides LDL-C, the management of low HDL-C and elevated triglycerides results in an independent reduction in cardiovascular risk. In the VA-HIT trial (171), over 5000 males with CVD were selected for low HDL-C levels and normal LDL-C. The average LDL-C was 112 mg/dL; triglycerides were 160 mg/dL; HDL-C were 32 mg/dL. In this population, treatment with gemfibrozil 1200 mg a day for 5 years resulted in a decrease of morbidity from CVD of 22%. The lipid profile of the patients treated compared to those on placebo revealed similar levels of LDL-C; an increase of HDL-C levels of 7% and a decrease in triglycerides levels of 24% in the treated group compared to the placebo group. These data show that managing HDL-C and triglycerides in patients with low HDL-C is effective in reducing CVD events independently of the effects on LDL-C. Other studies confirm the importance of treating patients with low HDL-C and elevated triglycerides. In the AFCAPS/TexCAP trial (170), the use of lovastatin in patients without evidence of CVD and average LDL-C of 150 mg/dL resulted in a significant reduction of CVD events which was significantly more pronounced in the group of patients who had low HDL-C levels. Similarly, in the Helsinki Heart study (172), treating patients with low HDL-C and elevated triglycerides, using gemfibrozil, resulted in a significant decrease in morbidity from CVD. These benefits were not seen in treated patients with no hypertriglyceridemia and normal HDL-C levels. Interestingly, a recent analysis of the Helsinki Heart Study (173) data revealed that gemfibrozil treatment decreased cardiovascular event more significantly in patients with BMI above 26 kg/m^2 than in patients who were lean. The data here reviewed support the notion that patients with obesity benefit most from CVD risk management. Specifically, the lipid management of the obese patient should include treatment of LDL-C, HDL-C and triglycerides (Fig. 19). The treatment of each of these components of the obesity-related dyslipidemia seems to have independent benefit in CVD risk reduction. The choice of hypolipidemic agent should be guided by the predominant lipoprotein abnormality. However, patients with the metabolic syndrome should probably be treated with a statin (or a resin or niacin) first and a fibrate as alternative choice whether in monotherapy or in combination therapy. The positive effect of statins on LDL-C, HDL-C and triglycerides often allows a thorough management of the lipid profile of patients with the metabolic syndrome using monotherapy. However, if hypertriglyceridemia and low HDL-C are uncontrolled, the choice should be of fibrates or nicotinic acid alone or in combination with a statin. Although there is general consensus on aggressive goals of therapy for patients with CVD, primary prevention is an area of current controversy. About 50% of patients who experience a CVD event die from their first event. This underscores the importance of managing aggressively patients at high risk for primary prevention of CVD. The desirable goals of lipid management in the obese patient is summarized in Fig. 20 . The data reviewed here clearly show that obesity is a complex condition that increases risk for CVD. We are now starting understanding the various components of the complex pathophysiologic mechanisms relating obesity to CVD. Future research will soon clarify the details of obesity-related CVD. The data already available support a potential benefit from a coordinated management at different pathogenic

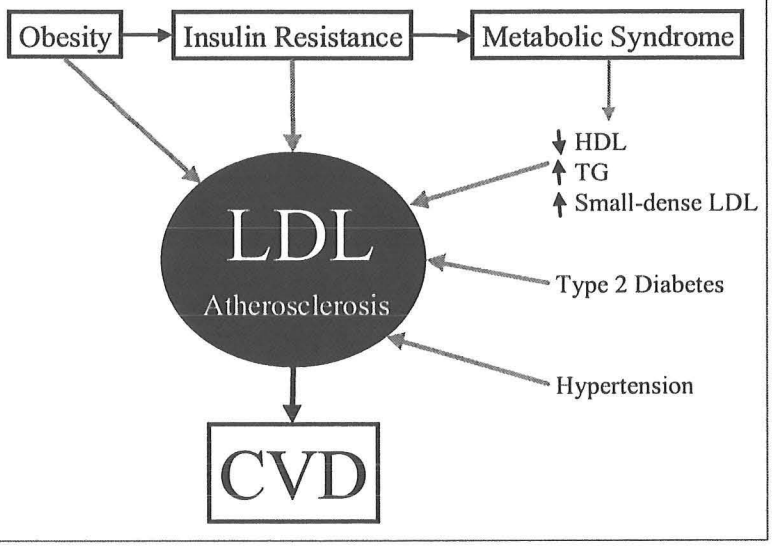
Fig. 20: Suggested goals of therapy for dyslipidemia in obese patients

	NCEP	Desirable
LDL-C		
+ CVD	< 100	< 100
≥ 2 Risk factors	< 130	< 130
≤ 2 Risk factors	< 160	< 130
HDL-C	> 35	> 40
Triglycerides	< 200	< 150

levels to reduce risk in this patient even in the absence of clinically evident CVD.

Recently, the AHA has defined obesity as a **major modifiable risk factor for CVD** (18). While waiting for the availability of a more effective management of the obesity epidemic, a major emphasis has to be put on the necessity to utilize the available tools to implement a comprehensive evaluation and an aggressive treatment of obesity itself, insulin resistance and the various components of the metabolic syndrome. The coordinated work of physicians, nurses and other health care providers in a multidisciplinary treatment of the obese patient is of fundamental importance to reduce CVD burden in our population (Fig. 21).

Fig. 21: Obesity, Insulin resistance, the metabolic syndrome and CVD.



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