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GENETIC POLYMORPHISM AND PATHOGENIC FACTORS INFLUENCING THE RISK OF METABOLIC SYNDROME AMONG HIV-INFECTED PATIENTS

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Abstract. The metabolic syndrome is characterized by the clustering of classic and emerging risk factors for cardiovascular disease and diabetes. If the diagnosis can be accomplished by simple clinical and biochemical tests, its pathophysiologic chain of events is complex and not comprehensively understood. Since the introduction of HAART changes in fat distribution, dyslipidemia, dysglycemia, and other metabolic abnormalities are increasingly observed, and they present major challenges for clinicians involved in screening, evaluation and treatment of HIV/AIDS. There is an increasing literature suggesting that all metabolic syndrome components are strongly inherited. Given the high prevalence of these metabolic complications among HIV-positive patients, an increasing number of authors suggest that it might be useful to test the genetic individual risk, prior to the introduction of HAART. In doing so, it will be possible to design individual HAART regimens for each patient and the clinician will be able to take early measures to prevent the cardiovascular and metabolic complications.
Keywords: metabolic syndrome, HIV, genes, HAART

Metabolic syndrome – definition and diagnosis

The term "metabolic syndrome" represents a cluster of risk factors for atherothrombotic cardiovascular disease and diabetes.

A variety of diagnostic criteria for the metabolic syndrome, proposed by different organizations, may cause confusion, although these criteria largely identify similar risk factors. Also, several different names have been used as alternatives for the metabolic syndrome: metabolic syndrome X, insulin resistance syndrome, dysmetabolic syndrome and cardiometabolic syndrome[1].

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However, even though there is no uniform semantic approach, there is a general agreement that the main components of the metabolic syndrome are: central obesity, impaired fasting blood glucose, elevated blood pressure, elevated triglycerides, and low high-density lipoprotein-cholesterol (HDL-C) [1].

From a clinical point of view, the metabolic syndrome provides a simple and easy-to-use diagnostic set for early detection of individuals at risk for atherothrombotic cardiovascular disease and diabetes[1].

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) in the United States, published in 2001 (revised in 2005), recognized the major contribution of the metabolic syndrome to cardiovascular risk. Table I presents the ATP III criteria for the metabolic syndrome[1].

Central obesity	Waist circumference > 102 cm in males or > 88 cm in females
Hypertriglyceridemia	Triglycerides > 150mg/dL (1.7mmol/L)/on medication for elevated triglycerides
Low HDL-cholesterol	HDL<40mg/dL (1.04mmol/L) in males or <50mg/dL (1.29mmol/L) in females/on medication for low HDL-cholesterol
Hypertension	Blood pressure > 130/85mg/on medication for hypertension
Hyperglycemia	Fasting plasma glucose > 110mg/dL (6.1mmol/L)/on medication for hyperglycemia

Table I. National Cholesterol Education Program Adult Treatment Panel III Criteria for the Metabolic Syndrome (three or more of the following)[1]

Pathogenic mechanisms

The metabolic syndrome and the risk for atherosclerotic cardiovascular disease are strongly associated. Insulin resistance is a core feature of this syndrome (table II)[3].

Patients with metabolic syndrome will commonly have either frank diabetes or a prediabetic state[4].

Dyslipidemia is characterized by low high-density lipoprotein cholesterol (HDL-C), high triglycerides (TG), and high low-density lipoprotein cholesterol (LDL-C). Increased fatty acid flow to the liver causes overproduction of TG-rich very low-density lipoprotein (VLDL), which in turn increases catabolism of HDL and leads to generation of small dense LDL. Atherosclerosis is promoted by these small, dense LDL particles[4].

The metabolic syndrome is determined both by genetic and environmental factors. The exact mechanisms of the metabolic pathways are not yet completely known. The pathophysiology is complex and has been only partially elucidated (figure 1)[6].

Adipose tissue produces a large number of signaling molecules named adipokines. Their functions are complex and they can modulate appetite, insulin sensitivity and inflammation.

The most important adipokines include tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), adiponectin and CRP[5].

CRP is also produced in the liver, under the influence of IL-6. CRP is a potential marker of cardiovascular risk and it appears to be directly involved in the development of atherosclerotic disease[5].

Insulin resistance is also associated with increased fibrinogen and PAI-1. These abnormalities are associated with increased risk of thrombosis because PAI-1 inhibits the activation of plasminogen, the main endogenous thrombolytic enzyme[5].

Raised blood pressure	
Dysglycemia	
Hyperuricemia	
Dyslipidemia	Increased VLDL-triglycerides Low HDL-cholesterol Increased small dense LDL particles
Endothelial dysfunction	Increased levels of adhesion molecules Decreased endothelial-dependent vasodilatation
Hypercoaguability	Increased PAI-1 Increased fibrinogen
Abnormal inflammatory markers	Increased hs-CRP

Table II. Abnormalities Associated with Insulin Resistance[4]

Abbreviations: Hs-CRP, high sensitivity C-reactive protein, PAI, plasminogen activator inhibitor.

Genes causing monogenic obesity	Leptin Leptin receptor Melanocortin receptor Pro-opiomelanocortin
Genes regulating free fatty acid metabolism	Adiponectin β-Adrenergic receptors Fatty acid binding protein-2 Lipases Uncoupling proteins
Genes affecting insulin sensitivity	Peroxisome proliferator activated receptor γ Glycoprotein PC-1 Insulin receptor substrates Skeletal muscle glycogen synthase 1 Calpain-10
Genes affecting lipid metabolism	CD36 Apolipoprotein E 11 β-Hydroxysteroid dehydrogenase type 1 Upstream transcription factor 1
Genes related to inflammation	Tumor necrosis factor-α C-reactive protein

Table III. Candidate Genes Associated with Metabolic Syndrome[6]

Cardiovascular disease risk assessment

A meta-analysis of risks for all-cause mortality, cardiovascular disease (CVD), and diabetes, showed that among studies that used the exact NCEP definition of the metabolic syndrome, relative risks associated with the metabolic syndrome were 1.27 (0.90–1.78) for all-cause mortality, 1.65 (1.38–1.99) for CVD, and 2.99 (1.96–4.57) for diabetes.

The authors concluded that the metabolic syndrome is a major cause of mortality (6-7% of the general mortality), of CVD (12-17%), and of diabetes (30-52%)[2].

Other authors demonstrated a twofold greater risk of mortality from coronary artery disease (CAD) and CVD in persons with metabolic syndrome; even those with only one or two metabolic syndrome

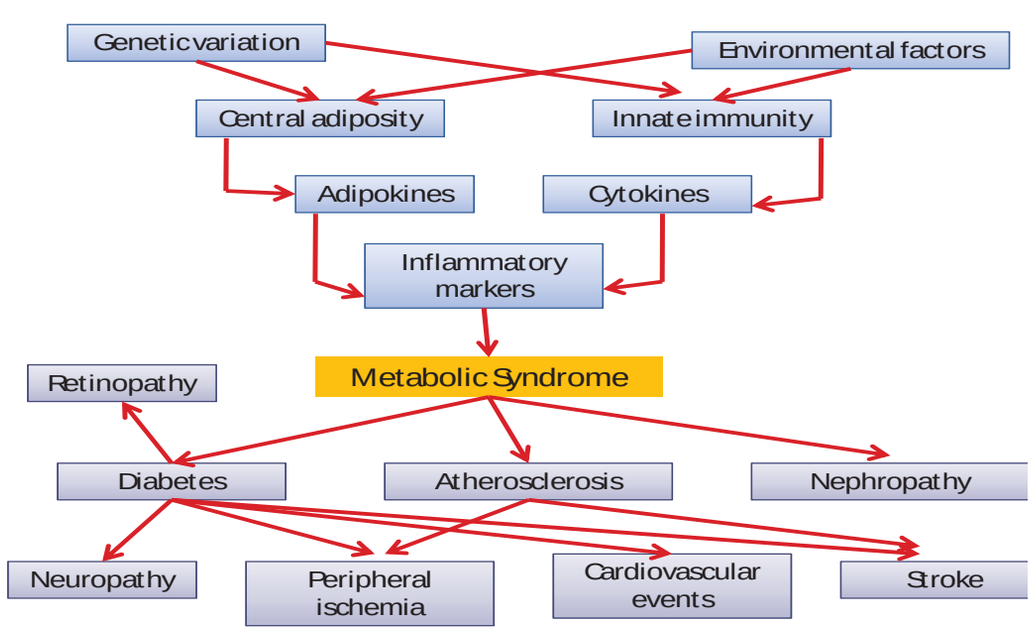

Figure 1. Metabolic Syndrome – Pathophysiologic chain of events (modified after Song Q[6])

risk factors were at an increased risk of death from CAD and CVD[2].

Genetic polymorphism

It is presently considered that all components of the metabolic syndrome are strongly inherited[6]. Common genetic variants in association with other gene variants and environmental factors may lead to disease development. According to their biologic relevance, several potential genes have been studied (table III). The most important genes correlated to the development of metabolic syndrome include: peroxisome proliferator-activated receptor (PPAR γ), adiponectin, CD36, β-adrenergic receptors, insulin receptor substrates (IRS), 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), CRP and tumor necrosis factor-α (TNF-α)[6].

Metabolic complications and HIV infection

Changes in fat distribution, dyslipidemia, dysglycemia, and other metabolic abnormalities represent major challenges in the treatment of human immunodeficiency virus (HIV) infection, considering their high prevalence.

The frequency of these metabolic disorders is higher (approximately 50%) than the frequency of the metabolic syndrome in the general population (25-30%)[9].

These metabolic complications were initially considered to be the result of antiretroviral toxicities. Highly active anti-retroviral therapy (HAART) has the potential to induce hypertriglyceridemia, low high-density lipoprotein (HDL) and insulin resistance. Clinical lipodystrophy is also considered a result of HAART.

However, metabolic changes were found in HIV infection before the HAART era.

Early during the course of HIV infection, the glucose homeostasis is normal, or there is an increased response to insulin. Also, HDL levels are lower[7].

As the immune function declines, a decrease in the LDL level occurs. Transition to AIDS is marked by an increase in VLDL, leading to hypertriglyceridemia. This increase in mediated by IFN-alpha which participates in the host response to HIV infection. The risk for atherosclerosis in AIDS is increased, because the LDL particles become small and dense, and HDL levels are lower[7].

The introduction of HAART has significantly increased the survival rates of HIV-infected patients. However, the numerous metabolic complications made the HAART-associated metabolic syndrome a recognized clinical entity.

The clinical features of this syndrome include somatic changes (lipodystrophy/lipoatrophy).

The metabolic abnormalities frequently follow fat redistribution: dyslipidemia (70% of patients), insulin resistance, type 2 diabetes mellitus (8%-10%), hypertension (up to 75%), coagulation abnormalities (25%), lactic acidemia, and elevated hepatic transaminases (nonalcoholic steatohepatitis)[13].

HIV-associated lipodystrophy/lipoatrophy was first described in 1998 and has a prevalence ranging from 18% to 83%. This syndrome was unreported before the introduction of HAART[12].

Lipoatrophy is characterized by the loss of subcutaneous fat in the face, arms, legs, abdomen, and/or buttocks. Lean tissue mass is unaffected, contrasting to the wasting syndrome of advanced HIV disease. Lipoatrophy occurs among patients who are responsive to HIV therapy[8].

Decrease in cytoplasmic retinoic-acid protein-1	Insulin resistance
Decrease in low density lipoprotein-receptor-related protein	High levels of plasmatic LDL
Decrease in peroxisome proliferator activated receptor type-gamma (PPAR-gamma)	Insulin resistance
Suppression of the breakdown of the nuclear form of sterol regulatory element binding proteins (nSREBP)	Hepatic tissue - increased fatty acid and cholesterol biosynthesis Adipose tissue - lipodystrophy, reduced leptin expression, insulin resistance
Suppression of the inhibition of the glucose transporter GLUT-4 activity in adipose tissue and muscle	Contributes directly to insulin resistance and diabetes

Table IV. PIs mechanisms of pathogenicity[10,12]

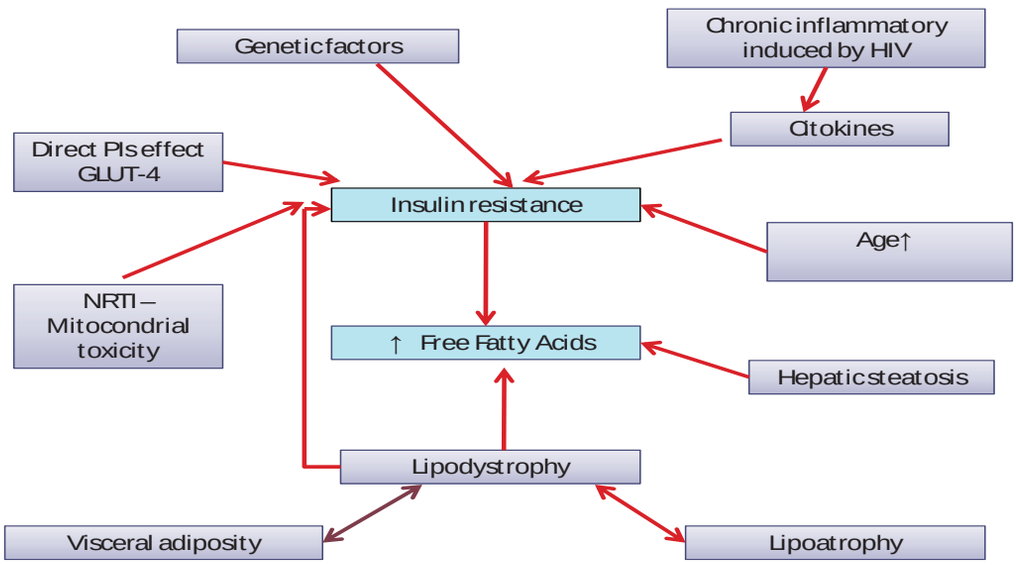

Figure 2. Etiologies for the development of HIV related insulin resistance (modified after Chow DC[18])

Fat accumulation is located on the abdomen, dorsocervical ("buffalo hump"), anterior neck, and breasts. Abdominal fat accumulation is an excess of visceral adipose tissue[8]. Enlargement of the breasts can occur both in men and women.

Pathogenic mechanisms and HAART

The pathogenesis of HAART-associated lipodystrophy and metabolic syndrome is complex and genetic factors may confer particular susceptibility (figure 2)[18].

HAART has direct effects on lipid metabolism, endothelial and adipocyte cell function, and mitochondria. PIs have a multitude of pathogenic features (table IV)[12].

Nucleoside reverse transcriptase inhibitors (NRTIs), and thymidine analogues, may cause mitochondrial toxicity as demonstrated by a decrease in subcutaneous adipose tissue mitochondrial DNA content. Mitochondrial dysfunction is responsible for a decreased differentiation of adipocytes, increased levels of free fatty acids and lipoatrophy[12].

Both PIs and NRTIs are associated with a decrease in adiponectin, which correlates positively with insulin resistance.[12]

HAART drugs can induce increased levels of proinflammatory cytokines, such as TNF-alpha and IL-6. These modifications also occur in non-HIV patients with metabolic syndrome[13]. TNF-alpha activates 11-beta-hydroxysteroid dehydrogenase type-1, which converts inactive cortisone to active cortisol, resulting in increased lipid accumulation in adipocytes and insulin resistance[12].

Genes associated to metabolic complications among HIV-patients

There is an increasing literature reporting the effect of gene polymorphisms regarding the risk of metabolic complications in HIV-positive patients. Most of these reports studied genes that code for apolipoproteins (APOE, APOC, APOA), hormones (resistin), intracellular and extracellular) regulators of lipid metabolism (Sterol Regulatory Element Binding Proteins – SREBPs, TNF-alfa).

APOE gene is mapped to chromosome 19, and codes for Apolipoprotein E, a main apoprotein of chylomicrons. Apolipoprotein E is essential for the normal catabolism of triglyceride-rich lipoproteins. Three common APOE alleles have been identified: APOE e2, APOE e3, and APOE e4.The most common isoform is e3, present in 40-90% of the population[19]. Common APOE variants influence lipoprotein metabolism in healthy individuals. Defects in APOE are a cause of hyperlipoproteinemia type III, Alzheimer disease, sea-blue histiocyte disease, lipoprotein glomerulopathy[19].

Recent studies report that allele-specific immunomodulatory effects involving inherited APOE

isoform are important enough to alter the lipid metabolism and the clinical course of HIV infection. APOE e4 is associated with enhanced HIV cell entry. APOE e4 and APOE e2 genotypes accelerate HIV mortality[14]. Some APOE genotypes, correlated to variants of apolipoproteins A5 and C3 have been associated with the severity of antiretroviral therapy-induced dyslipidemia and with higher prevalence of lipodystrophy[15].

APOC3 gene is mapped to chromosome 11 and codes for apolipoprotein C III[19].

Apolipoprotein C III is a VLDL component and some defects can induce the development of hypertriglyceridemia[19].

A recent study reported that APOC3 variant alleles (-455 1/-482 1) might be associated with dyslipidemia and lipoatrophy in HAART-treated patients[15].

The apolipoprotein encoded by APOA5 gene influences the triglyceride levels. Some genotypes in association with PIs therapy were associated with extreme hypertriglyceridemia (triglyceride level >500 mg/dL)[16].

Resistin is a cysteine-rich hormone produced by the adipose tissue. The physiologic role of resistin has been the subject of controversy regarding its implication in obesity and insulin resistance (resistin = *res*istance to *ins*ulin). A specific resistin single nucleotide polymorphism (SNP) called rs1862513 was previously linked to increased body mass index and diabetes in humans.

In a study published in 2008, researchers investigated the role of genetic variations in resistin and the risk of metabolic complications associated with HAART. 2 SNPs (rs321975 and rs3760678) were significantly more frequent in the high-risk group and were particularly associated with lipoatrophy. The PPARgamma agonists (such as pioglitazone and rosiglitazone) reduce resistin levels. The authors concluded that such agents could potentially have a beneficial impact on HAART-induced lipodystrophy[11].

Sterol Regulatory Element Binding Proteins (SREBPs) are key intracellular regulators of cholesterol, triglyceride, and glucose metabolism. SREBPs can bind to specific DNA sequences (sterol regulatory elements) that are found in the control regions of the genes that encode enzymes implicated in lipid and glucose metabolism. A study reported that in PI-treated patients, homozygous SREBP-1c 3 322C>G carriers (genotype 22), plasma total cholesterol (TC) remained unchanged, whereas in 3 322C>C carriers (genotypes 11/12), TC increased. Also, the increase in total cholesterol was associated with increases in insulin and leptin. The authors concluded that "genotype 22 carriers had a lower risk of being affected by PI-associated hyperlipoproteinemia than genotype 11/12 carriers"[22].

The role of TNF-alpha gene polymorphism has also been studied in relation to metabolic complications. In a genetic case-control association study, the frequency of a rare variant TNF-alpha genotype (-238) was significantly higher in HIV-positive patients with lipodystrophy than in those without lipodystrophy, but the results need to be confirmed by further studies[21].

The protective role of genetic variation was also observed. In a study published in 2008 the following genotypes were protective against lipoatrophy: ApoC3-455 CC, AR-beta-3 codon 64 TT, Fas-670 GG. The AR-beta-2 codon 27 CC genotype was associated with a lower risk of fat accumulation[14].

Conclusions

The genetic predisposition for metabolic complications during HAART is becoming more important than previously acknowledged. Given the relative low cost and feasibility of gene testing (at least in western countries) it is useful to determine this risk, as most of the cited authors suggest. It will be possible to avoid the rapid emergence of side effects by designing individual HAART regimens for each patient and by taking early measures to prevent them.

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