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METABOLIC SYNDROME AND MYOCARDIAL INVOLVEMENT IN HIV-INFECTED PATIENTS

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Rezumat
Terapia HAART folosită în prezent a modificat istoricul natural al infecției HIV, transformând practic această afecțiune într-o stare cronică care poate fi gestionată. Chiar dacă beneficiile utilizării HAART sunt cu mult mai mari decât riscurile posibile ale sindromului metabolic și bolilor cardiovasculare, este necesară o gestionare atentă a acestor pacienți, în special ca urmare a faptului că factorii de risc valabili pentru populația generală se suprapun cu cei specifici pentru această populație.
Screeningul cardiovascular pentru pacienții infectați cu HIV cărora li se administrează HAART trebuie să se facă în mod constant, printr-o colaborare între specialistul în boli infecțioase și medicul internist.
Cuvinte cheie: *HIV, HAART, sindrom metabolic, risc cardiovascular.*

Abstract
The current HAART has modified natural history of HIV infection and it has practically turned the disease into a manageable chronic condition. Even though the benefits of HAART use are overwhelmingly greater than possible metabolic syndrome and cardiovascular disease risks, close management of those patients is called for, especially due to the fact that general population risk factors now overlap with specific ones in this population.
Cardiovascular screening for HIV-infected patients who are receiving HAART must be done constantly with a collaboration between the infectious disease specialist and the internist.
Keywords: *HIV, HAART, metabolic syndrome, cardiovascular* risks.

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Cardiac risk in HIV-infected patients

Cardiac abnormalities in human immunodeficiency syndrome have been reported for the first time in 1983 following the autopsy of a 24-years-old patient who had Kaposi sarcoma on the entire anterior cardiac wall[1]. In autopsy studies, the prevalence of cardiac abnormalities varies between 8-73%. Antemortem, the cardiac dysfunction can be identified by clinical or paraclinical methods. Cardiac involvement in HIV-infected patients is a negative prognostic factor, it affects the quality of life and the survival rate.

The pathophysiology of HIV cardiomyopathy is multifactorial. Metabolic disorders, chronic inflammation, coronary artery disease, myocarditis, cocaine use, antiretroviral toxicity, neoplasia and malnutrition are involved in heart disease in HIV-infected patients.

Coronary heart disease is a very important non-infectious complication in these patients. Risk factors for HIV-associated coronary heart disease are the same as in the general population, but these patients have HIV-specific risk factors like inflammation, immune activation and endothelial dysfunction.

The traditional risk factors like sex, age, smoking, dyslipidemia, diabetes and hypertension are common in HIV-infected patients. Studies reported high prevalence of dyslipidemia among HIV-patients with and without antiretroviral therapy. Lipid metabolism abnormalities were reported in patients with AIDS before antiretroviral era. Hypercholesterolemia and hypertriglyceridemia develop with the administration of protease inhibitors. A study reported that one year after the introduction of protease inhibitors, the incidence of hypertriglyceridemia was 38.2% and hypercholesterolemia was 25%[2]. Protease inhibitors target the catalytic region of HIV-1 protease[3]. This region is homologous with regions of two human proteins that regulate lipid metabolism CRABP-1 (Cellular Retinoic Acid-Binding Protein Type 1) and LRP (Low Density Lipoprotein Receptor-Related Protein)[4]. Therefore, PI inhibit the action of CRABP-1 and bind to LRP, which leads to hyperlipidemia. By linking to CRBP-1, protease inhibitors interrupt the metabolism of retinoic acid and reduce PPAR-γ activity (peroxisome proliferator-activated gamma receptor), resulting in adipocyte differentiation but also in apoptosis of these cells. These phenomena lead to hyperlipidemia by reducing the peripheral lipid storage and increasing their release into the blood[5]. These patients had high plasma triglyceride levels which may correlate with the viral load.

The prevalence of systemic arterial hypertension is higher in HIV-infected

patients compared to the uninfected (21% vs 16%)[6]. An association between HAART agents and risk of hypertension has not been identified.

Antiretroviral agents are associated with insulin resistance and type II diabetes. The prevalence of diabetes mellitus in patients treated with HAART is between 8-10%[7]. Protease inhibitors can direct down-regulation of the glucose transporter (GLUT-4), the major transporter of glucose into fat cells and cardiac and skeletal muscle[8]. Another mechanism by which protease inhibitors (except for atazanavir) affect insulin sensitivity include direct effects on IRS-1 phosphorylation (substrate receptor-1 insulin) and on subsequent glucose uptake in adipocytes[9]. Also, chronic inflammation has its role in insulin resistance. Lipodystrophy can lead to the destruction of pancreatic beta cells[10].

Some retrospective studies demonstrate that the risk of cardiovascular disease was grater in HIV-infected patients on antiretroviral therapy than those without antiretroviral therapy[11]. Drugs like indinavir, lopinavir-ritonavir, didanosine and abacvir are associated with a high cardiovascular risk[12].

Metabolic syndrome and cardiovascular risk factors in hiv infected patients

Pathophysiology of Metabolic Syndrome in HIV-infected individuals

Since the description of abnormal fat distribution following a few years on HAART with Protease Inhibitors (PI), chiefly ritonavir plus saquinavir combination[3], metabolic changes in HIV individuals have been widely studied. The main features included dyslipidemia, insulin resistance, and lipodystrophy. Many of these phenotypic and metabolic changes fit metabolic syndrome criteria[14] and therefore, there is growing concern that metabolic complications associated to HIV and HAART may lead to increased risk for cardiovascular events

HIV infection is associated with deregulated inflammatory response, through suppressing genes necessary to extinguish inflammation. In such context, HIV-infected monocytic cells have downregulated expression of the tyrosine kinase RON, a negative regulator of the inflammatory process and HIV transcription as well, via ubiquitin-proteosome degradation[15]. This long term inflammatory environment along with higher white blood cells count act as a metabolic risk factor in the pathogenesis of HIV.

While obesity is a central component of metabolic syndrome, adipose tissue is a dynamic source of several proinflammatory cytokines, chemokines, growth factors and complement proteins, which can alter endothelial cells integrity and contribute to the atherosclerosic process. This constitutive low-grade inflammatory status is characterized by increased plasma levels of TNF-α and IL-6 and other mediators of inflammation[16]. The interplay between HIV-triggered low-grade inflammatory injury, inbalances in lipid and glucose metabolism and fat redistribution has already been described, with soluble urokinase plasminogen activator receptor (suPAR) emerging as a stronger predictor of dysmetabolism than TNF-α and IL-6.

Insulin resistance is thought to determine excessive adipokine production yielding to endothelial dysfunction. As it progresses towards metabolic syndrome and diabetes mellitus, the ongoing process of endothelial damage, along with inflammation, thrombosis and oxidation orchestrate at the vessel wall to produce atherosclerotic plaques. Accordingly, caloric restriction-

induced weight loss contributes to the regulation of a wide variety of inflammation-related molecules adipose tissue and upregulated the expression of molecules with anti-inflammatory properties[17].

HIV-related risk factors

Inflammation is thought to be a major determinant in the pathogenesis of both diabetes mellitus and atherosclerosis. However, the key inflammatory molecules involved in atheroma and diabetes mellitus in HIV individuals on HAART are poorly understood.

Epicardial and thoracic periaortic fat deposits have been associated to high levels of hsCRP, insulin resistance and subclinical atherosclerosis in HIV-infected patients on HAART and both have been related to metabolic syndrome[18]. In fact, epicardial fat storage, some lipodystrophy phenotypes and well established risk factors for atherosclerosis seem to be associated.

A case–control study performed among HIV-infected ART-naive Africans showed a high prevalence of metabolic syndrome and increased arterial stiffness, which is considered an early marker of atherosclerosis. In this report, prevalence of impaired fasting glucose and diabetes mellitus, levels of fasting triglycerides and the atherogenic dyslipidemia ratio were higher in HIV-individuals than in controls. Elevated blood pressure prevalence was high but comparable in both groups[19].

HIV infection acts as an independent risk factor for atherosclerosis development and cardiovascular damage and it has been responsible for the increased prevalence of metabolic syndrome and arterial function impairment. HIV-specific mechanisms include immune dysfunction and increased inflammatory response leading to increased thrombosis and changes in lipid levels and cholesterol metabolism, which are also responsible for metabolic syndrome and cardiovascular risk in the general population. Tat, a key molecule in HIV replication and pathogenesis can affect both mesenchymal stem cells survival and differentiation by downregulating the expression of VEGF-induced endothelial markers and this might play an instrumental role in vessel damage and in the atherosclerotic lesions observed in HIV infection[0].

The pathogenesis of dyslipidemia in HIV-infected individuals has been associated with increased apolipoprotein levels, increased hepatic synthesis of VLDL-c, decreased clearance of triglycerides and also with the effects of viral infection itself, acute-phase proteins and increase in circulating cytokines such as IL-6 and IFN-α . In fact, lipid unbalances are common in art-naive HIV-infected individuals even in the absence of major host-related risk factors for

dyslipidemia, such as high blood pressure, type 2 diabetes mellitus and obesity.

Subcutaneous adipose tissue from infected individuals bears reduced mRNA levels of cytochrome c oxidase subunit II compared to non-infected individuals. These concentrations decreased further in association with HAART[21].

Antiretroviral-related risk factors

HAART therapy has both positive and deleterious effects on cardiovascular risk. Cumulative evidence has pointed to the relation between different metabolic disorders and HAART use, including insulin resistance, hyperlipidemia, and lipodystrophy, even though it remains controversial whether these effects can be directly ascribed to antiretroviral drugs. Antiretroviral-driven suppression of HIV replication seem to act as double-edged sword since it can reduce and also increase HIV-related cardiovascular risk through its toxicity[22].

HAART toxicity depends on the antiretroviral drug used and may include adverse lipoprotein changes, insulin resistance, inflammation, platelet dysfunction, and vascular injury. Studies performed in vitro have demonstrated that some HAART regimens, such as those including zidovudine, some NNRTI (e.g. efavirenz) and indinavir induce toxicity through induction of cardiomyocyte and endothelial cell apoptosis leading to endothelial dysfunction and vascular damage. Thus, compared to untreated HIV infection, the net effect of starting antiretroviral therapy on cardiovascular disease risk is unknown as it may increase or decrease the overall risk[2]. Studies suggest that conventional risk factors will play major role in the development of cardiovascular disease in HIV patients, as seen in the general population and such risk factors urge to be targeted by prevention strategies.

Dyslipidemia in HIV population can result from both uncontrolled HIV disease and clinical restoration after HAART initiation. Individual, demographic and genetic traits besides the specific side effects of the antiretroviral combination have a great contribution to the type and degree of dyslipidemia seen in this population. According to the D:A:D, a consortium assessing adverse events of anti-HIV drugs, the risk associated to certain PI's (indinavir, lopinavir/ritonavir, abacavir) was consistently lower than the one calculated to the annual increment in risk associated to advanced age and current smoking habit[2]. The use of lopinavir/ritonavir, stavudine, efavirenz and nelfinavir, zidovudine/lamivudine and didanosine/stavudine have already been reported as cause of dyslipedemia by at least one of the following mechanisms: increased tryglycerides levels, increased LDL-c levels, and increased HDL-c levels.

Beside these specific cardiovascular risks, cardiovascular disease has been reported as adverse effect with some ARV drugs, independently of metabolic disorders. A meta-analysis indicated an increased risk of myocardial infarction in patients exposed to abacavir, and an increased risk associated with each additional year of exposure to indinavir (and lopinavir)[2]. A prospective observational study from the D:A:D consortium showed that combination antiretroviral therapy was independently associated with a relative increase of 1.26 times in the rate of myocardial infarction per year of exposure during the first four to six years of use[2]. Despite these minor metabolic unbalances described for many antiretroviral

drugs, it is important to keep in mind that the morbidity and mortality risks for HIV patients who are not on HAART are much higher than the risks seen with any antiretroviral drug or combination of drugs.

Myocardial involvement in HIV-infected patients

The spectrum of myocardial disease in HIV-infected patients ranges from incidental asymptomatic findings to symptomatic disease:

- Asymptomatic findings
- Focal myocarditis
- Abnormal myocardial structure/ function on imaging
- Symptomatic cardiomyopathy

A. Focal myocarditis

Before the antiretroviral era, in autopsy studies, the prevalence of focal myocarditis was around 33%[27,28]. Most of the patients diagnosed post-mortem with focal myocarditis were completely asymptomatic. Microscopically there are focal collections of mononuclear cells with/without necrosis and sometimes ventricular dilatation.

In the last years, the Dallas criteria have lost their value. Biochemical pigments that detect cellular antigens, such as anti-CD3 (T lymphocyte), anti-CD68 (macrophage), are more useful than the Dallas criteria.

Viral heart infection with Epstein-Barr, herpes simplex virus, cytomegalovirus or Coxsackie virus was found in all the patients with focal myocarditis. It is known that the myocardial cell does not have receptors for CD4, so the cell entry of the human immunodeficiency virus can not occur. However, other viruses may allow HIV to enter and replicate in myocardial cells. This mechanism is incompletely known.

B. Abnormal myocardial structure/ function on imaging

In addition to the general cardiovascular risk factors, antiretroviral therapy has an important role in metabolic disorders in these patients (especially protease inhibitors - PI) and it can also affect the myocardial cells by mitochondrial destruction (like nucleoside reverse transcriptase inhibitors - NRTI)[29]. Cardiometabolic risk in these patients has been provided by the echographic measurement of the epicardial adipose tissue, which is correlated with abdominal visceral fat[30]. Left ventricular dysfunction is often found in asymptomatic patients. A 196 patients study evaluated by echocardiography showed that almost half of the patients had a dyastolic dysfunction, independently associated with CD4 cell count, viral load and only 4% had systolic dysfunction of the left ventricle[31].

In a large meta-analysis from the ART era

including over 2000 HIV infected patients, the prevalence of ventricular dysfunction was over 50% (43% had diastolic dysfunction and 8% had systolic dysfunction)[32]. High blood pressure and advanced age have been associated with diastolic dysfunction, and tobacco smoking, low socioeconomic status, elevated PCR levels, low selenium plasma levels and history of acute myocardial infarction have been associated with systolic dysfunction.

The studies have different data about the impact of the viral load, the infection duration or the stage of disease Cardiac MRI can also identify subclinical myocardial abnormalities, showing evidence of inflammation and myocardial fibrosis. Myocardial fibrosis was three times more frequent on the patients with HIV infection. A 90-patients study reported almost 50% greater myocardial lipid on proton magnetic resonance spectroscopy compared to controls[33]. These patients had lower HDL values and higher LDL cholesterol and serum triglycerides. Compared to controls, HIV-infected patients had lower peak diastolic strain rate and higher myocardial mass[34].

The prevalence of systolic dysfunction has decreased in developed countries. Due to antiretroviral therapy, the diastolic dysfunction is now dominant. The exact impact of diastolic dysfunction is unknown. Further studies are needed to determine the prognosis of these patients. The HIV-infected patients can have asymptomatic myocardial imaging abnormalities, which do not correlate with the stage of the infectious disease and can be a risk factor to major cardiac events.

Symptomatic cardiomyopathy

The first case of dilated cardiomyopathy in a HIV infected patient was described in 1986[35].The incidence of symptomatic cardiomyopathy associated with HIV infection new cases is 1 to 2, and the prevalence was reported in approximately 4-10%[36]. Dilated cardiomyopathy appears late and it is often associated with the stage of the infectious disease.

A large study showed that 6,5% of the deaths of HIV infected patients receiving antiretroviral therapy (ART) were caused by cardiovascular events[37].

Conclusions

The current HAART has modified natural history of HIV infection and it has practically turned the disease into a manageable chronic condition. Special attention should be paid to both imperfect control of HIV replication and long-term adverse events linked to drugs used in the therapeutic scheme. Even though the benefits of HAART use are overwhelmingly greater than possible metabolic syndrome and cardiovascular disease risks, close management of those patients is called for, especially due to the fact that general population risk factors now overlap with specific ones in this population, even though the former are usually more prominent than the latter.

Thus, metabolic syndrome in HIV populations ought to be closely monitored and controlled by programmatic and comprehensive public measures. These findings call for an integrated management strategy, including smoking cessation policies, diet modification, and regular physical activity planning. Finally, comprehensive educational measures are needed and further research is instrumental to assess the barriers to implement preconized interventions and to achieving recommended treatment goals that are singular to the HIV-population[38].

HIV involvement in cardiac abnormalities is still

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incompletely elucidated. An autoimmune mechanism for myocardial dysfunction could be based on the observation that anti-myosin and anti-B cell receptors lead to myocardial destruction. This happens when HIV destroys proteins on the surface of myocardial cells. Another possible mechanism that could contribute to myocardial destruction could be hypergammaglobulinemia and the formation of immune complexes.

High active antiretroviral therapy in developed countries has reduced the prevalence of dilated cardiomyopathy, which influenced the prognosis of HIV-infected patients.

Cardiovascular screening for HIV-infected patients who are receiving HAART must be done constantly with a collaboration between the infectious disease specialist and the internist.

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