

METABOLIC DISORDERS IN PATIENTS WITH HIV

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Abstract

Human Immunodeficiency Virus (HIV) infection and subsequent antiretroviral therapy (ART) are known to be related to different metabolic disorders. Although ART decreased HIV-associated mortality and morbidity, mortality rates in patients with HIV and ART are 3 to 15 higher than those in the general population. More than 50% of the mortality is due to diseases like: diabetes mellitus (DM), hypertension, cardiovascular diseases (CVD), chronic renal disease and complications following bone fractures. In patients with HIV the metabolic disorders are mainly caused by mitochondrial toxicity, a side effect of ART, and they are represented by: dyslipidemia, lipoatrophy, insulin resistance and diabetes mellitus.

key words: insulin resistance, metabolic disorders, dyslipidemia, diabetes

Introduction

According to World Health Organization (WHO), 37 million subjects live with Human Immunodeficiency Virus (HIV) all over the world, of which only 54% are aware of their infection, and 1.2 millions of deaths due to Acquired Immune Deficiency Syndrome (AIDS) were reported [1]. In Romania, at the end of 2015 was reported a number of 13.766 people with HIV. The highest incidence was recorded in children in the 1990's and so most of the patients are now 25-29 years old [2].

HIV infection is a chronic, incurable disease which has a natural course without antiretroviral therapy (ART) to develop AIDS. The time frame for this development is different from individual

to individual, between eight and ten years, according to the age of the patient, the level of HIV ribonucleic acid (HIV-RNA) and the CD4 T cell count [3]. The development of ART changed this evolution and nowadays both the life expectancy and quality of life of these patients are higher. Although ART decreased HIV-associated mortality and morbidity, mortality rates in patients with HIV are 3 to 15 higher than those in the general population. More than 50% of the mortality is due to diseases like: diabetes mellitus (DM), hypertension, cardiovascular diseases, chronic renal disease and complications following bone fractures [4].

HIV infection and metabolic disorders

HIV infection itself contributes to the development of metabolic disorders. Studies have shown that people with HIV without ART, have a particular lipid profile characterized by low levels of total cholesterol (TC), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) but with high levels of triglycerides. In these individuals the rates of basal lipolysis and hepatic lipid production are increased, abnormalities that seem to be associated with elevated levels of some inflammatory cytokines, like interferon α . HIV infection has an important role in augmenting the chronic inflammation by increasing also the levels of high-sensitivity C-reactive protein and of interleukin 6 (IL-6) [5].

Regarding the way in which HIV infection affects the glucose metabolism several studies have shown that some of the inflammatory markers, like high sensitivity C-reactive protein and tumor necrosis factor (TNF) receptors 1 and 2, are linked with an increased risk of developing diabetes, highlighting the role of chronic inflammation in the appearance of dysglycemia [6]. In this population insulin resistance is increased through different other mechanisms like the presence of lipodystrophy [7], the effects of HIV itself [8,9], the co-infection with hepatitis C virus [10], the low levels of growth hormone [11], the low CD4 count [12], and the presence of hepatic steatosis [13]. Thus, the studies that used the standard of hyperinsulinemic-euglycemic clamp proved that in comparison with subjects without lipodystrophy, HIV patients with lipodystrophy achieve lower insulin-stimulated glucose disposal [14,15], impaired glucose uptake by skeletal muscles [15] and increased intramyocellular lipids [14]. Lipodystrophic patients are dealing with elevated plasma levels of insulin and free fatty acids [16], and they develop in a higher number hepatic steatosis

(which is linked to the hyperinsulinemia) [17]. It is known that fatty liver disease causes insulin resistance via many mechanisms, some of them involving hepatic adipokines, known to be part of the pathogenesis of type 2 diabetes [18]. In HIV patients, the presence of lipodystrophy and the development of insulin resistance are related with the growth hormone (GH) deficiency which is commonly described among these patients [11]. A low CD4 count (<200 cells/ μ L) is another factor which contributes to insulin resistance [19]. Moreover, low CD4 cell count was linked with impaired glucose tolerance (IGT) and DM in patients that had also infection with hepatitis C and hepatitis B virus [20].

ART and metabolic disorders

There are five different classes of drugs for the treatment of HIV: Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), Protease inhibitors (PIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Integrase inhibitors (INSTIs) and Entry inhibitors (co-receptor antagonists and fusion inhibitors) [21].

A side effect of ART is represented by a syndrome of lipodystrophy that includes metabolic complications and an altered distribution of fat [22]. Patients may develop lipoatrophy, lipohypertrophy or a combination of these two in the face, limbs, and breast or in the cervical or dorsocervical adipose tissue. Furthermore, the ectopic fat is often found in the liver, and muscles [6]. Several risk factors have been described for the appearance of this syndrome, including the longer duration of treatment, the older patients and the lower level of immunodeficiency. Some antiretroviral drugs are associated with lipodystrophy: the NRTIs linked most strongly to lipoatrophy are stavudine and zidovudine and those linked to lipohypertrophy are most of the PIs class: efavirenz and raltegravir [22]. Lipohypertrophy

mechanisms are different from those for lipoatrophy, and they haven't been described entirely. Some of them are represented by the high levels of inflammatory cytokines and triglycerides, and by the presence of free fatty acids deposits in the visceral fatty tissue and in the liver. Dyslipidaemia, hypertriglyceridemia, low-HDL-C and glucose metabolism disorders were described in high percentage in patients with lipodystrophy syndrome who were receiving ART [5].

Particularities of the dyslipidemia that appears after ART administration are represented by low levels of HDL-C and high levels of LDL-C (including small, dense LDL) and total cholesterol. PIs interfere with lipid metabolism, inhibiting adipocyte differentiation and lipogenesis; they also lower the hepatocyte clearance of chylomicrons and very low density lipoprotein (VLDL) and they augment triglycerides synthesis in the liver. So an atherogenic type of dyslipidemia is developed, with high levels of LDL-C and triglycerides and low levels of HDL-C with accumulation of Apo E and Apo CIII [23]. NRTIs are also known to determine an increase in LDL-C and in triglycerides, with one exception: tenofovir [5]. Regarding the NNRTIs, efavirenz increases the level of total cholesterol and triglycerides, while nevirapine maintains a normal level of HDL-C [24]. The entry inhibitors maraviroc and enfuvirtide didn't interfere with the lipid levels [25,26] and the use of maraviroc improved the lipid profile of the patients with dyslipidemia [26]. INSTIs are also known for their safer lipid profile compared with PI [27].

The prevalence of diabetes or milder glucose metabolism disorders in subjects with HIV has been reported in the range of 2-14% [28,29]. The D:A:D: study (Data Collection of Adverse events on Anti-HIV Drugs), maybe one of the largest studies on this population, showed an

incidence of type 2 DM (T2DM) of 4.2 per 1000 person-years. The factors associated with T2DM development were the low CD4 cell count (<200 cells/mL) and the presence of lipodystrophy [30]. According to MACS (Multicenter AIDS Cohort Study) the incidence of T2DM was 14% in HIV-positive men taking PI (ritonavir and indinavir) and NRTIs (stavudine, zidovudine and didanosine) [10]. In VACS (Veterans Aging Cohort Study) the association between the risk of diabetes and weight gain was linear for infected and uninfected subjects. However, a steeper slope was described for the association in HIV positive: for each 2.26 kg of weight gained, HIV infected had 14% increased risk of DM (HR, 1.14; 95% CI, 1.10-1.17) and uninfected individuals had 8% increased risk (HR: 1.08; 95% CI, 1.07-1.10) (p<0.01 for interaction) [31].

Studies revealed that the main mechanism for developing diabetes in HIV individuals receiving ART is insulin resistance. Patients on PI's described peripheral insulin resistance and impaired glucose tolerance due to the inhibition of glucose transporter GLUT 4 [32] and of glucose transport into the β -cell with secondary impairment of the insulin secretion [33]. Some cytokines like adiponectin and leptin were associated with glucose metabolism disorders [19]. In HIV patients with lipoatrophy who received for more than six months ART, hypoleptinemia, hypertriglyceridemia and hyperinsulinemia were described [34]. Also the levels of adiponectinemia are low in this population [35] while serum adiponectin levels were correlated negatively with insulin resistance [36]. Regarding the NRTIs, the other class of ART known for their role in the development of diabetes in these patients, it was observed that it inhibits DNA polymerase- γ , active in mitochondrial replication [37]. Afterwards the mitochondrial function is disturbed, an effect better seen in the muscle and

liver, where the fat isn't oxidized and lipotoxic insulin resistance occurs [38].

In the last publication of the American Diabetes Association's Standards of Medical Care in Diabetes (2016), it is mentioned for the first time that patients with HIV should be screened for glucose metabolism disorders before and after 3 months of ART or when ART medication is being changed by dosing fasting glucose [39].

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Conclusions

Each of these metabolic disorders must be identified quickly in order to be treated and so to increase the life quality of patients with HIV. It is important to develop screening programs adapted to the type of ART received by these patients in order to ensure a multidisciplinary management.

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