MANAGEMENT OF DIABETES MELLITUS IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME

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Abstract

Acquired immunodeficiency syndrome (AIDS) is a human immune system disease characterized by increased susceptibility to opportunistic infections, certain cancers and neurological disorders. The syndrome is caused by the human immunodeficiency virus (HIV) that is transmitted through blood or blood products, sexual contact or contaminated hypodermic needles. Antiretroviral treatment reduces the mortality and the morbidity of HIV infection but is increasingly reported to be associated with increasing reports of metabolic abnormalities. The prevalence and incidence of diabetes mellitus in patients on antiretroviral therapy is high. Recently, a joint panel of American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) experts updated the treatment recommendations for type 2 diabetes (T2DM) in a consensus statement which provides guidance to health care providers. The ADA and EASD consensus statement concur that intervention in T2DM should be early, intensive, and uncompromisingly focused on maintaining glycemic levels as close as possible to the nondiabetic range. Intensive glucose management has been shown to reduce microvascular complications of diabetes but no significant benefits on cardiovascular diseases. Patients with diabetes have a high risk for cardiovascular disease and the treatment of diabetes should emphasize reduction of the cardiovascular factors risk. The treatment of diabetes mellitus in AIDS patients often involves polypharmacy, which increases the risk of suboptimal adherence.

key words: acquired immunodeficiency syndrome, antiretroviral treatment, diabetes mellitus.

Introduction

Acquired immunodeficiency syndrome (AIDS) is a human immune system disease characterized by increased susceptibility to opportunistic infections, certain cancers and neurological disorders [1,2]. At the end of 2012, according to a statistics of the World Health Organization (WHO), 35.300.000 people were infected with the human immunodeficiency virus
(HIV) of which 9.700.000 had access to antiretroviral therapy [3]. According to the Compartment for Monitoring and Evaluation of HIV/AIDS, at the end of that year in Romania were registered 9880 patients (9546 adults and 334 children), of whom 7869 received antiretroviral therapy [4].

Antiretroviral therapy reduces morbidity and mortality of HIV infected individuals. Combinations of different classes of antiretrovirals generate the inhibition of viral replication and decrease the possibility of mutations. However, antiretroviral therapy is associated with metabolic alterations, namely changes in the carbohydrate homeostasis and an increased frequency of diabetes, fat redistribution and dyslipidemia. Thus, determination of fasting blood glucose in 1,278 men enrolled in a multicenter study presented by Brown TT et al revealed a prevalence of diabetes 4 times higher in patients treated with antiretroviral therapy than in HIV-seronegative men [5]. More recently, in a study published in 2013 in BioMed Central Infectious Diseases which included 2006 patients who were newly diagnosed with HIV/AIDS, the impaired glycemic's homeostasis was represented by hyperglycemia (defined as a fasting blood glucose value ≥110 mg/dl) in 19.99% of cases, and diabetes (defined by fasting blood glucose≥126 mg/dl) in 10.52% of cases [6].

The mechanisms involved in the alteration of glucose metabolism homeostasis in patients newly diagnosed with HIV/AIDS or those on antiretroviral treatment are:

1. Altered cellular uptake of glucose, secondary to the inhibition of glucose transporter 4 (GLUT 4) translocation induced by protease inhibitors [7]. Plasma membrane consisting of phospholipids is impermeable to polar molecules, like glucose. Its transport is provided by specific proteins located in the plasma membrane, respectively sodium-glucose cotransporters (which provides active transport of glucose) and glucose transporters (which ensures its diffusion). Stimulation of glucose transport in response to insulin is mainly the consequence of GLUT 4 translocation to the plasma membrane in the respective cytoplasmic sector (for muscle and for microtubule wall). Impaired trafficking and translocation of glucose transporters (GLUT 4 especially) involves insulin resistance.

2. The presence of high concentrations of free fatty acids in the portal and peripheral circulation induces insulin resistance by the competition they create to the utilisation of glucose in the insulin dependent tissues and generates the intensification of gluconeogenesis and hepatic glucose production [8].

3. HIV and antiretroviral therapy effects on fat redistribution may cause the alteration of cytokines involved in glycemic homeostasis, which was proved in studies by reduced adiponectin levels [9].

4. Overall, protease inhibitors may reduce pancreatic insulin secretion, but insulin resistance appears to represent the main alteration.

In 1997 the American Diabetes Association (ADA) proposed an etiopathogenetical classification of diabetes, classification accepted in 1999 by the WHO. The classification comprises four categories, namely: type 1 diabetes (T1DM), type 2 diabetes mellitus (T2DM), other specific types of diabetes, including drug-induced diabetes (in which is mentioned antiretroviral therapy) and gestational diabetes [10,11]. The subclass "specific types of diabetes" represents the association of diabetes with many diseases or conditions and its prevalence is estimated at 1-2% of the diabetic population [12]. The European AIDS Society Guidelines on the diagnosis and management of
AIDS recommended in 2009 to determine fasting blood glucose at diagnosis of HIV infection and consecutively after 6-12 months in patients with antiretroviral therapy. If the fasting glucose is modified (values between 110-125 mg/dl), an oral glucose tolerance test is recommended [13].

In patients diagnosed with diabetes, the importance of glycemic control has been demonstrated in numerous clinical trials, metabolic balance generating the reduction of microvascular complications. Unfortunately, the results of the major trials published in 2008-Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) haven’t confirmed that the intervention by intensive glycemic control will reduce the risk of cardiovascular events [14-16]. Meanwhile, diabetes is a clinical entity with increased cardiovascular risk and therefore specialist advice considering the management of all cardiovascular risk factors (serum lipid and blood pressure levels, antiplatelet therapy, smoking cessation).

Management of the diabetic patient includes: measures to optimize lifestyle, pharmacotherapy, self-control, complications screening and psychosocial support.

Lifestyle improvement

Optimizing lifestyle aims to achieve and maintain an ideal body weight and contribute to decreases in blood glucose, serum lipids and blood pressure or bringing them closer to the targets. Lifestyle optimization includes diet therapy, promotion of exercise and smoking cessation.

Diet therapy. The European AIDS Society Guidelines on the diagnosis and management of AIDS recommended that dietary interventions do not interfere with the absorption of antiretroviral therapy, keeping the balance between caloric intake and energy expenditure, limiting intake of refined carbohydrates, reducing consumption of fat <30% and cholesterol<300 mg/day, reducing alcohol consumption<20-40 g/day [13]. The ADA clinical practice recommendations published in 2010 [17] include: changing previous eating habits, access to a dietitian, individualization of diet in relation to age, sex, height, weight, level of exercise, preferences, local tradition and level of culture. Monitoring carbohydrate intake is an essential component of the strategy for achieving optimal glycemic control. Saturated fat intake should represent <7% of total caloric intake while intake of trans fat should be reduced to a minimum [17]. In the same time, ADA recommends restricting alcohol intake.

Promoting exercise. Exercise is recommended to be introduced gradually, depending on the individual skills and encourage extension of the duration and frequency of physical activity to 30-45 min/day, 3-5 days / week or 150 min/week [17].

Smoking cessation. Smoking is an independent cardiovascular risk factor and therefore education should advise for smoking cessation. Epidemiological studies have provided convincing evidence regarding the causal link between smoking and health risk. Studies in diabetic patients consistently showed an increased risk of cardiovascular disease and premature death in smokers. Smoking is also associated with premature occurrence of microvascular complications and may play a role in T2DM occurrence [18].

Pharmacotherapy

Glycemic control. Glycemic control targets recommended by ADA in 2013 for adults
outside pregnancy include a glycosylated hemoglobin (HbA1c) <7%, capillary fasting blood glucose between 70-130 mg/dl and postprandial blood glucose <180 mg/dl [19]. The European AIDS Society Guidelines on the diagnosis and management AIDS (2013) recommend a value of HbA1c<6.5-7% in the absence of hypoglycemia and a value of fasting blood glucose between 73-110 mg/dl [20].

Diabetes mellitus is characterized by beta cell insufficiency, insulin resistance and increasing hepatic glucose output. ADA and the European Society for the Study of Diabetes (EASD) published in September 2006 (and subsequently revised in 2009 and 2012) a consensus statement on the management of hyperglycemia in T2DM. Pharmacotherapy of glycemic control based on the ADA/EASD consensus applies the basic principle that diabetes is a progressive disease. As such, pharmacotherapy will also be progressive, permanently adapted to the achievement/failure of glycemic control targets [21].

Provided there are no contraindications, Metformin is the first choice due to the fact that it is well tolerated and the most cost -effective agent. In situations where it cannot be used, another oral agent (sulfonylurea/glinides, thiazolidinediones, dipeptidyl peptidase 4 (DDP4) inhibitors or in selected cases glucagon-like peptide 1 (GLP -1) receptor agonists should be considered. If the therapeutic target is not reached after about 3 months, one may consider the combination of metformin with a sulphonylurea, thiazolidinedione, DDP4 inhibitor, GLP-1 receptor agonist or basal insulin. Note that the order above is determined by historical reasons and does not denote a particular preference. Issues related to life expectancy, duration of diabetes, comorbidities and hypoglycemia risk should be considered for each patient before stepping up the treatment regimen [22].

It is recommended to start Metformin with a dose of 500-850 mg / day, with subsequent dose escalation as tolerated up to maximum 2.5 g / day. It should be noted that metformin therapy may enhance antiretroviral-induced lipodystrophy. After metformin therapy failure, the European AIDS Society Guidelines on the diagnosis and management of AIDS (2013) recommend dual non-insulin therapy and subsequently introducing insulin therapy. The guideline mentioned above indicates that there is currently little reliable data on the role of hypoglycemic therapy in cardiovascular prevention and the fact that there are no data on HIV-positive individuals [20].

In 2009, some experts believed that thiazolidinediones represent the therapy of choice in patients with AIDS associated lipoatrophy. This therapeutic class included 3 drugs: troglitazone (withdrawn in March 2000 due to liver toxicity), rosiglitazone and pioglitazone. In September 2010, the Committee for Medicinal Products for Human Use of the European Medicines Agency concluded that the benefits of rosiglitazone no longer outweigh its risks and that marketing authorization for all rosiglitazone-containing medicines should be suspended across the European Union [23]. More recently, in a statement posted on its website in July 2011, the same authority stated that the completion of the assessment of antidiabetic medicines containing pioglitazone confirmed that these medicines remain a valid treatment option for certain patients with T2DM, but there is a slightly increased risk of bladder cancer in patients receiving this therapy and recommended the need for periodic assessment of the efficacy and safety of individual treatment for each patient [24].
Management of dyslipidemia. In 2013, ADA recommended the following optimal values for lipid profile parameters: LDL (low-density lipoprotein) cholesterol <100 mg/dl in diabetic patients without manifest cardiovascular distress and <70 mg/dl in patients with overt cardiovascular disease; HDL (high-density lipoprotein) cholesterol >40 mg/dl in men and >50 mg/dl in women; and triglycerides <150 mg/dl [19]. The European AIDS Society Guidelines on the diagnosis and management of AIDS (2013) recommended optimal values of LDL cholesterol <80 mg/dl and standard values <115 mg/dl, while for triglycerides <155 mg/dl, respectively <190 mg/dl [20].

The classes of lipid lowering agents include: statins, resins, fibrates, nicotinic acid, cholesterol absorption inhibitors and omega 3 fatty acids. The lipid-lowering medication selection will be based on lipid control priorities as follows:

1. In the case where the main lipid abnormality is an increase in LDL cholesterol, the use of statins is the first option [13]. If there are contraindications for statin therapy based on resins or fibrates. Statins inhibit HMG-CoA (hydroxymethyl glutaryl CoA) reductase, the enzyme responsible for the intracellular conversion of HMG-CoA into mevalonic acid, a key step of endogenous cholesterol synthesis. The consequences are: reducing cholesterol synthesis, increasing expression of cellular receptors for LDL cholesterol, catabolism and clearance stimulation of circulating LDL cholesterol. Non lipid effects of statins administration include stabilization of plaque and anti-inflammatory and antithrombotic action. When choosing statin therapy it should be taken into account that they may influence the bioavailability of antiretroviral therapy through interaction with CYP3A4.

2. In the case of hypertriglyceridemia, the priority is lifestyle improvement and control of other metabolic parameters. In case of severe hypertriglyceridemia, in order to prevent acute pancreatitis, it is recommended to initiate fibrates therapy or nicotinic acid if fibrates are contraindicated. Fibrates have multiple mechanisms of action: they activate lipoprotein lipase (thereby reducing circulating triglyceride levels and, to a lesser extent, LDL cholesterol), they inhibit cholesterol biosynthesis by modulating the activity of HMG-CoA reductase, and they affect fibrinolysis and coagulation processes.

3. In the case of mixed dyslipidemia, the first choice will be statin, followed by fibrate combination in case of persistent elevated triglycerides. The European AIDS Society Guidelines on the diagnosis and management of AIDS (2009) recommend combination therapy after 4 months of fibrates with statins if the response is suboptimal [13].

Management of blood pressure. The target is to maintain blood pressure <140/80 mmHg. Patients with confirmed blood pressure ≥140/90
mmHg should receive pharmacologic therapy associated with interventions for lifestyle modification. The initiation of blood pressure lowering therapy in diabetic patients is recommended to be made with inhibitors of angiotensin converting enzyme or angiotensin receptor blockers. If one of those therapeutic classes is not tolerated, it will be changed with the other one. If necessary in order to reach the targets, it is recommended to associate other antihypertensive classes, preferable metabolically neutral such as calcium channel blockers or non-thiazide diuretics. Use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics requires careful monitoring of renal function and serum potassium levels [17,19].

**Antiplatlet treatment.** The treatment with aspirin 75-162 mg/day is recommended as a primary prophylactic strategy for type 2 diabetic patients with high cardiovascular risk. In case of allergies to aspirin clopidogel 75 mg/day is recommended. The usage of aspirin in patients under 21 years old is contraindicated because of the risk of Reye syndrome [19].

**Conclusions**

Treatment of diabetes mellitus in patients with HIV infection may imply the use of additional medications that may reduce the adherence to antiretroviral therapy. The influence on the antiviral drugs efficacy should be the primary criteria used in antidiabetic treatment selection. In the same time, the choice of antiretroviral therapies with minimal metabolic effects is recommended in patients with increased cardiovascular risk.

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