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FEATURES OF DIABETES MELLITUS IN HIV-INFECTED PATIENTS

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Abstract: Diabetes mellitus is one of the urgent problems of contemporary medicine, and today it is growing radiply. In diabetes, the risk of such diseases as lung tube, chronic hepatitis B,C and HIV increases. The increase in the number of HIV-infected patients and the prolonged life expectancy increase the frequency of joint management of these two diseases.
Key words: diabetes mellitus, HIV, hyperglikemia, ARVT.

Diabetes mellitus (DM, diabetes mellitus) is a systemic heterogeneous disease characterized by a chronic course, caused by absolute (type 1) or relative (type 2) insulin deficiency, which first causes disturbances in carbohydrate metabolism, and then in all types of metabolism, which ultimately leads to damage to all functional systems of the body [1,2,10].

Despite the obvious successes in the study of diabetes in recent decades, its prevalence has become a pandemic, which has affected almost all countries of the world. According to the IDF Diabetes Atlas from 2017, 424.9 million people with diabetes are registered in the world; by 2045, 628.6 million people are expected to have diabetes. The highest increase in the number of patients with diabetes will be observed in developing countries of the Pacific Ocean, the Middle East, and Southeast Asia. The global prevalence of diabetes among people aged 20 to 79 years has increased from 4.7 in 1980 to 8.8% in 2017, with an expected 9.9% by 2045.

Three quarters of people with diabetes live in middle- and low-income countries. According to expert estimates, 46.5% of patients with diabetes remain unregistered, most of them live in Africa [7,13].

Uzbekistan is no exception. Over the past 10 years, the number of patients with diabetes in terms of visits alone has increased by 37% [2,14]. According to epidemiological screening studies, today the prevalence of type 2 diabetes in Uzbekistan over the past 14 years has increased 1.6 times and amounted to 7.9% [13]. The progressive increase in the incidence of diabetes mellitus in the world, clinical manifestations and various complications leading to decreased ability to work and death of patients, have contributed to the fact that diabetes has become a universal problem of modern healthcare.

Diabetes is often associated with other diseases, such as tuberculosis, chronic viral hepatitis B, C, HIV, etc. [6,9,18].

HIV infection is a slowly progressive disease caused by the human immunodeficiency virus (HIV). The virus infects cells of the immune system that have CD4 receptors on their surface: T-helper cells, monocytes, macrophages, Langerhans cells, dendritic cells, microglial cells. As a result, the functioning of the immune system is inhibited, Acquired immune deficiency syndrome (AIDS) develops, the patient's body loses the ability to protect itself from infections and tumors, and secondary opportunistic diseases arise that are not typical for people with normal immune status. Today, many opportunistic infections (OIs) are rare in industrialized countries. The incidence of

infections associated with severe immunodeficiency, such as CMV and MAC infections, has now decreased to less than 10% of what was observed in the mid-1990s. Antiretroviral therapy not only led to a significant reduction in the incidence of OIs, but also significantly changed their course. While previously life expectancy after the onset of the first symptoms of AIDS was rarely more than three years, today patients can live with AIDS for 15 years or more [12,20].

Despite the progress of modern medicine in the treatment and prevention of HIV infection, according to WHO estimates, at the end of 2016 there were 37.3 million people living with HIV in the world, of which 2.6 million were cases of new infections. In addition, more than 1 million people die each year from HIV-related complications [18].

HIV spreads fastest in Eastern Europe, the incidence remains at a fairly high level in Asia. That is why the main goal of WHO is to optimize the prevention of transmission of this disease and existing methods of therapy, as well as to ensure timely monitoring of the effectiveness of therapy, minimizing side effects and thus increasing the overall effectiveness of treatment [19]. The rate of development of HIV infection depends on many factors, including the status of the immune system, age (elderly people have an increased risk of rapid development of the disease), strain of the virus, co-infections with other viruses, adequate nutrition, and therapy. An insufficient level of medical care and the presence of concomitant infectious diseases, such as tuberculosis, predispose to the rapid development of the disease.

American researchers have found that HIV infection predisposes to the development of another serious disease - type 2 diabetes. Details of the new study are reported in BMJ Open Diabetes Research & Care. Although the number of people infected with HIV has declined significantly in the United States over the past decade, the immunodeficiency virus lives in the blood of 1.2 million Americans. Moreover, every 8th HIV-infected person does not know about his illness [13]. The diabetes statistics are even more frightening. This disease affects 29 million people in the United States alone; another 86 million already have prediabetes [1,14].

Three quarters of people with diabetes live in middle- and low-income countries [13]. Risk factors for type 2 diabetes include obesity, lack of physical activity (even with normal body weight), age over 45 years, family history, and a history of gestational diabetes. Now it is proposed to add the presence of HIV infection to these risk factors. These two diseases belong to the group of chronic diseases, i.e. diseases that have the ability to progress, change or go into remission, take a protracted course [10]. The authors of the latest study claim that HIV is associated with an average 4% increased risk of type 2 diabetes, but a cause-and-effect relationship between the two diseases has not yet been proven, nor have the biological mechanisms underlying this association.

Study of diabetes in an HIV-infected population. The project was led by Dr. Alfonso Fernandez Romieu, a fellow in the Department of Epidemiology at Emory University in Atlanta. For the first time, he decided to calculate the incidence of diabetes in HIV-infected American adults, comparing it with the rest of the population. The analysis used data from the Medical Monitoring Project (MMP), a nationally representative study of 8,610 HIV-infected people. For comparison, data were taken from the National Health and Nutrition Examination Survey (NHANES), which included 5,604 healthy adult participants. Dr. Hernandez-Romiu compared the incidence of diabetes in both groups using statistical regression models, adjusting for other risk factors. HIV-infected participants were predominantly male (73%), 41% African American, over 45 years of age, and above the American average in terms of education and income. 25% were obese, and another 20% were positive for hepatitis C. In the healthy group, up to 50% were male, approximately 11% were African American, and the average age of participants was 45 years. Almost 60% had higher education. Less than 2% of participants were positive for hepatitis C. Type 2 diabetes was diagnosed in 10.3% of HIV-infected participants and only 8.3% of healthy study participants.

Taking into account the composition of the groups, it was calculated: the incidence of diabetes mellitus in HIV increases by 3.8 - almost 4%. According to the authors, modern highly effective antiretroviral therapy allows HIV-infected people to live to an advanced age, but in the future they are more susceptible to serious chronic diseases - this is a topic for future research [11].

Highly active antiretroviral therapy (HAART) is a method of treating HIV infection (HIV belongs to the family of retroviruses), consisting of taking three or four drugs. Thanks to HAART, most people living with HIV can now lead normal lives. According to a 2013 study, overall life expectancy with HAART (for residents of the United States and Canada, when starting therapy with a CD4 count above 350 cells/mm3), can be up to 70 years in some groups.

According to the literature, side effects of ART are divided into so-called. "early" and "late". “Early” effects include diarrhea, nausea, vomiting, thirst, abdominal pain, fatigue, insomnia, hair loss, and dyspepsia. Sometimes changes in the hematopoietic system can be observed, determined by simple tests, for example, a general blood test (decreased number of neutrophils, or neutropenia) or biochemical studies (increased ALT, AST levels). It should be remembered that all these side effects can be short-term, and also that their occurrence is associated not with ART in general, but with taking a specific drug of a certain group (NRTI, PI). “Late” effects of ART include those adverse events that can occur after many months or years of taking the drug [20]. The most serious of them include disorders of carbohydrate metabolism (increased blood sugar levels, up to the development of diabetes) and changes in lipid (fat) metabolism. It is very important to diagnose these changes in a timely manner, since, unlike “early” effects, they can go unnoticed by the patient and, if left untreated, increase the risk of cardiovascular diseases, even heart attack [6].

The undesirable late effect of ART drugs, such as an increase in blood sugar levels, can be easily stopped in the initial stages, as long as only fasting glucose levels are elevated - with the help of diet and lifestyle changes [15]. It is much more difficult to do this later, when disturbances in carbohydrate metabolism increase and the patient even develops type 2 diabetes. In a 4-week study in 12 healthy HIV-negative volunteers, which assessed the effect of indinavir on carbohydrate metabolism, an increase in glucose and insulin levels was detected when taking the drug at a dose of 800 mg 2 times a day. The glucose level at the start of the study was 4.9±0.1, at the end 5.2±0.2 mmol l ($p=0.05$), insulin - 61.7±12.2 and 83.9±12, respectively .2 pmol/l ($p<0.05$), insulin resistance index – 1.9±0.3 and 2.8±0.5 ($p<0.05$), glucose level during a glucose tolerance test 2 hours after a sugar load – 5.1±0.4 and 6.5±0.6 mmol/l ($p<0.05$), insulin level 223.1±48.8 and 390.3±108.8 pmol/l ($p= 0.05$) [8].

Further studies showed that not all PIs lead to impaired glucose transport. Thus, the use of atazanavir did not lead to disruption of carbohydrate metabolism. In a double-blind, randomized, crossover study on 30 healthy volunteers, it was found that during the use of atazanavir, unlike the combination of lopinavir/ritonavir, changes in carbohydrate metabolism did not develop.

Disorders of carbohydrate metabolism also develop with the use of NNRTIs [3,12]. In the above-mentioned study on 100 HIV-infected women, 80% of whom received NNRTIs, significant differences in fasting insulin levels were identified (81 ± 8 versus 45 ± 2 pmol/l , $p<0.05$), insulin 2 hours after a sugar load (496±47 vs. 267±22 pmol/l, $p<0.05$) and glucose 2 hours after a sugar load (6.88±0.22 vs. 5.72±0.17 mmol/l, $p<0.05$), while no differences in fasting glucose levels were obtained (4.66±0.06 43 versus 4.55±0.06 mmol/l) [16]. But in the same study already mentioned above, conducted on 37 patients 24 months after the start of ART, no differences were found in the HOMA index either in the group of patients receiving lopinavir/ritonavir + zidovudine/lamivudine, or in the group of patients receiving lopinavir \ritonavir + nevirapine) [4,17].

A study conducted on 30 HIV-infected children receiving ART and 20 children with the natural course of HIV infection (from 3 to 18 years old) also found no significant differences in the levels

of glucose, insulin, proinsulin, C-peptide and insulin resistance index [14].

The only antiretroviral drug that does not cause disturbances in carbohydrate metabolism is nevirapine; moreover, according to the FDA, while taking nevirapine, glucose tolerance even increases. There is also evidence that in HIV-infected patients, during the use of nevirapine, the level of insulin in the blood plasma decreases [19,21].

That is why for patients receiving ART therapy, regular monitoring of carbohydrate (fasting blood sugar) and lipid levels (level of total cholesterol and triglycerides, and, if necessary, a more extensive study, the so-called lipidogram, glucose tolerance test) is of paramount importance. exchange. In some regions, such as the African continent, such studies are recommended as routine screening for all patients with HIV infection as an effective means of reducing the risk of cardiovascular disease [5,8].

According to Russian authors, the emergence of highly active antiretroviral therapy for the treatment of infection caused by the human immunodeficiency virus (HIV infection) has led not only to a significant improvement in patient survival, but also to the need to study new pathological conditions that arise during the treatment of this infection, united by the concept "metabolic syndrome", namely insulin resistance, disorders of glucose and lipid metabolism, structural and functional disorders in adipose tissue with the formation of peripheral lipoatrophy, visceral obesity, etc. Long-term consequences of these processes may include cardiovascular diseases and type 2 diabetes mellitus [13.21].

Thus, widespread diabetes is often associated with HIV infection, the treatment of which involves the use of PIs and NRTIs, which, by negatively affecting carbohydrate metabolism, complicate the treatment of diabetes mellitus.

As the life expectancy of patients with HIV infection increases, the incidence of diabetes in this pathology increases. In turn, the use of drugs in the treatment of HIV infection, such as PIs and NRTIs, leads to disruption of carbohydrate metabolism, which contributes to the development of type 2 diabetes. If HIV infection occurs against the background of diabetes, the use of ART aggravates the course of this pathology.

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