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ORIGINAL ARTICLE

RISK ASSESSMENT FOR THE DEVELOPMENT OF METABOLIC SYNDROME IN PATIENTS WITH AIDS, AFTER THE FIRST YEAR OF ANTIRETROVIRAL THERAPY

PROCENA RIZIKA ZA RAZVOJ METABOLIČKOG SINDROMA KOD BOLESNIKA SA SINDROMOM STEČENE IMUNODEFICIJENCIJE POSLE JEDNOGODIŠNJE PRIMENE ANTIRETROVIRUSNE TERAPIJE

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Abstract

Introduction: Antiretroviral therapy (ART) in the treatment of HIV infection has allowed maximum control of viral replication and reconstruction of the immune system, which has contributed to the long-term survival. However, it has been observed that a long-term use of ART can lead to cumulative toxicity and metabolic abnormalities.

Aim: The aim of this study was to determine whether there is a difference in lipidogram, glycemia and body mass index (BMI) before and after the initiation of ART, and to determine in which of the antiretroviral drugs the changes in the values of the measured variables were most common.

Material and methods: The research was conducted at the Clinic for Infectious Diseases, Clinical Center of Kragujevac, as a prospective study involving 40 patients diagnosed with HIV infection. Biochemical parameters and BMI calculation were performed before the initiation of ART and one year after.

Results: The analysis of the observed variables indicated a statistically significant difference in total cholesterol ($p = 0.001$), HDL ($p = 0.002$), LDL ($p = 0.003$), triglycerides ($p < 0.001$), glucose ($p < 0.001$) and BMI ($p = 0.002$). By analyzing the administered ART therapy, statistical significance was achieved in the measured triglyceride values after the administration of ritonavir and lopinavir, while the highest BMI values, compared to initial ones, were observed after the administration of ritonavir, but without achieving statistical significance.

Conclusion: The results of the study showed that ART therapy has effect on the development of hyperlipidemia, which may be associated with an increased risk of developing cardiovascular disease and protease inhibitors of the older generation are highlighted, in particular. ART therapy in HIV-infected cells contributes to the development of a metabolic syndrome involving dyslipidemia, lipodystrophy and insulin resistance.

Keywords:
HIV,
antiretroviral therapy,
cardiovascular disease,
protease inhibitors,
hyperlipidemia

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Sažetak

Uvod: Antiretrovirusna terapija u lečenju infekcije virusa humane imunodeficijencije (HIV) omogućila je maksimalnu kontrolu virusne replikacije i rekonstrukciju imunog sistema, što je doprinelo dužem preživljavanju, čak i kod bolesnika sa uznapredovalom bolešću. Uočeno je, ipak, da dugotrajna primena antiretrovirusne terapije može dovesti do kumulativne toksičnosti i razvoja metaboličkih abnormalnosti.

Cilj: Cilj istraživanja je bio da utvrdimo da li postoji razlika u izmerenim vrednostima lipidograma, glikemije i indeksa telesne mase pre i nakon započinjanja antiretrovirusne terapije, kao i da utvrdimo kod kojih se antiretrovirusnih lekova najčešće javljaju promene u vrednostima izmerenih varijabli.

Materijal i metode: Istraživanje je sprovedeno u Kliničkom centru Kragujevac, Klinika za infektivne bolesti, u vidu prospektivne studije u kojoj je učestvovalo 40 bolesnika, kod kojih je dijagnostikovana HIV infekcija. Biohemijski parametri i izračunavanje indeksa telesne mase vršeni su pre i godinu dana nakon započetog lečenja antiretrovirusnom terapijom. Podaci su statistički obrađeni u statističkom programu *SPSS* (verzija *22.0*).

Rezultati: Analizom ispitivanih varijabli uočena je statistički značajna razlika u vrednostima ukupnog holesterola ($p = 0,001$), HDL ($p = 0,002$), LDL ($p = 0,003$), triglicerida ($p = 0,000$), glukoze ($p < 0,001$) i indeksa telesne mase ($p = 0,002$) pre i posle započinjanja antiretrovirusne terapije. Analizom primenjene antiretrovirusne terapije statistička značajnost je dostignuta kod izmerenih vrednosti triglicerida nakon upotrebe ritonavira i lopinavira, dok su najveće vrednosti indeksa telesne mase, u odnosu na početne, zabeležene kod primene ritonavira, ali bez postizanja statističke značajnosti.

Zaključak: Rezultati istraživanja su pokazali da antiretrovirusna terapija ima uticaja na razvoj hiperlipidemije koja može da bude povezana sa povećanim rizikom za nastanak kardiovaskularnih bolesti, a posebno se ističu inhibitori proteaze starije generacije. Antiretrovirusna terapija kod inficiranih HIV-om doprinosi nastanku metaboličkog sindroma koji obuhvata dislipidemiju, lipodistrofiju i insulinsku rezistenciju.

Ključne reči:
HIV,
antiretrovirusna terapija,
kardiovaskularna bolest,
inhibitori proteaze,
hiperlipidemija

Introduction

Human immunodeficiency virus (HIV) belongs to the retrovirus family and lentiviride subfamily. The main feature of retrovirus is the conversion of viral RNA into the DNA by reverse transcription mechanism under the effect of the reversible transcriptase encoding enzyme. There are two types of HIV, HIV-1 and HIV-2, both of which cause a chronic infection with progressive impairment of the immune system. Epidemiological and genetic data indicate that both infections have been present in human population for at least several decades, and HIV-2 has been present as an endemic form in West Africa, probably much longer. The HIV-2 is genetically more similar to monkey immunodeficiency virus, it is less virulent, and the infection has slow progression (1).

Acquired immunodeficiency syndrome (AIDS) is the terminal phase of chronic HIV infection. The first cases of AIDS were described in 1981 in America and next year all over the world. The diagnosis of AIDS in HIV infected patients is found in all patients with a total CD4 lymphocyte count of less than 200/mm3, as well as in those with AIDS-indicative diseases (invasive cervical cancer, Kaposi's sarcoma, progressive multifocal leukoencephalopathy, visceral toxoplasmosis, lymphoma, HIV wasting syndrome and others) (1).

Antiretroviral therapy has a major impact on the prognosis of patients with HIV infection. Before 1996, there were only a few antiretroviral drugs and the treatment of HIV infection consisted mainly of prophylaxis of common opportunistic pathogens and the treatment of AIDS-related diseases. The first drug approved for use in 1986 was zidovudine, a nucleoside reverse transcriptase inhibitor, and then didanosine and stavudine, which also belong to this group of antiretroviral drugs. Thereafter, non-nucleotide reverse transcriptase inhibitors such as efavirenz were synthetized, as well as protease inhibitors, out of which the most significant were indinavir, sakvinavir, lopinavir and ritonavir. Recent antiretroviral drugs include fusion inhibitors, CCR5 antagonists and integrase inhibitors. Since its discovery, antiretroviral therapy has made remarkable progress, especially thanks to the combination of antiretroviral drugs, known as Highly Active Antiretroviral Therapy (HAART) (2).

Antiretroviral therapy (ART) enabled maximum control of viral replication and the reconstitution of the immune system, thereby contributing to the prolonged survival of patients with advanced disease as well, extending the life expectancy of patients for several decades. However, the prolongation of life expectancy leads to the exposure of these patients to the cumulative toxicity of antiretroviral drugs. A significant number of patients have developed a cluster of metabolic abnormalities, called metabolic syndrome, which includes lipodystrophy, dyslipidemia and insulin resistance. The pathophysiology of cardiovascular disease in patients with HIV is complex

(3). HIV infection itself can accelerate the process of atherosclerosis by mechanisms associated with the activation of the immune system, chronic inflammation, coagulation disorders and lipid status (4). It was demonstrated that hyperlipidemia associated with an increased risk of cardiovascular disease could be found in 70% and diabetes mellitus type 2 in 8-10% of patients. The study proved the prevalence of lipodystrophy of 29.1%, with the increase over time and reaching 100% after ten years of therapy. An increased risk of cardiovascular disease was observed as well, with an estimated ten-year risk of 10% (5).

The objectives of the research were: 1) to determine whether there is a difference in the measured values of lipidograms (cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, glycaemia, before and after the initiation of ART; 2) to determine whether there is a difference in body mass index (BMI) values, before and after starting ART; 3) if there is a difference, to determine which group of antiretroviral drugs changes the values of the measured variables most frequently.

Material and methods

The research involved 40 patients with HIV infection, who were hospitalized and clinically treated at the Clinic for Infectious Diseases of the Clinical Center of Kragujevac.

The study started in October 2015 and lasted until March 2017. Only HIV positive patients in whom a treatment with antiretroviral therapy had been started, and were over 18 years of age, were included in the study. The study excluded patients who had already been diagnosed with some of the cardiovascular diseases such as ischemic heart disease, ischemic disease of the cerebrovascular system, cardiomyopathy, or the existence of risk factors for the development of cardiovascular disease in the sense of already diagnosed hypertension. Also, previously diagnosed diabetes mellitus, or the presence of insulin resistance were excluding factors. The following biochemical parameters were analyzed: triglycerides, cholesterol, LDL, HDL and fasting glucose. The examined variables were sampled before initiation of antiretroviral therapy and one year after continuous therapy. All patients in whom antiretroviral therapy was corrected during the one-year period, due to the existence of resistance or adverse effects, were excluded from the study. Laboratory analyzes were determined in the Laboratory Diagnostic Service of the Clinical Center of Kragujevac. For each patient, values of arterial pressure and BMI were measured. The atherosclerosis index was calculated according to the following formula: Index = LDL / HDL. In addition to monitoring certain parameters, one part of data were collected retrospectively, by the insight into medical documentation.

All statistical analyses were conducted using software package IBM SPSS Statistics 22. The results were analyzed using Student's t-test or Mann-Whitney test on the dependence of normal distribution determined by Kolmogorov-Smirnov test. The data were expressed as the mean ± standard error (SEM). All statistical analyses in this paper were conducted with confidence interval of 95%. Values of $p < 0.05$ were considered statistically significant.

Results

The study involved 40 patients, 32 male patients (80%), and 8 female patients (20%). The average age of male patients was 37 (± 9.72), while female patients were 43 (± 14.01) years old. The most significant risk factor in both groups was a risky sexual contact, male patients were dominated by a homosexual contact (69%), and female patients were dominated by heterosexual contact (20%). In only a few male patients, a sex risk factor for HIV infection was the earlier use of intravenous narcotic drugs (7,5%), while in one female patient, the only risk factor was blood transfusion (2,5%).

By analyzing total cholesterol values just before initiating antiretroviral therapy and one year after the initiation of antiretroviral therapy, there was a statistically significant difference (median values: 4.69 vs. 6.49; $p = 0.001$). (**table 1**).

On the other hand, the atherosclerosis index did not show statistical significance in the measured values. By analyzing triglyceride values, a year before and a year after starting ART, the statistical significance was observed (median values: 1.85 vs. 4.53; $p < 0.001$).

The non-parametric test showed that there was a statistically significant difference in fasting glucose values, in relation to the initial values before the introduction of the therapy ($p < 0.001$). Also, the statistical significance in the measured values (median values: 21.61 vs. 24.63; $p = 0.002$) was observed by analyzing the BMI values measured before and after the initiation of antiretroviral therapy.

The most commonly prescribed combination of ART in our study was abacavir/lamivudine and efavirenz in 16 (40%). Other prescribed combinations in our Center were abacavir/lamivudine/lopinavir/ritonavir and zidovudine/lamivudine/nevirapine and other. In patients treated with protease inhibitors, in the first place ritonavir ($p = 0,049$) and lopinavir ($p = 0.048$) statistical significance in triglyceride values was observed, compared to patients who were not treated with drugs from the group of protease inhibitors (non-nucleoside reverse transcriptase inhibitors and integrase inhibitors). All patients had nucleoside reverse transcriptase inhibitors like backbone therapy, except one.

Discussion

Today, there are several antiretroviral agents so that, in addition to previously known drugs from the group of nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, other groups, such as nucleotide reverse transcriptase inhibitors, integrase inhibitors, fusion inhibitors and coreceptor antagonists have been approved. In our study, most patients were treated with a combination of nucleoside

Table 1. Measured mean values of variables in patients with HIV infection just before initiating antiretroviral therapy and one year after the initiation of antiretroviral therapy

Parameter		average	SD	minimum	maximum	p
Cholesterol	before ART	4.69 mmol/L	± 1.01	2.46 mmol/L	6.66 mmol/L	P < 0.001
	after ART	6.49 mmol/L	± 2.26	3.76 mmol/L	16.23 mmol/L	
TGL	before ART	1.84 mmol/L	± 1.35	0.47 mmol/L	8.27 mmol/L	P < 0.001
	after ART	4.53 mmol/L	± 5.07	1.01 mmol/L	29.00 mmol/L	
HDL	before ART	0.99 mmol/L	± 0.99	0.26 mmol/L	1.59 mmol/L	P < 0.001
	after ART	1.29 mmol/L	± 1.29	0.69 mmol/L	2.91 mmol/L	
LDL	before ART	2.81 mmol/L	± 1.09	0.15 mmol/L	4.92 mmol/L	P = 0.003
	after ART	3.74 mmol/L	± 1.69	0.62 mmol/L	6.58 mmol/L	
Atherosclerotic index	before ART	2.90	± 1.12	0.22	5.12	P = 0.422
	after ART	3.09	± 1.2	0.9	5.62	
Glucose	before ART	4.69 mmol/L	± 0.51	3.3 mmol/L	5.70 mmol/L	P < 0.001
	after ART	5.35 mmol/L	± 0.61	5.20 mmol/L	6.50 mmol/L	
BMI	before ART	21.61 kg/m^2	±3.51	14.18 kg/m^2	30.10 kg/m^2	P = 0.002
	after ART	24.63 kg/m^2	± 5.06	16.96 kg/m^2	38.02 kg/m^2	

and non-nucleoside reverse transcriptase inhibitors or protease inhibitors. Drugs of a newer generation such as integrase inhibitors, or a newer generation of protease inhibitors, were not used enough to bring valid conclusions. Although it is still an incurable disease, thanks to antiretroviral therapy, HIV infection does not represent a deadly disease, but a chronic infection with which the patients live even in the case of the presence of viral resistance. Antiretroviral therapy leads to suppression of viral replication and so improves and maintains the function of the immune system, thereby reducing the risk of developing AIDS-associated diseases, as well as other complications (6,7).

It is known that the antiretroviral therapy has numerous side effects such as lipodystrophy, gastrointestinal disorders, metabolic disorders, insulin resistance and dyslipidemia, as indicated by our results.

The results of the study show an increase in the measured values of lipidogram, both of total cholesterol and of triglycerides, after one year of taking antiretroviral therapy. Also, the measured glycemic values after one year indicated the existence of statistical significance, which is in favor of other studies that indicate the relationship between antiretroviral therapy and insulin resistance (8). Previous studies showed that the incidence of type 2 diabetes mellitus is four times more common in HIV positive patients compared to the general population, and abacavir affects insulin resistance, in particular (9).

What certainly contributed to our results in the research is that the majority of patients have been treated with antiretroviral therapy of an older generation, which is known to have numerous side effects. Thus, one group of patients was treated with zidovudine, from a group of nucleoside inhibitors for which it was proven to be associated

with mitochondrial toxicity. On the other hand, the most common drugs from the group of protease inhibitors were lopinavir with ritonavir enhancer, which have numerous undesirable gastrointestinal effects with a known association with dyslipidemia and lipodystrophy (10,11). Studies dating from 2010, such as French Hospital Database on HIV (FHDH), demonstrated the existence of cumulative effects in protease inhibitors that are associated with increased cardiovascular risk (12). It is believed that the prolonged usage of an older generation of protease inhibitors with some nucleoside inhibitors such as zidovudine, stavudine and didanosine, is specifically related to the development of mitochondrial toxicity (13).

One should not forget that the HIV virus itself has been proven to cause an atherosclerosis by various mechanisms such as immune activation, chronic inflammation and coagulopathy disorder (14). A direct effect of HIV virus is associated with a damage of the endothelium due to atheism molecules and the stimulation of proliferation of vascular smooth muscles, which contributes to the development of arteriosclerosis (15). From all the above mentioned, it can be concluded that the long-term untreated infection, especially in the AIDS phase, is also associated with endothelial damage as a result of chronic inflammation.

Conclusion

Antiretroviral therapy has an effect on the rise in triglyceride and cholesterol levels, which represents one of the risk factors for the development of cardiovascular disease. Particularly emphasized are protease inhibitors of the older generation, such as lopinavir/ritonavir, also known to have an effect on the occurrence of a metabolic syndrome.

Despite the fact that antiretroviral therapy has a number of side effects, as well as the possibility to develop resistance, an early recognition of infection and the detection of a clinical stage of the disease is crucial for the introduction of an antiviral therapy. It is undoubtedly contributed not only to the prolongation of the life span of these patients, but also to the significantly higher quality of their life.

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