Received: March 19, 2024
Accepted: June 14, 2024

Acad Med J 2024;4(2):32-40
UDC:616-008:{616.98:578.828]-085.281.8(497.7)
DOI: https://www.doi.org/10.53582/AMJ2442032p
Original article

METABOLIC SYNDROME IN ANTIRETROVIRAL THERAPY TREATMENT EXPERIENCED BY PEOPLE LIVING WITH HIV

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Abstract

Introduction: Metabolic syndrome (MS) constitutes a group of risk factors that significantly affect the quality of life and life expectancy of people living with HIV.

Aim: To estimate the prevalence of MS among people living with HIV who receive antiretroviral therapy (ART) in the Republic of North Macedonia (RNM).

Material and methods: A study was conducted on 53 adult patients with confirmed HIV infection at the University Clinic for Infectious Diseases and Febrile Conditions, who are receiving ART. In all patients, the presence of MS was determined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel ATP III (NCEP ATP III), defined by at least three of five risk factors including: low values of HDL - high density lipoprotein cholesterol, elevated waist circumference, hypertriglyceridemia, increased values of fasting glucose and hypertension. The statistical analysis was made by utilizing the statistical program SPSS 23.0.

Results: The average age of patients was 35.7 ± 8.3, with a male predominance of 90.57%. All patients had undetectable values of HIV RNA viral load in serum and 79.25% had achieved immune reconstitution with a CD4 count above 350 cells/ml. The prevalence of MS among people living with HIV in RNM was 7.55%, or out of 53 respondents 4 had MS.

Conclusion: People with HIV infection in RNM who regularly receive ART have a low prevalence of metabolic syndrome.

Keywords: metabolic syndrome, HIV infection, antiretroviral therapy

Introduction

According to the data from the World Health Organization (WHO), 76% of people living with HIV infection received antiretroviral therapy (ART) by 2022. Nowadays, the use of ART does not cure HIV, but it allows suppression of viral replication of the HIV and immune reconstitution. Highly potent and effective ART has made it possible to reduce HIV-associated morbidity and mortality and extend the life expectancy of people living with HIV (PLHIV)[1]. Such success of ART is threatened by the possibility of metabolic syndrome in PLHIV.

Metabolic syndrome (MS) consists of a group of risk factors such as hypertension, abdominal obesity, dyslipidemia, and insulin resistance that significantly increase the risk of

cardiovascular disease and diabetes mellitus[2]. The first definition of MS was given by WHO in 1999. Since then, several definitions have been used in clinical practice, including the definition of the National Cholesterol Education Program (NCEP) ATPIII in 2005, International Diabetes Federation (IDF) in 2006, the definition of the American Association of Clinical Endocrinologists (AACE) in 2003, and the European Group for the Study of Insulin Resistance (EGIR)[3].

The pathogenesis of MS and metabolic irregularities in individuals living with HIV reflects a convergence of diverse factors. The availability of ART and the increased life expectancy, within demographic factors, aging, virus itself, individual genetic predispositions, conventional societal influences, and behavioral risk factors collectively contribute significantly to the onset of MS[4]. Compelling studies affirm a correlation between elevated viral load and the initiation of MS, pointing to a plausible link between the influence of the HIV virus on lipid metabolism[5].

Certain ART regimens have demonstrated a correlation with the manifestation of MS, pointing to a notable challenge for clinicians involved in the treatment of PLHIV. This challenge is particularly prominent in the careful selection of an ART regimen that balances efficacy with safety. Drawing from data derived from comprehensive studies conducted across Europe, the United States, and Australia, it is evident that patients exhibit a heightened baseline prevalence of conventional cardiovascular risk factors. These include dyslipidemia (42%), cigarettes consumption (47%), ex-smokers (16%), hypertension (5.6%), BMI exceeding 30 kg/m² (4.7%), and diabetes mellitus (3.5%)[6]. The authors discerned a heightened risk of myocardial infarction with prolonged exposure to ART during the initial seven years of theraputic utilization[6]. In a retrospective analysis involving 259 patients diagnosed with HIV infection and undergoing ART, the prevalence of MS was identified in 27% of patients based on the IDF criteria and 26% according to the ATP III criteria. Logistic regression analysis revealed an association between the use of the protease inhibitor (PI) Darunavir and the manifestation of MS. Additionally, existing data highlights a link between an ART regimen incorporating Dolutegravir (an integrase inhibitor INSTI) and the onset of metabolic syndrome[7].

The most recent recommendations by the European AIDS Clinical Society Guidelines (EACS) advocate for the initiation of ART with a triple regimen comprising two nucleoside reverse transcriptase inhibitors (NRTIs) alongside with Doravirine. This particular recommendation deviates from the prevalent trend, as it stands as the sole regimen endorsement not reliant on integrase inhibitors (INSTI). Noteworthy, clinical investigations have further emphasized the positive impact of Doravirine on metabolic profiles, with a neutral influence on weight gain[8].

The prevalence of MS among individuals with HIV infection varies globally, ranging from 7% to 52%[9]. This variation is influenced by factors such as the criteria used to define MS, population characteristics, size, and study design. Recent studies indicate a similar prevalence of MS in HIV-infected individuals compared to the general population. Notably, most of these studies were conducted in developed countries, where a higher proportion of patients exhibited obesity, smoked cigarettes, and were on ART regimens containing PI. In contrast, middle and lower developed countries may show different prevalence patterns, reflecting diverse sociodemographic and healthcare dynamics[9].

The variations in MS prevalence among individuals with HIV across countries emphasize the necessity for a regional localized evaluation of MS prevalence in our country. Assessing the prevalence and identifying associated risk factors for MS development in HIV patients undergoing

ART underscores the importance of routine monitoring. This approach not only facilitates the implementation of preventive programs, but also enables measures to avert cardiovascular diseases and diabetes mellitus, thereby enhancing the overall quality of life for PLHIV.

Aim

To estimate the prevalence of MS among HIV positive patients undergoing treatment with ART in the Republic of North Macedonia (RNM).

Materials and methods

Study design

An analysis encompassed 53 adult patients (aged >18) with confirmed HIV infection under the care of the University Clinic for Infectious Diseases and Febrile Conditions in Skopje. These individuals are currently receiving ART in accordance with the recommendations outlined in the EACS guidelines version 11.1, dated October 2022. Exclusions from the study criteria encompassed individuals under 18, pregnant individuals, those with a history of pre-exposure or post-exposure prophylaxis, and those presently dealing with active opportunistic infections or cancer.

The tests conducted in this study adhered strictly to the ethical principles outlined in the Declaration of Helsinki. Every participating individual was provided with a comprehensive written information about the research and willingly signed their consent to be part of the study. Additionally, approval to conduct the study was duly sought from the Ethics Committee of the Faculty of Medicine in Skopje.

MS Definition Criteria

In all patients, the presence of MS was determined based on the criteria established by the National Cholesterol Education Program Adult Treatment Panel ATP III (NCEP ATP III). This involves identifying at least three out of five risk factors:

1. Low levels of HDL - high density lipoprotein cholesterol (<1 mmol/l or 40 mg/dl for men and <1.3 mmol/l or 50 mg/dl for women),
2. Increased waist circumference (>102 cm for men, >88 cm for women),
3. Hypertriglyceridemia (>1.7 mmol/l or 150 mg/dl),
4. Elevated fasting glucose levels (>5.6 mmol/l or 100 mg/dl), and
5. Hypertension (systolic >130 mmHg or diastolic >85 mmHg)[5].

Demographic variables, such as gender and age, were extracted from patients' medical records and documented during the examination at the HIV outpatient clinic.

Laboratory Biochemical Investigations

To ascertain the presence of MS in all patients, comprehensive laboratory biochemical investigations were conducted. These encompassed the analysis of key biochemical parameters, including HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, and fasting glucose. Blood samples, totaling 16.5 ml, were meticulously collected from patients following a minimum 8-hour fasting period. Samples were distributed in three BD vacutainer tubes: a 6 ml CAT (Clot Activator Tube) for determining HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides, a PPT K2E 15.8 mg tube for assessing HIV RNA viral load in human plasma, and a K2E 3.6 mg tube for determining the number of CD4 cells/ml. The blood samples for laboratory biochemical tests underwent immediate analysis in the laboratory of the Clinic for

Infectious Diseases and Febrile Conditions in Skopje using standard biochemical testing procedures.

Detection of the Viral Load of HIV RNA in Human Plasma and CD4 Count

Quantification of HIV RNA levels in human plasma was meticulously carried out at the Clinic for Infectious Diseases and Febrile Conditions. This involved utilizing real-time polymerase chain reaction (RT-PCR) technologies, including COBAS AmpliPrep-COBAS TaqMan 48 Roche (with a lower limit of detection <20 copies/ml), Abbot System m2000sp/ m2000rt (with a lower limit of detection <40 copies/ml), and GeneXpert (with a lower limit of detection <40 copies/ml). Undetectable values of HIV RNA in serum were designated as <40 copies/ml. A detectable level of HIV RNA in serum was defined as >200 copies/ml, and virological failure was characterized by serum HIV RNA exceeding >1000 copies/ml.

Immunological deficiency was assessed by absolute photo-microscopy and light absorption detection utilizing a multicolor platform (Facs Presto-BD). This method allowed for both absolute and percentage detection of CD4 lymphocytes, expressed as the number of cells per milliliter (cell/ml), with each sample analyzed on an individual cartridge. Individuals with HIV infection exhibiting immunodeficiency were identified as those with a CD4 count <350 cells/ml, categorized as late presenters.

Physical Measures

Blood pressure was assessed using a mercury pressure device equipped with a standard cuff, following established guidelines with a reference value of 130 mmHg for systolic pressure and 85 mmHg for diastolic pressure. Prior to measurement, individuals were required to rest (seated in a chair) for at least 5 minutes with their feet on the floor. The measurements were conducted on the left hand (upper arm), and the recorded blood pressure values were calculated as the mean of two consecutive measurements, aligning with recommendations from the Joint National Committee (JNC7)[10]. Body weight was determined by means of scale measurements, expressed in kilograms. Waist circumference, a crucial anthropometric measure, was assessed using a metronome in centimeters during the examination at the HIV outpatient clinic.

Results

The study included 53 participants, all diagnosed with a confirmed HIV infection and consistently receiving ART. Notably, all participants exhibited undetectable levels of HIV RNA in human plasma. The age range of patients varied from 20 to 57 years, with a mean age of 35.7±8.3. Male gender was predominant, constituting 90.57% of subjects, resulting in a female-to-male ratio of approximately 1:10.

The prevalence of MS, determined by the criteria of the National Cholesterol Education Program Adult Treatment Panel ATP III, indicating the presence of at least three out of five risk factors, was 7.55%. To provide context, out of the total 53 subjects included in the study, MS was identified in 4 patients.

Body mass index (BMI) exhibited a range from 16.7 to 36.5 kg/m², with an average value of 23.89±4.3 kg/m². Notably, individuals with normal body weight constituted the majority, comprising 54.72% of the study participants based on BMI values.

For male patients, a minimum waist circumference of 66 cm was recorded, while for female patients, the minimum was 64 cm. The maximum values for waist circumference were 125 cm for men and 110 cm for women. On average, the waist circumference measured 87.69±

11.6 cm in men and 80.8±17.7 cm in women. Waist volume had an increased value in 9.43% of patients.

Systolic and diastolic pressure had an average value of 128.92±14.2 and 85.74±11.1 mmHg respectively, according to the median value; 50% of patients had a systolic pressure exceeding 130 mmHg and a diastolic pressure surpassing 85 mmHg. 30.19% of patients had elevated systolic pressure, whereas 39.62% of patients displayed elevated diastolic pressure (Table 1).

Table 1. Demographic and Physical Variables[1]

Variables	Statistical parameters	Normal n (%)	Elevated n (%)
Age (years)			
mean ± SD (min- max)	35.7±8.3 (20-57)		
Gender n (%)			
Female	5(9.43)		
Male	48(90.57)		
BMI (kg/m^2)			
mean ± SD (min- max)	23.89±4.3 (16.7-36.5)		
BMI (kg/m^2) n(%)			
<18.5 underweight	5(9.43)		
18.5 – 24.9 normal	29(54.72)		
25 – 30 overweight	15(28.3)		
>30 obesity	4(7.55)		
Waist circumference (cm)			
Male mean ± SD (min- max)	87.69±11.6 (66-125)	48(90.57)	5(9.43)
Female mean ± SD (min- max)	80.8±17.7 (64-110)		
Systolic pressure (mmHg)			
mean ± SD (min- max)	(128.92±14.2) (104-180)	37(69.81)	1(30.19)
median (IQR)	130(120-135)		
Diastolic pressure (mmHg)			
mean ± S) (min- max)	(85.74±11.1) (70-121)	32(60.38)	21(39.62)
median (IQR)	82(80-90)		

[1]Data from University Clinic for Infectious Diseases and Febrile Conditions, Skopje, N. Macedonia

Glycemia demonstrated an average value of 5.59±0.9 mmol/L, with half of the patients registering a serum glucose level higher than 5.4 mmol/L. As for the lipid status, the mean triglyceride level was 1.24±0.7 mmol/L, with a median of 1.09 mmol/L. Cholesterol levels manifested a mean of 4.79±0.98 mmol/L and a median of 4.8 mmol/L, while HDL showcased a mean value of 1.25+0.3 (0.6-2.6) mmol/L and a median of 1.22 mmol/L. LDL levels were 2.94±0.8 mmol/L, with a median of 2.8 mmol/L. The average count of CD4 cells was 637.75±315.4, with more than 608 cells/ml detected in half of the patients (Table 2).

Forty-two (79.25%) patients had a CD4 cell count above 350 cells/ml, while 6 (11.32%) patients had elevated glucose

Table 2. Laboratory Biochemical Parameters

Variables	Statistical parameters
CD 4 cells	

mean ± SD (min- max)	637.75±315.4 (114-1655)
median (IQR)	608(454-765)
CD 4 %	
mean ± SD (min- max)	31.85±9.2 (12-51.8)
median (IQR)	33.1(26.4-37.3)
Glycose (mmol/L)	
mean ± SD (min- max)	5.59±0.9 (4.6-9.5)
median (IQR)	5.4(5-5.9)
CRP (mg/l)	
mean ± SD (min- max)	2.94±6.1 (1-37)
median (IQR)	1(1-1)
Triglycerides (mmol/L)	
mean ± SD (min- max)	1.24±0.7 (0.47-3.71)
median (IQR)	1.09(0.75-1.49)
Cholesterol (mmol/L)	
mean ± SD (min- max)	4.79±0.98 (2.8-7)
median (IQR)	4.8(4-5.3)
HDL (mmol/L)	
mean ± SD (min- max)	1.25±0.3 (0.6-2.6)
median (IQR)	1.22(1-1.4)
LDL (mmol/L)	
mean ± SD (min- max)	2.94±0.8 (1.3-5.1)
median (IQR)	2.8(2.5-3.4)

Alterations in lipid status above the reference values were registered in 4 (7.55%) patients for triglycerides, in 17 (32.08%) patients for cholesterol, 4 (7.55%) patients for LDL, while in 11 (20.75%) patients reduced values of HDL were registered (Figure 1).

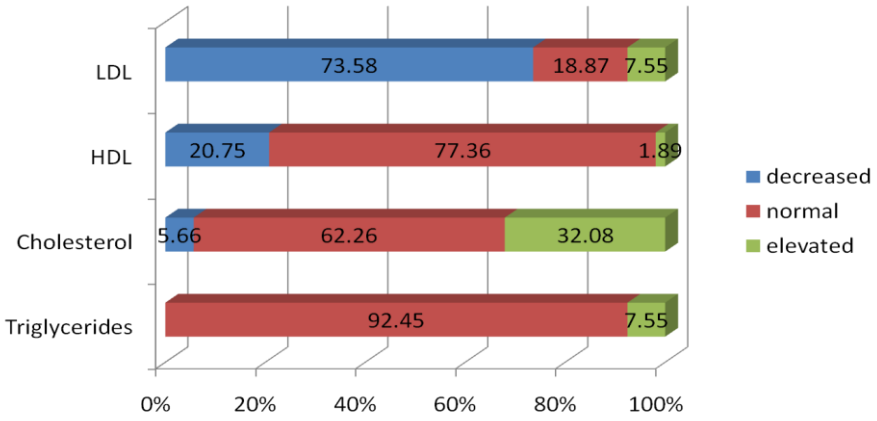

Fig 1. Lipid Status

Statistical analysis of data obtained in the study was made by means of the statistical program SPSS 23.0. The normality of data distribution was assessed using the Shapiro-Wilk's test. The results are presented in both tabular and graphical formats.

Categorical (attributive) variables are depicted using absolute and relative numbers. For numerical (quantitative) variables, the presentation includes mean, standard deviation, minimum and maximum values, as well as median and interquartile range.

Discussion

The study revealed a relatively low prevalence of MS at 7.55% (4 patients) as per the criteria of the National Cholesterol Education Program Adult Treatment Panel ATP III (NCEP ATP III). It is important to note that MS prevalence can vary across studies due to differences in the criteria used for assessment. For instance, a national study in Iran in 2007 reported MS prevalence of 34.7% (ATP III criteria), 37.4% (IDF definition), and 41.6% (ATPIII/AHA/ NHLBI). In Tunisia, the prevalence was 45.5% (IDF criteria) and 24.3% (ATP III)[4].

Observational studies in Europe and America have indicated a prevalence of MS in HIV-infected individuals ranging from 7% to 52%, whereas in Africa, a meta-analysis reported a prevalence of 13%-58%. [5] In China, the prevalence in 2017 was approximately 15.5%[2]. Sub-Saharan Africa displays variability, with MS prevalence ranging from 11.1% to 47%, influenced by factors such as study type, ART regimen, and ART experience[9]. In some highly developed countries, the estimated prevalence of MS fluctuates around 25%. Globally, the prevalence of metabolic risk factors in individuals with HIV infection is estimated to be between 16.7% and 31.3%[3].

The prevalence results we obtained for MS in people with HIV infection in the Republic of North Macedonia align with findings from a meta-analysis encompassing 65 studies across five continents. In Badiou's 2008 study in France, the prevalence of MS was 7.3%, and Martin's study from the same year reported a prevalence of 7.1%. In 2010, Cahn's study in Colombia found 8.4% prevalence of MS, while Calza's 2011 study in Italy reported 9.1%. Starling's 2008 study in the United States revealed 9.0% prevalence of MS in persons with HIV infection. Additionally, Wand's 2007 study, conducted on respondents from several countries, demonstrated a prevalence of 8.5%[11].

The observed low prevalence of MS in our study group can be attributed to a lower representation of specific risk factors associated with MS. These factors include demographic elements such as a younger age profile and a predominant male population. Furthermore, the fact that more than half of the patients exhibited normal body weight, with a BMI within the range of 18.5-24.9 (54.72%), and only a small percentage (9.43%) having an increased abdominal volume, contributed to the overall lower prevalence of MS in our study cohort. Regarding NHANES III data, the prevalence of MS has increased in the adult population from 29% to 32% over the last decade. Particularly noteworthy is the significant increase in MS prevalence among women aged 20-39, nearly doubling from 11% to 19%. Additional studies in the United States have identified associations between increased risk of MS and factors such as high BMI, older age, and alcohol consumption[2].

The absence of viral suppression is correlated with an elevated risk of developing MS. Additionally, metabolic disturbances have been observed in individuals who are ART naive, suggesting that either the virus itself or the inflammation associated with uncontrolled viral replication may contribute to the occurrence of these metabolic issues. In the studied patient group, all individuals attained viral suppression with undetectable values of HIV RNA in serum (HIV RNA <40 copies/ml), and a significant majority (79.25%) achieved immune reconstitution (CD4 count >350 cells/ml). This suggests that another risk factor for the occurrence of MS is underrepresented in our patient cohort.

Among the risk factors established as criteria for the occurrence of MS in the studied population of HIV-infected individuals, elevated cholesterol levels were prevalent in 32.08%, low HDL cholesterol values in 20.75%, and elevated blood pressure in 30.19% for systolic and 39.62% for diastolic measurements. Metabolic disorders, including dyslipidemia, insulin resistance, and lipodystrophy (characterized by peripheral fat loss and relatively central fat accumulation), are well-documented in HIV-infected individuals undergoing ART. Variances in the impact of lipid profiles associated with various combinations of ART have been substantiated in diverse studies. Stern *et al.* validated an escalation in risk factors, including hypertriglyceridemia, hyperglycemia, BMI, and cholesterol, among patients on ART, particularly pronounced within the initial three months of treatment and notably higher in patients receiving protease inhibitors. [6] Conversely, an ART regimen incorporating Doravirine, a newer non-nucleoside reverse transcriptase inhibitor, has demonstrated a beneficial impact on the lipid profile and the occurrence of MS in individuals with HIV infection. This effect has been corroborated by the outcomes of a randomized, active-controlled, double-blind phase 3 study, DRIVE-AHEAD, and the multicenter DRIVE-FORWARD study[12].

Conclusion

Individuals with HIV infection in the Republic of North Macedonia, who consistently undergo ART and maintain undetectable HIV RNA viral load values in serum, exhibit a low prevalence of metabolic syndrome.

The heightened presence of specific risk factors, defined as criteria for metabolic syndrome, such as hypercholesterolemia, low HDL cholesterol levels, and hypertension, in patients with HIV infection poses an increased risk for the development of metabolic syndrome. This underscores the importance of routine monitoring to assess the presence of metabolic syndrome and associated risk factors among patients with HIV in the Republic of North Macedonia.

The low prevalence of metabolic syndrome (MS) among individuals living with HIV in the Republic of North Macedonia contributes to a decreased likelihood of cardiovascular morbidity and mortality.

Conflict of interest statement. None declared.

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