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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Metabolic syndrome in HIV infected adults in Poland

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Abstract

Background: Metabolic syndrome (MS) is usually diagnosed based on the presence of abdominal obesity, elevated blood pressure (BP), elevated fasting plasma glucose, high serum triglycerides (TG), and low high-density lipoprotein (HDL) cholesterol levels. Whether HIV is associated with a higher prevalence of MS than in the general population remains unclear.

Aim: The aim of the study was to determine the incidence of MS in the population of HIV-infected adults and its association with clinical, virological, and biochemical features.

Methods: Two hundred and seventy HIV-infected Caucasian adult patients were enrolled in the study and evaluated based on clinical records in the years 2013–2015.

Results: Metabolic syndrome was diagnosed in 60 of 270 (22%) patients, 47 (24%) males and 13 (17%) females, mostly (72%) aged above 40 years. The percentage of patients with diagnosed MS in specific age groups in comparison to the general Polish population for females aged < 40 years was 7% vs. 4%, and males in the same age — 18% vs. 9%, for females aged 40–59 years — 47% vs. 24.4%, and males — 33% vs. 28.3%. Particular components of MS in the MS population were found as follows: body mass index > 30 kg/m^2 in 29%, waist circumference exceeding 94 cm in men and 80 cm in woman — 87.5%, TG ≥ 150 mg/dL — 82%, HDL cholesterol < 40/50 mg/dL (males/females) — 42%, systolic/diastolic BP ≥ 130 mmHg/≥ 85 mmHg — 83%, and fasting glucose > 100 mg/dL — 42%. In stepwise multivariate logistic regression analysis, age (odds ratio [OR] 1.052, 95% confidence interval [CI] 1.018–1.088, p = 0.003) and nadir CD4 < 350 cells/mm^3 (OR 3.576, 95% CI 1.035–12.355, p = 0.04) were associated with MS. Patients with MS compared with those without this disorder had low, intermediate, high, and very high cardiovascular risk in 10% vs. 23%, 73% vs. 70%, 7% vs. 5%, and 10% vs. 2%, respectively (p = 0.006).

Conclusions: Prevalence of MS in the HIV-infected population is higher than in the general Polish population. Age and low nadir CD4 were found to be associated with MS.

Key words: HIV, HCV, metabolic syndrome, hypertension, cardiovascular risk

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INTRODUCTION

Metabolic syndrome (MS) is usually diagnosed based on the following medical conditions: abdominal obesity, elevated blood pressure (BP), elevated fasting plasma glucose, high serum triglycerides (TG), and low high-density lipoprotein (HDL) cholesterol levels. It is estimated that around one quarter of the adult population in the world have MS [1]. Individuals affected by MS have significantly increased risk of heart attack or stroke, compared with those without MS. Furthermore, MS results in a fivefold greater risk of developing type 2 diabetes. Insulin resistance and central obesity are significant risk factors of MS with the additional coexistence of genetic factors, physical inactivity, ageing, proinflammatory state, and hormonal changes [2]. According to the new Joint Interim Societies (JIS) definition of MS, obesity is diagnosed using waist circumference instead of body mass index (BMI) because it has been shown to better correlate with visceral adiposity and insulin resistance as well as type 2 diabetes and cardiovascular disease (CVD) [3].

Whether human immunodeficiency virus (HIV) infection is associated with a higher prevalence of MS than in the general population remains unclear, probably because of overlapping of host, viral, and antiretroviral therapy factors that contribute to the components of this syndrome, which can be different in particular geographic regions, races, and

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specific populations. The prevalence of MS in the HIV-infected population varies from about 10% to over 50%, depending on the studied population and region [4–11].

The aim of our study was to determine the incidence of MS and its components among HIV-infected adults in Poland with the evaluation of the association of these parameters with clinical, virological, and biochemical features.

METHODS

A total of 270 HIV-infected adult Caucasians (mean age 37 years, interquartile range [IQR] 21–71; 193 men and 77 women) were enrolled, which included 172 (64%) HIV/hepatitis C virus (HCV) co-infected.

The average time from the diagnosis of HIV infection was 10 years (IQR 2–27). 251 (93%) individuals were treated with antiretroviral drugs (highly active antiretroviral therapy [HAART]), and the average duration of the treatment was seven years (IQR 1–18). Therapeutic schemes were based on nucleoside reverse transcriptase inhibitors (NRTI) with protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), or other drugs in 62.5%, 21%, and 16.5%, respectively. Laboratory and clinical parameters from the routine medical records from the years 2013–2015 were analysed.

Analysis of the BP was based on the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines from 2013 and were as follows: grade 1 hypertension: 140–159 mmHg and/or 90–99 mmHg; grade 2 hypertension: 160–179 mmHg and/or 100–109 mmHg, grade 3 hypertension: ≥ 180 mmHg and/or ≥ 110 mmHg [12].

Hypercholesterolaemia, hypertriglyceridaemia, and hypo-HDL were defined as values exceeding 190 mg/dL, 150 mg/dL, and < 40 mg/dL in males and < 50 mg/dL in females, respectively. Low-density lipoprotein (LDL) was defined as optimal when < 115 mg/dL, < 100 mg/dL, and < 70 mg/dL for patients with low or intermediate, high, and very high cardiovascular risk, respectively [13].

Risk of CVD was assessed by Pol-SCORE scale taking into account: age, gender, smoking, systolic BP, and LDL and was categorised as low risk when less than 1%, between 1% to less than 5% as intermediate risk, between 5% to less than 10% as high risk, and 10% and more as very high risk [14]. Patients with diabetes were included in the adequate risk range. There were no patients with chronic kidney disease as well as those with diagnosed or clinically evident CVD. However, electrocardiograms or any other cardiovascular tests or procedures were not performed routinely in every patient, which is a limitation of the study and can result in underestimation of the very high-risk population.

Values of the analysed clinical and biochemical criteria of MS complied with the International Diabetes Federation (IDF) definition from 2005 as well as a new JIS definition [3]. Waist circumference according to the European Group for the Study of Insulin Resistance (EGIR) from 1999 was defined as abnormal when ≥ 94 cm in men and ≥ 80 cm in women. IDF definition allows diagnosis of MS when central obesity is diagnosed (BMI > 30 kg/m^2 or BMI ≤ 30 kg/m^2 and waist circumference exceeding ethnic specific value), and additionally the definition required the presence of two of the following four elements: TG ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in woman, systolic BP (SBP) ≥ 130 mmHg or diastolic BP (DBP) ≥ 85 mmHg, fasting glucose > 100 mg/dL, including diabetes, and those with a prior diagnosis or treatment of any of these conditions. According to the new JIS definition, diagnosis of MS is based on any three of the following five risk factors: abnormal waist circumference with population-specific and country-specific criteria; TG ≥ 150 mg/dL, HDL cholesterol < 40/< 50 mg/dL in males and females, respectively, SBP ≥ 130 mmHg or DBP ≥ 85 mmHg and fasting glucose > 100 mg/dL, with the inclusion of patients taking medication to manage hypertriglyceridaemia, low HDL-cholesterol, hypertension, and hyperglycaemia [3].

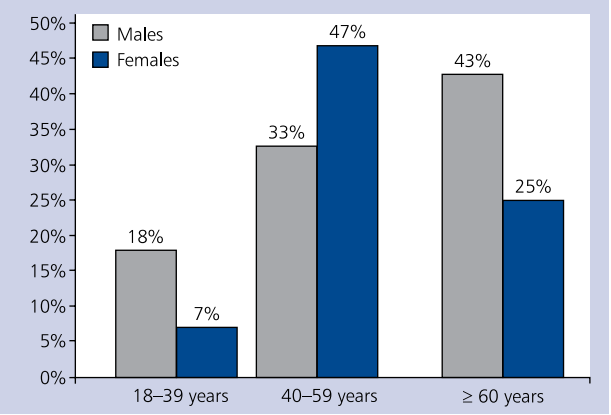

Figure 1. Incidence of metabolic syndrome in particular age groups by gender

Statistical analysis

Statistical analysis was performed on licensed software Statistica, version 12.0 and Windows 10 operating system, using the U Mann-Whitney and χ^2 tests. The Spearman test was used for correlation analyses. Stepwise multivariate logistic regression analysis was also performed. P values less than 0.05 were considered statistically significant.

RESULTS

According to the IDF and JIS definitions MS criteria were met in 53 (20%) and 57 (21%) of patients, respectively. MS was diagnosed in 60 (22%) patients, 47 (24%) men and 13 (17%) woman. Forty-two per cent of patients with diagnosed MS according to the JIS definition had four or all five criteria fulfilled. MS was diagnosed in 15% of patients aged 18–39 years, 36% — aged 40–59 years, and in 36% of patients aged over 60 years (Fig. 1). Particular

Table 1. Metabolic syndrome (MS) criteria and other parameters in patients with MS and without MS

	With MS (n = 60)	Without MS (n = 210)	p
Waist circumference: ≥ 94 cm in men or ≥ 80 cm in women	49 (87.5%)	44 (28%)	< 0.005
BMI > 30 kg/m^2	17 (29%)	9 (4%)	< 0.005
TG ≥ 150 mg/dL	49 (82%)	37 (18%)	< 0.005
HDL cholesterol: < 40 mg/dL in men or < 50 mg/dL in women	25 (42%)	13 (6%)	< 0.005
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg	50 (83%)	88 (42%)	< 0.005
Fasting glucose > 100 mg/dL	25 (42%)	32 (15%)	< 0.005
Cigarette smoking	30 (50%)	118 (57%)	NS
Alcohol abuse	7 (12%)	42 (20%)	NS
Illicit drug use	10 (17%)	42 (20%)	NS
HCV infection	35 (58%)	137 (65%)	NS
Arterial hypertension:	35 (59%)	47 (22%)	< 0.005
Grade 1	26 (44%)	26 (12%)	
Grade 2	6 (10%)	17 (8%)	
Grade 3	3 (5%)	4 (2%)	
HIV infection diagnosis:			0.03
≤ 10 years	22 (37%)	109 (52%)	
> 10 years	38 (63%)	101 (48%)	
HIV infection treatment	58 (97%)	193 (92%)	NS
Duration of treatment:			0.005
≤ 10 years	35 (59%)	162 (78%)	
> 10 years	24 (41%)	47 (22%)	
Treatment based on:			NS
PI	36 (60%)	121 (58%)	
NNRTI	7 (12%)	45 (21%)	
Other drugs	14 (23%)	27 (13%)	
Viral load < 50 copies/mL	35 (58%)	111 (53%)	NS
CD4+:			NS
≤ 350 cells/mm^3	26 (43%)	78 (37%)	
> 350 cells/mm^3	34 (57%)	132 (63%)	
Nadir CD4+:			0.01
< 100 cells/mm^3	17 (29%)	63 (30%)	
100–350 cells/mm^3	37 (62%)	94 (45%)	
> 350 cells/mm^3	6 (9%)	52 (25%)	

Data are presented as number (percentage). BMI — body mass index; TG — triglycerides, HDL — high-density lipoprotein; SBP — systolic blood pressure; DBP — diastolic blood pressure, PI — protease inhibitors, NNRTI — non-nucleoside reverse transcriptase inhibitors; NS — nonsignificant

criteria of MS in special groups and other parameters are presented in Tables 1–3. In the stepwise multivariate logistic regression, only increasing age (odds ratio [OR] 1.052, 95% confidence interval [CI] 1.018–1.088, p = 0.003) and nadir CD4 < 350 cells/mm^3 (OR 3.576, 95% CI 1.035–12.355, p = 0.04) remained associated with MS when evaluated in the multivariate model. The other parameters taken into account in the multivariate model were: HCV coinfection, antiretroviral treatment, duration of treatment (< 10 years, > 10 years), treatment scheme (based on PI, NNRTI or other drugs), duration of HIV infection (< 10 years, > 10 years), viral load (< 50 copies/mL, > 50 copies/mL), and CD4+ number (< 350 cells/mm^3, > 350 cells/mm^3).

Analysis of the whole study group revealed low, intermediate, high, and very high CVD risk in 19.5%, 71%, 5.5%, and 14% of cases, respectively. Patients with MS compared with those without MS had low, intermediate, high, and very high cardiovascular risk in 10% vs. 23%, 73% vs. 70%, 7% vs. 5%, and 10% vs. 2%, respectively (p = 0.006). From all the patients, 190 (70%) achieved optimal concentration of

Table 2. Metabolic syndrome criteria in patients with diagnosed metabolic syndrome compared across genders

Criterion	Males (n = 47)	Females (n = 13)	p
Waist circumference: ≥ 94 cm in men or ≥ 80 cm in women	37 (84%)	12 (92%)	NS
BMI > 30 kg/m^2	14 (30%)	3 (23%)	NS
TG ≥ 150 mg/dL	39 (83%)	10 (77%)	NS
HDL cholesterol: < 40 mg/dL in men or < 50 mg/dL in women	16 (34%)	9 (69%)	0.02
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg	40 (85%)	10 (77%)	NS
Fasting glucose > 100 mg/dL	21 (45%)	4 (31%)	NS

Data are presented as number (percentage). BMI — body mass index; TG — triglycerides; HDL — high-density lipoprotein; SBP — systolic blood pressure; DBP — diastolic blood pressure; NS — nonsignificant

Table 3. Metabolic syndrome criteria in the patients with and without hepatitis C virus (HCV) coinfection

Criterion	HCV (+) (n = 172)	HCV (–) (n = 98)	p
Metabolic syndrome diagnosed	35 (20%)	25 (26%)	NS
Waist circumference: ≥ 94 cm in men or ≥ 80 cm in women	53 (31%)	40 (41%)	NS
BMI > 30 kg/m^2	12 (7%)	14 (14%)	0.05
TG ≥ 150 mg/dL	53 (31%)	51 (52%)	NS
HDL cholesterol: < 40 mg/dL in men or < 50 mg/dL in women	23 (13%)	15 (15%)	NS
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg	87 (51%)	51 (52%)	NS
Fasting glucose > 100 mg/dL	33 (19%)	24 (24%)	NS

Data are presented as number (percentage). BMI — body mass index; TG — triglycerides; HDL — high-density lipoprotein; SBP — systolic blood pressure; DBP — diastolic blood pressure; NS — nonsignificant

LDL. Optimal LDL was less common in the group with MS compared with the remainder (58% vs. 74%, p = 0.02).

DISCUSSION

The actual prevalence of MS in the HIV-infected population is still debatable, but the available data indicate that it can be regarded as high, ranging from 11.2% up to 45.4% [15]. Therefore, there is growing concern that metabolic complications associated with HIV and antiretroviral drugs, place this population in a CVD high-risk category. HIV infection is associated with disturbed inflammatory response and immune dysfunction, leading to increased thrombosis and changes in lipid levels as well as cholesterol metabolism, which are also responsible for MS and CVD risk in the general population [16]. This long-term inflammatory state acts as a metabolic risk factor in the pathogenesis of HIV infection. Krishnan et al. [17] found that CD4+ T-cell count > 50 cell/mm^3 was associated with decreased risk and HIV-1 RNA > 400 copies/mL with increased risk of MS. It was not confirmed in our study; however, we found that MS was observed more commonly in patients with lowest nadir CD4 in comparison to those with nadir CD4 > 350 cells/mm^3 (p = 0.01).

In the presented study, MS was diagnosed in 22% of patients using two definitions of MS — IDF from 2005 and new JIS definition called "harmonised". Each definition allowed recognition of MS in 20% and 21% of patients, respectively. These numbers are comparable to those in the general Polish population [18]. However, we found that the percentage of patients with diagnosed MS in specific age groups was much higher than in the general Polish population (WOBASZ study), for females aged < 40 years it was 7% vs. 4% and in males in the same age it was 18% vs. 9% [19]. Similarly, for females aged 40–59 years it was 47% vs. 24.4% and for males — 33% vs. 28.3%. The exception was the group of patients aged 60+ years — for females 25% vs. 46.3% and for males — 43% vs. 34.5%, which is probably linked to fewer and younger aged woman in our oldest sample because the mentioned Polish population study included patients aged up to 74 years, proportionally, while in our study only four women were 60 years old or above. Direct comparison of the data is also difficult and affected by the use of different MS definitions: NCEP-ATP III definition in the WOBASZ study, which is known to underestimate the prevalence of MS in comparison to the definitions used by us [20]. However, a very interesting finding was the considerable variation in the occurrence of the syndrome in particular regions of Poland. In North-Eastern Poland, the same as our study population, the prevalence of MS was 25% for men and 18% for women, in comparison to 24% and 17% among our HIV-infected population [21].

Analysis of the most common MS criteria observed in our study revealed that they were different than in the general Polish population [19]. While in HIV-infected individuals with diagnosed MS, the most common was increased waist circumference (men — 84%, women — 92%) followed by increased BP and TG level, in the general population, according to the WOBASZ study, increased BP dominated, followed by abdominal obesity and elevated TG level. However, BMI > 30 kg/m^2 was found in only 29% of MS patients in comparison to almost 34% for the general Polish population [21]. It is known that HIV-1 infection itself is able to induce adipose tissue alterations crucial to lipodystrophy development through modifications of adipose tissue gene expression. Adipose tissue is a dynamic source of many proinflammatory cytokines, chemokines, growth factors, and complement proteins, which can disturb endothelial cell integrity and lead to atherosclerosis. This low-grade inflammation is characterised by increased plasma levels of tumour necrosis factor-alpha, interleukin-6, and the newly described soluble urokinase plasminogen activator receptor — described as a strong predictor of disturbed metabolism [16]. In our cohort with MS increased TG levels were seen in 77% of women and in 83% of men compared with 22.3% and 33.8%, respectively, in the general Polish population with MS, similarly to decreased HDL cholesterol — 69% and 34% vs. 12.5% and 9.8%, respectively. This confirms the observation that hypertriglyceridaemia is a result of distinct defects in regional adipocyte function as well as dysregulated lipolysis, and combined with low HDL cholesterol is a defining hallmark of MS in HIV patients on HAART [15, 20]. Other factors involved in the pathogenesis of dyslipidaemia in HIV infection are: increased apolipoprotein levels, increased hepatic synthesis of VLDL-cholesterol, decreased clearance of TG, viral replication itself, acute-phase proteins, and increased circulating cytokines [15].

Dysfunction of glucose metabolism depends on the specific drug in use and may result in insulin resistance, glucose metabolism changes, and diabetes mellitus. In vitro assay with PIs and NRTIs revealed adipocyte dysfunction and decreased adiponectin, which is a positive regulator of insulin sensitivity, due to increased expression and secretion of proinflammatory cytokines [22]. Among our patients with MS, 31% of women and 45% of men had hyperglycaemia, in comparison to 12.5% and 19.6% in the general Polish population with MS [20]. Regarding increased glucose concentration or diabetes, there was no difference between HIV- and HIV/HCV-infected patients in our study. However, HCV is known to disturb the glucose metabolism by direct and indirect influence on intracellular insulin signalling, which leads to insulin resistance, impaired glucose tolerance, or even type 2 diabetes mellitus [23]. Similarly to Cheng et al. [24], we also did not observe any difference in MS incidence between populations with and without HCV coinfection, despite the known direct cytopathic influence of HCV on lipid profile resulting in reduction of cholesterol and/or TG levels [25]. These perturbations seem to resolve after successful viral clearance.

It is also important that in our study almost half of the patients with diagnosed MS according to JIS definition had four or even all five criteria fulfilled, which suggests a very strong presentation of MS in HIV-infected people.

HAART has a positive as well as a harmful effect on cardiovascular risk through its toxicity. Moreover, slight degree of chronic inflammation may persist despite successful HAART. Antiretroviral drug toxicity depends on the drug used, and these could be adverse lipoprotein changes, insulin resistance, platelet dysfunction, and vascular injury. Key inflammatory molecules involved in atherosclerosis and diabetes mellitus in people receiving antiretroviral drugs are poorly understood [16]. In our study the influence of antiretroviral drugs on MS was not confirmed. However, most of the patients in our cohort were treated with PI-based regimens, which was found to be an independent risk factor of MS in previous studies [17].

Many studies suggest that the final effect of starting HAART on CVD risk is unsure because it may increase or decrease the overall risk, and conventional risk factors may be decisive in the development of CVD in HIV-infected patients [26]. Cigarette smoking is one of the most important cardiovascular risk factors. In our study half of the patients were cigarette smokers, similarly as in other studies concerning HIV-infected populations and almost twice as much as in the general Polish population [21, 27]. It is interesting that cessation of smoking was found to reduce CVD risk more than the antiretroviral therapy adjustment or use of lipid-lowering drugs, which also suggests that traditional risk factors may play a major role in CVD development in this special population.

In our study CVD risk was assessed by SCORE scale, and we found that in the group with MS the percentage of patients with very high risk was five times as high as in the group without MS, and the percentage of patients with low risk was two-times lower in the group with MS than in the group without MS. Tat, a crucial molecule in the HIV replication process, can affect mesenchymal stem cell survival and differentiation, and this might play an important role in vessel damage and formation of atherosclerotic lesions in HIV-infected individuals [28].

It is still a matter of discussion whether the classic cardiovascular risk scales that take into account traditional risk factors but not HIV-related factors such as chronic inflammation are appropriate in the HIV-infected population. In a study by Stein et al. [29] ultrasonographic measures of CVD were used: carotid artery intima-media thickness and brachial artery flow-medicated vasodilation, to assess subclinical and functional atherosclerosis in treatment-naïve HIV-infected patients. They found that traditional CVD risk factors, such as aging, body size, and lipids levels, better predicted atherosclerosis than inflammatory markers, cytokines, CD4 cell count, and HIV viral load. Aging is actually a key word as-

sociated with HIV because today, thanks to improvements in the effectiveness of antiretroviral therapy, people living with HIV have longer life expectancy and exhibit many clinical conditions commonly observed in elderly patients.

CONCLUSIONS

As we demonstrated, the prevalence of MS in the HIV-infected population is higher than in the general Polish population, increasing with age irrespective of the patient's gender. Low nadir CD4 was found to be associated with MS, which confirms the impact of immune system impairment. Although antiretroviral treatment is known to disturb lipid profile, its effect on MS was not confirmed in our study.

Conflict of interest: *none declared*

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