Diabetes Mellitus,

Hyperinsulinaemia and Metabolic Syndrome during HIV infection: a single-centre experience

Running headline: diabetes mellitus and metabolic syndrome during HIV infection
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Summary

Metabolic complications in HIV-infected patients treated with antiretroviral combinations may include insulin resistance, diabetes mellitus, dyslipidaemia and lipodystrophy syndrome. Metabolic syndrome is an aggregation of central obesity and glucose and lipid metabolism alterations that confers an increased risk of cardiovascular disease, and it strictly reproduces the antiretroviral therapy (HAART)-associated metabolic and morphologic abnormalities. In this study we report the prevalence of diabetes mellitus, hyperinsulinaemia, and metabolic syndrome among 755 adult patients with HIV infection referring to our outpatients' unit.

Key words: Diabetes mellitus, HIV, infection, hyperinsulinaemia, metabolic syndrome.

Introduction

Mortality and morbidity associated with human immunodeficiency virus (HIV) infection have dramatically declined since the advent of highly active antiretroviral therapy (HAART). However, a wide spectrum of metabolic complications (including insulin resistance, diabetes mellitus, dyslipidaemia, and fat redistribution syndrome) has emerged in recent years, leading to an increased risk of cardiovascular disease[1-3].

The clustering of these metabolic and morphologic abnormalities has a considerable overlap with metabolic syndrome, which is a significant and multifaceted risk factor for cardiovascular disease in the general population. Metabolic syndrome is an association of disturbances in glucose and lipid metabolism with central obesity and arterial hypertension, and approximately affects 20-30% of the general population[4,5]. A better understanding of epidemiological and pathogenetic correlations between HIV infection, HAART and metabolic syndrome might allow for more effective clinical management of these patients.

Patients and methods

All the consecutive HIV-positive patients affering at our tertiary care hospital for routine clinical and laboratory follow-up between July and December 2009, were enrolled into the study and evaluated for the prevalence of hyperinsulinaemia, diabetes mellitus, and metabolic syndrome. Biochemical laboratory analyses included serum levels of glucose, insulin, triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol. Serum glucose, insulin, and lipid levels were measured after a 12-hour overnight fast. Insulin level was not assessed in patients taking insulin therapy.

Diagnosis of type 2 diabetes mellitus and disorders of glucose metabolism was defined using the American Diabetes Association criteria[6]. Diabetes mellitus was diagnosed by a fasting glucose $\geq$126 mg/dL or a non-fasting glucose >200 mg/dL (in at least two blood tests) in the absence of symptoms of diabetes. DM was also diagnosed in patients taking insulin or oral anti-diabetic drugs. Impaired fasting glucose (IFG) was diagnosed by a fasting glucose ranging from 100 to 125 mg/dL (in at least two blood tests). Hyperinsulinaemia was diagnosed by a fasting insulin level $\geq$25 ng/mL (in at least two blood tests), but insulin assessment was not performed in patients with diagnosis of diabetes mellitus. Patients with a glucose or insulin level above the diagnostic value for hyperinsulinaemia, diabetes mellitus or IFG underwent a second blood test to confirm the diagnosis. Lipodystrophy was determined by physical examination which recorded fat loss and/or fat accumulation (in the face, neck, dorsocervical region, arms, breasts, abdomen, buttocks, and legs), or mixed form. Metabolic syndrome was defined using ATP-III criteria[7] and diagnosis required three or more of the following: (a) waist circumference >88 cm in women and >102 cm in men; (b) systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg; (c) triglycerides $\geq$150 mg/dL; (d) HDL cholesterol < 40 mg/dL; (e) glucose $\geq$110 mg/dL.

Data are expressed by mean values $\pm$ standard deviation (SD). Statistical evaluation was carried out by Student t test, Mantel-Haenszel chi-square test, or Fisher exact test (where appropriate), with significance levels placed at $p<0.05$.

Results

A total of 755 patients were enrolled into the study, and their epidemiological, clinical, and laboratory characteristics are summarized in Table 1. Diabetes mellitus was diagnosed in 34 subjects out of 755 (4.5%), while IFG was found in 71 (9.4%): then 105 subjects (13.9%) showed a fasting glucose concentration persistently above the normal value. Hyperinsulinaemia was diagnosed in 86 out of 721 non-diabetic patients (11.9%).

A diagnosis of frank diabetes mellitus was made by confirmed fasting glucose level higher $\geq$126 mg/dL in 22 out of 34 diabetic patients (64.7%) and by current anti-diabetic therapy in 12 (35.3%). Concomitant anti-diabetic drugs included insulin in 5 cases and oral agents (metformin, repaglinide or rosiglitazone) in the remaining 7 cases. Diabetic patients were characterized by a significantly higher mean age, and a significantly greater prevalence of black race in comparison with non-diabetic subjects. Moreover, duration of antiretroviral therapy, prevalence of lipodystrophy syndrome, and mean body mass index were significantly higher among diabetic subjects, in comparison with patients without diabetes. On the other hand, no significant differences regarding other demographic features, smoking status, stage of HIV infection, immuno-virological parameters, current antiretroviral therapy, chronic HCV or HBV infection, serum lipid values, blood pressure, and waist circumference were observed between diabetic and non-diabetic individuals (Table 1).

Among patients with hyperinsulinaemia in comparison with those without hyperinsulinaemia the following variables reached a statistical significance: higher mean age (46 vs. 35 years; p=0.021), higher prevalence of lipodystrophy syndrome (59% vs. 36%; p<0.001), higher prevalence of chronic HCV infection (42% vs. 28%; p=0.042), higher mean concentration of triglycerides (268 mg/dL vs. 211 mg/dL; p=0.032), and higher body mass index (26.3 Kg/m^2 vs. 22.5 Kg/m^2; p=0.038).

Metabolic syndrome was diagnosed in 69 out of 755 enrolled patients (9.1%). With regard to diagnostic criteria of metabolic syndrome, among these 69 subjects hypertriglyceridaemia was diagnosed in 63 patients (91%), low HDL cholesterol level in 58 (84%), hyperglycaemia in 45 (65%), high waist circumference in 43 (62%), and high systolic and/or diastolic blood pressure in 40 (58%). Subjects with metabolic syndrome showed the following statistically significant differences in comparison with subjects without metabolic syndrome: higher mean age, greater prevalence of black race, higher prevalence of lipodystrophy syndrome, longer mean duration of antiretroviral therapy, higher mean concentrations of glucose, total cholesterol and triglycerides, lower mean concentration of HDL cholesterol, higher mean systolic blood pressure, greater mean waist circumference and body mass index, and higher insulinaemia. On the other hand, no significant differences between subjects with and those without metabolic syndrome were registered with regard to other demographic features, smoking status, stage of HIV infection, immuno-virological parameters, current antiretroviral therapy, and chronic HCV or HBV infection (Table 1).

Table 1. Epidemiological, clinical, laboratory, and therapeutic faatures of the 755 patients enrolled in our study.

	Diabetes			Metabolic syndrome		
Baseline characteristics	Not present (n=721)	Present (n=34)	p value	Not present (n=686)	Present (n=69)	p value
Males [No. (%)]	475 (66)	25 (73)	0.88	445 (65)	55 (80)	0.59
Mean age [years (SD)]	37 (11)	48 (13)	<0.001	36 (11)	47 (11)	<0.001
Race [No. (%)]: - white - black - other	701 (97) 17 (2.6) 3 (0.4)	30 (88) 4 (12) 0	0.67 0.031 0.87	671 (98) 12 (1.7) 3 (0.4)	60 (87) 9 (13) 0	0.62 0.024 0.65
Current smokers [No. (%)]	255 (35)	8 (23)	0.59	239 (35)	24 (35)	0.88
Mean CD4 lymphocyte count [cells/mm^3 (SD)]	437 (231)	486 (255)	0.72	449 (251)	502 (288)	0.71
Patients with plasma HIV RNA <50 copies/mL [No. (%)]	605 (84)	29 (85)	0.91	583 (85)	51 (74)	0.66
Mean plasma HIV RNA in patients with detectable viremia [log_{10} copies/mL (SD)]	4.32 (1.15)	4.17 (1.22)	0.45	4.09 (1.08)	4.21 (1.17)	0.72
HIV stage [No. (%)] - asymptomatic - symptomatic non-AIDS - AIDS	491 (68) 205 (28) 25 (3.5)	20 (59) 9 (26) 5 (15)	0.86 0.82 0.54	477 (70) 185 (27) 24 (3.5)	34 (49) 29 (42) 6 (8.7)	0.63 0.58 0.75
Patients naïve to antiretroviral therapy [No. (%)]	96 (13)	3 (8.8)	0.52	79 (12)	20 (30)	0.58
Patients treated with [No. (%)]: - NRTIs + NNRTI - NRTIs + PI - Others	312 (43) 298 (41) 15 (2.4)	16 (47) 13 (38) 2 (6.4)	0.69 0.63 0.56	309 (45) 284 (41) 14 (2.3)	19 (28) 27 (39) 3 (4.3)	0.41 0.85 0.71
Mean duration of antiretroviral therapy [years (SD)]	5.1 (1.2)	7.2 (1.9)	0.031	5.3 (1.4)	7.5 (2.2)	0.028
Patients with lipodystrophy syndrome [No. (%)]: - fat loss - fat accumulation - mixed form	288 (40) 61 (8.4) 44 (6.1) 183 (25)	18 (53) 6 (18) 4 (12) 8 (24)	0.041 0.025 0.037 0.82	255 (37) 55 (8) 30 (4.4) 170 (25)	51 (74) 12 (17) 18 (26) 21 (30)	0.022 0.041 0.028 0.59
Patients with chronic HCV infection [No. (%)]:	218 (30)	12 (35)	0.61	207 (30)	23 (33)	0.71
Patients with chronic HBV infection [No. (%)]:	35 (4.8)	1 (2.9)	0.69	31 (4.5)	5 (7.2)	0.62
Mean total cholesterol [mg/dL (SD)]	205 (82)	196 (75)	0.71	194 (75)	241 (97)	0.039
Mean HDL cholesterol [mg/dL (SD)]	41 (11)	38 (10)	0.74	48 (13)	32 (11)	0.012
Mean triglycerides [mg/dL (SD)]	225 (103)	241 (119)	0.59	218 (97)	286 (112)	<0.001
Mean glucose [mg/dL (SD)]	84 (34)	131 (55)	<0.001	92 (45)	119 (47)	0.018
Mean systolic blood pressure [mmHg (SD)]	116 (19)	121 (21)	0.72	118 (21)	137 (26)	0.004
Mean diastolic blood pressure [mmHg (SD)]	73 (10)	76 (10)	0.89	77 (12)	85 (14)	0.45
Mean waist circumference [cm (SD)]	83 (16)	87 (19)	0.62	84 (9.2)	98 (12)	0.003
Mean BMI [Kg/m^2 (SD)]	23.1 (4.5)	26.5 (5.2)	<0.001	23.4 (5.5)	28.7 (7.4)	0.004
Mean insulin [ng/mL (SD)]	13.6 (6.2)	n.a.	n.a.	15.2 (5.9)	38.5 (12.3)	<0.001

SD, standard deviation; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; n.a., not applicable; HCV, hepatitis C virus; HBV, hepatitis B virus

Discussion

The prevalence of diabetes mellitus in HIV-infected patients is very variable in different retrospective and prospective studies, and usually ranges from 2% to 14%, while prevalence of all glucose metabolism disorders (including diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance) ranges from 25% to 35% [7]. Incidence of diabetes mellitus in cohort studies was found to be significantly associated with previous or current antiretroviral therapy (and particularly with exposure to zidovudine, stavudine or protease inhibitors), presence of lipodystrophy, central obesity, immunological status, chronic hepatitis C, increasing age, and black or Asian ethnicity[8-13].

At the same time, prevalence of metabolic syndrome in HIV-infected subjects receiving HAART is unclear, ranging from 8% to 25%. Risk factors for metabolic syndrome include body mass index, lipodystrophy syndrome, past or present use of nucleoside analogues (such as stavudine or didanosine) or protease inhibitors, HIV viral load, and serum inflammatory markers[7,14-16], and the relative risk of developing diabetes mellitus was significantly increased (4-fold to 9-fold) in subjects suffering from metabolic syndrome[7,14]. Results of our study were in agreement with the literature data. Prevalence of diabetes mellitus, hyperinsulinaemia and metabolic syndrome among our HIV-infected patients was 4.5%, 11.9% and 9.1%, and a longer duration of antiretroviral therapy and presence of lipodystrophy were significantly associated with both diabetes mellitus and metabolic syndrome.

Further prospective studies are requested in order to determine whether the presence of metabolic syndrome in HIV-positive population produces a multiplicative increase in cardiovascular risk above and beyond the additive risks of its components.

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