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Overweight HIV Patients with Abdominal Fat Distribution Treated with Protease Inhibitors are at High Risk for Abnormalities in Glucose Metabolism – A Reason for Glycemic Control

S. C. Blass[1], S. Ellinger[1], M. Vogel[2], P. Ingiliz[2], U. Spengler[2], P. Stehle[1], A. von Ruecker[3], J. K. Rockstroh[2]

[1]Department of Nutrition and Food Sciences, Nutritional Physiology, University of Bonn, Bonn, Germany,
[2]Department of General Internal Medicine I, University of Bonn, Bonn, Germany,
[3]Department of Pathology, University of Bonn, Bonn, Germany

Abstract
Background: In HIV patients, disorders in glucose metabolism seem to be side effects of highly active antiretroviral therapy (HAART) which may be favoured by obesity, abdominal fat accumulation and familial disposition for diabetes mellitus (DM). The aim of our study was to identify patients at high risk for abnormalities in glucose metabolism taking into account HAART, familial disposition for DM and anthropometric parameters.
Methods: Plasma glucose, insulin, c-peptide and insulin resistance (homeostasis model assessment, HOMA) were determined in 44 HIV patients [16 without HAART, 19 with protease inhibitors (PI), 9 without PI (non-PI)] and in 11 healthy subjects. Glucose tolerance was determined by standard procedures. Body mass index (BMI), triceps skin fold thickness and waist circumference were measured and the waist-to-hip-ratio was calculated. Familial disposition for DM was assessed by questionnaire.
Results: Impaired fasting glucose was observed in 28% of HAART-treated patients (21% with PI, 7% non-PI), in 13% of HAART-naive but none in healthy controls. 58% of PI, 44% of non-PI, 38% of HAART-naive and none of healthy controls had a HOMA-index > 2.5 which indicates insulin resistance. HAART-treated patients had significantly higher fasting glucose levels (PI: 97 ± 11 mg/dL, p = 0.048; non-PI: 109 ± 58 mg/dL, p = 0.009) compared to healthy controls (72 ± 8 mg/dL). HOMA-Index was higher in PI treated patients (3.74 ± 3.08) than in HIV negative controls (0.95 ± 0.28, p = 0.018). The duration of HAART (p = 0.045), overweight and familial disposition for DM (p = 0.017) significantly affected fasting glucose among PI users. Waist circumference affected c-peptide (p = 0.046) concentration in these patients.
Conclusion: HIV patients on long-term PI therapy with overweight and familial disposition for DM are at high risk to develop abnormalities of glucose metabolism. Thus, measurements of HOMA-Index, BMI and waist circumference should be routinely done especially in PI medicated patients.

Key words: HIV, protease inhibitors, glucose metabolism, insulin resistance, obesity, waist circumference
Abbreviations: HAART, highly active antiretroviral therapy; DM, diabetes mellitus; HOMA, homeostasis model assessment; PI, protease inhibitors; BMI, body mass index; IR, insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; WC, waist circumference

Introduction

Highly active antiretroviral therapy (HAART) has dramatically decreased the mortality of HIV-infected individuals [1, 2]; however, long-term side effects of HAART present a significant problem in clinical practice and indeed, are the most common reason for discontinuation of antiretroviral therapy [3].

Abnormalities in glucose and lipid metabolism are deemed responsible for hepatosteatosis and increased risk for myocardial infarction. The disorders of carbohydrate metabolism range from insulin resistance (IR) to manifest diabetes mellitus (DM) [4]. As reviewed recently, 30-90% of patients treated with protease inhibitors (PI) as well as 20% of patients with other HAART developed impaired glucose tolerance (IGT) and IR. The incidence of manifest hyperglycaemia and DM varies from 1-11% in PI treated patients [5]. The broad range may be due to inconsistent patient cohorts, different PI use as well as different parameters and laboratory methods for assessment of IR and the use of different reference values. Thus, standardized assessments and screening tools are needed to determine the true prevalence of IR and further abnormalities in carbohydrate metabolism [5]. However, the role of classical factors for DM as obesity, lifestyle and genetic disposition that contribute to disorders in carbohydrate metabolism [2] has not been reported so far in HIV patients.

Hence, the aim of this study was to identify HIV patients with abnormalities of carbohydrate metabolism considering HAART-regime and the contribution of anthropometric factors and familial disposition for DM.

Methods

Study Population

HIV-seropositive patients, older than 18 years from the Outpatient HIV Clinic at University of Bonn were included in this cross-sectional study. Diagnosis of HIV infection was confirmed by detection of HIV mRNA (Versant™ HIV-1 RNA 3.0 Assay, Bayer Diagnostics, Fernwald, Germany; viral load > 50 copies of HIV-mRNA/mL plasma). Exclusion criteria were: previously known manifest diabetes, gastrointestinal diseases with malabsorption, pregnancy, lactation, intake of glucocorticoids and drug abuse. All patients attending at our outpatient department between February and June 2005 were consecutively enrolled into one of the three study groups (PI based HAART, PI-free HAART [non-PI HAART; patients who never received PI], HAART-naive patients [patients who never received HAART]). Sex/age-matched healthy subjects from the staff were recruited as controls. All participants provided written, informed consent prior to enrolment into the study. The study was conducted according to the declaration of Helsinki and was authorized by the local Ethics committee.

Data Collection

Clinical data and familial disposition for diabetes mellitus (by questionnaire) were recorded by anamnesis. Familial disposition for diabetes mellitus was defined as occurrence of type 2 diabetes mellitus in first- and second-degree relatives. Data on immunological status (count on $CD3^+$, $CD4^+$, $CD8^+$ cells and $CD^+4/CD8^+$-ratio), quantitative HIV RNA level, duration of HIV-infection and HAART, HIV-associated lipodystrophy, antiretroviral use and CDC-classification were collected.

Laboratory Data

Oral glucose tolerance was investigated by bolus ingestion of 75 g glucose solution (Dextro O.G-T.; Roche, Mannheim, Germany) after an overnight fast. Plasma glucose levels were measured before, 60 min and 120 min after glucose ingestion by the hexokinase method. Basal insulin (normal range: 6-27 mU/L) and c-peptide level (normal range: 1-4 ng/mL) were determined in serum by radioimmunoassay. Oral glucose tolerance was evaluated according to the criteria of the American American Diabetes Association 2005 [6] (normal: fasting glucose < 100 mg/dL and 2 h glucose < 140 mg/dL; impaired fasting glucose (IFG): 100 -126 mg/dL and IGT: 2 h glucose 140-199 mg/dL; diabetic: fasting glucose ≥ 126 mg/dL and 2 h glucose ≥ 200 mg/dL). IR was calculated using the homeostasis model assessment (HOMA-Index): [fasting insulin (μU/l) x fasting glucose (mmol/L)/22.5] [7].

Anthropometric Data

Body mass index (BMI kg/m^2) was assessed and classified according to the guidelines of the International Obesity Task Force 1998 (normal: 18.5 – 24.9; overweight: 25.0 – 29.9; obesity: ≥ 30.0). Waist circumference (WC) and hip circumference were determined by standardized methods and the waist-to-hip ratio was calculated. Triceps skin fold thickness was measured by standard procedures.

Statistical Analysis

The results are presented as means ± SD, median and quartiles. Differences in laboratory parameters between the groups "HAART with PI", "HAART non-PI", "HAART-naive" and "controls" were calculated by one-way ANOVA. In case of significant differences the Tukey-Test was performed. Factors affecting parameters of glucose metabolism were determined by univariate analysis. Statistical significance was assumed for $p < 0.05$. SPSS software, version 12.0 was used for all tests.

Results

Study Population

Forty-four HIV-seropositive patients were recruited into this study: 19 patients with PI-containing HAART, 9 patients with non-PI containing HAART

Table 1. Clinical data of HIV patients and healthy controls.

	HAART with PI (n = 19)	non-PI HAART (n = 9)	HAART-naive (n = 16)	Controls (n = 11)
Sex (female/male)	(1/18)	(5/4)	(2/14)	(2/9)
Age [yrs][1]	44 (29-68)	39 (34-59)	37 (24-45)	33 (24-58)
Familial disposition for DM [n]	6 (32%)	2 (22%)	4 (25%)	2 (18%)
Duration HAART [month][2]	41 (12; 104)	46 (26; 72)	0	—
CDC-classification (A/B/C)	7/5/7	3/2/4	14/1/1	—
Viral load [copies/μL log^{10}][3]	0.69 ± 1.37^a	0.23 ± 0.68^b	4.49 ± 0.48^{ab}	—
CD4 cell count/μL[3]	526 ± 342	490 ± 316^d	308 ± 137^c	794 ± 206^{cd}
CD4/CD8-ratio[3]	0.54 ± 0.36^f	0.57 ± 0.36^g	0.38 ± 0.14^e	2.8 ± 1.06^{efg}

[1]median, range in parentheses, [2]median, quartile in parentheses, [3]mean ± SD;
HAART: highly active antiretroviral therapy; PI: protease inhibitors; DM: Diabetes mellitus. Identical letters indicate significant differences between the groups: a,b,c,e,f,g: $p<0.001$; d: $p<0.05$ (Tukey-test)

Table 2. Frequency of individual antiretroviral substances used in the different treatment groups.

	HAART with PI (n = 19)	non-PI HAART (n = 9)
PI		
Lopinavir/Ritonavir	16	—
Atazanavir	3	—
NRTI		
AZT + 3TC	2	1
Amtricitabin	2	—
Lamivudin	9	3
3TC + ABC	1	2
Zidovudin	1	—
AZT + 3TC + ABC	1	4
FTC + TDF	1	1
Tenofovir	13	2
Stavudin	1	1
Abacavir	1	—
NNRTI		
Efavirenz	—	1
Nevirapin	—	4

HAART: highly active antiretroviral therapy; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor

Table 3. Data on glucose metabolism in HIV patients and healthy controls.

	HAART with PI (n = 19)	non-PI HAART (n = 9)	HAART-naive (n = 16)	Controls (n = 11)
Basal glucose [mg/dL]	97 ± 11[b]	109 ± 58[a]	87 ± 11	72 ± 8[ab]
Without new onset diabetics	96 ± 9[c]	86 ± 14	87 ± 11	72 ± 8[c]
2 h Glucose [mg/dL]	107 ± 53	123 ± 92	85 ± 14	91 ± 16
Basal insulin [mU/L]	15.17 ± 11.55[d]	12.84 ± 8.88	9.34 ± 5.11	5.3 ± 1.41[d]
Basal c-peptide [ng/mL]	2.6 ± 1.4	2.4 ± 1.5	2.0 ± 1.1	1.5 ± 0.4
HOMA-Index	3.74 ± 3.08[e]	3.63 ± 3.56	2.15 ± 1.06	0.95 ± 0.28[e]

Data: mean ± SD; HAART: highly active antiretroviral therapy; PI: protease inhibitors; HOMA: homeostasis model assessment. Identical letters indicate significant differences between the groups: a: $p<0.01$; b,d,e: $p<0.05$, c: $p<0.001$ (Tukey-test).

and 16 HAART-naive ones. Additionally, 11 sex-/age matched healthy controls were enrolled. The characteristics of these groups considering clinical data are summarized in Table 1. The frequency of the specific antiretroviral drugs used in the different treatment groups is shown in Table 2.

Glucose Metabolism

Fasting plasma glucose level (mg/dL) was significantly higher only in patients treated with HAART (non-PI: 109 ± 58, $p = 0.009$; PI: 97 ± 11; $p = 0.048$) compared to controls (72 ± 8). If patients with a new onset diabetes were excluded, significantly higher fasting glucose levels could only be observed in PI treated patients compared to controls ($p<0.001$). Plasma glucose levels after 120 min and c-peptide concentration in serum did not differ between the HIV-groups and controls. In PI treated patients insulin concentration (15.17 ± 11.55 mU/L; $p = 0.013$) and HOMA-Index (3.74 ± 3.08; $p = 0.018$) were significantly higher than in controls (insulin 5.3 ± 1.41 mU/L; HOMA: 0.95 ± 0.28). Regarding the remaining HIV groups compared to controls concerning HOMA-Index and c-peptide, there were no statistically differences (see Table 3).

Unexpectedly, in one (5%) of 19 PI treated and 2 (22%) of 9 non-PI medicated patients a new-onset diabetes was detected. An IFG was observed in 2 (22%) non-PI, 6 (32%) PI treated and in 2 (13%) HAART-naive patients. Just one (5%) patient of the PI group developed an IGT.

Three (16%) patients of the PI group and one (11%) of the non-PI group had c-peptide concentrations above the normal range. The upper reference level of 27 mU insulin/l was exceeded in 2 (11%) PI and in 1 (11%) non-PI treated patients. I R (HOMA-Index > 2.5) could be observed in 11 (58%) PI, in 4

Table 4. Prevalence of derangements of carbohydrate metabolism in HIV patients and healthy controls.

	HAART with PI (n = 19)	non-PI HAART (n = 9)	HAART-naive (n = 16)	Controls (n = 11)
IFG (basal glucose 100 -126 mg/dL)	32% (n = 6)	22% (n = 2)	13% (n = 2)	—
IGT (2h glucose>140 mg/dL)	5% (n = 1)	—	—	—
New onset Diabetes mellitus[1]	5% (n = 1)	22% (n = 2)	—	—
Insulin resistance (HOMA>2.5)	58% (n = 11)	44% (n = 4)	38% (n = 6)	—
Basal c-peptide > 4 ng/mL	16% (n = 3)	11% (n = 1)	—	—
Hyperinsulinemia (basal insulin > 27 mU/L)	11% (n = 2)	11% (n = 1)	—	—

[1]criteria: basal glucose ≥ 126 mg/dL or 2h glucose ≥ 200 mg/dL
HAART: highly active antiretroviral therapy; PI: protease inhibitors; IFG: impaired fasting glucose; IGT: impaired glucose tolerance.

(44%) non-PI treated and in 6 (38%) HAART-naive patients, but in none of the matched healthy controls (see Table 4).

Risk Factors on Glucose Metabolism and Anthropometric Measurements

There were no statistically significant differences in waist circumference, waist-to-hip ratio and BMI between HIV groups and controls.

PI treated patients had a tendency towards lower triceps skin fold thickness (6.4 ± 11.4 mm) than patients in the non-PI group (12.0 ± 20.1 mm), however, this differences failed to receive significance ($p = 0.053$) (see Table 5).

Abnormalities in glucose metabolism were observed especially in PI treated patients, but also in patients with other HAART. Overweight (BMI > 25 kg/m^2) combined with familial disposition for DM significantly affected the fasting glucose level in PI treated patients ($p = 0.017$). The combination of overweight and familial disposition for diabetes mellitus had a significant influence on basal glucose level in healthy controls ($p = 0.039$). As well, the duration of HAART had a significant effect on fasting glucose in PI treated patients ($p = 0.045$). Fasting insulin concentration ($p = 0.032$) and HOMA-Index ($p = 0.046$) were significantly affected by overweight (BMI > 25 kg/m^2) in PI medicated patients.

In PI treated patients, waist circumference had a significant impact on c-peptide level ($p = 0.046$) whereas the waist-to-hip ratio had no significant influence on any parameter of glucose metabolism in any group.

Discussion

The aim of this study was to investigate if HAART (with PIs or other agents) influence the glucose metabolism and if abnormalities in glucose metabolism are affected by anthropometric factors and a familial disposition for DM.

Glucose Metabolism

In our study, abnormalities in glucose metabolism were mainly associated with PI-use, which is in line with previous findings from other groups [4, 5, 8-11].

Table 5. Anthropometric data of HIV patients and healthy controls.

	HAART with PI (n = 19)	non-PI HAART (n = 9)	HAART-naive (n = 16)	Controls (n = 11)
BMI [kg/m^2]	25.1 ± 4.2	27.4 ± 3.9	24.8 ± 3.1	24.1 ± 3.2
BMI ≥ 25 [kg/m^2] [n]	7 (37%)	6 (67%)	8 (50%)	4 (36%)
WHR	0.91 ± 0.12	0.91 ± 0.12	0.89 ± 0.50	0.86 ± 0.76
WHR > reference values [n][1]	8 (42%)	6 (67%)	2 (13%)	2 (18%)
TSFT [mm]	6.4 ± 11.4	12.0 ± 20.1	8.8 ± 15.6	6.0 ± 15.2
WC [cm]	93.4 ± 16.3	96.7 ± 12.6	90.3 ± 8.5	89.9 ± 12.1
WC > reference values [n][2]	11 (58%)	6 (67%)	6 (38%)	5 (46%)

Data: mean ± SD, HAART: highly active antiretroviral therapy; PI: protease inhibitors; BMI: body mass index; WHR: waist-to-hip ratio; TSFT: triceps skin fold thickness; WC: waist circumference; [1]reference values: ≥ 0.85 cm for women and ≥ 0.95 cm for men according to WHO (2000), [2]reference values: ≥ 80 cm for women and ≥ 94 cm for men according to WHO (2000).

Increased fasting glucose in non-PI patients in this study could be explained by two patients with new onset diabetes. These patients suffer from overweight or obesity, respectively. In HIV-patients, an increase of BMI is associated with accumulation of visceral fat mass [12] which increases the risk for diabetes mellitus [13]. If these patients were excluded, fasting glucose level was only higher in PI patients than in controls as reported by others [4, 5, 8-11]. However, Shlay et al. 2007 [12] did not found any differences between HAART strategies in the long-term. By the oral glucose tolerance test, three patients with an unknown diabetes mellitus could be detected. One non-diabetic patient showed IGT.

The higher basal insulin concentration in PI treated patients compared to the other patient groups is in line with the results of cross-sectional studies reported previously [10, 11]. It cannot be excluded that the duration of HAART exerted an independent effect on basal insulin. A prospective cohort study with 422 HIV patients has shown that 5-year duration of HAART increases basal insulin in all HIV-patients using either PI, NNRTI or a combination of PI and NNRTI [12]. After one month only increased insulin concentrations were observed in PI-treated ones [12]. As our patients were 3.5 years on HAART, it can be speculated that duration of HAART treatment may be an important factor.

Various protease inhibitors (indinavir, nelfinavir, lopinavir, saquniavir and ritonavir) have shown to induce IR [14]. Our results (58% of PI treated patients suffer from IR) thus confirm that protease inhibitors treatment is associated with IR. Importantly, in our study 38 % of the HAART-naive patients suffered from IR, whereas IR was not found in any of the healthy controls. Therefore, regardless of HAART, all HIV-infected patients should be routinely monitored for IR to minimize the risk for future development of diabetes mellitus. This was also recently recommended by Shlay et al. 2007 [12] due to the increase in HOMA-index in all patients under HAART. However, due to the strong variance of HOMA-index, we cannot recommend this surrogate marker for IR as a reliable screening tool.

In 2003, the American Diabetes Association published new reference values for the category "impaired fasting glucose", whose incidence has not been investigated so far in HIV patients. Surprisingly, the incidence of IFG especially in patients with PI, but also in the other HIV groups, is much higher than the incidence of IGT which has been investigated in several studies [2, 10, 11]. Thus, screening for IFG might be a more effective tool for detecting derangements in carbohydrate metabolism early in HIV patients. Our findings support the recommendations of Grinspoon (2003) [15] for routine determination of fasting plasma glucose level for all HIV infected patients. In PI treated patients the prevalence of diabetes mellitus (5%) is in line with the findings of Carr et al. 1999 (7%) [16] and Howard et al. 2005 (6%) [2], who analysed the data according to the reference values of the American Diabetes Association.

Risk Factors on Glucose Metabolism

Obesity and familial disposition of diabetes mellitus were associated with IFG and seem to promote this abnormality of glucose metabolism [17]. This is in line with the observations of our study in which a BMI > 25 kg/m^2 in combination with familial disposition of diabetes mellitus affects fasting glucose in PI-treated patients. However, these risk factors are not specific for PI medicated patients as overweight also affects fasting glucose level in HIV-negative controls. Duration of HAART has an impact on plasma fasting glucose level and seems to increase the risk for IGT in PI-treated subjects as suggested from others [10-12].

A study with healthy subjects confirmed the correlation between BMI and IR [18]. As well, the majority of healthy people with categorical obesity (BMI ≥ 30 kg/m^2) suffer from postprandial hyperinsulinemia and low insulin sensitivity [19]. Since overweight (BMI ≥ 25 kg/m^2) affects the fasting insulin level and HOMA index in PI treated patients in this study, PI seems to potentiate the risk for IR which results from overweight. Thus, these patients may benefit from a reduction of weight to obtain a BMI within the normal range.

Janssen et al. 2002 [20] have shown that the risk for dyslipidemia and metabolic syndrome depends on WC which strongly correlates with fasting hyperglycaemia [21]. In our study, WC affected c-peptide level in PI treated patients significantly. Thus, the determination of WC in addition to BMI would provide important information on a patient's risk for abnormalities in carbohydrate metabolism and should be routinely performed in HIV patients treated with PI.

To our knowledge, this is the first study investigating a broad spectrum of parameters and abnormalities in glucose metabolism of HIV patients taking into account risk factors for DM. Although the small sample size limits the power of this pilot study, it provides information which parameter may be useful for screening.

In conclusion, overweight and familial disposition for diabetes mellitus seem to favour abnormalities in carbohydrate metabolism in HIV patients treated with HAART, especially HAART containing PI. Considering our results, every HIV patient at high risk for abnormalities in carbohydrate metabolism should be routinely screened using fasting glucose as well as BMI and waist circumference. Moreover, an oral glucose tolerance test should be performed in all patients at high risk for diabetes mellitus as well.

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Address for correspondence:
Prof. Dr. med. Juergen K. Rockstroh
Department of General Internal Medicine I
University Hospital of Bonn
Sigmund-Freud-Str. 25
53105 Bonn
Germany
Tel.: +49 228 287 16558
Fax: +49 228 287 15034
E-mail: Juergen.Rockstroh@ukb.uni-bonn.de