Prevalence of Metabolic Syndrome in HIV-Infected Patients Receiving Highly Active Antiretroviral Therapy Using International Diabetes Foundation and Adult Treatment Panel III Criteria

Associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and hypoadiponectinemia

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OBJECTIVE — Metabolic syndrome is a cluster of risk factors for cardiovascular disease and type 2 diabetes. Definitions exist to identify those "at risk." Treatment of HIV infection with highly active antiretroviral therapy can induce severe metabolic complications including lipodystrophy, dyslipidemia, and insulin resistance. The purpose of this study was to report the prevalence of metabolic syndrome in HIV-infected patients and compare insulin resistance and total body, limb, and visceral fat and adipokines in those with and without metabolic syndrome.

RESEARCH DESIGN AND METHODS — This was an international cross-sectional study of a well-characterized cohort of 788 HIV-infected adults recruited at 32 centers. Metabolic syndrome prevalence was examined using International Diabetes Federation (IDF) and U.S. National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria, relative to body composition (whole-body dual-energy X-ray absorptiometry and abdominal computed tomography), lipids, glycemic parameters, insulin resistance, leptin, adiponectin, and C-reactive protein (CRP).

RESULTS — The prevalence of metabolic syndrome was 14% (n = 114; 83 men) by IDF criteria and 18% (n = 139; 118 men) by ATPIII criteria; the concordance was significant but only moderate (κ = 0.46, $P < 0.0001$). Many patients (49%) had at least two features of metabolic syndrome but were not classified as having metabolic syndrome as their waist circumferences or waist-to-hip ratios were in the non–metabolic syndrome range. Metabolic syndrome was more common in those currently receiving protease inhibitors ($P = 0.04$). Type 2 diabetes prevalence was five- to ninefold higher in those with metabolic syndrome. With IDF criteria, subjects with metabolic syndrome showed disturbances in inflammation and adipokines: they had higher CRP (5.5 ± 7.0 vs. 3.9 ± 6.0 mg/l, $P < 0.003$) and leptin (9 ± 9 vs. 4 ± 6 ng/ml, $P < 0.0001$) and lower adiponectin (12 ± 8 vs. 15 ± 10 μg/ml, $P < 0.0001$) levels. By ATPIII criteria, those with metabolic syndrome had higher leptin (6 ± 8 ng/ml, $P = 0.006$) and lower adiponectin (15 ± 10 vs. 18 ± 8 μg/ml, $P < 0.0001$) levels.

CONCLUSIONS — Metabolic syndrome prevalence in HIV-positive adults was lower than that reported for the general population. Metabolic syndrome was associated with a substantially increased prevalence of type 2 diabetes in this specific cohort. Many subjects without metabolic syndrome had at least two metabolic syndrome components (particularly elevated lipid levels) but did not meet waist circumference or waist-to-hip ratio cutoff metabolic syndrome criteria in this group with high rates of body fat partitioning disturbances.

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Highly active antiretroviral therapy (HAART) in HIV infection produces a spectrum of metabolic complications, including dyslipidemia, insulin resistance, and changes in body fat compartmentalization (peripheral lipoatrophy and central fat accumulation). We first described and characterized the lipid and metabolic abnormalities associated with lipodystrophy, noting many similarities with the metabolic syndrome (1–4). We also reported the early natural history of HIV lipodystrophy (2), poor responses to peroxisome proliferator–activated receptor-γ agonists and fibrates (5,6), and the impact of HAART on molecular processes in lipid, insulin, and glucose metabolism (7). The metabolic effects of HAART in contributing to increased risk of premature and accelerated atherosclerosis in HIV infection are recognized (8–11).

Metabolic syndrome has been identified as a significant and multifaceted risk

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Abbreviations: ATPIII, U.S. National Cholesterol Education Program Adult Treatment Panel III; CRP, C-reactive protein; CVD, cardiovascular disease; HAART, highly active antiretroviral therapy; IDF, International Diabetes Federation.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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factor for cardiovascular disease (CVD) by the U.S. National Cholesterol Education Program Adult Treatment Panel III (ATPIII) report (12). Metabolic syndrome encompasses disturbances in glucose, insulin, and lipid metabolism, associated with abdominal obesity (13). Metabolic syndrome doubles coronary heart disease mortality, after adjustment for age, sex, cholesterol level, physical activity, and smoking (14). In the Kuopio Ischemic Heart Disease Risk Factor Study, men with metabolic syndrome had a threefold increase in coronary death, after adjusting for age, LDL cholesterol, smoking, and family history (15).

Metabolic syndrome affects 24% of the adult population in the U.S. (16). The International Diabetes Federation (IDF) recently published its universal classification (17), which permits epidemiological study across different populations, using evidence-based abdominal obesity cutoffs that are sex and ethnicity specific.

Metabolic syndrome prevalence in HIV-infected patients receiving HAART is unclear. A Spanish study reported a prevalence of 17% by ATPIII (18) criteria. In this study we report the prevalence of metabolic syndrome in HIV-infected subjects and its associations with peripheral lipoatrophy/visceral obesity, glucose tolerance, insulin resistance, and novel adipokines implicated in the pathogenesis of atheroma and type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Patients were part of the cross-sectional Lipodystrophy Case Definition cohort, described in detail elsewhere (19): $n = 788$ (663 men) of which 75% were Caucasian ($n = 587$), 11% were African American, 8% were Asian, and 6% were Hispanic, and 451 had clinical lipodystrophy. All but 56 had received HAART at some time (self-reported). All had the following measured: 12-h overnight fasting total cholesterol, HDL cholesterol, triglycerides, insulin, glucose, adiponectin, leptin, and C-reactive protein (CRP) (19). Lipodystrophy was determined by a lipodystrophy-specific questionnaire and standardized, lipodystrophy-specific physical examination, which recorded lipoatrophy and/or diffuse fat accumulation in the face, neck, dorsocervical spine, arms, breasts, abdomen, buttocks, and legs. Subjects with at least one moderate or severe lipodystrophic feature (except isolated abdominal obesity) apparent to both physician and patient were assigned as case patients. Subjects with no lipodystrophic feature of any severity were control subjects as were subjects without any lipodystrophic feature (19).

Lifestyle data available included self-reported current smoking status, physical activity (sedentary, low, moderate, or high), and dietary intent (increase, maintain, or lose weight). Data were also available for current HAART and lipid-lowering, antihypertensive, and diabetes drugs.

Measures of adiposity included BMI, waist and hip circumferences, total body (kilograms and percentage), trunk, and peripheral fat by dual-energy X-ray absorptiometry (DEXA), and subcutaneous and visceral abdominal fat by single-slice computed tomography (CT) (at L4) as described elsewhere (19). All patients gave written informed consent, and research and ethics committees at each study location approved data collection.

Metabolic syndrome was defined using IDF (17) and ATPIII criteria (13). IDF criteria are waist circumference >80 cm in women and >94 cm in men (17) plus two of the following: triglycerides >1.7 mmol/l, HDL <1.29 mmol/l, glucose >5.6 mmol/l, systolic blood pressure >130 mmHg, or diastolic blood pressure >85 mmHg (17). ATPIII criteria are three of the following: waist circumference >88 cm in women and >102 cm in men, triglycerides >1.7 mmol/l, HDL <1.20 mmol/l in women or <1.0 mmol/l in men, glucose >6.1 mmol/l, or blood pressure >130/85 mmHg (13).

Data are means ± SD. Data were analyzed by *t* tests for group comparisons using Stata Statistical Software version 8.2 (Stata, College Station, TX).

RESULTS

— Among 788 HIV-infected adults in the Lipodystrophy Case Definition ($n = 451$ with lipodystrophy), there was a high prevalence of lipid disturbances: 307 subjects (39%) had fasting total cholesterol >5.5 mmol/l and 440 (56%) had fasting triglycerides >1.7 mmol/l. Metabolic syndrome prevalence by IDF criteria was 14%: 12% of all men and 25% of all women; a higher prevalence (18%) was found by ATPIII criteria (Table 1). The difference in prevalence between metabolic syndrome classifications was significant (McNemar's $\chi^2 = 6.36$, $P = 0.01$). Subjects classified as having metabolic syndrome were slightly older but were similar for HIV disease severity (Table 1). Current HAART type and duration were similar in those with and without metabolic syndrome for nucleosidase reverse transcriptase inhibitors and non-nucleosidase reverse transcriptase inhibitors (Table 1) (duration data not shown). Protease inhibitor use was associated with a significantly higher prevalence of metabolic syndrome (Table 1). Of the 56 HAART-naïve subjects, one had metabolic syndrome (IDF and ATPIII criteria) ($P < 0.005$).

Eighty-nine patients received lipid-lowering drugs (11%); use was twice as prevalent in those with than in those without metabolic syndrome (ATPIII 22 vs. 9%, $P < 0.0001$; IDF 19 vs. 10%, $P < 0.004$). Antidiabetes drug use was more prevalent in those with than in those without metabolic syndrome ($n = 25$) (ATPIII 11 vs. 2%, $P < 0.0001$; IDF 6 vs. 3%, $P < 0.0001$). Of the cohort, 30% smoked tobacco ($n = 229$), with similar use in those with or without metabolic syndrome (both classifications) (data not shown); physical activity was similar in both groups (Table 1). Self-reported dietary intent and alcohol use differed between those with and without metabolic syndrome but not consistently between the classifications (Table 1).

The same 76% of subjects were classified as not having metabolic syndrome and the same 9% as having metabolic syndrome by both definitions; the observed agreement between the two classifications was 85% ($\kappa = 0.46$, $P < 0.0001$). Of subjects classified as having metabolic syndrome by ATPIII criteria, 48% were also identified by IDF criteria. ATPIII criteria identified almost 50% more men but 30% fewer women.

Subjects with metabolic syndrome had significantly greater adiposity, including BMI, waist circumference, total, truncal and peripheral fat (DEXA), and visceral fat (CT) (Table 2). The prevalence of diabetes was five- to ninefold greater in those with metabolic syndrome (IDF 14 vs. 3%, $P < 0.0001$; ATPIII 18 vs. 2%, $P < 0.0001$); family history of diabetes was similar between those with and without metabolic syndrome (IDF 30 vs. 22%, $P = 0.06$; ATPIII 28 vs. 22%, $P = 0.14$). As expected by definition, blood pressure, glucose, and triglycerides were significantly higher and HDL cholesterol was significantly lower in those with metabolic syndrome; total cholesterol was significantly greater only by ATPIII criteria, LDL cholesterol was similar in both groups, and CRP was higher in those with metabolic syndrome but only with the IDF criteria (Table 3).

Table 1—*Demographic details of a cohort of 788 HIV-infected patients with and without metabolic syndrome by IDF and ATPIII criteria*

	IDF			ATPIII		
Characteristic	Metabolic syndrome	No metabolic syndrome	*P* value	Metabolic syndrome	No metabolic syndrome	*P* value
n	114	674		139	649	
Male	83 (73)	580 (86)	0.0003	118 (85)	545 (79)	
Age (years)	45 ± 10	41 ± 9	<0.0001	46 (9)	41 (9)	<0.0001
BMI (kg/m^2)	27 ± 4	23 ± 3	<0.0001	26 (5)	23 (3)	<0.0001
Systolic BP (mmHg)	130 ± 15	122 ± 15	<0.0001	134 ± 16	121 ± 14	<0.0001
Diastolic BP (mmHg)	81 ± 10	76 ± 10	0.23	81 ± 10	75 ± 10	<0.0001
HIV duration (years)	8.1 ± 4.0	7.8 ± 5.0	0.05	9.0 (4)	7.5 (5)	0.01
Lipodystrophy cases	83 (73)	368 (55)	0.31	110 (79)	341 (53)	<0.001
CDC categories						0.05
Category A	59 (52)	338 (50)		60 (43)	337 (52)	
Category B	31 (27)	153 (23)		31 (22)	153 (24)	
Category C	24 (21)	184 (27)		48 (35)	159 (24)	
Current drug therapies						
NRTI	102 (89)	572 (86)	0.3	124 (89)	550 (86)	0.29
Lamivudine	82 (72)	417 (63)		92 (66)	409 (64)	
Zidovudine	37 (32)	217 (33)		45 (32)	209 (33)	
Stavudine	55 (48)	266 (40)		63 (45)	258 (40)	
Abacavir	85 (21)	47 (23)		29 (21)	103 (16)	
Didanosine	13 (11)	129 (19)		23 (17)	119 (19)	
NNRTI	41 (36)	258 (39)	0.57	49 (35)	250 (39)	0.41
Nevirapine	17 (15)	116 (17)		18 (13)	115 (18)	
Efavirenz	23 (20)	134 (20)		30 (22)	127 (20)	
Delaviridine	1 (1)	10 (2)		1 (<1)	10 (2)	
Protease inhibitors	68 (60)	329 (49)	0.04	82 (59)	315 (49)	0.04
Indinavir	28 (25)	91 (14)		30 (22)	89 (14)	
Nelfinavir	21 (18)	95 (14)		18 (13)	98 (15)	
Saquinavir hard gel	7 (6)	31 (5)		10 (7)	28 (4)	
Saquinavir soft gel	2 (2)	49 (7)		8 (6)	43 (6)	
Ritonavir <400 mg/day	16 (14)	99 (15)		30 (22)	85 (13)	
Ritonavir >400 mg/day	9 (8)	49 (7)		16 (12)	42 (7)	
Lopinavir/ritonavir	9 (8)	63 (9)		16 (12)	56 (9)	
Amprenavir	4 (4)	27 (4)		6 (4)	25 (4)	
Alcoholic beverages*						
<7	98 (86)	519 (7)	0.16	122 (88)	495 (77)	0.007
7–13	11 (10)	96 (14)		15 (11)	92 (14)	
>14	5 (4)	49 (7)		2 (1)	52 (8)	
Physical activity						
Sedentary	35 (31)	204 (31)	0.12	47 (34)	495 (77)	0.19
Low	40 (35)	167 (25)		35 (25)	172 (27)	
Moderate	26 (23)	192 (29)		44 (32)	174 (27)	
High	13 (11)	101 (15)		13 (9)	101 (16)	
Dietary intent						
Increase weight	22 (11)	133 (20)	0.008	28 (20)	117 (18)	0.11
Maintain weight	81 (71)	461 (69)		88 (63)	454 (71)	
Decrease weight	21 (18)	71 (11)		23 (17)	69 (11)	

Data are means ± SD or *n* (%). *Standard drinks consumed each week. *P* values are for *t* test comparisons for antiretroviral drug use in those with and without metabolic syndrome. BP, blood pressure; CDC, Centers for Disease Control and Prevention; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors.

Insulin resistance was two- to threefold higher in those with metabolic syndrome; hyperinsulinemia was doubled (Table 3). As expected, because of higher fat mass, leptin was higher in patients with metabolic syndrome; hypoadiponectinemia was also found (Table 3). Lipodystrophy was present in the majority of patients with metabolic syndrome: 73% by IDF criteria ($P < 0.001$) and 79% by ATPIII criteria ($P < 0.0001$). In patients without metabolic syndrome, lipodystrophy was less frequent (53–55%).

In subjects with metabolic syndrome (IDF criteria), the presence of lipodystro-

Table 2—*Body composition parameters in HIV-infected patients with and without metabolic syndrome*

	IDF			ATPIII		
Body composition	Metabolic syndrome	No metabolic syndrome	*P* value	Metabolic syndrome	No metabolic syndrome	*P* value
n	114	672		139	649	
Anthropometry						
Waist (cm)	98 ± 9	84 ± 10	<0.0001	93 ± 12	85 ± 10	<0.0001
Hip (cm)	98 ± 9	91 ± 9	<0.0001	95 ± 11	92 ± 10	0.0001
Waist-to-hip ratio	1.00 ± 0.09	0.93 ± 0.09	<0.0001	0.98 ± 0.1	0.93 ± 0.1	<0.0001
DEXA measures						
Total fat (kg)	19 ± 7	12 ± 8	<0.0001	15 ± 10	13 ± 8	0.0009
Total fat (%)	26 ± 8	19 ± 9	<0.0001	21 ± 11	20 ± 8	0.15
Peripheral fat (kg)	7 ± 4	5 ± 4	<0.0001	6 ± 4	5.4 ± 4.0	0.5
Peripheral fat (%)	21 ± 10	17 ± 10	<0.0001	17 ± 10	17 ± 10	0.4
Trunk fat (kg)	12 ± 4	7 ± 4	<0.0001	10 ± 6	7 ± 4	<0.0001
Trunk fat (%)	29 ± 8	20 ± 9	<0.0001	24 ± 10	21 ± 9	0.002
Lean tissue (kg)	54 ± 11	50 ± 9	<0.0001	54 ± 10	50 ± 9	<0.0001
Lean tissue (%)	74 ± 9	81 ± 9	<0.0001	79 ± 11	80 ± 9	0.15
CT measures						
VAT (cm^2)	198 ± 107	107 ± 72	<0.0001	176 ± 102	107 ± 75	<0.0001
SAT (cm^2)	206 ± 122	120 ± 102	<0.0001	158 ± 138	127 ± 101	0.004

Data are expressed as means ± SD. DEXA, dual-energy X-ray absorptiometry; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

phy was not associated with worse metabolic features except for a lower adiponectin level (Table 4). In contrast, those with lipodystrophy but no metabolic syndrome had a significantly worse metabolic profile, not unlike that of metabolic syndrome with lipodystrophy (Table 4). In those without metabolic syndrome, the presence of clinically evident lipodystrophy was associated with significantly higher total cholesterol, triglycerides, insulin resistance, glucose, and CRP and lower HDL cholesterol, adiponectin, and leptin (similar for IDF and ATP-III criteria) (IDF data shown in Table 4). In those without metabolic syndrome but with lipodystrophy, metabolic disturbances were similar to those seen with metabolic syndrome (Table 4), suggesting that the presence of lipodystrophy has metabolic implications equivalent to those for meeting metabolic syndrome classifications. Only 18% of subjects with lipodystrophy (n = 451) met the metabolic syndrome criteria. Analyses were similar if the ATPIII criteria were used.

In subjects without metabolic syndrome, metabolic disturbances were prevalent: hypertriglyceridemia (>1.7 mmol/l) was twice as prevalent in those with lipodystrophy (n = 223, 61%), compared with those without lipodystrophy (n = 110, 35%) ($P < 0.0001$). Similarly, in those without metabolic syndrome, the prevalence of fasting glucose >5.6 mmol/l was 19% (n = 70) in those with

Table 3—*Fasting lipids, insulin, glucose, insulin resistance, adipokines, and blood pressure in HIV-infected patients with and without metabolic syndrome by IDF criteria*

	IDF			ATPIII		
	Metabolic syndrome	No metabolic syndrome	*P* value	Metabolic syndrome	No metabolic syndrome	*P* value
n	114	674		139	649	
Total cholesterol (mmol/l)	5.6 ± 1.0	5.3 ± 2.0	0.1	5.8 ± 2.0	5.3 ± 1.5	0.002
LDL cholesterol (mmol/l)	3.1 ± 1.0	3.0 ± 1.0	0.7	2.0 ± 1.0	3.1 ± 1.0	0.07
HDL cholesterol (mmol/l)	0.97 ± 0.3	1.18 ± 0.40	<0.0001	0.9 ± 0.3	1.2 ± 0.4	<0.0001
Triglycerides (mmol/l)	3.44 ± 2.0	2.60 ± 3.0	0.006	4.3 ± 3.0	2.4 ± 3.0	<0.0001
Glucose (mmol/l)	5.80 ± 2.0	5.0 ± 1.0	<0.0001	6.1 ± 2.0	4.9 ± 0.8	<0.0001
Insulin (mIU/l)	149 ± 157	87 ± 138	<0.0001	181 ± 262	77 ± 89	<0.0001
C-peptide (ng/ml)	2.5 ± 6	1.2 ± 1	<0.0001	1.9 ± 2.0	1.3 ± 3.0	0.03
Insulin resistance (HOMA)	6 ± 8	3 ± 6	<0.0001	7.8 ± 12	2.5 ± 3.0	<0.0001
hsCRP (mg/l)	5.5 ± 7.0	3.9 ± 6.0	0.003	4.7 ± 7.0	4.0 ± 6.0	0.25
Leptin (ng/ml)	8 ± 9	4 ± 6	<0.0001	6.3 ± 8.0	4.5 ± 6.0	0.006
Adiponectin (μg/ml)	12 ± 8	15 ± 10	<0.0001	15 ± 10	18 ± 8	<0.0001

Data are means ± SD. HOMA, homeostasis model assessment; hsCRP, high-sensitivity CRP.

Table 4—*Impact of clinical lipodystrophy on metabolic parameters in those with and without metabolic syndrome in the Lipodystrophy Case Definition Cohort by IDF criteria*

	Metabolic syndrome			No metabolic syndrome		
	Lipodystrophy	No lipodystrophy	*P* value	Lipodystrophy	No lipodystrophy	*P* value
n	83	31		368	396	
Total cholesterol (mmol/l)	5.7 ± 0.2	5.5 ± 0.3	0.67	5.5 ± 2.0	5.1 ± 1.0	0.002
LDL cholesterol (mmol/l)	3.0 ± 1.0	3.0 ± 1.0	0.48	3.1 ± 1.0	3.0 ± 1.0	0.35
HDL cholesterol (mmol/l)	0.96 ± 0.3	1.02 ± 0.28	0.33	1.1 ± 0.3	1.3 ± 0.4	<0.0001
Triglycerides (mmol/l)	3.6 ± 2.0	2.9 ± 2.0	0.09	3.2 ± 4.0	1.9 ± 2.0	<0.0001
Glucose (mmol/l)	5.8 ± 2.0	5.7 ± 2.0	0.75	5.2 ± 1.0	4.8 ± 0.7	<0.0001
Insulin (mIU/l)	160 ± 179	119 ± 67	0.22	103 ± 167	69 ± 95	0.002
C-peptide (ng/ml)	2.7 ± 7	2.0 ± 2	0.59	1.4 ± 2.0	1.0 ± 1.0	0.003
Insulin resistance (HOMA)	6.7 ± 9	4.2 ± 2	0.14	3.7 ± 7.4	2.2 ± 3.0	0.001
Leptin (ng/ml)	8.8 ± 10	6.8 ± 5	0.34	3.6 ± 5.0	4.7 ± 7.0	0.04
Adiponectin (μg/ml)	11 ± 7	15 ± 10	0.01	12 ± 10	18 ± 10	<0.0001

Data are means ± SD. HOMA, homeostasis model assessment.

lipodystrophy versus 11% ($n = 33$) in those without lipodystrophy ($P = 0.001$).

Waist circumference is the IDF entry point for metabolic syndrome; body fat disturbances found in HIV treatment may therefore affect detection of metabolic syndrome. Of 674 subjects without metabolic syndrome by IDF criteria, 269 (40%) had at least two of the other diagnostic criteria. In addition to the 114 subjects who met all IDF criteria, 49% met the nonanthropometric criteria for metabolic syndrome.

CONCLUSIONS — Metabolic syndrome prevalence in this large international cohort of HIV-infected patients was 14–18%. Hyperlipidemia was threefold higher: 39% had hypercholesterolemia and 56% had hypertriglyceridemia. Metabolic syndrome was associated with five- to eightfold increased diabetes prevalence. Metabolic syndrome was associated with higher measures of all body fat indexes, including the direct gold standard measures of total, peripheral, and visceral adiposity. Increased CRP, hyperleptinemia, and hypoadiponectinemia were found in metabolic syndrome.

There was an 85% agreement in patient classification between IDF and ATPIII criteria. Discordance arose from differences in the key criterion: the waist-to-hip ratio (ATPIII) and waist circumference (IDF). In this cohort of HIV-infected patients, of whom 57% have lipodystrophy, it is not surprising that the ATPIII criteria detected more subjects: lipodystrophy-induced peripheral fat wasting would tend to increase the waist-to-hip ratio. By both classifications, metabolic syndrome prevalence was less than that in the general population, which is surprising given the high prevalence of hyperlipidemia, diabetes, and insulin resistance found. The prevalence of metabolic syndrome found in this large, international cohort was similar to that from a smaller Spanish study (18), which showed a rate of 17% using ATPIII criteria.

The metabolic complications of HAART in patients with HIV infection introduce this patient group to future risk from CVD and diabetes, despite improvements in morbidity and mortality conferred by immune reconstitution. We have previously described the metabolic complications of HAART and described the lipodystrophy syndrome (1–4). The long-term effects of these metabolic complications indicate the need for concern and active prevention of atheroma and diabetes. The Data Collection on Adverse Events from Anti-HIV Drugs (DAD), an international collaboration of over 22,000 patients, found that 27% had hypercholesterolemia and 40% had hypertriglyceridemia (9); of those with lipodystrophy 57% had hyperlipidemia (9). Comparisons with the Framingham Offspring Study showed a greater prevalence of lipid disorders in HAART recipients than in those with a family history of heart disease (9). Longitudinal follow-up of the DAD cohort showed a 26% increase in the rate of myocardial infarction per year of exposure to HAART during the first 4–6 years of treatment (10). An increased risk of other cardio- and cerebrovascular events has also been shown, comparable to that in myocardial infarction (20). Beyond the severe lipid abnormalities associated with HAART, disorders of lipid metabolism and endothelial function that promote atherogenesis have also been reported. In mildly hypercholesterolemic HAART recipients, VLDL, chylomicrons, and intermediate-density lipoprotein were higher than in HAART-naïve HIV-positive patients (21). Flow-mediated dilatation was significantly lower in patients receiving HAART, with strong relationships between lipids and arterial reactivity (21). Studies of noninvasive measures of arterial function and structure suggested the following effect of HIV infection per se and metabolic syndrome in HIV-infected patients: flow-mediated dilation is impaired, similar to that found in diabetes (22). Further, patients with HIV infection and metabolic syndrome had increased intima-media thickness, again similar to that found in diabetes (22).

Inflammation is recognized as a major contributor in the pathogenesis of both diabetes and atherosclerosis. Little is known about key inflammatory molecules involved in atheroma and diabetes in HIV-positive HAART recipients. Insulin resistance is associated with increased CRP levels, an independent predictor of CVD. We have reported that circulating CRP is directly related to adipose tissue mass after controlling for genetic influences (23). In this study, CRP was higher in those with metabolic syndrome by IDF criteria only; it is feasible to hypothesize that CRP was higher in those with metabolic syndrome by IDF only, as these subjects had higher measures of adiposity than those with metabolic syndrome by ATPIII criteria (total fat 26 vs. 21%) (Table 1).

The adipokine adiponectin has pleomorphic actions, is a biomarker of insulin resistance, and is a potent indicator of underlying metabolic complications. We have shown reduced adiponectin levels in HIV lipodystrophy (5). In this study, adiponectin was 20% lower in metabolic syndrome, again, not surprisingly, because hypoadiponectinemia is associated with visceral obesity. Hypoadiponectinemia may play a role in the accelerated atherogenesis in HIV-infected patients: in concert with increased CRP (indicative of increased systemic inflammation), the lower adiponectin level may promote atherogenesis in this group who also have a high prevalence of hyperlipidemia.

This cohort was drawn from large tertiary referral centers in urban settings in western nations, which raises the possibility that education, socioeconomic status, and nutrition may differ from other HIV-infected HAART recipients elsewhere. Further, the purpose of the cohort was to clarify features of lipodystrophy: 57% had lipodystrophy, more than the percentage seen in the overall population of HIV-infected HAART recipients in whom lesser lipodystrophy is expected. The higher lipodystrophy prevalence rates and skewing of BMI toward "normal" may partly explain the prevalence difference of metabolic syndrome in this cohort compared with that in the general U.S. population in which much higher obesity rates are found (16). The cross-sectional nature of this study permits only associations to be drawn between metabolic syndrome and body composition and metabolic indexes; prospective studies are required to answer questions such as the impact of HAART on development of metabolic syndrome and the combined effects of HIV infection and metabolic syndrome on end points such as CVD and diabetes. These caveats considered, results from this cohort are still highly informative, given the detailed metabolic measures, measures of novel risk factors in addition to body composition, and CT measures of visceral obesity.

This study requires consideration within the context of the international debate of whether metabolic syndrome detection provides utility in identifying at-risk individuals over and above individual risk factor detection (24,25). It is not within the scope of this article to address this debate; however, prospective outcome data are necessary to determine whether the presence of metabolic syndrome produces a multiplicative increase in risk above and beyond the additive risks of its components. Such data do not exist for HIV-infected patients. Patients with HIV-associated lipodystrophy may be a subset in whom diabetes and cardiovascular risk may not be sufficiently predicted by anthropometric cutoffs, because these may not indicate the extent of lipid disturbances and insulin resistance. Whether those who meet metabolic syndrome diagnostic criteria are at even higher risk is unknown.

The circumstances of HIV infection and HAART should highlight to clinicians a patient subset for specific prevention, particularly in the presence of lipodystrophy. Metabolic syndrome may provide a useful epidemiological tool for population comparisons in HIV medicine. Diagnostic dependence on anthropometry, however, may obscure many subjects with multiple other metabolic syndrome phenotypes. Whether metabolic syndrome detection in HIV-infected HAART recipients identifies a group at higher risk of diabetes and CVD above the composite of individual risk factors is unknown and requires longitudinal data with appropriate outcome measures. Further research is also needed to define therapeutic strategies that may reduce CVD and diabetes burden in this high-risk patient group.

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