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Endothelial Function in HIV-infected Persons

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Abstract

Background—Several reports have suggested an increased risk of coronary disease in HIV-infected patients on protease inhibitors (PI). Impaired endothelium-dependent vasodilation is a putative surrogate marker of coronary atherosclerotic disease.

Methods—This study evaluated the effect of HIV infection and antiretroviral treatment on endothelial vasomotor function using brachial artery flow-mediated dilation (FMD). 75 HIV-infected patients were compared to 223 presumed HIV-uninfected control patients.

Results—HIV-infected subjects had significantly impaired FMD compared to controls (7.3 ± 4.4% versus 11.1 ± 6.4%, $p<0.0001$). When adjusted for smoking, gender and BMI the difference remained statistically significant between the two groups ($p<0.0001$). In a cross-sectional analysis of the HIV-infected patients, we found significant associations between FMD and active intravenous drug use, hazardous drinking, HIV viral load and alpha HDL triglyceride levels, but not PI therapy. In multivariate analysis, only current intravenous drug use and lower alpha HDL triglyceride level were significantly associated with FMD.

Conclusions—HIV-infected patients have significant impairment of endothelial function and this impairment is worse among those with elevated levels of HIV replication, particularly intravenous drug users.

Introduction

Since the introduction of antiretroviral therapy, mortality among persons with AIDS has declined substantially [1-5]. As people live longer with HIV disease, they develop chronic manifestations of HIV infection, such as lipodystrophy, dyslipidemia, and glucose intolerance [6-10]. More recently, concern has arisen that the onset of coronary artery disease is also accelerated in HIV-infected patients [11]. Several studies have tried to link the endocrine abnormalities associated with PI use with an increased risk of coronary artery disease in HIV-infected patients [12-17]. However, this association remains controversial [19].

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The pathogenesis of atherosclerotic disease in HIV infection is unknown. Endothelial dysfunction is an early event in atherogenesis [19-21], and brachial artery ultrasound is a well established non-invasive method of assessing endothelium-dependent vasodilation [23-25]. Some studies have demonstrated an association of endothelial dysfunction with PI use in HIV-infected persons [25-26], while others have not [27]. Therefore we compared the endothelial function of HIV-infected persons and that of persons without HIV-infection, using brachial artery ultrasound. In addition, we examined factors that were associated with endothelial function in HIV-infected patients.

Methods

Patient Population

HIV-infected patients were enrolled from the Boston Medical Center infectious disease clinic. The patients were recruited from a pool of patients participating in a longitudinal study of hepatitis C infection. A control group of presumed HIV-uninfected persons without clinically defined diabetes mellitus (fasting glucose ≥126 mg/dl or taking hypoglycemic medications), hypertension (blood pressure ≥ 140/90 mmHg or taking blood pressure lowering medications), or cardiovascular disease was drawn from a database of subjects previously studied at Boston Medical Center; this cohort has been described elsewhere [28]. The Boston Medical Center Institutional Review Board approved the study, and all participants gave informed consent. We excluded pregnant women, patients on hemodialysis, and patients with uncontrolled hypertension at the time of the study visit. Study subjects were defined as being on a PI if they were on such regimen for at least three consecutive months at the time of the visit. They were defined as not being on a PI if they did not meet this criterion. Metabolic syndrome was defined by the presence of at least three of the following factors: central obesity as specified by waist measurement, presence of dyslipidemia with low HDL levels, high triglycerides, evidence of high fasting blood sugar and presence of hypertension — as defined by the National Cholesterol Education Panel [29].

Study Protocol

Using a standardized questionnaire, we recorded smoking history, family history of coronary artery disease, diabetes mellitus and hypertension. We collected blood and measured fasting blood sugar and insulin level, high sensitivity C reactive protein (hsCRP), fasting lipid profile and lipoprotein values. We also measured body mass index (BMI), waist to hip ratio, brachial to ankle ratio. All study subjects fasted overnight and took their last anti hypertensive medication at least 24 hours before the study. Subjects restrained from exercise on the day of the study visit and from smoking at least 4 hours before the study.

We used flow-mediated dilatation (FMD) as measured by brachial artery ultrasound, as an indicator of endothelial function. We performed the measurements based on an established protocol [30]. Briefly, study subjects were positioned in a comfortable supine position. After a 15-minute rest, we recorded baseline end-diastolic brachial artery diameter and brachial artery flow velocity above the antecubital fossa. Ischemia of the forearm was induced by inflating a blood pressure cuff on the upper arm for 5 minutes at a pressure of at least 100mm Hg above the systolic blood pressure. Peak hyperemic flow was recorded within 15 seconds after cuff release and brachial artery diameter was recorded 60 seconds after cuff release. Following reactive hyperemia, we allowed 10 minutes of rest for restoration of baseline conditions. To assess vascular response to an exogenous source of nitric oxide, we recorded brachial artery diameter and velocity before and after sublingual administration of nitroglycerin (0.4 mg). Nitroglycerin was not given if patient's systolic blood pressure was < 100mm Hg, if the patient had a history of adverse reaction to nitrates, if the patient refused, or if the patient had used

sildenafil within seven days of study. The same technician performed ultrasound on all study patients and was blinded to their HIV treatment.

Statistical Analysis

We analyzed the data using the SAS version 8.02 SE (SAS, Cary, North Carolina). We reported the descriptive statistics as mean ± SD. FMD and nitroglycerin-mediated dilation (NMD) were expressed as percentage of increase from baseline. Differences between groups were evaluated by the non-parametric Wilcoxon rank test. We used a stepwise regression to select covariates that affected FMD between HIV-infected patients and controls. Based on current published literature on endothelial dysfunction [31-33] age, BMI, smoking, total cholesterol, fasting blood sugar and gender were included in the model. HIV serology was also included in the model, as were any variables that were associated with FMD at a p value of 0.15 or less. We used a similar approach to identify covariates that affected FMD among the HIV-affected patients.

Results

Clinical Characteristics

Seventy-six patients with positive serology for HIV-1 confirmed by western blot were enrolled. One study subject's results were not analyzed because of the poor quality of the imaging studies. Data from 227 subjects with presumed negative serology for HIV-1 were selected from the database of studies previously studied at Boston Medical Center. The clinical characteristics of the two groups are displayed in Table 1. HIV-infected patients were older, were more likely to be African-American and had more abnormal lipid profiles.

Brachial Artery Ultrasound Results

HIV-infected patients had significantly lower flow-mediated vasodilation compared to HIV-uninfected controls (7.3 ± 4.4% versus 11.1 ± 6.4%, respectively, $p<0.0001$). Non-endothelium-dependent NMD did not differ between the two groups (17.4 ± 8.2% versus 20.1 ± 9.1%, respectively, $p=0.11$). Table 2 displays flow-mediated dilation (FMD) and NMD values by subject characteristics. Older age, smoking, male gender, higher BMI, higher low density lipoprotein (LDL), and lower high density lipoprotein (HDL) were all associated with significantly lower values for both FMD and NMD. Patients with triglycerides (TGL) values above 200mg/dl displayed also lower values of FMD but no significant difference in NMD.

Predictive Value of Endothelial Function

As shown in table 3, independent predictors of endothelial dysfunction in multivariate modeling were HIV status, smoking, gender and BMI. This model accounts for 27% of the variability of FMD as measured by brachial artery ultrasound. Patients with HIV had significant endothelial dysfunction compared to the HIV uninfected controls, adjusted parameter estimate of 3.2% (95% CI: 5.2% to 1.8%), $p<0.0001$.

Factors associated with FMD among HIV-infected patients

To further examine the effect of HIV infection on endothelial function, we performed an analysis of factors associated with FMD among the HIV-infected patients. Forty of the subjects were current or former intravenous drug users. Of these, 15 were current users and 25 were former users. The median duration of intravenous drug use was 24 years (range 4-34 years). Of the 15 current users, 12 (80%) were using heroin and 8 (53%) were using cocaine. Of the 25 former users, 22 (88%) had used heroin and 22 (88%) had used cocaine. Of the 75 subjects, 32 were on a Protease Inhibitor (PI) regimen and 43 on a non-PI regimen. Demographic distribution, hepatitis C status, intravenous drug use and smoking status were similar in PI and

non-PI groups (table 4). Patients on PI had higher LDL levels compared to patients on non-PI regimen (120 mg/dl ± 36 versus 103 mg/dl ± 71, respectively, p=0.03). Overall PI therapy was not associated with the metabolic syndrome or worsening endocrine abnormalities. However, patients on PI-regimen were more obese as documented by waist measurements, p=0.04.

Table 5 shows the results of univariate associations between demographic and laboratory variables, FMD and NMD among the HIV-infected patients. In addition to the factors shown in the table, the following parameters were also examined: waist size, waist-to-hip ratio, hemoglobin A1c, fasting glucose, fasting insulin, high sensitivity C-reactive protein, apolipoprotein B, total cholesterol, pre-beta VLDL cholesterol, total triglycerides, LDL, HDL, lipoprotein (a) cholesterol, lipoprotein (a) triglycerides, and beta low density triglycerides. None were statistically significantly associated with FMD. HIV viral load was significantly associated with FMD, as were use of intravenous drugs during the past year and hazardous drinking. There was an association between PI use and FMD, but this did not reach statistical significance, and FMD was better in the PI group than the non-PI group. In stratified analysis, mean FMD was 2.4 percentage points higher in the PI group compared to the non-PI group among blacks, but was only 0.8 percentage points higher in the PI group compared to non-PI group among the non-black population.

In multivariate analysis, independent predictors of FMD were active intravenous drug use (3.3%; 95% CI 0.9% - 5.7%, p=0.007) and alpha HDL triglyceride (3.2%: 95% CI 1.3% - 5.1%, p=0.002). This model explained 26% of the variability of FMD among the HIV-infected patients. However, when active intravenous drug use was taken out of the model, HIV viral load became a significant predictor (2.1%; 95% CI 0.2% - 4.0%, p = 0.04).

Discussion

This study showed a strong association between HIV-1 infection and endothelial dysfunction. This finding is consistent with several studies that have described the association of coronary artery disease with the HIV infection [12,34]. Joshi et al. have documented significant inflammation involving the coronary arteries of children infected with HIV [35]. This inflammatory state is a well known precursor of the cascade of event leading to arteriosclerosis. Furthermore, HIV infection by itself may be considered a procoagulant state. Various biological markers of endothelial cell dysfunction which may contribute to this procoagulant environment have been described [36-41].

Our study also showed a strong correlation among HIV-infected persons between active intravenous drug use and impaired FMD. Although multiple comparisons were performed, the strength of this association was such that it is not likely attributable to chance. Intravenous drug use (mainly cocaine use) is a well-known risk factor for coronary artery disease [42]. Repetitive toxic effects of cocaine or other illicit substances could damage the endothelium leading to repeating cycles of cell loss and decreased ability of the endothelium to release nitric oxide in response to physiologic stimulus. It is also possible that cocaine or other drugs may be factors in down-regulation of endothelium-dependent vasorelaxation. In support of this notion, Havranek et al. used plethysmography to compare forearm blood flow response to intra-arterial acetylcholine between chronic cocaine users and control subjects. Mean forearm blood flow was lower in chronic cocaine users compared to controls [43]. In our cohort we found 12 (28%) active drug users in the non PI group compared to 3 (10%) in the PI group. This could have led potentially to a higher FMD value in the PI group. However, the multivariate analysis did not reveal such an association.

When intravenous drug use was removed from the multivariate model, HIV viral load became a significant predictor of FMD. This suggests that at least part of the effect of active drug use

is mediated by HIV viral load. This mediation is biologically plausible, as active drug use is known to adversely affect adherence to antiviral medications, and poor adherence would be expected to be associated with higher HIV viral load. Of note, 12 (80%) of the active durg users we studied had viral loads that were not completely suppressed. Our results therefore support the observation by Blum, et al. that HIV viral load may be an independent risk factor for endothelial dysfunction [44].

On the other hand, this study did not substantiate the observation by others [25] that PI-induced dyslipidemia and insulin resistance was associated with endothelial dysfunction. Although the results reveal a slightly worse lipid profile among the PI-treated group, our analysis did not show any significant worsening of FMD values associated with lipid status or presence of insulin resistance, and patients on PI treatment displayed slightly better endothelial function than patients not on PI therapy. While our study population was 57% black compared to 5% in the study by Stein, et al., and effect modification by race was observed, this effect modification does not explain the lack of effect of PI on FMD.

The role of metabolic abnormalities in HIV-infected patients receiving PI therapy and their potential association with accelerated cardiovascular and cerebrovascular disease in HIV-infected patients therefore remains controversial [45]. In a recent paper, improvement of lipoprotein profile with the use of pravastatin in HIV-infected patients on PI did not lead to significant improvement of FMD [46]. Some small case series [11,12,47] and large retrospective cohorts [13-14] have demonstrated an excess of cardiovascular events associated with PI therapy among HIV-infected persons. However, the largest observational study with the longest follow up to date failed to confirm these observations [18].

While HIV infection appears to be associated with substantial impairment of endothelial function, the degree to which this impairment translates to increased risk for cardiovascular disease in persons with HIV infection is still unknown. Modena et al, prospectively evaluated brachial artery FMD in 407 postmenopausal women with a new diagnosis of hypertension but with no known artherosclerosis (23). Failure to improve FMD with 6 months of antihypertensive therapy was an independent predictor of coronary events over the next five years. If FMD has the same predictive value in HIV infection, the subjects we studied are at substantial risk of cardiovascular disease. On the other hand, if the decreased FMD values we observed improve when HIV viral load is reduced, the long-term risk for cardiovascular disease may be small.

Our study had several potential limitations. Both diet and exercise can potentially affect FMD. We had patients fast before the study, so the short-term effects of the last meal should not be an issue, but we cannot exclude the possibility that long-term diet might have varied among the patient groups. Similarly, exercise affects risk factors that influence endothelial function, such as HDL and glucose, and also may have direct effects on the endothelium. In addition, it is possible that an association between endothelial function and PI therapy was missed because of confounding by indication, i.e., that persons who were at risk for developing impaired endothelial function were preferentially prescribed a non-PI-containing regimen. However, the patients not on PIs were not, for the most part, those who had failed on a PI regimen, and clinical predictors of dyslipidemia on PI therapy have not been identified.

We conclude that HIV-infected persons have substantial impairment in endothelial vasomotor function, and that this impairment is worse among those with elevated levels of HIV replication, particularly intravenous drug users. In our study, impaired endothelial function was not associated with PI therapy but was associated with lower alpha HDL triglyceride level, a presumed marker of metabolic imbalance. Prospective studies are needed to determine if

effective antiretroviral treatment can lead to improved endothelial function in persons with HIV infection.

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Table 1

Baseline Characteristics of HIV-infected Patients and Controls

Characteristics	**HIV positive**	**n=75**	**HIV negative**	**n=227**	**p**
Age, *mean (sd)*	44.2 (8.4)	75	41.9(11.4)	227	**<0.01**
Female gender	44%	33	47%	107	0.63
Race					
Black	57%	43	38%	87	**<0.01**
Non-black	43%	32	62%	140	
Smoker (%)	62	47	45	102	**0.01**
HDL, *mean mg/dL (sd)*	44.1 (14.7)	73	54.9 (15.2)	214	**<0.01**
LDL, *mean mg/dL (sd)*	110.7 (36.1)	73	107.5 (30)	211	0.92
Total cholesterol, *mean mg/dL (sd)*	180.9 (47.8)	73	181 (32.8)	216	0.58
Triglycerides, *mean mg/dL (sd)*	158.2 (95.9)	73	95.1 (59.8)	214	**<0.01**
Fasting glucose, *mean mg/dL (sd)*	90.8 (15.6)	74	92.4 (11.1)	198	0.09
Body mass index, *mean (sd)*	26.6 (4.5)	73	26.8 (5.9)	163	0.45

HIV = human immunodeficiency virus; HDL = high-density lipoprotein; LDL = low-density lipoprotein

Table 2

Univariate Analysis of Risk Factors for Impaired Endothelial Function Among 302 Study Subjects

Category	FMD % (sd)	n	p	NMD % (sd)	n	p
Age:						
> 40	9.5 (5.8)	166	**0.02**	8.1 (4.5)	111	**<0.01**
< 40	11.1 (6.4)	136		9.4 (6.9)	77	
HIV:						
Positive	7.3 (4.4)	75	**<0.01**	17.4 (8.2)	38	0.11
Negative	11.1 (6.3)	227		20.1 (9.1)	150	
Smoker:						
Yes	8.8 (5.3)	149	**<0.01**	17.7 (7.5)	97	**0.01**
No	11.6 (6.6)	153		21.5 (10)	91	
Gender:						
Male	8.2 (4.9)	162	**<0.01**	16.5 (6.9)	111	**<0.01**
Female	12.5 (6.6)	140		24 (9.8)	77	
Race:						
Black	10.4 (6.5)	130	0.79	19.8 (9.4)	93	0.78
Non Black	10 (5.9)	172		19.3 (8.6)	95	
Body mass index:						
> 30	7.9 (4.6)	51	**<0.01**	15.7 (6.6)	35	**<0.01**
< 30	10.9 (6.6)	185		20.4 (9.1)	102	
LDL:						
> 100 mg/dl	9.6 (5.6)	163	**0.05**	18.3 (8.5)	102	**<0.01**
< 100 mg/dl	11.3 (6.8)	121		22.2 (9.4)	75	
HDL:						
> 40 mg/dl	10.9 (6.4)	221	**<0.01**	20.6 (9.2)	143	**0.02**
< 40 mg/dl	8.1 (4.9)	66		16.8 (7.8)	36	
Total cholesterol:						
> 200 mg/dl	9.0 (4.7)	76	0.07	18.7 (9.0)	53	0.20
< 200 mg/dl	10.7 (6.6)	213		20.3 (9.0)	128	
Triglycerides:						
> 200 mg/dl	7.7 (5)	26	**0.02**	17.7 (9.9)	15	0.17

Category	FMD % (sd)	n	p	NMD % (sd)	n	p
< 200 mg/dl	10.6 (6.3)	261		20 (9)	164	
Fasting glucose:						
> 110 mg/dl	10.2 (5.3)	12	0.89	16.9 (5.2)	10	0.46
< 110 mg/dl	10.3 (6.2)	260		19.7 (9.2)	162	

FMD= flow-mediated dilation; NMD=nitroglycerin-mediated dilation; HIV=human immunodeficiency virus; HDL=high-density lipoprotein; LDL=low-density lipoprotein

Table 3

Multivariate Analysis of Risk Factors for Impaired Endothelial Function Among 302 Study Subjects

Category	Percent FMD Difference (95% CI)	p
HIV infection	3.6 (1.8 to 5.2)	<0.01
Smoker	1.8 (3.4 to 0.2)	0.02
Male Gender	4.2 (5.7 to 2.5)	<0.01
Body mass index >30	3.1 (4.9 to 1.2)	<0.01

R^2=0.27

Table 4

Baseline Demographic and Clinical Characteristics of the HIV-Infected Patients

Characteristics	Study Patients (n=75)	By Group		p
		PI (n=32)	Non PI (n=43)	
Age, *mean (sd)*	44 (8)	45 (9)	44 (8)	0.67
Female gender, *n (%)*	33 (44)	12 (37)	21 (49)	0.87
Race, *n (%)*				
Black	42 (56)	19 (59)	23 (53)	0.64
White	16 (21)	7 (22)	9 (21)	
Hispanic	15 (20)	6 (19)	9 (21)	
Hepatitis C positive, *n (%)*	47 (65)	18(56)	29 (67)	0.32
Child-Pugh score, *n* [a] *(sd)*	7.4 (14.7)	5.1(0.3)	8.6(18)	0.61
Current smoker, *n (%)*	47 (65)	17 (57)	30 (71)	0.19
Hazardous drinking, yes *(%)*		19	23	0.63
Injection drug use, *n (%)*				
Current	15 (20)	3 (9)	12 (28)	0.12
Former	25 (33)	13 (41)	12 (28)	
Never	35 (47)	16 (50)	19 (44)	
Family history of coronary artery disease, *n (%)*		6 (20)	11 (26)	0.42
History of hyperlipidemia, *n (%)*		4 (13)	3 (8)	0.51
History of lipodystrophy, *n (%)*		2 (7)	1 (3)	0.45
Waist, *mean cm (sd)*	91 (16)	96 (21)	88 (11)	**0.04**
Waist to hip ratio, *mean (sd)*	0.9 (0.1)	0.94 (0.1)	0.88 (0.1)	**0.01**
Body mass index, *n (%)*	27 (4)	27(4)	26 (4)	0.22
Ankle brachial index, *n (sd)*	1 (0.1)	1(0.1)	1(0.1)	0.46
Nadir CD4 cell count, *mean (sd)*	270 (250)	226 (227)	301 (264)	0.11
HIV-1 RNA, log10 copies/ml, median	90	49	497	**0.02**
AIDS, *n (%)*	36 (48)	18 (56)	18 (42)	0.21
Use of HIV PIs, *n (%)*				
Nelfinavir		15 (47)		
Lopinavir-Ritonavir		10 (31)		
Indinavir		6 (19)		
Saquinavir		1 (3)		
Use of NRTIs [b], *n (%)*				
Lamivudine		24 (75)	26(60)	0.18
Zidovudine		11 (34)	24 (56)	**0.06**
Stavudine		18 (56)	5(12)	**<0.01**
Didanosine		7 (22)	5(12)	0.23
Tenofovir		5 (16)	2 (5)	0.10
Abacavir		2 (6)	13 (30)	**0.01**
Use of NNRTIs, *n (%)*				
Efavirenz			14 (32)	

Characteristics	Study Patients (n=75)	By Group		p
		PI (n=32)	Non PI (n=43)	
Nevirapine			5 (12)	
Exposure to antiretrovral therapy, *n (%)*				
Not on antiretroviral at study visit [c]	12 (16)			
On therapy at study visit				
0-6mo		1 (3)	4 (13)	
6mo-1yr		3 (9)	5 (16)	
1yr-3yrs		8 (25)	15 (48)	
> 3yrs		17 (53)	6 (19)	

PI=protease inhibitors; HIV=human immunodeficiency virus ; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor

[a] n=41

[b] All patients on HAART were at least on 2 NRTIs

[c] 12 patients were on no therapy. Among them 4 were antiretroviral naïve, 4 were off therapy for more than 2 years, 3 were off therapy for more than 3 months, one was off therapy for 3 months.

Table 5

Univariate Analysis of Risk Factors for Impaired Endothelial Function Among 75 HIV-Infected Patients

Category	FMD% (sd)	n	p	NMD %(sd)	n	p
Race:						
Black	8.1 (4.8)	43	0.15	17.2 (8.6)	23	1.0
Non-black	6.3 (3.7)	32		17 (8)	14	
Age:						
> 40	7.5 (4.6)	49	0.61	16.2 (8.8)	27	0.07
< 40	7.0 (4.1)	26		19.7 (6.6)	10	
Gender:						
Male	6.7 (4)	42	0.22	14.9 (4.8)	19	0.33
Female	8.2 (4.8)	33		19.5 (10.5)	18	
Protease inhibitors:						
Yes	8.3 (4.5)	32	0.07	17.4 (6.9)	17	0.47
No	6.6 (4.3)	43		16.9 (9.5)	20	
AIDS Diagnosis						
Yes	7.5 (4.7)	36	0.93	17.5 (9.8)	14	0.96
No	7.2 (4.2)	39		16.9 (7.5)	23	
HIV Viral Load						
≥50 copies	6.3 (4.1)	41	0.03	15.1 (6.3)	23	0.15
<50 copies	8.6 (4.5)	34		20.5 (10.3)	14	
Smoking status:						
Current	7.2 (4.2)	47	0.87	16.4 (7.4)	25	0.57
Non-current	7.7 (4.8)	25		18.7 (10.2)	12	
Injection drug use:						
Current	4.7 (3.8)	15	**<0.01**	13.5 (5)	8	0.19
Non-current	8 (4.3)	60		18.1 (8.8)	29	
Hazardous drinking:						
Yes	5.6 (4.7)	16	**0.02**	17.7 (11.5)	9	0.73
No	7.8 (4.3)	59		16.9 (7.3)	28	
Body mass index:						
> 30	7.7 (4.0)	16	0.60	14.2 (6.3)	11	0.12

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Category	FMD% (sd)	n	p	NMD %(sd)	n	p
< 30	7.2 (4.6)	59		18.4 (8.8)	26	
Alpha HDL triglycerides:						
> 20 mg/dl	8.4 (4.8)	44	**<0.01**	18 (9.3)	24	0.81
< 20 mg/dl	5.8 (3.4)	31		15.6 (6.3)	13	
Metabolic syndrome:						
Yes	8.1 (3.3)	12	0.27	14.6 (8.4)	8	0.20
No	7.2 (4.6)	63		17.8 (8.3)	29	

FMD= flow-mediated dilation; NMD=nitroglycerin-mediated dilation; HCRP= High sensitive C reactive protein; LDL=low-density lipoprotein; HDL=high-density lipoprotein; VLDL=very low-density lipoprotein

[a] cutoff is 35 for females

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