

Lipid and Lipoprotein Profile in HIV-Infected and Non-Infected Diabetic Patients: A Comparative Cross-Sectional Study Design, Southwest Ethiopia

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Background: Lipoproteins are complexes of lipids and proteins that are essential for the transport of cholesterol, triglycerides, and fat-soluble vitamins. The linkage between chronic diseases like diabetes mellitus and HIV infection increases the complication of the diseases and worsens the clinical outcome of the patients.

Purpose: To assess and compare lipid and lipoprotein profiles among HIV-infected and non-infected diabetic patients, and to identify independent predictor variables for abnormal lipid and lipoprotein profiles.

Patients and Methods: A comparative cross-sectional study design was used to carry out the research, and a convenient sampling technique was used to include 96 adult diabetic patients (48 HIV-infected and 48 non-infected diabetics). Socio-demographic and clinical data were collected by interviewer-administered questionnaire. Five milliliter blood sample was collected and processed for lipid and lipoprotein profile measurement. Multivariate and bivariate logistic regressions were used to identify independent predictor variables for abnormal lipid and lipoprotein profiles.

Results: The prevalence of diabetic dyslipidemia was 41.7% and 37.5% in HIV-infected and non-infected diabetic patients, respectively. Hypercholesterolemia was more commonly detected among HIV-infected diabetic patients than non-HIV-infected, 25.0% versus 18.8%, respectively. Similarly, hypertriglyceridemia was more commonly observed in HIV-infected (31.3%) than non-infected diabetic patients (20.8%). About 25.0% HIV-infected diabetic patients had combined hyperlipidemia (hypercholesterolemia plus hypertriglyceridemia); and about 4.2% had hypoalphalipoproteinemia or isolated low HDL-C. Being female and long duration of diabetes mellitus were independent predictor variables for abnormal lipid and lipoprotein profiles in HIV-infected patients. Similarly, being female and high blood pressure were independent predictor variables in non-HIV-infected diabetic patients.

Conclusion: High prevalence lipid and lipoprotein abnormalities were detected in HIV-infected diabetic patients even though the abnormalities were also common in non-HIV comorbid diabetic patients. Hence, proactive screening and treatment of blood glucose, lipid, and lipoprotein abnormalities are critically important and should be part of comprehensive HIV care.

Keywords: diabetes mellitus, hypertriglyceridemia, lipoproteins, hypercholesterolemia, HIV-infection

Introduction

Lipids occur in all types of cells with great contribution to cellular structure and as the richest source of energy^{1,2}; these are chemically heterogeneous group and

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insoluble in water or plasma so that they need carrier proteins or lipoproteins to be transported.^{3–5} Lipoproteins play a cardinal role in transporting hydrophobic lipids, primarily, triglycerides and cholesterol via body fluids from the liver to peripheral tissues and the transport of cholesterol from peripheral tissues to the liver.^{3,6,7} Dietary triglycerides and cholesterol are transported to the periphery and liver by exogenous lipoprotein metabolic pathway, whereas endogenously synthesized hepatic lipids are transported to the periphery by endogenous lipoprotein metabolic pathway that is mediated by very low-density lipoprotein (VLDL).^{4,8,9} The triglycerides of chylomicrons are hydrolyzed by lipoprotein lipase (LPL) releasing free fatty acids that are taken up by adjacent myocytes or adipocytes.^{3,8} Similarly, the triglycerides of VLDL are hydrolyzed by LPL in adipose tissue and muscle producing intermediate density lipoproteins (IDLs) that contain roughly similar amounts of cholesterol and triglyceride.^{3,4,10} About 40–60% of IDLs are removed by the liver and the remainder is remodeled by hepatic lipase to form low-density lipoprotein (LDL) that contains greater than 50% of total plasma cholesterol.^{4,11} Another lipoprotein is high-density lipoprotein (HDL) that contains trace amount of triglycerides and significantly useful in transporting excess cholesterol from the plasma membrane of the peripheral cells to liver and intestine.^{3,12,13}

Serum cholesterol, particularly the LDL, is one of the most important identified risk factors for coronary heart disease (CHD). High triglyceride is also generally accepted as a significant risk factor. On the other hand, an elevated HDL is considered as protective of CHD.³ Sedentary lifestyle, cigarette smoking, advancing age (M>45 years, F>55 years), hypertension and diabetes mellitus are the major risk factors for CHD.^{3,4} Dyslipidemia is a common characteristic of diabetes mellitus, and there is a link between atherosclerosis and hyperlipidemia in diabetic patients.^{9,14} The risk of CHD is stronger in diabetic patients at any serum cholesterol level with hypertriglyceridemia than in general population.¹⁵ The linkage between HIV and diabetes mellitus makes the diagnosis and management of these diseases more difficult and also increasing the complications and leading to worsen the clinical outcome of the patients.^{16,17} Co-morbid medical conditions including diabetes mellitus, dyslipidemia and other metabolic disorders are challenging in managing people living with HIV and diabetes mellitus.^{9,18–25} Like other general populations, HIV-infected individuals are exposed to different socioeconomic and cultural factors, including

sedentary lifestyle and unhealthy dietary practices. Such problems are highly prevalent in low-income countries.²⁶ Diabetes and other metabolic abnormalities among HIV-infected individuals are not well studied in low-income countries including Ethiopia where the availability of health-care resources is limiting. Therefore, the objective of this study was to assess and determine lipid and lipoprotein profile in HIV-infected diabetic patients and to compare the findings with HIV-non-infected diabetic patients.

Materials and Methods

Study Objective, Period and Setting

The study was conducted in Jimma Zone public health institutions from February 05, 2019, to June 28, 2019. Jimma zone is located in Oromia Regional State southwest Ethiopia. Jimma Zone has one tertiary hospital, two general hospitals and four primary hospitals. The Jimma University Medical Center is the only teaching and referral hospital in southwest Ethiopia with about 800 beds capacity and over 20 million catchment populations.

Study Design, Sample Size Determination and Sampling Technique

A comparative cross-sectional study design was used to carry out the study. The sample size was calculated by using a double population proportion formula, $n = (Z_{\alpha/2} + Z_{\beta})^2 * (p_1(1-p_1) + p_2(1-p_2)) / (p_1 - p_2)^2$, by considering $P_1 = 0.127^{34}$ for HIV-infected diabetic patients and $P_2 = 0.385^{35}$ for non-HIV-infected diabetic patients with 95% confidence interval and 80% power. A convenient sampling technique was used to include 96 adult diabetic patients (48 HIV-infected and 46 non-HIV-infected). Severely ill and individuals on lipid profile-lowering drugs were excluded from the study as it severely interfere the lipid profile result.

Data Collection and Blood Chemistry

Socio-demographic and clinical data were collected by trained data collectors using an interviewer-administered questionnaire. Anthropometric data and blood pressure measurements were performed by clinical nurses working in chronic illness clinic according to World Health Organization (WHO) guidelines.²⁷

The body mass index (BMI) was calculated as weight/height square expressed as kg/m². Study subjects with BMI value of 25.0–29.99 kg/m² were categorized as

overweight and those with $\geq 30.0 \text{ kg/m}^2$ as obese. Blood pressure values of $\geq 140 \text{ mmHg}$ for systolic and/ or $\geq 90 \text{ mmHg}$ for diastolic were categorized high blood pressure or hypertension.²⁸

About 5-milliliter blood sample was collected from each study subject and processed based on the standard operating procedure for sample processing. After serum had been separated from whole blood cell, the samples were analyzed for lipid parameter (triglyceride and total cholesterol), and lipoproteins (high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) by using Horiba ABX SAS (Montpellier, France) chemistry analyzer by strictly applying the basic test principle for each lipid and lipoprotein parameter.

The lipid profile and lipoprotein serum results were interpreted based on WHO dyslipidemia guideline, as hypercholesterolemia: if serum total cholesterol level $> 160 \text{ mg/dl}$; hypertriglyceridemia: if serum triglyceride level $\geq 200 \text{ mg/dl}$; elevated low-density lipoprotein cholesterol: if serum LDL-C level $\geq 160 \text{ mg/dl}$; low high-density lipoprotein cholesterol: if HDL-C $< 40 \text{ mg/dl}$ for male and $< 30 \text{ mg/dl}$ for female.⁵

Statistical Analysis

After proper cleaning for completeness and consistency, the data were entered into the Epi-data version 3.1 and later exported to SPSS version 21.0 for analysis and interpretation. Descriptive statistics were used to explain data in numbers and proportions. Binary and multivariate logistic regression analyses were used to assess the relationship between independent and predictor variables. P value < 0.05 was used as a threshold level for statistical significance.

Results

Socio-Demographic and Clinical Characteristics of Study Subjects

A total of 96 (48 HIV-infected and 48 non-HIV-infected) diabetic patients were included in the study with the mean \pm SD age of 51.6 ± 10 years for HIV-infected and 48.8 ± 9.8 years for non-HIV-infected diabetic patients; age range of 30–70 and 28–66 years for HIV-infected and non-infected study subjects, respectively. The proportion of male study participants were higher in HIV-infected diabetic patients as compared to non-HIV-infected (75% versus 47.9% respectively). The majority of the study subjects, 87.5% for HIV-infected and 81.3% for non-HIV-infected,

belonged to the age group of 40 years or older. About 29.2% and 10.4% HIV-infected patients were overweight and obese, respectively. Concerning duration of diabetes mellitus, majority of HIV-infected diabetic patients, 60.4%, were less than 5 years, whereas about 58.3% of non-HIV-infected diabetic patients were greater or equal to 5 years. Almost comparable proportion of study groups had been taking oral glucose lowering agents; 56.3% and 52.1% HIV-infected and non-infected diabetic patients, respectively. About 64.6% and 70.8% HIV-infected diabetic patients were on a TDF+3TC+EFV drug regimen and had CD4 count greater or equal to 500 cells/ mm^3 , respectively. Concerning substance use, about 29.2% and 18.8% of HIV-infected and non-infected diabetics, respectively, had the habit of cigarette smoking during the study period (Table 1).

The prevalence of diabetic dyslipidemia was 41.7% and 37.5% in HIV-infected and non-infected diabetic patients, respectively. About 25.0% HIV-infected diabetic patients had high total cholesterol level as compared to 18.8% among non-HIV-infected diabetic patients. Similarly, higher rate of hypertriglyceridemia was observed among HIV-infected than non-HIV-infected diabetic patients (31.3% versus 20.8%, respectively). The serum abnormality of APO-B containing lipoprotein that carries about 50% of total cholesterol or LDL-C was about 35.4% in HIV-infected and 29.2% in non-HIV-infected diabetic patients. Again, the low level of non-APO-B containing lipoprotein or HDL-C was more common in HIV-infected diabetic patients than non-HIV-infected (29.2% versus 18.8%, respectively). From the total HIV-infected diabetic patients about 25.0% and 4.2% had combined hyperlipidemia and hypoalphalipoproteinemia respectively showing increased serum level of total cholesterol and triglyceride together, and isolated low level of HDL-C (Table 2).

The multivariate logistic regression analysis revealed that being female (AOR: 6.30, 95% C.I: 1.398–28.390, P: 0.0165) and long duration of diabetes (≥ 5 years) (AOR: 4.93, 95% C.I: 1.091–22.297, P: 0.038) were independently associated with abnormal lipid and lipoprotein profile in HIV-infected diabetic patients. Similarly, being female (AOR: 9.23, 95% C.I: 1.661–51.308, P: 0.011) and high systolic blood pressure (AOR: 3.92, C.I: 1.012–15.214, P: 0.048); high diastolic blood pressure (AOR: 13.04, 95% C.I: 1.804–94.25, P: 0.011) were independent predictor variables for abnormal lipid and lipoprotein profile in non-HIV-infected diabetic patients. Being female

Table 1 Socio-Demographic and Clinical Characteristics of HIV-Infected and Non-Infected Diabetic Patients

Variable	Category	HIV-Infected, N(%)	HIV-Non-Infected, N(%)	Total, N(%)
Sex	Male	36(75.0)	23(47.9)	59(61.5)
	Female	12(25.0)	25(52.1)	37(38.5)
Age (years)	18–39	6(12.5)	9(18.8)	15(15.6)
	≥40	42(87.5)	39(81.3)	81(84.4)
Marital status	Married	39(81.3)	38(79.2)	77(80.2)
	Others	9(18.8)	10(20.8)	19(19.8)
Occupation	Employed	25(52.1)	22(45.8)	47(48.9)
	Unemployed	23(47.9)	26(54.2)	49(51.04)
Residence	Urban	31(64.6)	35(72.9)	66(68.8)
	Rural	17(35.4)	13(27.1)	30(32.3)
Educational status	No formal education	6(12.5)	7(14.6)	13(13.5)
	Formal education	42(87.5)	41(85.4)	83(86.5)
BMI (kg/m ²)	Normal	29(60.4)	39(81.3)	68(70.8)
	Overweight	14(29.2)	7(14.6)	21(21.9)
	Obesity	5(10.4)	2(4.2)	7(7.3)
Systolic blood pressure	Normal (<140mmHg)	25(52.1)	30(62.5)	55(57.3)
	Abnormal (≥140mmHg)	23(47.9)	18(37.5)	41(42.7)
Diastolic blood pressure	Normal (<90mmHg)	23(47.9)	15(31.3)	38(39.6)
	Abnormal (≥90mmHg)	27(56.3)	33(68.8)	60(62.5)
Duration DM	<5 years	29(60.4)	20(41.7)	49(51.0)
	≥5 years	19(39.6)	28(58.3)	47(49.0)
Anti-hyperglycemia	Insulin	19(39.6)	15(31.3)	34(35.4)
	Metformin	27(56.3)	25(52.1)	52(54.2)
	Others	2(4.2)	8(16.7)	10(10.4)
ART drug regimen	TDF+3TC+EFV	31(64.6)	-	31(64.6)
	AZT+3TC+EFV	14(29.2)	-	14(29.2)
	ABC+3TC+EFV	2(4.2)	-	2(4.2)
	Other	1(2.1)	-	1(2.1)
CD4 count (in cells/mm ³)	<500	14(29.2)	-	14(29.2)
	≥500	34(70.8)	-	34(70.8)
Smoking	Yes	14(29.2)	9(18.8)	23(24.0)
	No	34(70.8)	29(60.4)	63(65.6)
Khat chewing	Yes	7(14.6)	11(22.9)	18(18.8)
	No	41(85.4)	27(56.3)	68(70.8)

Abbreviations: ART, anti-retroviral therapy; BMI, body mass index; mmHg, millimeter of mercury; ABC, abacavir; AZT, zidovudine; EFV, efavirenz; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

Table 2 Dyslipidemia and Lipoprotein and Lipid Profile in HIV-Infected and Non-Infected Diabetic Patients

Variable	Category	HIV-Infected DM, N(%)	Non-HIV-Infected DM, N(%)	Total, N(%)
Dyslipidemia	Yes	20(41.7)	18(37.5)	38(39.6)
	No	28(58.3)	30(62.5)	58(60.4)
Total cholesterol	Elevated	12(25.0)	9(18.8)	21(21.8)
	Normal	36(75.0)	39(81.3)	75(78.1)
Triglyceride	Elevated	15(31.3)	10(20.8)	25(26.0)
	Normal	33(68.8)	38(79.2)	71(74.0)
LDL-C	Elevated	17(35.4)	14(29.2)	31(32.3)
	Normal	31(64.6)	34(70.8)	65(67.7)
HDL-C	Low	14(29.2)	9(18.8)	23(24.0)
	Elevated	34(70.8)	39(81.3)	73(76.0)
Combined hyperlipidemia	Yes	12(25.0)	9(18.8)	21(21.9)
	No	3(6.3)	1(2.1)	4(8.3)
Hypoalphalipoproteinemia (HDL-C <38mg/dl)	Yes	2(4.2)	0(0.0)	2(4.2)
	No	12(25.0)	9(18.8)	21(21.9)

Abbreviations: LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

was about 6.3 times more likely to develop dyslipidemia than male in HIV-infected diabetic patients. The odds of developing dyslipidemia among HIV-infected diabetic patients with abnormal systolic blood pressure was about 3.53 times more likely than those with normal systolic blood pressure. HIV-infected diabetic patients with longer duration of diabetes mellitus (≥ 5 -years) were about 4.93 times more likely to develop dyslipidemia as compared to those with less duration of diabetes mellitus (< 5 years) (Table 3).

Discussion

The total prevalence of dyslipidemia was 39.6%, and it was a little bit more common in HIV-infected diabetic patients (41.7%) as compared to non-HIV-infected diabetic patients (37.5%). Comparable prevalence of dyslipidemia was reported from Khartoum with the range of 13–70% diabetic dyslipidemia in HIV-infected patients.²⁹ About 21.8% diabetic patients were hypercholesterolemic, of which about 25.0% and 18.8% were from HIV-infected and non-infected diabetic study groups, respectively. HIV-infected diabetic study subjects were more hypertriglyceridemic than the HIV-non-infected study subjects, 31.3% versus 20.8% respectively and the total hypertriglyceridemia was about

26.0%. Similar findings in which HIV-infected diabetic patients were more hypercholesterolemic and hypertriglyceridemic than non-HIV-infected diabetic patients were reported from Massachusetts.⁶ In contrast to this, the study reported from Australia showed that there was no difference in serum concentration of triglyceride in HIV-infected and non-infected diabetic patients.³⁰ Some study subjects had both elevated cholesterol and triglyceride together, which are considered to be risk factors for coronary heart disease (CHD), and thus about 25.0% HIV-infected and 18.8% non-infected diabetic patients had combined hyperlipidemia. Elevation of LDL-C is considered as an established risk factor for CHD and the elevation of this lipoprotein was more common among HIV-infected diabetic patients than non-infected, 35.4% versus 29.2%, and a total of 32.3% study subjects had abnormal level of this lipoprotein. The highest concentration of HDL-C is very helpful in maintaining the equilibrium of cholesterol in peripheral cells by removing excess cholesterol via the reverse cholesterol transport pathway. Thus, its high blood concentration has anti-atherogenic property, whereas its low concentration is considered to be an independent risk factor for atherosclerosis. A majority, 70.8% and 81.3%, of HIV-infected and non-infected diabetic patients, respectively, had the highest

Table 3 Multivariate Logistic Regression Analysis in HIV-Infected and Non-Infected Diabetics

Variable	Category	HIV-Infected		HIV-Non-Infected	
		AOR(95% CI)	P value	AOR(95% CI)	P value
Sex	Male	0.16(0.035–0.715)	1	0.11(0.019–0.602)	1
	Female	6.30(1.398–28.390)	0.0165	9.23(1.661–51.308)	0.011
Systolic BP (mmHg)	Normal	0.28(0.063–1.266)	1	0.26(0.066–0.988)	1
	Abnormal	3.53(0.790–15.775)	0.099	3.92(1.012–15.214)	0.048
Diastolic (mmHg)	Normal	0.35(0.098–1.233)	1	0.08(0.011–0.554)	1
	Abnormal	2.87(0.811–10.177)	0.102	13.04(1.804–94.25)	0.011
Alcohol use	Yes	4.10(0.898–18.722)	0.07	2.82(0.758–10.501)	0.122
	No	0.24(0.053–1.113)	1	0.36(0.095–1.320)	1
Khat chewing	Yes	4.72(0.763–29.248)	0.10	1.54(0.393–6.026)	0.536
	No	0.212(0.034–1.311)	1	0.65(0.166–2.546)	1
Duration of diabetes mellitus	<5 years	0.20(0.045–0.917)	1	0.42(0.08–2.285)	1
	≥5 years	4.93(1.091–22.297)	0.038	2.36(0.438–12.771)	0.317

Abbreviations: AOR, adjusted odds ratio; BP, blood pressure; mmHg, millimeter of mercury; HIV, human immunodeficiency virus.

concentration of HDL-C although 29.2% HIV-infected and 18.8% non-HIV-infected diabetic patients had low serum concentration of HDL-C. This finding is comparable with the finding reported from Tunisia in which HDL-C value in selected study subjects was 26.6%.³¹ From the total HIV-infected diabetic patients with low concentration of HDL-C, 4.2% study subjects had an isolated decrease in HDL-C or hypoalphalipoproteinemia, which might be due to mutation of apolipoprotein A-I. This finding is almost comparable to the finding reported from Japan with 6.0% hypoalphalipoproteinemia,³² but much less than the finding from Indonesia with 30% hypoalphalipoproteinemia.³³ Even though the BMI measurement was abnormal among non-HIV-infected diabetic patients, the prevalence of abnormal BMI was twice among the co-morbidities.

The multivariate analysis revealed that being female and long duration of diabetes were independent risk factors for hyper- and hypolipoproteinemia, and hyperlipidemia in HIV-infected diabetic patients. Similarly, being female and abnormal diastolic blood pressure were independent predictor variables for the same abnormality in non-HIV-infected diabetic patients. The non-HIV-infected diabetic patients with abnormal diastolic blood pressure had about 13 times more likely to develop dyslipidemia than those with normal diastolic blood pressure. Similarly, female non-HIV-infected diabetic patients had more than

nine times more likely to have abnormal lipoproteins and hyperlipidemia.

This shows that HIV infection is likely to worsen metabolic abnormalities among diabetic patients. In addition to the co-morbidities, social determinants of health include access to healthy foods, quality of health care access; and economic stability to choice and pay for quality of medical care might contribute to higher prevalence of serum lipid and lipoprotein abnormality in diabetic patients.

Limitation of the Study

The sample size was small even though we used all HIV-infected diabetic patients in the study area. Due to the impact from cross-sectional study, design we could not determine whether the exposure or outcome came first.

Conclusion

More lipid and lipoprotein abnormality was detected in HIV-infected diabetic patients, although the abnormality was common in non-HIV co-morbid diabetes mellitus. Being female and long duration of diabetes mellitus were independent predictor variables for abnormal lipid and lipoprotein profile in HIV-infected and HIV-negative diabetic patients. Thus, appropriate diagnosis and management of lipoprotein disorders is critically important and lipid abnormalities

should be assessed aggressively and treated as part of comprehensive diabetic care. Hence, proactive screening and treatment of blood glucose, lipid, and lipoprotein abnormalities should be part of comprehensive HIV care.

Abbreviations

ABC, abacavir; AOR, adjusted odds ratio; ART, antiretroviral therapy; AZT, azidothymidine; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CD4, cluster of differentiation; EFV, efavirenz; HDL-C, high-density lipoprotein-cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein-cholesterol; mmHg, millimeter of mercury; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

Data Sharing Statement

Data are available from the corresponding author on reasonable request.

Ethical Clearance and Consent to Participant

The study has been conducted in accordance with the principles stated in the Declaration of Helsinki, and thus an ethical approval had been taken from the Institutional Review Board of Jimma University Institute of Health. Official permission was also obtained from Jimma Zone Health Office and heads of each hospital involved. Additionally, written informed consent was obtained from all study participants. Confidentiality of the collected data was ensured through anonymity.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors reported there is no financial or any other conflict of interest.

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