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Assessment of Lipid Profile among Patients Infected with Visceral Leishmaniasis and Healthy Controls

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ABSTRACT: Visceral leishmaniasis remains a major public health concern in many parts of the tropical and subtropical world. The infection is also accompanied by lipid profile alterations. The aim of the study was to assess lipid profile among patients infected with visceral leishmaniasis and healthy control in Northwest Ethiopia**.** A total of 140 study participants (70 case and 70 healthy controls) were enrolled. A Five milliliter venous blood was collected at the time of diagnosis. Serum was extracted from the sample and analyzed by A25 Biostem, Spanchemistry analyzer using enzymatic calorimetric methods. The data was described using mean, standard deviation, and percentage. Independent t-test was used to see the mean difference among groups and linear regression was employed to determine the associated factors for the outcome variable. P-value <0.05 was considered as statistically significant. Study participants with visceral leishmaniasis had lower levels of mean total cholesterol (69.7± 22.83 vs 179±42.87), high density lipoprotein cholesterol (18.3±7.79 vs 88±31.53), and low density lipoprotein cholesterol (35.3±15.19 vs 64.6±18.11) in mg/dl as compared with the control group. On the other hand the case group showed significant mean increase in circulating triacylglycerol (169±67.43 vs 116±46.4) and very low density lipoprotein cholesterol (33.8±13.49 vs 23.8 ±10.8) in mg/dl in contrast to the control group. Body mass index, infection by leishmaniasis, parasite load, waist circumference, occupation and educational level were variables yielded significant associations with serum lipid profile. Marked elevation in serum triacylglycerol and very low density lipoprotein cholesterol and significant lower level of high density lipoprotein cholesterol found in patients make the patients more prone to dyslipidemia. As consequence, dyslipidemia also important risk factor for the development of atherosclerosis and coronary heart disease.

Keywords: Ethiopia; Lipid profile; Visceral leishmaniasis.

INTRODUCTION

Leishmaniasis is a vector-transmitted protozoan disease distributed throughout tropical and subtropical regions. It is caused by the genus *Leishmania* having 20 different species which are pathogenic to humans. It is an intracellular parasite transmitted by the bite of *phlebotomine* sand fly (El-on, 2009). Globally, more than 12 million people are infected with leishmaniasis and 350 million are at risk. Leishmaniasis is endemic in 98 countries and responsible for a burden of 2.35 million disability adjusted life years. Visceral Leishmaniasis (VL) is the second protozoal disease next to malaria in its annual worldwide fatalities. Over 90% of VL cases occur in six main countries: Bangladesh, India, Nepal, Sudan, Ethiopia, and Brazil (Pan American Health Organization /World Health Organization, 2014).

Ethiopia is the second most affected country in VL among the Sub-Saharan African countries. It is a major cause of death for thousands of people in the area. The Northwest Ethiopia namely Metema, Humera, Wolkait, Shiraro and Libo/Fogera are known as endemic foci for the disease (Deribe et al., 2012). Cholesterol plays an important role in the maintenance of membrane fluidity, formation of membrane rafts and promote phagocytosis essential for proper antigen presenting cell (APC) function, response and entry of *Leishmania* parasite (Bansal et al., 2005). The pathogen exploits and modulates the host membrane machinery (host lipidome) through different mechanisms. Such approaches include the use of water soluble carriers that efficiently remove cholesterol from membranes, cholesterol-binding compounds that sequester the cholesterol in the membrane, cholesterol-modifying enzymes and biosynthetic inhibitors of cholesterol (Pucadyil and Chattopadhyay, 2006). VL patients demonstrate reduced serum total cholesterol (Tc), high density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) as a function of splenic parasite load. This leads to dyslipidemic condition which is a burden to very high morbidity, mortality, and medical costs (Dean and Smith, 2007). The lipid alteration is a

cause for the subsequent development of other disease like dyslipidemia. Lipid abnormality is a prognostic indicator for increased morbidity and mortality connected with various pathological conditions (Muldoon et al., 2007). Therefore, assessment of lipid profile among VL patient to evaluate the lipid alteration related to the disease is crucial. This study aimed at assessing lipid profile among VL patients and healthy control group.

METHODS AND MATERIALS

Study population

Seventy patients who were diagnosed with VL at Metema and University of Gondar Hospitals from January to March 2015 were considered. The diagnosis of VL was established by the presence of high titers of antileishmania antibodies via indirect immunofluorescence assay and indirect haemagglutination antibodies, as well as demonstration of intracellular parasites in bone marrow aspiration in patients with compatible clinical and laboratory findings. None of the enrolled patients were receiving any hypolipidaemic agents or had any clinical or laboratory evidence of any disease known to affect lipid metabolism, such as neoplasia, renal or liver failure, and hypo- or hyperthyroidism. Seventy age- and sex-matched healthy volunteers (control population) were also included in the present study. All individuals signed an informed consent for the participation in the study. The study was approved by the Ethics Committee of the University of Gondar.

Data collection and laboratory methods

Socio-demographic characteristics data were collected using semi-structured questionnaire after pre-test in 5% of the participants. The height and weight of study participants were measured using the nearest meter (m) and Kilo gram (Kg) respectively. Body Mass Index (BMI) was calculated by dividing the subjects weight (Kg) by height square. It was done after filling the written and verbal consent form. Five milliliters of fasting venous blood was collected in sterile plain vacutainer tube and properly labeled with specific code of the patient. Then samples were allowed to clot for 30 minutes and then the clotted samples were centrifuged at 4000 rpm for 5 minutes to obtain the sera. The sera were separated into sterile tubes and were used for lipid profiles assay. The samples were processed in the clinical chemistry laboratory of University of Gondar Hospital by A25 Biostem, Spanchemistry analyzer using enzymatic calorimetric methods. Whereas Very Low Density Lipoprotein cholesterol (VLDL-c) was calculated by Friedewald calculation as of (Triacylglecerol (TAG)/5).

Data management and quality assurance

The questionnaire was prepared in English and translated to Amharic and the interview was carried out by well trained professionals. The quality control of the test was assessed using laboratory manuals and standard operating procedures of quality assurance of University of Gondar Hospital laboratory. Fasting blood sample for about 8 hrs was collected at the time of diagnosis before starting the treatment to have safe procedure and reliable specimen. Then, the sample was transported into clinical chemistry laboratory and processed and analyzed based on the manufacturer's manual. Quality control was also done daily in order to check the optimal reactivity of the reagent and the proper function of analyzer. Normal and pathological controls were performed to ensure the result was within the normal interval before actual sample was done. The result of parameters was properly cross checked with the questionnaire and interpreted accordingly.

Data analysis and interpretation

Data was checked, coded and entered to Epi-info version 3.5.1 (CDC, Atlanta-USA) and exported in to SPSS (IBM, USA) version 16 for analysis. Data was described by the use of means, standard deviation, and percentage. Independent t-test was used to see the mean difference among groups and linear regression analysis was employed to determine factors associated with outcomes of the study. P-value < 0.05 was considered as statistically significant.

Ethical consideration

Ethical approval was obtained from the Research and Ethical Committee of School of Biomedical and Laboratory Sciences in University of Gondar with ref no SBMLS/927/07. Permission approval was also obtained from each hospital. After getting permission and verbal consent from hospitals directors, individual written consent was obtained from each participant before administering the questionnaire and taking sample. We never disclosed any information by the name of participants to assure confidentiality.

RESULTS

Socio-demographic characteristics

The mean ($\pm$SD) age of the participants was 27.2 ($\pm$6.42) and 28.51 ($\pm$5.74) years for cases and control

respectively. Majority of the participants were single (64.3%) and (74.3 %) in both categories. Higher percentages of the participants were from rural background for both case and control (75.7% and 85.7%) respectively. As to occupation, 74.3% and 67.1% of the study participants were engaged in farming activities in both case and control group respectively. Coming to their educational level, most (44.3%) individuals were not educated in case group and elementary (61.4%) in the control group (Table 1).

Table 1. Socio-demographic characteristics of the study participants, North-west Ethiopia.

Variables	Cases		Controls	
	Frequency	Percentage	Frequency	Percentage
Age in year				
< 20	11	15.7	9	12.9
20-34	51	72.9	53	75.7
35-39	3	4.3	5	7.1
40-44	3	4.3	2	2.9
≥ 45	2	2.9	1	1.4
Marital status				
Single	45	64.3	52	74.3
Married	21	30	14	20
Divorced	3	4.3	2	2.9
Widowed	1	1.4	2	2.9
Residence				
Rural	53	75.7	60	85.7
Urban	17	24.3	10	14.3
Occupation				
Daily laborer	8	11.4	5	7.2
Civil servant	2	2.9	12	17.1
Merchant	8	11.4	6	8.6
Farmer	52	74.3	47	67.1
Education Level				
Not educated	31	44.3	10	14.3
Elementary	25	35.7	43	61.4
High school	12	17.1	13	18.6
College	2	2.9	4	5.7

Anthropometric measurements and lipid profile

There was a statistically significant mean reduction (P-value = 0.000) in both Waist Circumference (WC) and BMI in case group compared to control group. A statistically significant mean differences (P-value =0.000) in both serum Tc, HDL-c and LDL-c levels were observed in case group in comparison with the controls group. On the contrary, the finding revealed that there was a statistically significant elevation (P-value = 0.000) in serum TAG and VLDL-c in VL infected group compared to the control ones (Table 2).

Table 2. Mean and standard deviation of anthropometric and lipid profile measurement of study participants in North-west Ethiopia.

Variables	Cases (Mean±SD)	Controls (Mean±SD)	P-value
WC (cm)	75.5 (5.59)*	82.2 (9.94)	0.000
BMI (Kg/m^2)	16.8 (1.80)*	22.9 (3.17)	0.000
TC (mg/dl)	69.7 (22.83)*	179.2 (42.87)	0.000
HDL-c (mg/dl)	18.3 (7.79)*	88.0 (31.53)	0.000
LDL-c (mg/dl)	35.3 (15.19)*	64.6 (18.11)	0.000
TAG (mg/dl)	169.0 (67.43)*	116.3 (46.40)	0.000
VLDL-c (mg/dl)	33.8 (13.49)*	23.8 (10.80)	0.000

WC: Waist circumference, BMI: Body mass index, Tc: Total cholesterol, HDL-c: High density lipoprotein cholesterol, LDL-c: Low density lipoprotein, TAG: Triacylglycerol, VLDL-c: Very low density lipoprotein cholesterol, *: statistically significant at $P < 0.05$.

Factors associated with lipid profile

The presence of disease along with its parasitic load was significantly associated with all kinds of lipid panel. Both yielded a negative significant association to Tc, HDL-c and LDL-c and a positive significant association to TAG. Participants who were in case group had lower level of Tc, HDL-c and LDL-c reduced by 99.5, 56.56 and 29.5 units respectively compared to non-case (control) group. A unit increase in parasite load from one grade to the next one indicated a reduction of serum Tc, HDL-c and LDL-c by 5.16 and 1.54 and 2.76 units respectively and to elevation of TAG level by 2.01 units.

BMI also showed significant association to all serum lipid profile except for TAG. It was positively associated to Tc and LDL-c and negatively associated to HDL-c. An increase in BMI by 1 unit was associated with an increase in Tc and LDL-c by 15.27 and 5.91 units respectively and reduced serum HDL-c by 7.91 units.

In addition, WC showed a positive significant association to Tc. The results indicated that an increase by one additional unit to WC, elevate the Tc by 0.81 units. On the contrary, occupation and educational status were factors that showed a significant negative association to serum LDL-c. In the study, being a farmer was linked to reduction of serum LDL-c by 3.4 compared to non-farming occupation. The educational status (being educated) had also shown a significant inverse relation to the level of serum LDL-c for about 4.31 units compared to none educated study participants (Table 3).

Table 3. Linear regression analysis of factors associated with lipid level of study participants in North-west Ethiopia.

Variables	Tc		HDL-c		LDL-c		TAG	
	β (95% CI)	PV	β (95% CI)	PV	β (95% CI)	PV	β (95% CI)	PV
Status(case)	-99.35(-119.82 - -78.88)	.000*	-56.56 (-70.826 - -42.287)	.000*	-29.5 (-39.047 - -19.944)	.000*	61.0 (24.535 - 97.466)	.001*
Age (per year)	-.795 (-1.81 - 0.22)	.124	0.26 (-1.064 - .351)	.321	-.28 (-.756 - .191)	.240	-.32 (-2.128 - 1.487)	.726
MS (Married)	-11.05 (-21.94 - 0.16)	.052	-1.12 (-8.715 - 6.474)	.771	-6.98 (-12.072 - 1.906)	1.59	0.871 (-17.817 - 20.997)	.871
Residence (Urban)	13.18 (-3.13 - 29.49)	.112	-.214 (-11.585 - 11.157)	.970	5.19 (-2.418 - 12.804)	.179	-18.73 (-47.793 - 10.32)	.204
Occupation (Farmer)	.009 (-0.63 – 7.64)	.848	0.915 (-4.597 - 5.120)	.915	-3.418 (-6.670 - -0.166)*	.040*	0.360 (-6.645 - 18.185)	.360
Ed. Level (Educated)	-5.16 (-12.29 – 1.98)	.155	1.85 (-3.128 - 6.825)	.464	-4.29 (-7.626 - -.964)*	.012*	1.44 (-11.277 - 14.156)	.823
Income	-.454 (-7.32 – 6.41)	.896	-.134 (-4.917 - 4.649)	.956	1.39 (-1.812 - 4.591)	.392	3.05 (-9.170 - 15.276)	.622
Family size	-.919 (-2.74 – 0.91)	.321	-1.56 (2.830 -.1287)	.087	-.61 (-0.240 - 1.462)	.158	-0.172 (-3.422 - 3.078)	.917
BMI	15.27 (3.23 - 27.31)*	.013*	-7.91 (-34.82 - -16.309)*	.044	5.91 (0.295 - 11.534)*	.039*	0.417 (-21.039 - 21.872)	.969
WC	0.81 (0.57 – 1.56)*	.035*	0.18 (-3.45 - 0.700)	.503	0.178 (-.172 - 0 .527)	.317	0.878 (-.457 - 2.213)	.196
Parasite load	-5.16 (-8.87 - -1.44)*	.007*	-1.54 (-2.728 - -.349)*	.012*	-2.76 (-5.269 - -.263)*	.031*	2.01 (0.755 - 13.772)*	.034*

β = Un Standardized coefficient, * = statistically significant at P<0.05, MS = Marital Status, BMI = Body mass index, WC = waist circumference, Tc = Total cholesterol, HDL-c = High density lipoprotein cholesterol, LDL-c = Low density lipoprotein cholesterol, TAG = Triacylglycerol, PV = P-value, CI = Confidence interval.

DISCUSSION

The present study found that the levels of serum Tc, HDL and LDL` were significantly decreased among VL infected patients (P = 0.0001) compared to the controls group. On the contrary, VL patients had significant high level of circulating TAG and VLDL (P= 0.0001) when it was compared to the control group. These results are in agreement with the findings of (Liberopoulos et al., 2002; Bekaert et al., 2009; and Soares et al., 2010) who reported hypocholesterolemia, low level of HDL-c and LDL-c and hypertriglyceridemia in a patient with VL.

The decrease in Tc levels in VL infections may be related with certain cytokines and acute-phase protein levels such as IL-1b, IL-6 and TNF (Khovidhunkit et al., 2006). The autoimmune phenomena occur in patient during immunological mechanism also influence cholesterol metabolism in various ways: by forming immune complex, accelerate degradation and impairing responsible enzyme (Malmendier et al., 2011). The host membrane cholesterol are required for binding and internalization of Leishmnaiasis using complentary approaches (Yao and Wilson, 2016)

The impressive decrease in HDL-c levels at the time of VL diagnosis may be implicated due to cytokines that stimulate the displacement of apoA-I by serum amyloid resulting in modification of HDL particles (Khovidhunkit et al., 2006) and decreased hepatic synthesis and secretion of apolipoproteins (Gordon et al., 2011).

The sequestration and/or degradation of lipoproteins in the enlarged spleen and liver are another possible mechanism that reduced level of circulating HDL-c in the tissues where the parasites accumulate (Malmendier et al., 2011). The inhibitory effect of cytokines on reduction of lecithin cholesterol acyltransferase (LCAT) synthesis and activity also markedly affect the HDL-c concentration (Auerbach and Parks, 2009).

The other finding observed in the current study in patients with VL was a marked low level LDL-c concentration. This decreased level could be associated with elevated concentrations of IL-6, TNF and cytokines provoked by parasitic infection. The effect of IL-6 to stimulates the expression LDL receptor in hepatic cells (Gierens et al., 2012), accelerated by the effect TNF to increases the activity LDL receptor leads to the increased uptake of LDL particles and decreased LDL-C levels in the serum (Khovidhunkit et al., 2006). Moreover, the cytokines suppress the production of apo (B-100) and the synthesis of respective lipoproteins (Ettinger et al., 2005).

The observed hypertriglyceridemia could be related to decrease lipoprotein and hepatic lipase activities. TNF and excess level of Apo E synthesis by the disease-induced activated macrophages are responsible for impairment of lipase activity (Dijk et al., 2009). This is continued by stimulating hepatic fatty acid synthesis resulting in elevated VLDL production and retardation of VLDL clearance (Rouzer and Cerami, 2007; Vasilis et al, 2018).

BMI yielded significant positive association with Tc and LDL-c, and negative correlation with HDL-c. The direct and inverse association between BMI and (Tc, LDL-c) and HDL-c respectively is supported by various studies (Lior et al., 2011; Zamani et al., 2012; Carmem et al., 2014 and Mohammed et al., 2017) which revealed a significant association between BMI and lipid profile. The association might be related to adiponectin secreted from adipocyte, which is a potent modulator of glucose and lipid metabolism and an indicator of metabolic disorders. The increase in BMI decreases the concentration of adiponectin that has metabolic effect on serum lipid profile (Martin et al., 2005).

WC was significant predictors for change in Tc, HDL-c and LDL-c. This result is supported by the findings of (Cugentto, 2008; Luiz et al., 2013) who reported a significant association between WC and lipid parameters. As WC is an indicator of visceral fat mass, an increase in visceral fat releases excess free fatty acids into the portal vein. This continuous exposure to liver leads to peripheral and hepatic dysfunction causing atherogenic dyslipidemia (Bjorntorp, 2010).

CONCLUSION

Visceral Lieshmaniasis is associated with marked reductions in Tc, HDL-c and LDL-c levels and an increase in TG and VLDL concentration when compared to healthy control group. Additionally, BMI was a significant predictor for the alteration of all serum lipid level. WC was another variable which significantly correlated to Tc, HDL-c and LDL-c. The marked change in serum lipid concentration seems to be an additional feature of VL associated disorders of lipid metabolism. This problem needs to be monitored along with the treatment of the disease before it develops to subsequent diseases. The clinical relevance of these findings in terms of subsequent diseases progression remains unknown. Large observational studies are required to establish a possible role of VL in lipid alteration and development of subsequent disease.

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DECLARATIONS

Competing interests

The authors declare that they have no competing interests.

Author contributions

MY conceived and designed the study, performed analysis, interpreted data, and drafted the manuscript. BB, AA and MA assisted with the design, performed analysis and interpretation of data, and MC and AK perform the lab works. All the authors critically reviewed, read and approved the final version of the manuscript.

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