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HTLV1 infection and long term association with liver function and lipid indices; 10 years' follow-up

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Abstract

Background Human T-cell leukemia virus type 1 (HTLV-1) is a well-known retrovirus, particularly prevalent in northeastern Iran, where it is associated with a range of disorders, including liver dysfunction. Previous studies have demonstrated that HTLV-1 infection can alter lipid profiles, yet no research has examined lipid indices and liver function tests in these patients in the long term.

Methods This data is part of the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study. A total of 1116 participants were randomly selected, including 837 healthy individuals and 279 HTLV-1-infected patients. Following a 10-year follow-up period, Serum levels of liver enzymes were measured. Lipid indices such as the Atherogenic Index of Plasma (AIP), Body Adiposity Index (BAC), Castelli risk index (CRI-I, CRI-II), Lipid Accumulation Product (LAP), Visceral Adiposity Index (VAI), Triglyceride-glucose index (TyG), and Triglyceride and HDL-C Ratio (THR) were calculated.

Results Multivariable-adjusted regression analysis demonstrated a significant coefficient for the Visceral Adiposity Index (VAI) in HTLV-infected patients compared to healthy controls (B: -0.014, 95% CI: -0.02, 0.00, $p=0.046$). However, no significant differences were observed in other lipid indices between HTLV-infected patients and healthy individuals. Regarding liver enzymes, significant variations were noted in HTLV-infected patients compared to healthy controls: Aspartate Aminotransferase (AST) (B: 2.978, 95% CI: 1.34, 4.61, $p<0.001$), Alanine Aminotransferase (ALT) (B: 3.687, 95% CI: 1.59, 5.78, $p=0.001$), Alkaline Phosphatase (ALP) (B: 18.232, 95% CI: 6.81, 29.65, $p=0.002$), and Gamma-Glutamyl Transferase (GGT) (B: 3.714, 95% CI: 0.18, 7.24, $p=0.039$).

Conclusion Individuals with HTLV-1 infection exhibit reduced VAI but elevated levels of liver enzymes such as AST, ALT, ALP, and GGT, indicating liver damage. These findings emphasize the virus's involvement in liver pathology. Also, HTLV-I is associated with reduced visceral fat tissue.

Keywords HTLV-I, MASHAD study, Liver, Lipid profile

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Introduction

It has been 40 years since the human T-cell leukaemia virus (HTLV)-1 was discovered by the Gallo group at the National Cancer Institute/National Institutes of Health (NCI/NIH) as the first human retrovirus [1]. Among the four types of HTLV, HTLV-I is the most pathogenic for humans [2]. Mashhad, a south province in Iran, is an endemic region for HTLV-I (2.12%) [3, 4] a as well as other endemic regions of the world such as Suriname (1.2% in 1995) [5], Guinea-Bissau 5% (in 2011) [6], and Brazil (0.07–15.9%) [7]. HTLV-1 manifests many diseases, including ATL, HTLV-1– associated myelopathy/tropical spastic Para-paresis (HAM/TSP), inflammatory disorders, especially uveitis, arthritis, and dermatitis, and an immune-deficient state, resulting in bronchiectasis [8]. Evidence has shown that HTLV infection can increase the risk of contracting diabetes [9–11], Kidney disease [12, 13], CVD [11] and other chronic diseases [14]. In some studies, it has been seen that in patients with HTLV-I, the lipid profile and the level of liver enzymes can be affected.

In HTLV-1-positive people, following the reduction of the immunity level, the possibility of getting secondary infections increases [15]. Some secondary infections, including hepatitis B and C, can cause liver damage, such as liver fibrosis and hepatic osteosis, and increase the likelihood of liver cancer [16]. Also, HTLV-1 infection alone can cause liver disorders [10, 11] or liver cancer [17–19]. Therefore, due to liver damage, liver factors such as ALT, AST, ALP, CPK and SAMA ST can be affected [20]. Also immune disorders can arise from liver damage [21] And it is possible HTLV-1 positive people become more vulnerable to viral infections.

Lipid profile is one of the factors influencing the development progress of chronic diseases like liver disease [22–24]. Evidence suggests that chronic viral infections have a negative correlation with lipid profile components, including cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) [25, 26]. On the other hand, an elevated lipid profile may be implicated in susceptibility to HTLV-1 infection and HTLV-1-associated myelopathy, HAM/TSP [27].

Therefore, due to the lack of similar studies, the aim of this study is to investigate the lipid indices and liver enzymes in HTLV-I patients and healthy controls.

Methods

Study population

The study used serum samples from 1,116 participants in the "Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD)" study [28]. Among them, 279 were HTLV-1 positive, and 837 were HTLV-1 negative [28, 29]. Because the number of people with HTLV-1 was small compared to the total population and creating SPARS data, we randomly selected 837 people (three times the number of patients) from those who did not have HTLV-1. Participants were excluded if the liver and lipid factors deviated by more than three standard deviations from the available data. Additionally, thorough screenings for viral hepatitis were conducted, and affected individuals were excluded.

All participants were fully informed and provided written consent. The Ethics Committee of Mashhad University of Medical Sciences (MUMS) and the Institutional Review Board of Mashhad University Medical Center approved the study protocol. This project is financially supported by Mashhad University of Medical Sciences (Funding number: 4021736).

HTLV-1 infection assessment

The serum samples of all participants of the MASHAD study were screened for HTLV-1-specific antibodies by ELISA at baseline (Dia. Pro Diagnostic, Italy). Positive cases were assessed for the HTLV-1 genome using PCR for TAX- and LTR-specific primers to confirm the infection. If either of the genes were present, patients were confirmed to be infected by HTLV-1. A total of 279 HTLV-1-infected patients who were enrolled in the current study were identified.

Measurement of lipid indices

After a 10-year follow-up, all participants were invited, and blood samples were collected after a 14-hour overnight fast. Blood glucose, serum Triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) were estimated using enzymatic methods on an automated analyzer. A non-stretched tape measure to the nearest 0.1 cm was used. Waist circumference (WC) was obtained at the minimum circumference between the iliac crest and the last rib. Also, Hip circumference (HC) was measured from the widest part of the hips. Then we calculated Atherogenic Index of Plasma (AIP) [30], Atherogenic Coefficient (AC), Castelli risk index (CRI-I, CRI-II) [31], Lipid Accumulation Product (LAP) [32], Visceral Adiposity Index (VAI) [33], Triglyceride-glucose index (TyG) [34], Triglyceride and HDL-C Ratio (THR) [35].

$$\mathrm{AIP} = \log\left(\frac{TG(\frac{mg}{dl})}{HDL-C(\frac{mg}{dl})}\right)$$

$$\mathrm{AC} = \mathrm{TC} - \frac{HDL-C(\frac{mg}{dl})}{LDL-C(\frac{mg}{dl})}$$

$$\mathrm{CRI\text{-}I} = \frac{TC(\frac{mg}{dl})}{HDL-C(\frac{mg}{dl})}$$

$$\text{CRI - II} = \frac{LDC - C(\frac{mg}{dl})}{HDL - C(\frac{mg}{dl})}$$

$$\text{LAP} = \text{WC(cm)} - (58 \times \text{TG}(\frac{mmol}{L}))$$

VAI:

$$\text{Male: } \frac{WC(cm)}{39.68 + (1.88 \times BMI)} \times \frac{TG(\frac{mg}{dl})}{1.03} \times \frac{1.31}{HDL - C(\frac{mg}{dl})}$$

$$\text{Female: } \frac{WC(cm)}{39.68 + (1.89 \times BMI)} \times \frac{TG(\frac{mg}{dl})}{0.81} \times \frac{1.52}{HDL - C(\frac{mg}{dl})}$$

$$\text{TyG} = \log(\frac{\text{TG}(\frac{mg}{dl}) \times fasting\,Glucose(\frac{mg}{dl})}{2})$$

$$\text{THR} = \frac{TG(\frac{mg}{dl})}{HDL - C(\frac{mg}{dl})}$$

Table 1 Lipid indices and liver function test in HTLV-1 positive patients and healthy control individuals

	HTLV-I negative (N = 837)	HTLV-I positive (N = 279)	P value
Age (y)	47.17 ± 7.78	50.14 ± 8.01	< 0.001
Sex (male)	346 (72.4%)	92 (49.1%)	0.002
Weight, Kg	72.34 ± 12.96	69.11 ± 12.73	0.001
BMI (kg/m^2)	27.91 ± 4.86	27.63 ± 4.66	0.41
SBP (mmHg)	134.93 ± 20.43	134.58 ± 20.41	0.82
DBP (mmHg)	81.81 ± 13.41	79.69 ± 12.48	0.011
Cholesterol (mg/dl)	204.75 ± 45.47	208.85 ± 44.07	0.220
Triglyceride (mg/dl)	142.67 ± 72.30	146.11 ± 84.52	0.560
HDL (mg/dl)	48.48 ± 11.12	49.87 ± 10.92	0.090
LDL (mg/dl)	115.59 ± 34.57	115.75 ± 31.70	0.950
AIP (mg/dl)	0.43 ± 0.24	0.42 ± 0.25	0.800
AC	3.56 ± 1.12	3.65 ± 1.20	0.270
CRI_I	4.56 ± 1.12	4.65 ± 1.20	0.280
CRI_II	2.46 ± 0.79	2.41 ± 0.78	0.350
LDL_HDL	2.77 ± 0.90	2.83 ± 0.93	0.370
LAP	55.97 ± 49.73	56.69 ± 44.17	0.840
TyG	8.53 ± 0.64	8.58 ± 0.62	0.250
THR	3.55 ± 3.15	3.73 ± 3.30	0.430
VAI	1.47 ± 0.33	1.40 ± 0.31	0.004
LAP	52.17 ± 32.88	52.09 ± 36.95	0.960
LDL: HDL ratio	2.46 ± 0.79	2.41 ± 0.78	0.350
LDL: TG ratio	0.96 ± 0.44	0.94 ± 0.42	0.690
AST (mg/dl)	21.93 ± 8.22	24.16 ± 14.52	0.003
ALT (mg/dl)	18.79 ± 12.27	20.81 ± 19.22	0.049
ALP (mg/dl)	222.38 ± 71.15	239.35 ± 84.52	0.002
GGT (mg/dl)	24.90 ± 25.66	26.29 ± 30.50	0.490
CPK (mg/dl)	123.40 ± 77.69	121.96 ± 71.92	0.810
Bilirubin Direct (mg/dl)	0.25 ± 0.10	0.24 ± 0.08	0.050
Bilirubin total (mg/dl)	0.84 ± 0.33	0.82 ± 0.30	0.440

Data presented as mean ± standard division and mean (percent); sample t-tests or Mann-Whitney U tests has been done

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TG: serum Triglyceride, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, TC: total cholesterol, AIP: Atherogenic Index of Plasma, AC: Atherogenic Coefficient, CRI-I: Castelli risk index I, CRI-II: Castelli risk index II, LAP: Lipid Accumulation Product, VAI: Visceral Adiposity Index, TyG: Triglyceride-glucose index, THR: Triglyceride and HDL-C Ratio, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, GGT: Gamma-Glutamyl Transferase, CPK: Creatine Phosphokinase

Evaluation of liver function

we assessed various liver function tests such as Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), Creatine Phosphokinase (CPK), Bilirubin Direct, and Bilirubin Total using commercial kits (Pars Azmun, Karaj, Iran) and the BT-3000 auto-analyzer machine (Biotechnica, Rome, Italy).

Statistical analysis

All statistical analyses were performed using the SPSS version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The significance level was set at $p < 0.05$.

To compare the lipid profile parameters and liver factors between the HTLV-1 positive group and the control group, independent sample t-tests or Mann-Whitney U tests were utilized depending on the normality of the data distribution. Normality of continuous variables was assessed using the Kolmogorov Simonov test. Furthermore, to evaluate the relationship between HTLV-I infected status with lipid indices and liver enzymes, β-coefficients were computed via univariate and multivariate linear regression models, with adjustments made for potential confounding factors including age, sex and BMI.

Results

The analysis of demographic characteristics (see Table 1) revealed that the HTLV-1 positive group had a significantly higher average age and lower diastolic pressure. Additionally, the majority of the HTLV-1 negative group consisted of men (72.4%), while HTLV-1 positive subjects were almost evenly distributed between men and women (49.1% men). Table 1 Also displays the mean (±SD) values of lipid indices and liver function tests in HTLV-1-positive patients and healthy control individuals. The most significant finding was the difference in the VAI index, which was lower in the HTLV-1 positive group than in the control group ($P < 0.05$). Additionally, AST, ALT, and ALP levels were higher in HTLV-I patients than in the control group ($P < 0.05$), while bilirubin direct levels were significantly lower in patients compared to the control group, with a p-value of 0.05. However, this p-value, while meeting the conventional threshold for statistical significance, should be interpreted with caution due to its borderline nature.

The multivariable-adjusted coefficients and 95% CIs for the lipid indices and liver function test are presented in Table 2. It presents the significant coefficients and corresponding p-values for VAI (B: -0.014, 95% CI: -0.02, 0.00, $p=0.046$), AST (B: 2.978, 95% CI: 1.34, 4.61, $p<0.001$), ALT (B: 3.687, 95% CI: 1.59, 5.78, $p=0.001$), ALP (B: 18.232, 95% CI: 6.81, 29.65, $p=0.002$) and finally GGT (B: 3.714, 95% CI: 0.18, 7.24, $p=0.039$).

Discussion

In this study, we aimed to investigate the lipid indices and liver enzymes in two groups of HTLV-1-positive patients and a control group due to the lack of similar studies. Our findings showed that the lipid profile did not differ significantly between HTLV-1 patients and healthy controls. This result is consistent with Derakhshan et al.'s study, which reported no significant difference in cholesterol, TG, and LDL between asymptomatic carriers and healthy controls. However, HDL levels were lower in asymptomatic carriers compared to healthy controls [27]. Carvalho et al. found no difference in TG and VLDL levels between infected or uninfected men. However, they observed that these levels were higher in HTLV-1-infected women compared to healthy individuals ($p=0.02$) [36]. Notably, both of these studies had a smaller sample size compared to our study.

In our investigation of lipid indices, we observed that HTLV-1-infected individuals exhibited a lower VAI compared to healthy controls. This study represents a pioneering exploration of VAI in HTLV-I-infected patients.

Table 2 Multivariable-adjusted coefficients and 95% CIs for lipid indices and liver function test in HTLV-1 positive patients and healthy control individuals

Variables	HTLV-I positive	
	Coef (95% CI)	*P*-value
Cholesterol	4.094 (-2.50, 10.69)	0.224
Triglyceride	5.293 (-6.05, 16.64)	0.360
HDL	0.748 (-0.86, 2.36)	0.363
LDL	1.087 (-3.96, 6.13)	0.673
TyG	0.028 (-0.06, 0.11)	0.538
THR	0.119 (-0.22, 0.46)	0.498
LDL: HDL ratio	0.001 (-0.11, 0.11)	0.988
LDL: TG ratio	-0.003 (-0.06, 0.06)	0.930
VAI	-0.014 (-0.02, 0.00)	0.046
LAP	-0.560 (-5.62, 4.50)	0.828
AST	2.978 (1.34, 4.61)	< 0.001
ALT	3.687 (1.59, 5.78)	0.001
ALP	18.232 (6.81, 29.65)	0.002
GGT	3.714 (0.18, 7.24)	0.039
CPK	0.799 (-11.15, 12.75)	0.896
Bilirubin direct	-0.013 (-0.02, 0.00)	0.076
Bilirubin total	-0.006 (-0.05, 0.04)	0.835

Data adjusted by age, sex and BMI

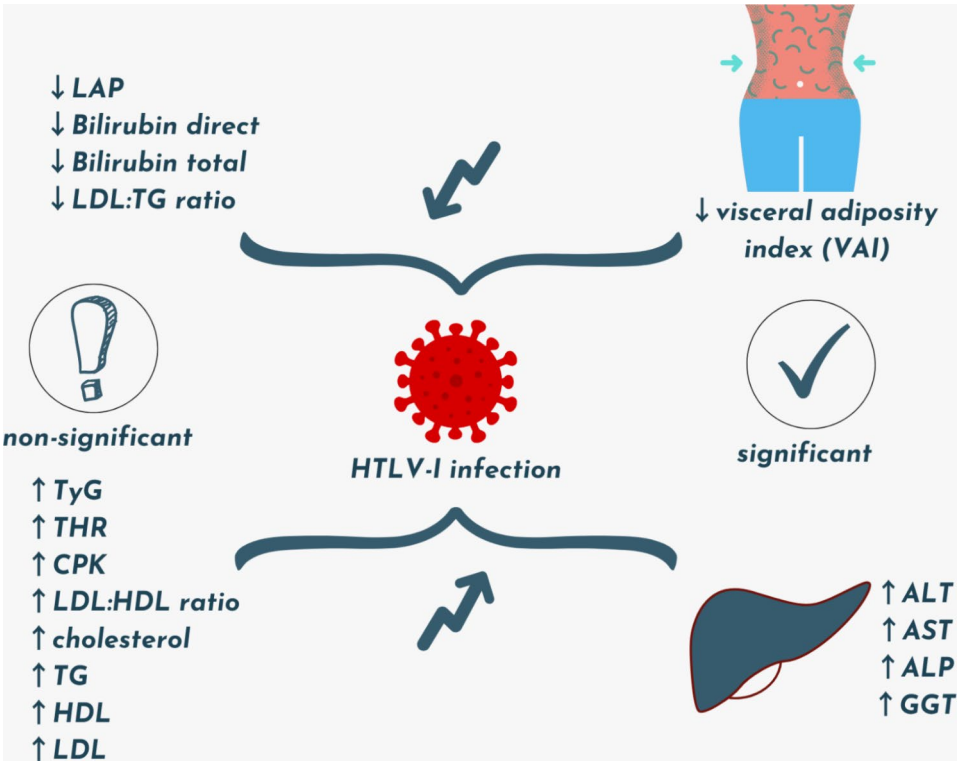
Furthermore, in alignment with related research, the Bacelo et al.'s study, Symptomatic participants compared to asymptomatic, had a lower body mass index (BMI) (25.47±5.06 kg/m2 vs. 30.08±5.61 kg/m2; $p<0.001$), Mid-Upper Arm Circumference (MUAC) (29.56±5.13 cm vs. 33.22±4.21 cm; $p=0.0011$), and fat mass per cent (%FM) (30.75%vs 36.60%; $p=0.0064$), however, had a higher lean mass per cent (%LM) (68.95% vs. 63.40%; $p=0.0299$) [37]. However, Controversy, Saghi et al. observed that the mean WC in the carrier (Asymptomatic) group was significantly higher than the healthy control group ($p=0.008$) [38]. Chronic HTLV infection may lead to a progressive and constant inflammatory response [39]. Inflammation can influence the VAI through its effects on adipose tissue and metabolic health. Research shows systemic inflammation is associated with altered chromatin accessibility in preadipocytes, which may contribute to changes in adipose tissue distribution and function [40]. Inflammation can also increase the energetic protein catabolism [41].

Regarding liver enzymes, we found that HTLV-1 infection is associated with elevated ALT, AST, ALP, and GGP levels. To our knowledge, no study has investigated the level of these enzymes in people infected with HTLV-1 virus. However, studies have been done on other similar viruses. Hsu et al. showed that patients had higher ALT levels ($p<0.01$) in HCV patients compared to controls [26]. A recent case-report study demonstrated that HTLV-1 infection could cause liver damage through the development of adult T-cell lymphoma/leukaemia (ATLL), which can lead to acute liver failure. ATLL, arising from HTLV-1 infection, can infiltrate the liver, resulting in massive hepatic ischemia and widespread necrosis of the hepatocytes, leading to acute hepatitis and liver injury [42].

One of the strengths of our study is the large sample size, especially in an area where HTLV-1 is considered endemic. Additionally, the status of HTLV-1 infection was accurately confirmed by relevant tests, and the control group was matched with the patient group regarding age and sex. Finally, we measured these patients' lipid profiles, lipid indices, and liver function tests for the first time. It is important to note that our study had limitations, such as the absence of differentiation between asymptomatic HTLV-1 carriers and those experiencing symptoms. This differentiation is crucial as individuals with symptoms typically exhibit higher viral loads. It is necessary to make this distinction when examining the virus's impact on different serum levels. Additionally, we lacked data on alcohol consumption due to ethnic considerations and did not gather information on the drug history of the individuals, which could have affected the results. Furthermore, we did not assess viral loads and

clinical symptoms in patients with HTLV-I, which was a limitation of our study.

Our findings open up exciting avenues for future research. We recommend further studies to examine the anthropometric indices of patients with HTLV-1, as this could provide a deeper understanding of the impact of this viral disease on the distribution of fat and muscle in different parts of the body. Additionally, our findings suggest a potential link between HTLV-1 infection and various types of liver diseases. We encourage researchers to explore the prevalence of these diseases in individuals with HTLV-1, as this could significantly advance our understanding of the disease.



Conclusion

This study's results show that HTLV-infected patients had lower VAI and also experienced increased amounts of liver enzymes ALT, AST, GGP and ALP. The findings suggest that individuals with HTLV-1 infection may experience liver damage prior to the development of long-term complications such as HAM/TSP or ATLL. Further studies are required to investigate the association of HTLV-I infection with the occurrence of chronic liver diseases and diseases related to lipid profiles.

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Author contributions
Susan Darroudi (corresponding author, designed the study)Farzam Kamrani, Amirhossein Esfandiari, Hojat Ghahvechi (Wrote manuscript, data analysis) Samaneh Abolbashari (data gathering) Habibollah Esmaily, Majid Ghayour-Mobarhan (study design, scientific consultant)Zahra Meshkat (virology scientific consultant).

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Data availability
This study was conducted on the basis of MASHAD study cohort data. Data is available upon request.

Declarations

Ethical approval and consent to participate
Ethical Approval and Consent to participate -All individuals were well informed and their written consent was drawn. Accordingly, the study protocol was validated by the Ethics Committee of the Mashhad University of Medical Sciences (MUMS) and the Institutional Review Board of Mashhad University Medical Center. This project is supported by Mashhad University of Medical Sciences. Funding number: 4021736.

Consent for publication
This section as not applicable. It is not applicable to the Consent of Image Publication for this manuscript. The figures were designed only in this manuscript to present the results of the current paper.

Competing interests
The authors declare no competing interests.

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