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Short Communication

Are lipid disorders involved in the predominance of human T-lymphotropic virus-1 infections in women?

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ABSTRACT

Introduction: The human T-lymphotropic virus-1 (HTLV-1) is associated with chronic inflammatory diseases such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a chronic inflammatory disease. Disturbances in lipid metabolism are involved in inflammatory and demyelinating diseases. **Methods**: Plasma levels of triglycerides, total cholesterol, and fractions of HTLV-1–infected individuals of both sexes with different clinical progressions were determined. **Results**: Elevated levels of triglyceride and very low-density lipoproteins (VLDL) were exclusively detected in HTLV-1–infected women from asymptomatic and HAM/TSP groups compared with uninfected individuals ($p = 0.02$). **Conclusions**: Elevated triglyceride and VLDL levels in HTLV-1–infected women may be related to the predominance of HAM/TSP in women.

Keywords: HTLV-1. Lipid disorders and sex differences.

The human T-lymphotropic virus 1 (HTLV-1) is associated with neoplastic disorders as well as degenerative inflammatory diseases, including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), which is observed in approximately 3-5% of HTLV-1–infected individuals[1]. Currently, 5-10 million people are infected with HTLV-1 worldwide[2], and Brazil has the largest absolute number of individuals infected with HTLV-1/2. The transmission of HTLV-1 may occur by transfusion of contaminated blood products, needle sharing, breastfeeding, or unprotected sex[2][3]. Furthermore, transmission rates and neurological effects of the disease are high in women: HAM/TSP affects 2-3 times more women than men. Sexual transmission from men to women is common, and mother-to-child transmission seems to be more frequent in female infants than in male infants[4].

The HTLV Interdisciplinary Research Group (GIPH) conducted a cross-sectional study to investigate the high incidence of dermatological findings in 30 subjects from 3 generations of a family residing in the southeast region of Brazil. The index patient was a man with HAM/TSP. All 30 patients underwent serological tests for HTLV, using enzyme-linked immunosorbent assay (ELISA; OrthoClinical Diagnostics, USA) and western blot (Genelabs Diagnostics, USA), and 15 (50%) patients were found to be seropositive. The results showed that the HTLV-1 infection was predominance in the women of this family, wherein in generation II, HTLV-1 infection occurred in 52,9% of girls and 47.5% of boys (17 babies: 9 girls, 8 boys). Surprisingly, all infected children in generation III were girls (14 babies: 7 girls, 7 boys)[5]. Although the basis for this sex difference is poorly understood, Lima et al.[6] evaluated 88 HAM/TSP patients and showed that this disease had a faster progression in women if the disease started before menopause, suggesting that sex hormones could be implicated in the sex differences of infection[6].

Lipoproteins that carry triglycerides and cholesterol in the blood are divided into 5 categories: chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The chemical composition of lipoproteins is influenced by the action of enzymes that participate in complex and dynamic biochemical pathways involving cholesterol and triglycerides, which overlap and interact with each other[7][8][9].

Considering the relevance of biochemical events occurring during HTLV-1 infection, in the present study, we aimed to determine the differences in the pathogenesis of HTLV-1 between sexes. To achieve this, we compared the lipid profiles of infected individuals of both sexes, presenting different clinical progression, from asymptomatic (AS) and HAM/TSP (HT) to uninfected (NI) individuals.

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The study population comprised 54 HTLV-1-infected individuals, classified as AS (16 men and 19 women; median age: 43.6 years) and HT (10 men and 9 women; median age: 57 years). The NI group comprised 18 individuals: 8 men and 10 women, and the median age was 33 years. Upon confirmatory diagnosis of HTLV-1 infection (positive serology on ELISA and western blot), a patient's clinical status was determined by two specialist physicians, according to the established clinical score and impairment scale recommended by the American Spinal Injury Association (ASIA)[4].

Individuals infected with HTLV-1 were categorized into the AS group and contacted by the *Fundação HEMOMINAS* in Belo Horizonte, State of Minas Gerais, Brazil. Patients from the AS group had no clinical complaints and presented with normal motor and sensory functions. Patients from the HT group received medical assistance at the Sarah Kubitschek Hospital in Belo Horizonte, Minas Gerais, Brazil. These individuals presented with the classic symptoms of HAM/TSP, according to the standard neurological ASIA impairment scale classification. The NI individuals included in this study presented with negative serology for other relevant blood-borne pathogens, including human immunodeficiency virus, hepatitis C virus, hepatitis B virus, syphilis, and Chagas disease. The use of corticosteroids or other immunosuppressive chemotherapy was considered an exclusion criterion prior to the blood collection procedure.

Informed written consent was obtained from all participants. This work was approved by the Ethical Committee at the *Fundação HEMOMINAS*, Belo Horizonte, Minas Gerais, Brazil.

Sample collection and analysis were conducted in July 2005. The enzymatic colorimetric methods developed by Labtest were used to determined levels of triglycerides, total cholesterol, and HDL in serum or plasma were determined as given below.

The triglyceride levels were measured by determining the levels of quinone imines formed by reacting them with lipoprotein lipase and then with enzymes to ultimately produce quinone imine dye. The level of cholesterol was determined by measuring the amount of quinidine formed by cholesterol esters, according to manufacturer's guidelines. The levels of VLDL and LDL cholesterol were estimated by using the Friedewald formula if the triglyceride levels were <400mg/dl[12].

Statistical analysis was performed using non-parametric methods, analysis of variance (ANOVA), and the Kruskal-Wallis test, followed by the Dunn multiple comparison test. Statistical tests were performed using GraphPad Prism 3.0.3 software (San Diego, CA, USA). Values of $p < 0.05$ were considered statistically significant.

Analysis of the lipid profiles showed that infected women presented with significantly higher levels of triglycerides and VLDL ($p = 0.02$) compared to uninfected women. No difference in lipid levels was observed between infected or uninfected men **(Figure 1)**. Significant differences in the lipid levels with regard to the different clinical outcomes were only detected in female patients. In addition, the lipid content among women was generally higher in the HT and AS groups **(Figure 2)**. Individuals from both infected groups showed higher levels of triglycerides and VLDL than the NI group. No differences in the levels of total cholesterol, HDL, or LDL were detected among the infected or NI groups, men or women, and among the different clinical statuses (data not shown).

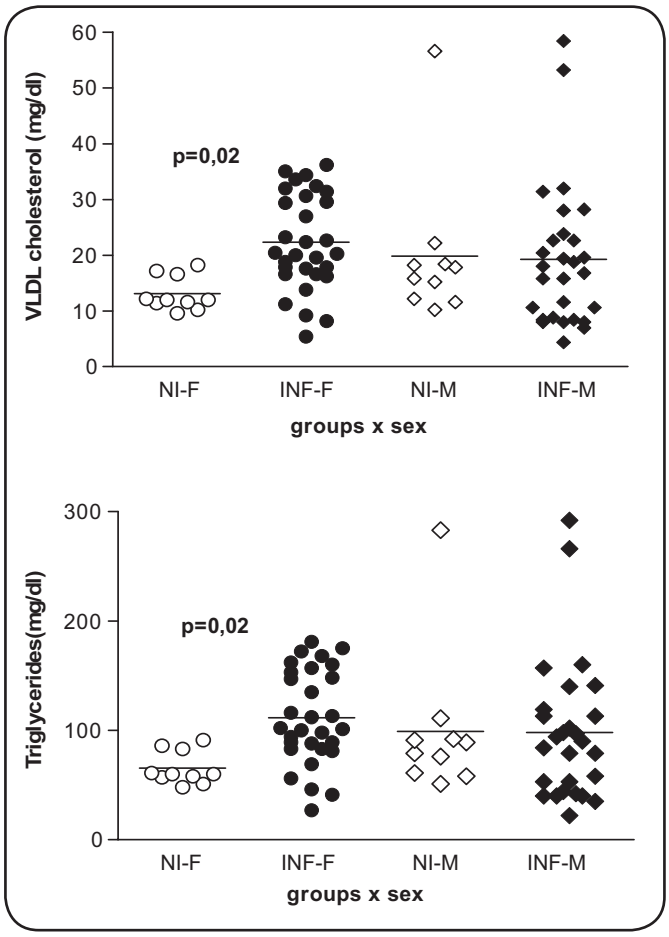

FIGURE 1 - Levels of triglycerides and VLDL fractions of 72 individuals according to sex. The uninfected group consisted of 18 individuals (10 women, 8 men) and the infected group consisted of 54 individuals (28 women, 26 men). VLDL: very low density lipoprotein; **HTLV-1:** human T lymphotropic virus type 1; **NI-F:** uninfected women; **INF-F:** HTLV-1 infected women; **NI-M:** uninfected men; INF-M: HTLV-1 infected men.

The results of the present study indicate that triglyceride and VLDL levels were higher in HTLV-1-infected women than in NI women, suggesting that these differences may be related to the pathogenesis of HTLV infection in women. Women with HAM/TSP show faster progression of the disease when the disease starts before menopause, suggesting that sex hormones could be implicated in sex-specific infection by HTLV-1[6].

Viral infection triggers the production of interferons, which in turn prompts the cells to combat infection. One of the proteins involved in those mechanisms is the soluble LDL molecule, which regulates anti-viral activity by interfering with virus assembly or release from cells[13]. Furthermore, virus-infected cells release a VLDL receptor fragment, which attaches to the virus and inhibits the viral infection. The increase in the levels of triglycerides and VLDL could represent a mechanism employed by the infected cell that could block the binding site for the virus on its cellular receptor and consequently curb the

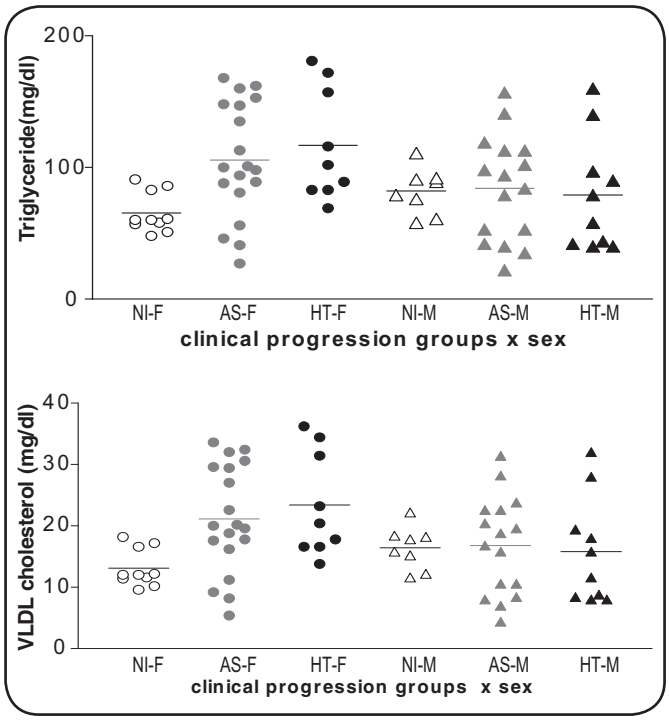

FIGURE 2 - Levels of triglycerides and VLDL fractions of 72 individuals (all participants of the GIPH cohort): asymptomatic (AS) patients (19 women, 16 men); HAM/TSP (HT) patients (9 women, 10 men); and uninfected (NI) volunteers with negative serology for HTLV-1 (10 women, 8 men). VLDL: very low density lipoprotein; **GIPH:** Interdisciplinary HTLV-I/II Research Group; **HAM/TSP:** HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis **HTLV-1:** Human T lymphotropic virus type 1; **NI-F:** uninfected women; **AS-F:** asymptomatic women; **HT-F:** HAM/TSP women; **NI-M:** uninfected men; **AS-M:** asymptomatic men; **HT-M:** HAM/TSP men.

infection[10][11][13]. However, a persistent infection could cause a major disruption in the balance between lipid metabolism and production of cytokines (tumor necrosis factor-α, interferon-λ, and interleukin-6), leading to tissue damage and hypercholesterolemia, heart disease (atherosclerosis), and autoimmune diseases (rheumatoid arthritis)[9]. Chronic inflammatory diseases could disrupt lipid metabolism, leading to lesions of the endothelium and higher levels of monocyte chemoattractant protein-1 (MCP-1), which would increase migration of monocytes towards the lesion[9][13].

In conclusion, lipid disorders have been implicated in many neurodegenerative diseases. The chronic demyelinating disease in HTLV-1-infected people and the consistently high levels of VLDL and triglycerides in HTLV-1-infected women may be involved in the pathogenesis of HAM/TSP.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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