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Correlation between Leptin Levels and CD4 Count in HIV Patients Receiving Highly Active Antiretroviral Therapy (HAART)

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ABSTRACT

Background: HIV/AIDS is an immuno-deficiency disease with CD4 T lymphocytes as the main target. Although antiretroviral therapy has increased life expectancy of HIV patients, its adverse effect, lipodystrophy, causes a decrease in leptin production by adipose tissue and reduces leptin effect on T lymphocytes' stimulation. Previous studies had examined the correlation between leptin levels and CD4 count, although the results were inconclusive. This study aims to assess the association between leptin levels and CD4 count in HIV patients receiving HAART.
Methods: This is a cross sectional study conducted at the outpatient clinic of Tropical and Infectious Disease Haji Adam Malik General Hospital Medan between April and July 2020. Correlations between variables were assessed through Pearson's or Spearman's correlations. Data were analyzed using the SPPS program where $p < 0.05$ was considered significant.
Results: A total of 40 HIV patients were analyzed. The mean ages of the subjects were 33.62 ± 7.61 years. The mean leptin levels were 1198.97 ± 832.47 ng/mL and the mean CD4 count was 330.55 ± 163.98 cells/mm^3. There were no significant differences in leptin levels between HIV stage III and IV (1067.71 ± 902.39 vs. 1090.80 ± 1185.74, $p = 0.961$). No significant differences were found between CD4 count and HIV clinical stage (392.34 ± 164.70 vs. 339.0 ± 177.46, $p = 0.904$). There was a significant association between leptin levels and CD4 count in HIV patients receiving HAART ($r = 0.351$, $p = 0.026$).
Conclusion: Leptin levels were significantly correlated with CD4 count in HIV patients receiving HAART.

Keywords: Leptin, CD4 lymphocyte count, HIV, highly active antiretroviral therapy.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus targeting Cluster of Differentiation 4 (CD4) T lymphocytes and eventually causes severe immunodeficiency state in infected individuals. Acquired Immunodeficiency Syndrome (AIDS) is the most severe phase of HIV infection, characterized by CD4 count less than 200 cells/mm^3 or developing certain opportunistic infections. [1,2] The mainstay treatment for HIV/AIDS by using a combination of at least 3 antiretroviral drugs (highly active antiretroviral therapy / HAART) had successfully decreased morbidity, secondary complication, and increased life expectancy in HIV patients. [3] Nevertheless, HAART has some adverse metabolic effect as it reduce the amount of adipose tissue partially or completely. [4]

Adipose tissue produces and secretes leptin into the circulation. Leptin is a hormone that reduces food intake by upregulating anorexigenic neuropeptides, such as α-melanocyte- stimulating hormone. Leptin has also been shown to exert a specific effect on T lymphocyte responses. [5,6] Leptin regulates proliferation of naive and memory T cells and modulates helper T cells (Th) by increasing Th1 cytokine production and suppressing Th2 cytokines. [7] Leptin increases the number and function of T cells by direct signaling through leptin receptors on T cells and indirectly by affecting T cell environment. [8]

Leptin levels are associated with the amount of adipose tissue. In HIV patients on HAART, there is a decrease in leptin levels due to lipodystrophy. HAART-associated lipodystrophy (HALS), a common adverse effect of HAART, occurs in approximately 20% of patients on HAART and is typically characterized by a loss of subcutaneous adipose tissue in the face and extremities. [4,9,10] Leptin deficiency causes a reduction in the total number of T cells, CD4+ Th cells, and a change in dominance from Th1 to Th2 cells. [8]

Previous studies had examined the association between leptin levels and immune status, which was reflected in CD4 count, in HIV patients although there were controversies in the results. [10- 12] Hence, the aim of this study is to assess the association between leptin levels and CD4 count in HIV patients receiving HAART.

MATERIAL AND METHODS

This is a cross-sectional study at the outpatient clinic of Tropical and Infectious Disease Haji Adam Malik General Hospital Medan. Patients were enrolled between April and July 2020. Men and women were eligible if they were 18 to 60 years of age, HIV-diagnosed and on antiretroviral therapy for at least 2 months, and adhere to drug consumption. The exclusion criteria were HIV patients with comorbidities (diabetes, cardiovascular disease, renal dysfunction, malignancy, and autoimmune disease), opportunistic infection, and hormonal dysregulation. Study samples were selected consecutively. All of the patients were given informed consent and venous blood samples were collected to determine leptin levels and CD4 count. Leptin levels were examined using Enzyme-linked Immunosorbent Assay (ELISA) method with a normal range of 4,760-20,676 ng/mL. CD4 count was measured using flow cytometry with a normal value of > 500 cells/mm^3.

All statistical analysis was performed through a computerized program SPSS 24^{th} version (Statistical Product and Service Solution). The Shapiro-Wilk test was used to determine whether the variables were normally distributed. In normally distributed variables, all data were expressed as mean ± standard deviation while in abnormal distribution; all data were expressed as median and (minimum-maximum). Pearson's or Spearman's correlations were used to evaluate the correlation between leptin levels and CD4 count according to the variable distribution. A p-value <0.05 was considered statistically significant.

RESULTS

Table I. Baseline characteristics of HIV patients.

Variable	Total (n=40)
Age (years)	33.62 ± 7.61
Gender	
• **Male**	28 (70%)
• **Female**	12 (30%)
Body mass index (kg/m^2)	21.13 ± 3.53
HIV clinical stage	
• **Stage I**	-
• **Stage II**	-
• **Stage III**	35 (87.5%)
• **Stage IV**	5 (12.5%)
Antiretroviral regimen	
• **Tenofovir, Lamivudin, Efavirenz**	35 (87.5%)
• **Lamivudin, Zidovudin, Efavirenz**	3 (7.5%)
• **Tenofovir, Lamivudin, Lopinavir**	1 (2.5%)
• **Tenofovir, Lamivudin, Nevirapin**	1 (2.5%)
Duration of treatment	2.48 ± 2.26
Leptin levels	1198.97 ± 832.47
CD4 count	330.55 ± 163.98

Baseline clinical characteristics of the 40 patients enrolled in this study were shown in Table 1. The mean ages of the subjects were 33.62 ± 7.61 years. The mean body mass index was 21.13 ± 3.53 kg/ m^2. Majority of the subjects (87.5%) were

diagnosed with HIV stage III and the antiretroviral regimen mostly prescribed (87.5%) was Tenofovir, Lamivudin, Efavirenz regimen. The mean duration of treatment was 2.48 ± 2.26 years. The mean leptin levels of the subjects were 1198.97 ± 832.47 ng/mL and the mean CD4 count was 330.55 ± 163.98 cells/mm^3.

In each HIV clinical stage, leptin levels were lower than normal value and leptin levels were higher in HIV stage III than in stage IV (1067.71 ± 902.39 vs. 1090.80 ± 1185.74), although this finding was not statistically significant (Table 2). There were no significant differences in CD4 count between HIV stage III and IV (392.34 ± 164.70 vs. 339.0 ± 177.46). There was a weakly positive correlation between leptin levels and CD4 count in HIV patients receiving HAART (Table 3).

Table II. Leptin levels and CD4 count in each HIV clinical stage.

Variable	HIV clinical stage		p-value
	III	IV	
Leptin levels	1067.71 ± 902.39	1090.80 ± 1185.74	0.961
CD4 count	392.34 ± 164.70	339.0 ± 177.46	0.904

Table III. Correlation between leptin levels with CD4 count.

Variable	CD4 count	
Leptin levels	r = 0.351*	p = 0.026

r ≤ 0.20 : very weak correlation, r = 0.21 - 0.40 : weak correlation, r = 0.41 - 0.60 : moderate correlation, r = 0.61 - 0.80 : strong correlation, r = 0.81 - 1 : very strong correlation.

DISCUSSION

In this study, leptin levels and CD4 count are not significantly different in each HIV stage, although leptin levels are low in all stage. This is contrary to previous study which reported a significant difference in leptin levels among HIV patients with low viral load compared to those with high viral load. [12] In Saliya et al. research, majority of the HIV patients who require antiretroviral therapy is malnourished due to low energy intake followed by increased basal energy requirements due to HIV and other co-infections. [13] Alteration in body fat in HIV-infected individuals have largely focused on lipodystrophy induced by antiretroviral therapy. Low CD4 T cell counts may contribute to fat loss in chronic HIV conditions (via lipodystrophy- induced TNF, limited dietary intake, malabsorption, etc.). The infected macrophages in the lipodystrophic adipose tissue also have different characteristics. When activated, macrophages secrete proinflammatory cytokines, such as TNF-α and IL-6 which control adipocyte metabolism, decrease leptin production, and induce insulin resistance and lipolysis. [12]

Our study found a weakly positive correlation between leptin levels and CD4 count. This is consistent with previous study which reported a higher leptin levels in HIV patients with a higher CD4 count. [12] Onyemelukwe et al. had also reported a moderately positive correlation between leptin levels and CD4 count. [14] Leptin induces proinflammatory cytokine expression by macrophages and monocytes, and plays a direct role in hepatocytes to increase CRP expression. Mature CD4+ cells express long isoform leptin receptors, and leptin stimulates the T cell proliferation in vitro, polarizing the proliferation of naïve CD4+ T cells to the Th1 phenotype, and increases the levels of interferon-γ and other cytokines produced by Th1 cells. Leptin also increases the expression of activation markers, such as CD69, CD25, and CD71 on CD4+ and CD8+ T cells in vitro after stimulated by different doses of antigen. [15]

Although this is the first study in North Sumatra that examined the association between leptin levels and CD4 count in HIV patients receiving HAART, there are a few limitations. This study was conducted with a smaller sample size which might make the study can not be generalized. In addition, there are many independent variables that can affect the results of this study. For example, adherence to taking ARV drugs and the patient's baseline CD4 cell count. Therefore, further research is needed with different research methods.

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Conflict of Interest:

The authors declare that there is no conflict of interest.

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