Relationship CD4 cell counts and serum hepcidin in HIV patients at “Dr. Wahidin Sudirohusodo” Hospital

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ORIGINAL ARTICLES

Relationship CD4 cell counts and serum hepcidin in HIV patients at "Dr. Wahidin Sudirohusodo" Hospital

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ABSTRACT

Background and aim. HIV remains a major global public health problem in Indonesia and many countries around the world. WHO reports that there will be approximately 39 million people living with HIV by the end of 2022. CD4 lymphocytes are the main target of HIV infection and causes a decrease in the body's immune resulting in immune dysfunction. Hepcidin is an anti-microbial peptide hormone synthesized by the liver in response to inflammatory stimuli and regulates iron homeostasis. Hepcidin expression is facilitated by IL-6 produced during inflammation, and a risk factor for HIV-1 disease progression and pathogenesis. Data regarding hepcidin levels in HIV-infected patients are sparsely reported, currently shown to increase HIV-1 transcription.

Methods. This study involved 45 subjects of HIV patients. Sampling using consecutive sampling, with samples in the form of CD4 cell count and serum hepcidin in HIV patients at "Dr. Wahidin Sudirohusodo" Hospital. Laboratory examinations were performed using the Flowcytometry method for CD4 cell count and using the ELISA method for hepcidin serum.

Results : Analysis of the relationship between CD4 count and Hepcidin levels using the Pearson Correlation Test showed that there was no significant correlation between CD4 counts and hepcidin levels ($p>0.05$). Based on the negative R value, there is a tendency that the lower the CD4 count, the higher the Hepcidin level.

Conclusions. There is no significant relationship between serum hepcidin levels and CD4 counts, but there is a tendency that the lower the CD4 cell counts, the higher the hepcidin levels.

Keywords: HIV infection, CD4, Hepcidin, Inflammation

INTRODUCTION

Human Immunodeficiency Virus (HIV) belongs to the retrovirus family which is a group of RNA viruses.[2] HIV affects almost all aspects of the human immune system, both innate immunity and specific adaptive immunity both cellular and humoral, resulting in immune dysfunction. HIV causes disease pathology through several mechanisms, including immune deficiency leading to opportunistic infections, autoimmune reactions, hypersensitivity reactions and a tendency for malignancy in advanced stages. The role of chronic immune activity and chronic inflammation is hypothesized to be directly linked to high levels of chronic immune activation and disease progression.[3] CD4 lymphocytes are the primary target in HIV infection. Various factors play a role in the reduction of CD4+ lymphocyte cell numbers including direct cytopathic effects of HIV on CD4+ cells and their progenitors, induction of apoptosis through immune activation, destruction of stem cells and bone marrow stromal cells.[11]

Hepcidin is an anti-microbial peptide hormone synthesized by the liver in response to inflammatory stimuli and a regulator of iron homeostasis. The activity of hepcidin depends on its ability to bind to feroportin (FPN 1). Feroportin 1 is the receptor for hepcidin and hepcidin binding causes ferroportin to be internalized and degraded in endolysosomes. The inflammation-related regulation of hepcidin is the release of IL-6, leads to activation of STAT-3 which will induce hepatocytes to produce hepcidin. [16] Increased hepcidin expression may be a consequence of inflammation, higher systemic hepcidin and the resulting transfer of iron from the circulation to macrophages may also contribute to HIV development through increased HIV spread and CD4 cell destruction.[4]

Some studies on elevated serum hepcidin levels in HIV patients have been reported. Research by I Ketut et al. (2019) reported high serum hepcidin levels and CD4 count <350 cells/μL are risk factors for anemia of chronic disease (ACD) in HIV patients with antiretroviral therapy.[9] In another study by Kerkhoff et al. (2016) also reported high hepcidin concentrations were strongly associated with disseminated disease, anemia, and poor prognosis in patients with HIV-associated tuberculosis, and significant upregulation of hepcidin during the acute and chronic phases of HIV-1 infection.[10] Study by Armitage et al (2014) found that hepcidin increased during the acute phase of HIV-1 infection, baseline hepcidin levels could predict later viral load, and hepcidin remained high even in chronically infected individuals receiving antiretroviral therapy.11 In a study by Minchella et al. (2015) found that the median serum hepcidin level in HIV-infected patients with anemia was higher than those without anemia.[12]

MATERIALS AND METHODS

Patient population

The study population was all patients diagnosed with HIV at "Dr. Wahidin Sudirohusodo" Hospital, Makassar. Samples are subjects who meet the inclusion criteria.

Inclusion criteria

Inclusion criteria

HIV patients both inpatient and outpatient at "Dr. Wahidin Sudirohusodo" Hospital Makassar aged >18 years, and participants who agree in the study and sign an Informed Consent.

Clinical data and sample collection

Sample collection employed the consecutive sampling method on eligible patients. Blood serum was taken from HIV patients in "Dr. Wahidin Sudirohusodo" Hospital, who had previously filled out a willingness form to take part in this study. Research samples were taken by competent nurses or laboratory staff (laboran). Blood was taken from the mediana cubiti vein as much as 3 cc and put into a citrate tube. Blood samples were examined using bioactive Human Hepcidine-25 based on the principle of ELISA (enzyme-linked immunosorbent assay) and on CD4 examination using Flow cytometry.

Statistical analysis

Data analysis utilized SPSS version 25. using the sample characteristics Kolmogorov-Smirnov test to assess Data Normality, Independent t-test, and Pearson Correlation test.

Statistical significance was defined as a P value of <0.05. The results obtained will be displayed in the form of a narrative supplemented by tables and figures.

RESULTS

Study population

This study collected 45 subjects with characteristic as shown in Table 1. Gender distribution was male 38 subjects (84.4%) and female 7 subjects (15.6%). The age range was between 19-59 years with an average of 34.9 years. Based on the CD4 value <200, there were 19 subjects (42.2%) and at the CD4 value> = 200, there were 26 subjects (57.8%), the range of hepcidin levels was between 0.08-4.78 with a mean of 2.27. Description of confounding factors in this study with pulmonary TB (7 subjects), CKD (3 subjects), anemia (26 subjects), malignancy (3 subjects).

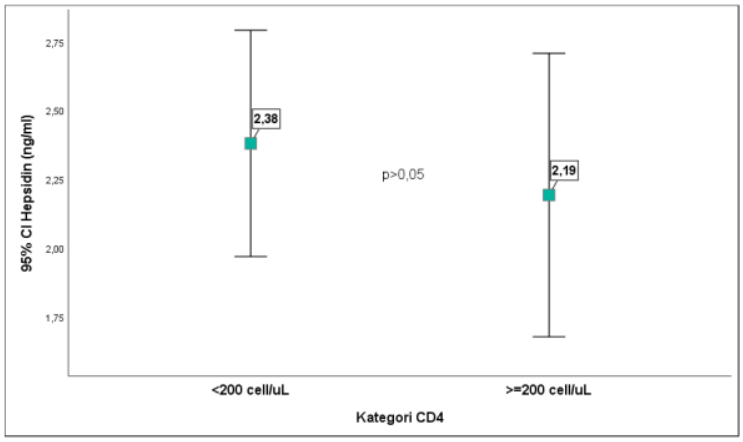
Table 1. Characteristics of Research Subjects (n:45)

Variable		n	%	Min	Max	Mean	SD
Gender	Female	7	15,6				
	Male	38	84,4				
Age	<40 year	34	75,6	19	59	34,9	8,6
	>=40 year	11	24,4				
Pulmonary tuberculosis	Yes	7	15,6				
	No	38	84,4				
CKD	Yes	3	6,7				
	No	42	93,3				
Anemia	Yes	26	57,8				
	No	19	42,2				
Malignancy	Yes	3	6,7				
	No	42	93,3				
CD4 cell counts	<200 cell/uL	19	42,2				
	>=200 cell/uL	26	57,8				
Hepcidin (ng/ml)				0,08	4,78	2,27	1,11

N=number of samples; SD=standard deviation; CKD=chronic kidney disease; CD4= Cluster Differentiation 4

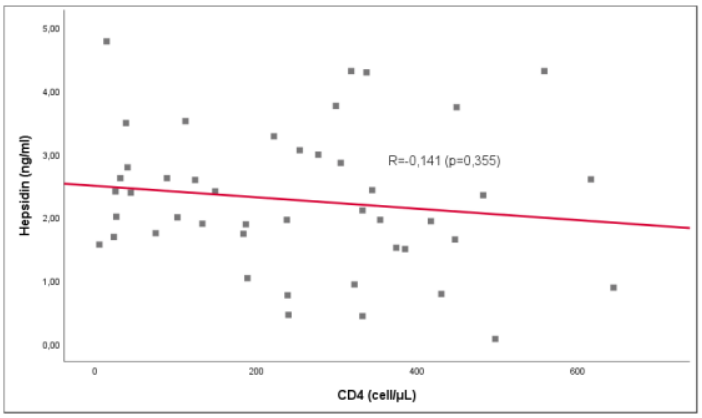
Correlation of HIV patients based on CD4 counts with Hepcidin serum

The correlation between HIV patients with CD4 counts <200 cells/uL and CD4 counts >= 200 cells/uL and hepcidin levels can be seen in figure 4. In this study, that there was no significant correlation between CD4 counts and hepcidin levels (p>0.05). Based on the negative R value, there is a tendency that the lower the CD4 count, the higher the hepcidin level.



Pearson Correlation Test R = Correlation Coefficient

Figure 4. The correlation between HIV patients with CD4 counts <200 cells/uL and CD4 counts >= 200 cells/uL and hepcidin levels



Independent-t test

Figure 5. Comparison of Hepcidin Level according to CD4

Figure 5 showed Mean Hepcidin levels were found to be higher in CD4<200 cells/uL (2.38) than in CD4>=200 cells/uL (2.19), but this difference was not significant (p>0.05), as the range of Hepcidin levels was mostly overlapping between CD4<200 cells/uL and CD4>=200 cells/uL. This shows that there is no significant relationship between CD4 count and Hepcidin levels.

Correlation of CD4 count with hepcidin level according to therapy status

Table 2 showed that there was no significant correlation between CD4 count and hepsidin levels in both ARV and ARV-naive status (p>0.05), but based on the correlation coefficient (R), there was a greater trend in ARV patients (R=-0.172) than ARV-naive (=-0.008), with low CD4 counts having high hepsidin levels

Table 2. Correlation between CD4 count and hepcidin level on therapy status

Therapy status	Variable	statistics	Hepcidin (ng/ml)
ARV	CD4 (cell/µL)	R	-0,172
		p	0,356
		n	31
ARV Naive	CD4 (cell/µL)	R	-0,008
		p	0,977
		n	14

Pearson's Correlation test

Table 3 showed that in ARV patients, higher hepsidin levels were found in CD4 counts <200 than in CD4 counts >=200, but not statistically significant (p>0.05), while in ARV-naive patients, lower hepsidin levels were found in CD4 counts <200 than in CD4 counts >=200, but not statistically significant (p>0.05).

Table 3. Comparison of Hepsidin Level based on CD4 Counts and Therapy Status

Therapy status	CD4 category	n	Mean	SD	p
ARV	<200 cell/uL	9	2,51	1,10	0l,477
	>=200 cell/uL	22	2,15	1,33	
ARV-Naive	<200 cell/uL	10	2,26	0,60	0,732
	>=200 cell/uL	4	2,41	1,04	

The role of confounding factors for hepcidin

The role of confounding factors on hepcidin levels was assessed in table 2, the comparison test of hepcidin levels between the categories of each confounding factor was carried out, and the mean hepcidin levels were found to be higher in HIV patients with no

Pulmonary TB (2.27), HIV patients with CKD (2.85), HIV patients with Anemia (2.42) and Malignancy (2.34), but all were not statistically significant (p>0.05). The results above indicate that, in this study, there was no significant role of confounding factors on hepcidin levels.

Table 4. Comparison of hepcidin levels based on confounding factors

Variables		n	Hepcidin (ng/ml)		p
			Mean	SD	
Pulmonary tuberculosis	Yes	7	2,26	0,46	0,980
	No	38	2,27	1,20	
CKD	Yes	3	2,85	0,77	0,356
	No	42	2,23	1,13	
Anemia	Yes	26	2,42	0,97	0,298
	No	19	2,07	1,27	
Malignancy	Yes	3	2,34	1,03	0,917
	No	42	2,27	1,13	

Independent-t test

DISCUSSION

Analysis of the relationship between CD4 cell counts and hepcidin levels using Pearson's Correlation test showed that mean hepcidin levels were found to be higher in CD4 values <200 cells/uL (2.38) than in CD4 values >=200 cells/uL (2.19), but this difference was not significant (p>0.05).

Expression of hepcidin is facilitated by IL-6 and other cytokines produced during inflammation, and underlying inflammation is a risk factor for HIV-1 disease progression and pathogenesis.6 I ketut et al (2019) reported that high serum hepcidin levels and CD4 counts <350 cells/μL were risk factors for anemia chronic disease (ACD) in HIV patients on cARV therapy. Kerkhoff et al (2016) reported that high hepcidin concentrations were strongly associated with disseminated disease, anemia, and poor prognosis in patients with HIV-associated tuberculosis, and significant upregulation of hepcidin during the acute and chronic phases of HIV-1 infection. Min Xu et al (2010) concluded that the interaction between ferroportin-mediated iron export and hepcidin-mediated ferroportin degradation may play a role in the regulation of HIV-1 transcription and may be important for understanding HIV-1 pathogenesis. However, this study is not in line with some of the previous studies above due to the different time since diagnosis of HIV infection which could potentially impact the results, but this is obvious and impossible to avoid.

There was no significant correlation between CD4 count and hepcidin levels in patients taking ARVs and patients not taking ARVs (p>0.05), but based on the correlation coefficient (R), there was a greater tendency for patients with low CD4 counts to have high hepcidin levels in ARV patients. In ARV patients, higher hepcidin levels were found in CD4 counts <200 compared to CD4 counts >=200, but not statistically significant, while in ARV naïve patients, lower hepcidin levels were found in CD4 counts <200 compared to CD4 counts >=200, but not statistically significant. Chronic immune activation is an important clinical feature of HIV infection, which determines several abnormalities in host metabolic homeostasis. Analysis of our study cohort showed no significant abnormalities in ARV-naive status and ARV status.

This is in line with the research of Roldan et al (2017) reported that no significant differences in hepcidin and IL-6 levels in HIV patients with antiretroviral therapy and with mild anemia.[13] Masaisa et al. (2011) reported that subjects with ferroportin Q248H had significantly lower values for serum hepcidin than subjects who did not have mutations, this is rare because as is known the factor in hepcidin production is inflammation / infection and decreased hepcidin regulation is thought to occur in anemia or iron deficiency.[8] Szymczak et al. (2021) also reported that of the 89 patient samples studied, asymptomatic HIV-1 infection was found with low levels of IL-6 and hepcidin, thus showing no clinically significant differences.[14]

In this study it was found that there was no significant role of confounding factors on CD4 values with hepcidin levels, but it was found that the mean hepcidin levels were higher in HIV-infected patients accompanied by anemia as many as 26 patients or 57.8% with a mean (2.42), compared to other confounding factors but all of them were not statistically significant (p>0.05). This is in line with previous research conducted in Minchella et al. (2015) which found that the median level of serum hepcidin in HIV-infected patients with anemia was higher than those without anemia.[12]

Limitations in this study include the absence of detailed data grouping regarding the length of ARV therapy and in more than 50% of all cases are patients with anemia, but no measurement of iron status in the patients studied.

CONCLUSION

There is no significant correlation between serum hepcidin levels and CD4 count in HIV patients but there is a tendency that the lower the CD4 count the higher the hepcidin levels.

Conflict of interest:

Each author relates that they have no financial relationships that would provide a conflict of interest concerning the work that has been submitted, including stock ownership, equity holdings, consulting, patent/licensing agreements, etc.

Ethics committee approval:

The Ethics Committee for Biomedical Research on Humans at Hasanuddin University's Faculty of Medicine in Makassar, South Sulawesi, Indonesia, approved for this study. Based on recommendation letter Number: 950/UN4.6.4.5.31,/ PP36/ 2023, Dec 2023, with protocol number: UH23110829

Author's contributions:

FS (Concept, Design, Sources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Manuscript Writing). SK (Concept, Planning, Guidance, Interpretation and Analysis). AF (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). SB (Concept, Planning, Guidance, Evaluation, and Knowledge Search the Literature). MA (Concept, Planning, Guidance, Evaluation, and Knowledge Search the Literature). AS (Concept, Analysis and Interpretation, Critical Review).

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