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# The relationship between hepcidin and anemia in controlled and uncontrolled Type-2 Diabetes Mellitus (T2DM) patients at Sanglah Hospital, Bali, Indonesia

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## ABSTRACT

**Background:** Anemia in patients with diabetes mellitus (DM) is often associated with anemia of chronic disease caused by inflammation or iron metabolism disorders. Hepcidin is known to function in initiating the internalization and degradation of ferroportin. It can inhibit the release of iron from cells where an increase in hepcidin levels will reduce iron absorption in the intestine, resulting in a decrease in serum iron levels. This study aims to determine the relationship between serum hepcidin levels and anemia in patients with Type-2 Diabetes Mellitus (T2DM).

**Methods:** This cross-sectional study was conducted on 77 consecutive T2DM patients who met the inclusion and exclusion criteria and received health services at Sanglah Hospital, Bali, Indonesia, during the study period. The variables assessed in this study included T2DM status (controlled and uncontrolled), anemia, hemoglobin, HbA1c, erythrocyte sedimentation rate, and hepcidin. Data were analyzed with SPSS version 20 for Mac.

**Results:** There was no significant difference in age, sex, disease duration, SGOT, SGPT, leukocytes, platelets, and ESR between controlled and uncontrolled T2DM groups ($p>0.05$). However, there was a significant difference in eGFR and hemoglobin levels between controlled and uncontrolled T2DM groups ($p<0.05$). Mann-Whitney U test found a significant difference in hepcidin levels between controlled and uncontrolled T2DM groups (MD=138.14; 95%CI=10.65-286.94; $p=0.046$). A weak significant negative correlation was found between hemoglobin and hepcidin levels by the Spearman correlation test ($r=-0.259$; $p=0.043$).

**Conclusion:** There was a significant difference between the mean hemoglobin and hepcidin levels in the controlled T2DM group compared to uncontrolled T2DM group patients. A weak statistically significant negative correlation was found between hepcidin levels and anemia in T2DM patients.

**Keywords:** Hepcidin, Anemia, T2DM, Controlled, Uncontrolled.
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## INTRODUCTION

Diabetes Mellitus (DM) is a chronic and progressive metabolic disease in impaired carbohydrate, fat and protein synthesis caused by defects in insulin secretion, insulin action, or a combination of both.[1] Hyperglycemia in DM can cause increased expression of inflammatory markers such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α).[2] These cytokines have an anti-erythropoiesis effect which causes a decrease in the hematocrit value due to inflammation.[3] Inflammation in Type-2 Diabetes Mellitus (T2DM) closely associated with anemia of chronic disease.[4] There is decreased erythrocyte survival, impaired iron excretion from macrophages or enterocytes and poor response of erythroid precursors to erythropoietin.[5] Anemia is the most common complication in DM patients, which can be detected by performing several examinations, including complete blood count (hemoglobin), iron test (serum ferritin level examination, Soluble Transferrin Receptor (sTfR) transferrin level, transferrin saturation), and hepcidin.[4,5]

Hepcidin is an antimicrobial peptide hormone synthesized by the liver, distributed in plasma and secreted in the urine.[6] Hepcidin functions in the initiation of the internalization and degradation of ferroportin to inhibit the release of iron from cells. Increased hepcidin levels will reduce iron absorption in the intestines, resulting in a decrease in serum iron levels and causing disruption of the erythropoiesis process and impaired synthesis of hemoglobin contained in erythrocytes.[6] Previous studies by Fernandes-Real JM et al., Aso Y et al., and Sam AH et al., reported a decrease in hepcidin concentrations in the type 2 DM group, indicating a loss of insulin signaling

with an increase in iron stores.[7-9] In the case-control study by Aigner E et al., who assessed the effect of glucose on serum iron and hepcidin, found an increase in serum hepcidin in the group given glucose compared to the control group that was only given water.[10] In addition, a previous study was also showed an increase in hepcidin in the uncontrolled DM group compared to the controlled DM group.[11]

Based on those mentioned above, this study aims to evaluate the relationship between hepcidin and anemia in controlled and uncontrolled Type-2 Diabetes Mellitus (T2DM) patients at Sanglah Hospital, Bali, Indonesia.

## METHODS

This research was conducted using a cross-sectional design from August to October 2020 at the Endocrinology Polyclinic and Clinical Pathology Laboratory of Sanglah Hospital Denpasar, Bali, Indonesia. A total of 77 patients were selected by consecutive sampling as study participants after meeting the inclusion criteria, namely at least 18 years of age who had been diagnosed with type 2 DM, and meeting the exclusion criteria, namely patients with chronic kidney failure, infection, impaired liver function (with increased SGOT and SGPT values), and patients who had a transfusion within 3 months, and patients who were pregnant. Subsequently, venous blood samples were taken to examine hemoglobin levels, HbA1c, erythrocyte sedimentation rate, and hepcidin levels.

Hemoglobin examination used venous blood collected in an EDTA tube, then examined using a Dyn Ruby Cell Hemato-analyzer from Abbott with the principle of cyanide-free hemoglobin. HbA1c examination using the Cobas c601 device with the principle of HbA1c examination based on Turbidimetric Inhibition Immunoassay (TINIA) for whole blood. The results came out with two values, namely hemoglobin levels and A1c values, then converted into HbA1c percentage values based on DCCT/NGSP, which was calculated from the HbA1c/Hemoglobin ratio with the formula: HbA1c (%) = (HbA1c/Hb x 100%) x 0.915 + 2.15 %. While the examination of serum hepcidin levels was carried out by the sandwich ELISA method. Normal levels are 50 pg/mL–170 pg/mL. ELISA inspection quality assurance is carried out by precision testing using the within-run method.

Data analysis was performed with the Statistical Program for Social Sciences (SPSS) version 21 for Mac. All data obtained in this study were analyzed descriptively and the results will be presented in the form of mean ± standard deviation (SD) and median (minimum-maximum). The normality test of the data used the Saphiro-Wilk test, followed by the average comparison test using the Mann Whitney U Test and the correlation test using Spearman with a significance level of $p < 0.05$.

## RESULTS

The subjects of this study were patients with type 2 diabetes who met the inclusion and exclusion criteria, divided into two groups, namely the controlled T2DM group of 36 people who had HbA1c levels 7%, and the uncontrolled T2DM group consisting of 41 people with HbA1c levels. >7%. Characteristics of research subjects can be seen in **Table 1**.

Examination of SGOT and SGPT enzymes showed no increase in transaminase enzyme levels beyond the upper limit of normal (normal value of SGOT enzyme = 11-33 U/L, SGPT = 11-50 U/L) (Table 1). This situation indicates that the research subjects were not experiencing liver disease in either the controlled DM group or the uncontrolled DM group.

In the estimated Glomerular Filtration Rate (eGFR) value, the two groups had a statistically significant difference of eGFR value (p=0.043) (**Table 1**). The controlled T2DM group had a mean eGFR of 81.48±24.68 ml/min/1.73m$^2$, and the mean eGFR value in the uncontrolled DM group was 90.30±16.73 ml/min/1.73m$^2$ (**Table 1**).

The range of hemoglobin levels in this study was from 9.4 g/dL to 17.2 g/dL. The uncontrolled DM group had a significantly lower hemoglobin level (p=0.025). The leukocyte counts in both groups did not show a statistically significant difference (p=0.060). On the platelet count, both controlled and uncontrolled T2DM groups were still within normal limits. The erythrocyte sedimentation rate was found to increase in both groups but not significantly different (p=0.877) (**Table 1**).

In a comparative test using the Mann-Whitney U Test, there was a significant difference in hepcidin levels between the groups (p=0.046), and hepcidin levels were higher in the uncontrolled T2DM group (581.84±441.46 pg/ml) (**Table 2**).

Statistical analysis with Spearman's rank correlation test showed a weak significant negative correlation between hemoglobin levels and hepcidin levels (r=-0.259; p=0.043). In addition, there was a statistically significant positive correlation

**Table 1. Characteristics of research subjects**

| Characteristics | Controlled T2DM (Hba1c ≤7%) (n=36) | Uncontrolled T2DM (Hba1c >7%) (n=41) | p |
|---|---|---|---|
| Age (Years) | 54.88±10.54 | 52.58±9.96 | 0.328 |
| Sex, n (%) | | | |
| Male | 22 (52.40) | 20 (47.60) | 0.278 |
| Female | 14 (40.00) | 21 (60.00) | |
| Disease duration (Months) | 27.91±10.21 | 34.21±17.11 | 0.054 |
| SGOT (U/L) | 20.34±7.19 | 25.00±17.85 | 0.147 |
| SGPT(U/L) | 28.53±19.71 | 30.52±19.95 | 0.663 |
| eGFR (ml/minutes/1.73m$^2$) | 81.48±24.68 | 90.30±16.73 | 0.043* |
| Hemoglobin (g/dL) | 12.43±2.05 | 11.49±3.09 | 0.025* |
| Leukocytes (10$^3$/µL) | 8.14±2.15 | 9.23±2.79 | 0.060 |
| Platelets (10$^3$/µL) | 295.81±72.25 | 302.45±93.19 | 0.730 |
| ESR (mm/jam) | 58.25±11.11 | 55.41±33.87 | 0.877 |

ESR: Erythrocyte Sedimentation Rate; eGFR: estimated Glomerular Filtration Rate; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; *Independent T-Test: statistically significant if p-value less than 0.05.

**Table 2. Mann-Whitney U Test Hepcidin levels in the T2DM group**

| Variable | Controlled T2DM (HbA1c ≤7 %) (n=36) | Uncontrolled T2DM (HbA1c>7%) (n=41) | MD | 95% CI | p |
|---|---|---|---|---|---|
| Hepcidin (pg/mL) | 443.70±173.20 | 581.84±441.46 | 138.14 | 10.65-286.94 | 0.046* |

T2DM: Type 2 Diabetes Mellitus; MD: Mean Difference; CI: Confidence Interval; **Mann-Whitney U Test*: statistically significant if p-value less than 0.05

**Table 3. Spearman's rank correlation test among several variables to hepcidin levels**

| Variable | | Hepcidin |
|---|---|---|
| Hemoglobin | r | -0.259 |
| | p | 0.043* |
| HbA1c | r | 0.298 |
| | p | 0.040* |
| Erythrocyte Sedimentation Rate | r | 0.127 |
| | p | 0.042* |

*Statistically significant if p-value less than 0.05; r=coefficient correlation

between HbA1c levels and hepcidin levels (r= 0.298; p= 0.040) and erythrocyte sedimentation rate on hepcidin levels (r=0.127; p=0.042) (**Table 3**). This indicates that an increase in hepcidin levels will correlate with a decrease in hemoglobin levels and an increase in hepcidin levels will correlate with an increase in HbA1c levels and the erythrocyte sedimentation rate.

## DISCUSSION

In this study, the age range of type 2 DM patients was from 35 years to 76 years, with the mean age in the controlled DM group was 52.58 years and the average age in the uncontrolled DM group was 54.88 years. This result is in accordance with Wild S et al., statement that the highest prevalence of type 2 DM in the world is at the age of more than 45 years.[12] Research conducted by Handayani SA in Semarang concluded that the age of more than 45 years has a risk of suffering from type 2 diabetes by 7.5 times compared to those aged less than 45 years.[13] This is due to the diminishing ability of insulin due to insulin resistance or insulin production.[10] Insulin by pancreatic beta cells decreases with the aging process that continues in the body of old adults and old age.[10-12] The proportion of T2DM patients by sex was more common in men than women in the controlled T2DM group and the uncontrolled T2DM group, the proportion of female sex was higher. This result is similar to the study conducted by Silangit T et al, which found among 200 patients with type 2 diabetes, 121 (60%) patients were males.[14] However, a previous study found that patients with T2DM in the uncontrolled T2DM group were more prevalence in female.[15] This is because women are more at risk of developing diabetes because women have a greater chance of increasing body mass index due to the monthly cycle and post-menopausal syndrome so that the distribution of body fat becomes easy to accumulate due to the hormonal process.[16,17]

In the average eGFR value of the two research groups, there is kidney damage with a mild decrease in GFR value. According to previous studies, after 40 years, kidney filtration begins to decrease by about 1% per year.[18,19] The decrease in GFR will be faster if there are comorbidities such as hypertension, diabetes, and heart disease.[20]

Anemia in this study used the cut-off value of hemoglobin for anemia criteria based on WHO, namely hemoglobin in adult males <13 mg/dL and hemoglobin in women <12 mg/dL.[21] The range of hemoglobin levels in this study was from 9.4 g/dL to 17.2 g/dL. The average hemoglobin level in the controlled DM group was 12.43±2.05 g/dL, and the average hemoglobin in the uncontrolled DM group was 11.49±3.09 g/dL. The hemoglobin level in the uncontrolled T2DM group was significantly lower than the hemoglobin level in the controlled T2DM group. The average MCV value of the controlled T2DM group and the uncontrolled T2DM group showed that it was still in the normal range (80-100 fL). These results indicate that the anemia that occurs is anemia with normochromic erythrocyte characteristics. This result is similar to the study conducted by Setianingsih E et al. among 89 patients with controlled and uncontrolled T2DM.[22] It was found that uncontrolled type 2 diabetes had lower hemoglobin levels than controlled type 2 diabetes.[22] In a case-control study conducted by Aljohani AH et al., showed that the incidence of anemia increased in patients with uncontrolled T2DM.[23] Shaheen ES reported in his research that 75% of type 2 DM patients had anemia and as many as 44.6% of the types of anemia were normochromic normocytic.[24]

In this study, the mean hepcidin level was significantly higher in the uncontrolled T2DM group compared to the controlled T2DM group. In a case-control study by Al-Adhami IAA et al., in Yamen found that hepcidin levels were significantly increased in type 2 DM patients who had a mean fasting glucose of more than 200 mg/dL.[25] In a case-control study by Aigner E et al., who assessed the effect of glucose on serum iron and hepcidin, found an increase in serum hepcidin in the group that was given glucose compared to the control group that was only given water, this is because one of the extrahepatic sources of hepcidin is pancreatic cells.[10] When glucose stimulates insulin release, hepcidin production simultaneously occurs, glucose stimulates pancreatic cells to secrete hepcidin.[10] Previous studies using the competitive ELISA hepcidin examination method were also found no difference in hepcidin levels in the healthy control group and the patient group with DM, but there was a correlation between hepcidin levels and iron parameters such as hemoglobin and ferritin.[11,26,27]

There was an increase in the erythrocyte sedimentation rate in the two study groups, but not significantly different. The normal values for the erythrocyte sedimentation rate (ESR) in men are 15 mm/hour and 20 mm/hour for women.[28] In this study, there was no significant difference of the average ESR in the controlled T2DM group and the uncontrolled T2DM group. According to a study conducted by Bikramjit P et al, there was an increase in the ESR more than 50 mm/hour in patients with T2DM who had an HbA1c value of 7% and an increase in the ESR more than 90 mm/hour in DM patients who had an HbA1c value of more than 9%.[29]

Hepcidin is a 25 amino acid peptidase hormone that inhibits iron entry into the plasma compartment through 3 sources of iron supply, namely absorption of food in the duodenum, the release of iron from macrophages and release of stored iron from hepatocytes.[30] Hepcidin is mainly produced in the liver, but hepcidin is also produced in small amounts in other tissues such as the heart, kidney, pancreas and hematopoietic cells. Hepcidin is a major regulator of iron homeostasis, where its synthesis is mainly controlled by bone marrow erythropoiesis activity, iron storage, and the presence of inflammatory conditions in the body.[31] Inflammation in the body is often associated with an increase in the erythrocyte sedimentation rate. The erythrocyte sedimentation rate can be caused by kidney disease, anemia, infection, autoimmune disease and malignancy. Hepcidin is also a type II acute-phase protein.[30-32] Impaired regulation of hepcidin synthesis is an important factor in the pathogenesis of certain diseases, where hepcidin deficiency causes iron overload or hemochromatosis. In contrast, an increase in hepcidin causes anemia of chronic disease.[33]

This study showed a weak significant negative correlation between hemoglobin levels and hepcidin levels in T2DM patients, indicating that high hepcidin levels correlated with a decrease in hemoglobin levels (anemia) in type 2 DM patients. These results are consistent with this study. A study conducted by Albendary E et al., reported a significant negative correlation between hepcidin levels and hemoglobin levels in patients with gestational diabetes (r=-0.408; p=0.005).[34] According to Hong JH et al. who conducted a study on the relationship of hepcidin in 1,150 T2DM patients without renal impairment, also found a negative correlation between hemoglobin levels and hepcidin levels (r=-0.526; p=0.001).[35] In the study of Zaritsky J et al., who tested the relationship between serum hepcidin and indicators of anemia, iron status and inflammation, found an increase in hepcidin levels and a correlation between hepcidin and anemia parameters such as hemoglobin.[36] The previous study also reported that an increase in hepcidin plays a role in impaired iron regulation and the process of erythropoiesis so that hepcidin can be used as a parameter in iron deficiency anemia and one of the causes of inadequate erythropoietin response.[36] Guo X et al., also reported a significant correlation between hepcidin levels and hemoglobin levels in the group of patients with T2DM.[26]

## CONCLUSION

The average hemoglobin level of the controlled type 2 DM patient group is higher than the average hemoglobin level of the uncontrolled group of type 2 DM patients. The mean hepcidin level in the controlled type 2 DM patient group was lower than that in the uncontrolled type 2 DM group. There was a significant difference between the mean hemoglobin and hepcidin levels in the controlled T2DM group compared to uncontrolled T2DM group patients. In addition, there was a statistically significant negative relationship between hepcidin levels and anemia in patients with type 2 diabetes.

## CONFLICT OF INTEREST

There is no competing interest regarding manuscript.

## ETHICS CONSIDERATION

Ethics approval has been obtained from the Ethics Committee, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia with number 1849/UN14.2.2.VII.14/LT/2020 prior to the study being conducted.

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None.

## AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data acquisition, data analysis, until reporting the study results through publication.

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