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Evaluation of Serum Ferritin in Type 2 Diabetes Mellitus: An Observational Study from North Sulawesi, Indonesia

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Abstract: Diabetes mellitus is still an important health problem in Indonesia because the incidence is increasing every year and most patients do not achieve good and proper glycemic control. Analysis of blood ferritin levels in type 2 diabetes mellitus patients is considered limited in many areas. As a marker of iron stores in the body, elevated serum ferritin has been associated with microvascular and macrovascular complications of diabetes mellitus. This study aimed to determine the correlation between serum ferritin levels and fasting blood glucose, glycated hemoglobin (HbA1c), and other biochemical parameters in type 2 diabetes mellitus patients in North Sulawesi, Indonesia. A total of 108 diabetes mellitus patients were included in this cross-sectional study. Subjects were tested for blood pressure, body mass index, fasting blood glucose, hemoglobin, glycated hemoglobin (HbA1c), ferritin, urea, creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, cholesterol, and triglyceride. The averages of HbA1c% in the good, moderate, and poor groups were 5.70 ± 0.5%, 7.2 ± 0.6, and 10.1 ± 1.6, respectively. Increased fasting blood glucose, ferritin, urea, creatinine, and uric acid levels were observed along with worsening glycemic status. There were significant correlations between serum ferritin and fasting blood glucose, glycated hemoglobin, and alanine aminotransferase ($p < 0.05$). There were significantly different mean ferritin values in the three groups of glycated hemoglobin, suggesting ferritin can be used as an indicator of control of glycemia and diabetic complications.

Keywords: Diabetes Mellitus, Ferritin, Glycated Hemoglobin, HbA1c, Blood Glucose

1. Introduction

Diabetes mellitus, a metabolic disorder characterized by hyperglycemia, is still an important global health problem, because it can cause high morbidity and mortality rates. More than 50% of diabetic patients have comorbidities, so the prevalence of diabetic vascular complications such as retinopathy, nephropathy, and other vascular dysfunctions is also increasing [1]. Indonesia ranks seventh out of ten countries with the highest number of people with diabetes (10.7 million) [2]. The incidence of type 2 diabetes mellitus in Indonesia is increasing every year and about 87.5% of patients do not achieve good and appropriate glycemic control [3]. The financial burden of family and community health is significantly increased by diabetes mellitus and its complications, which in turn contributes significantly to the national burden of healthcare costs [4]. North Sulawesi ranks among the top five of 34 Indonesian provinces with the highest prevalence of diabetes mellitus, according to data from the Indonesian Basic Health Research conducted in 2018 [5]. Analysis of fasting blood glucose (FBG) and glycated hemoglobin related to blood ferritin levels in diabetes mellitus patients is considered limited in this area.

Serum ferritin, an acute phase reactant, is a marker of the body's iron stores. Ferritin testing is generally used to assess iron status in healthy individuals and anemia patients.

There are several ways that increased iron stores can cause diabetes mellitus [6]. Elevated serum ferritin has been linked to long-term microvascular and macrovascular complications of diabetes mellitus in a number of studies [7–9].

The aims of this study were to determine the relationship between serum ferritin levels and fasting blood glucose and glycated hemoglobin (HbA1c), and also to assess whether there was any association of clinical and other biochemical parameters with change in HbA1c and ferritin levels in type 2 diabetes mellitus patients.

2. Material and Methods

2.1. Study Design and Patients

A cross-sectional study was conducted at Noongan Regional General Hospital, Minahasa Regency, North Sulawesi, Indonesia. The timeline of sample collection was May-August 2021. This study was approved by the Medical Research Ethics Committee of R. D. Kandou General Hospital (No. 074/EC/KEPK-KANDOU/V/2021). Written informed consent was taken from all subjects. Populations were all inpatients and outpatients with diabetes mellitus (fasting blood glucose ≥126 mg/dL or previous history of diabetes mellitus).

Sample collection used total sampling method, which included all subjects who were examined during the study period and met the inclusion and exclusion criteria, and were willing to participate in this study. Exclusion criteria included the following: a. patients with hemoglobin levels <10 mg/dL, b. anemia therapy in the last 2 months, c. pregnant patient, d. patients with heart failure, liver disease, hematological disorders, and infection, and e. chronic alcoholics.

2.2. Clinical and Laboratory Data Collection

Systolic and diastolic blood pressure of the participants was measured with an automatic digital aneroid sphygmomanometer. The height was measured with a stadiometer (cm) and weight was measured with a weighing scale (kg). The patients' body mass index (BMI) values were calculated using the formula of weight (kg)/height (m^2). Venous blood was taken from all subjects after overnight fasting.

Serum samples were used for chemical parameters estimation and ethylenediaminetetraacetic acid (EDTA) samples for hemoglobin (Hb) and glycated hemoglobin (HbA1c). Blood glucose, urea, creatinine, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, and triglyceride (TG) were assayed using Sysmex BX-3010 chemistry analyzer. Hemoglobin analysis was conducted using Sysmex XN-1000™ hematology analyzer. HbA1c was tested using Epithod®616 analyzer. Serum ferritin was estimated using Roche COBAS e-411. All analysis were performed according to the manufacturer's protocol.

2.3. Statistical Data Analysis

Statistical analysis was performed using the SPSS version 26 software. Diabetic patients were divided into three groups based on HbA1c as follows: good control HbA1c <6.5%, moderate control 6.5-8%, and poor control >8% [7]. The data was represented by number, percentage, and mean and standard deviation (SD). Continuous variables of independent measurements showing normal distribution were analyzed using an independent samples t-test and one-way analysis of variance, while data with abnormal distribution were analyzed using the Mann-Whitney rank sum test and Kruskall-Wallis on the rank test. Variables with abnormal distribution were analyzed using the Spearman's correlation coefficient to identify the relationship between the variables and the direction. A p-value of <0.05 was considered significant.

3. Results

One hundred and eight blood specimens were collected from diabetes mellitus patients. The patients ranged in from 33 to 80, with an average of 57.2±9.4 years. The majority of subjects were in the age group of 45-54 and 55-64 years, each 36 patients (33.3%), followed by the age group ≥65 years (25%). Sixty of 108 patients were females (55.6%), 8.3% of patients were receiving insulin, 2.8% were receiving insulin in combination with an oral antidiabetic, and 88.9% of patients were taking oral antidiabetics. We observed that majority of subjects had overweight BMI (51%).

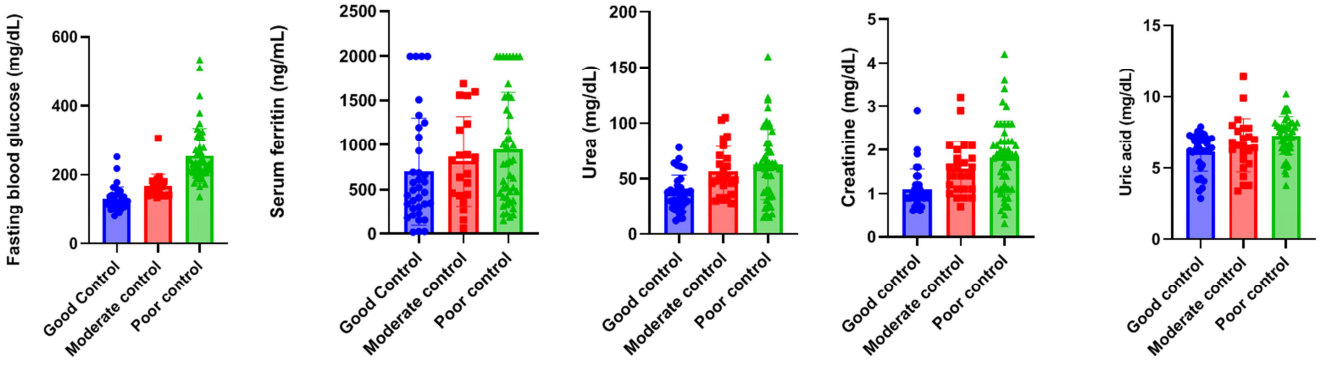
Diabetic patients were divided into three groups based on their HbA1c: good control 35 cases (32.4%), moderate control 24 cases (22.2%), and poor control 49 cases (45.4%). Baseline characteristics of the groups are shown in Table 1.

Fasting blood glucose, ferritin, urea, creatinine, and uric acid levels were observed to rise as the glycemic status deteriorated (Figure 1). With a correlation coefficient (r) of 0.844, which indicates a very strong and positive correlation (directly proportional), there was a correlation between HbA1c levels and FBG, as shown in Figure 2a. The null hypothesis was rejected on the basis of the significance test, which indicated that there was a significant relationship between HbA1c levels and FBG levels. The correlation coefficient (r) between ferritin levels and FBG was 0.206, indicating a weak and directly proportional relationship. The fact that the *p*-value was 0.040 (<0.05) indicated that there was a significant correlation between the levels of FBG and serum ferritin (Figure 2b). The correlation coefficient (r) between ferritin levels and HbA1c was 0.199, indicating that there was a very weak and positive correlation. Figure 2c shows that there was a significant relationship between ferritin concentrations and HbA1c, with a *p*-value of 0.048 ($p<0.05$).

Another biochemical parameter, alanine aminotransferase, had a significant correlation with ferritin (r 0.429 and *p*-value 0.023). The others parameters in the Spearman's correlation analysis did not show significant correlations with ferritin.

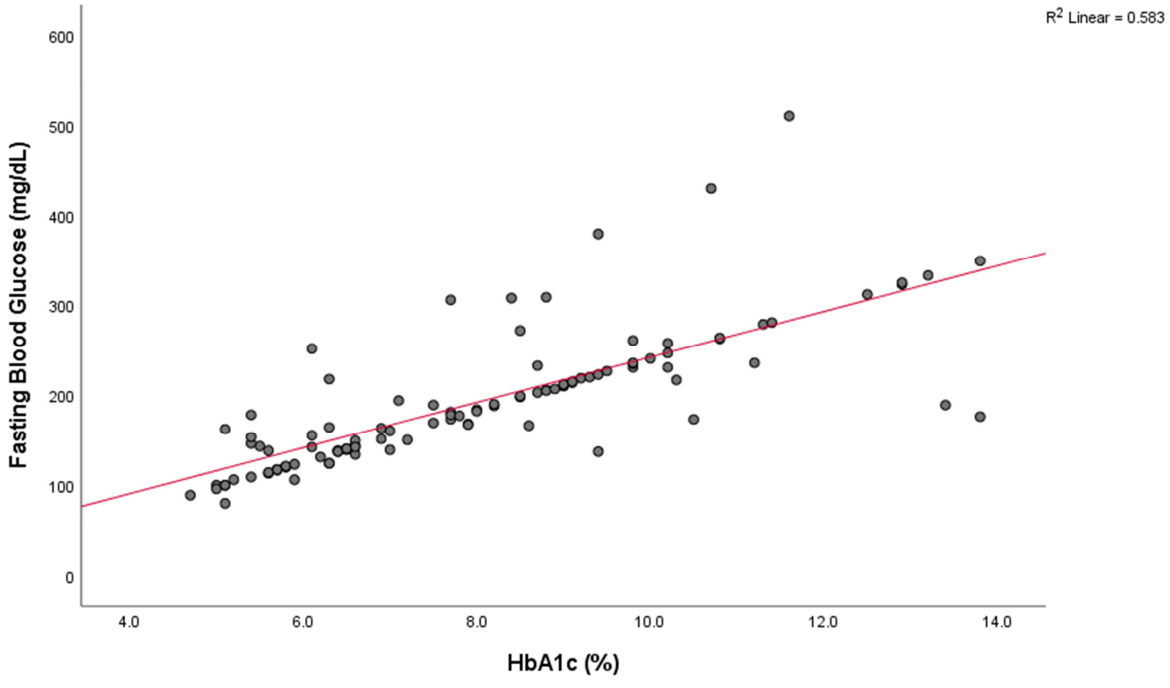
Table 1. *Baseline characteristics of diabetic patients.*

Characteristic	Good control		Moderate control		Poor control		*p*-value
	mean ± Standard Deviasi	median (min-max)	mean ± Standard Deviasi	median (min-max)	mean ± Standard Deviasi	Median (min-max)	
BMI (kg/m^2)	24.5±3.0	25.3 (14.9-29.4)	25.5±3.0	25.6 (20.3-33.9)	25.0±3.5	25.2 (18.4-33.9)	0.735
SBP (mmHg)	138.0±24.4	140 (90-190)	129.8±21.2	130 (100-200)	132.0±22.5	130 (100-180)	0.198
DBP (mmHg)	83.4±17.1	90.0 (60.0-151)	81.5±12.5	80.0 (60.0-110)	81.7±22.5	80.0 (50.0-110)	0.357
Hemoglobin (g/dL)	12.7±1.9	13.4 (6.8-15.1)	11.9±2.0	11.6 (7.9-15.1)	11.8±2.0	12.0 (7.0-15.5)	0.086
HbA1c (%)	5.70±0.5	5.70 (4.70-6.40)	7.2±0.6	7.15 (6.50-8.00)	10.1±1.6	9.65 (8.20-13.80)	<0.001*
FBG (mg/dL)	131.1±34.3	123 (80.0-252)	167.4±34.7	165 (134-306)	254.8±79.8	231 (137-534)	<0.001*
Ferritin (ng/mL)	699.1±603.9	495 (18-2000)	816.9±503.5	754 (62-1686)	955.9±634.3	793 (149-2000)	0.125
Urea (mg/dL)	37.2±16.1	36.0 (12.0-78.0)	56.6±22.5	50.0 (12.0-78.0)	62.9±31.4	61.0 (15.0-160.0)	<0.001*
Creatinine (mg/dL)	1.1±0.5	1.0 (0.6-2.9)	1.6±0.6	1.5 (0.7-3.2)	1.8±0.8	1.9 (0.3-4.2)	<0.001*
Uric acid (mg/dL)	6.1±1.4	6.4 (2.9-7.9)	6.6±1.9	6.6 (3.4-11.4)	7.3±1.3	7.6 (3.8-10.2)	0.001*
ALT (U/L)	23.0±10.4	19.0 (10.0-42.0)	35.5±18.2	31.0 (16.0-66.0)	32.0±20.5	27.0 (10.0-69.0)	0.306
AST (U/L)	23.6±8.6	19.0 (14.0-37.0)	34.3±15.0	33.0 (14.0-60.0)	26.3±12.8	19.5 (14.0-45.0)	0.341
Cholesterol (mg/dL)	199.9±27.4	210 (149-228)	163.3±60.7	159 (76-251)	191.2±40.3	242 (137-242)	0.368
TG (mg/dL)	163.2±62.8	143 (87-291)	146.9±59.9	140 (58-224)	133.2±36.5	138 (67-180)	0.656

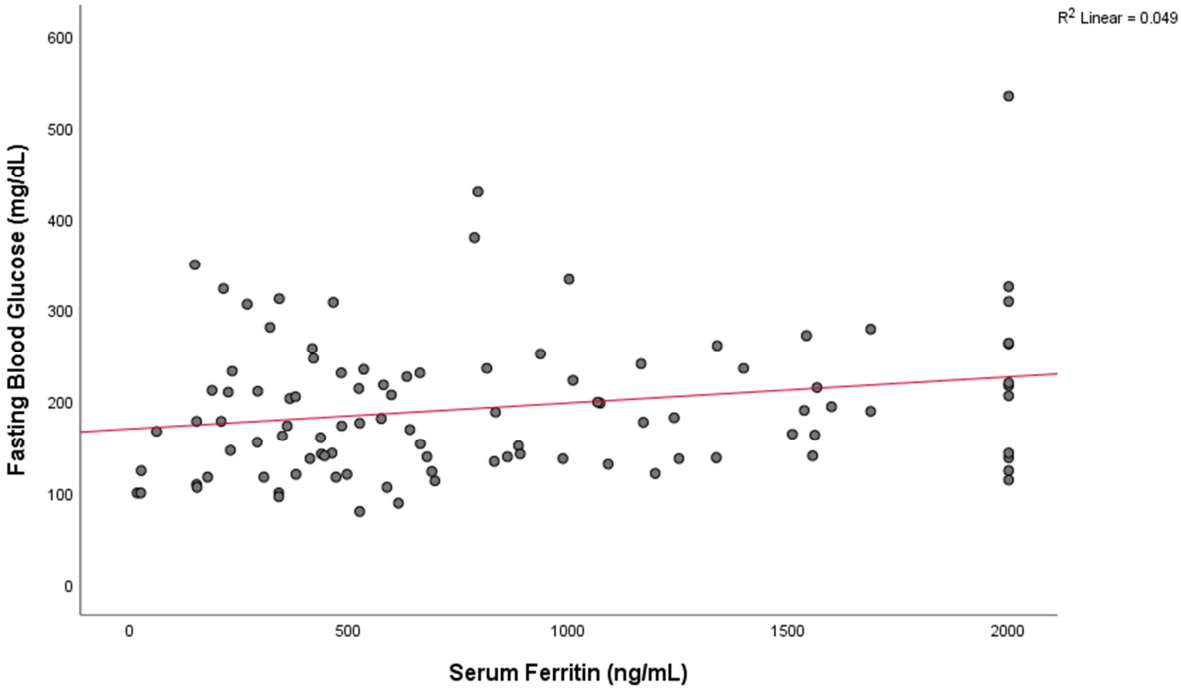


(a) fasting blood glucose, (b) ferritin, (c) urea, (d) creatinine, and (e) uric acid.

Figure 1. *Comparison of biochemical parameters levels based on HbA1c groups.*



(a)



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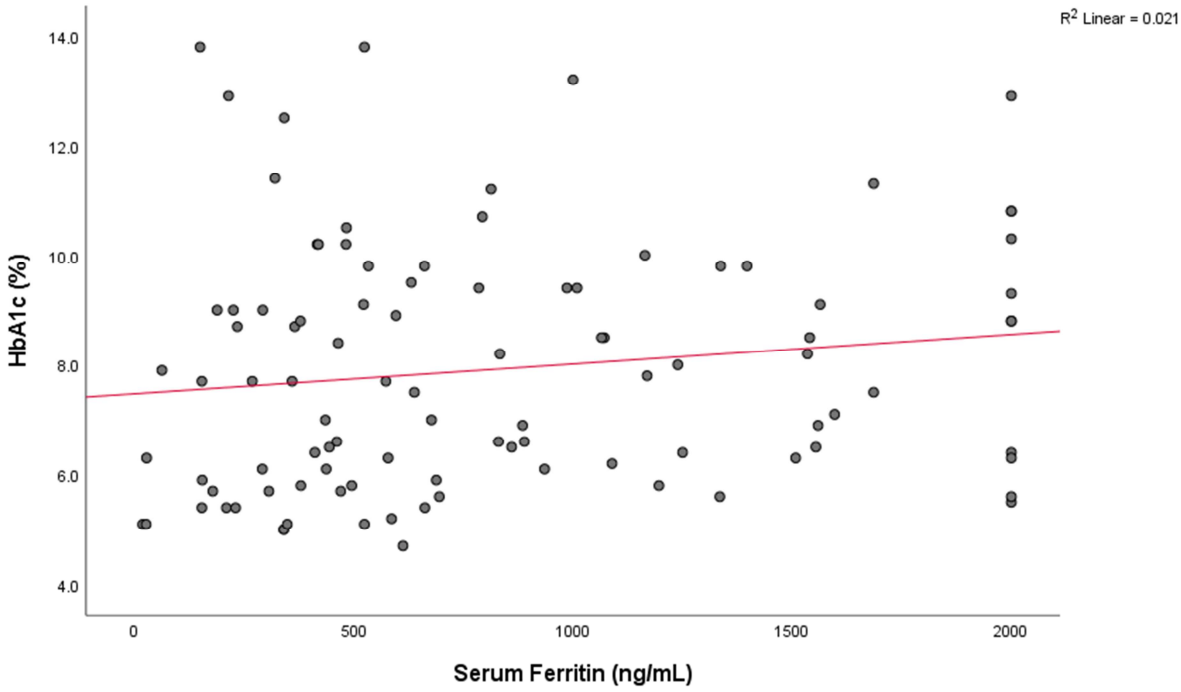

(c)

Figure 2. *Correlation between (a) HbA1c and fasting blood glucose (b) ferritin and fasting blood glucose, and (c) ferritin and HbA1c.*

4. Discussion

The results of this study indicate that diabetes mellitus is mostly suffered by subjects aged 45-54 and 55-64 years old. The average peak age of type 2 DM diagnosis is between 45-60 years [10]. The prevalence of subjects ≥65 years (25%) was similar to those of U.S. adults, which varies from 22 to 33% [11]. Older adults with diabetes are particularly vulnerable to having acute and chronic microvascular and cardiovascular complications from this disease [12]. This study also shows that females are more likely than males to have diabetes mellitus. This finding agrees with prior studies, however contradicts Borah's study [13–15].

This study indicates that the poor control group has the highest fasting blood glucose and serum ferritin. These findings are consistent with those of previous studies [5, 13–17]. Several possible mechanisms have been suggested for the correlation between elevated serum ferritin and the incidence of type 2 diabetes, although the precise mechanism is unknown. Iron deposition in the liver, one of these mechanisms, can increase hepatic glucose production and cause hepatic insulin resistance [8, 18, 19]. Furthermore, elevation of oxidative stress due to increased formation of hydroxyl radicals catalysed by iron, can cause systemic insulin resistance and hyperglycemia [20–22]. Other studies have suggested that iron excess contributes to insulin resistance and subsequently to decreased insulin secretion [23, 24]. Lastly, higher ferritin levels in non-alcoholic fatty liver disease (NAFLD) reflect abnormal iron metabolism or inflammation, and NAFLD is a risk factor for the development of type 2 diabetes [25].

Our study shows a very strong and directly proportional correlation between fasting blood glucose and HbA1c. There are many studies conducted worldwide indicating significant relationship between the two [8]. However, a meta-analysis conducted by Ketema *et al*. [26] reported, although correlation coefficient was 0.61 between FPG and HbA1c values, in the absence of HbA1c, it was discovered that monitoring of postprandial plasma glucose (PPG) was a better parameter for predicting or achieving target HbA1c values than FPG alone.

The averages of HbA1c% in the good, moderate, and poor groups in this study were 5.70±0.5%, 7.2±0.6, and 10.1±1.6, respectively. The mean HbA1c% value was significantly highest in the poor group among others, indicating that patients' glycemic control worsened [8]. Poor glycemic control may be caused by inactivity, a poor diet, or a lack of medication compliance for diabetics. This study shows a positive correlation between increased serum ferritin and poor glycemic control, reflected by higher HbA1c%. This finding is supported by various studies [6, 7, 15, 16, 27–29]. Apart from serum ferritin and HbA1c%, the urea, creatinine, and uric acid levels were significantly higher in the poor group than others. This finding is similar to result of Amartey *et al.* [30] that kidney dysfunction is more prevalent in diabetics than in non-diabetics. As a result, in diabetic patients, serum levels of urea and creatinine can be used as useful prognostic markers and predictors of renal failure [31, 32].

In the present study, there is a significant correlation between ferritin and alanine aminotransferase, as one of the hepatic enzymes. Cugy *et al.* [33] in a cohort study reported a significant relationship between ferritin and hepatic enzymes and inflammatory markers (ALT, AST, and gamma glutamyl transferase). In NAFLD, the most common abnormality in the liver is an elevated serum alanine aminotransferase (ALT) level [34].

This study has limitations. First, the small sample size may weaken the statistical power of our results. Second, this was a cross sectional study without longitudinal follow-up, therefore we were unable to determine a causal relationship between serum ferritin and fasting blood glucose, glycated hemoglobin, and alanine aminotransferase or other variables of diabetes mellitus.

5. Conclusion

This study concluded that there are significant correlations between serum ferritin and fasting blood glucose, glycated hemoglobin, and alanine aminotransferase. Mean ferritin values are significantly different in the three groups of glycated hemoglobin, therefore ferritin can be used as an indicator of control of glycemia and diabetic complications. Further studies on the causal relationship between elevated serum ferritin and laboratory parameters of diabetes mellitus are warranted.

Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

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