Poor Glycemic Control Correlates with Iron Deficiency Anemia in Type 2 Diabetes Mellitus

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Abstract

Background: Glycated hemoglobin (HbA1c) has been used extensively to diagnose and monitor diabetes mellitus (DM). Patients with type 2 DM are at risk of experiencing comorbidities and complications such as iron deficiency anemia (IDA). This study aimed to determine the correlation of HbA1c with iron deficiency anemia (IDA) in type 2 DM.

Methods: This cross-sectional study was conducted on 115 types 2 DM patients at a hospital in South Jakarta, Indonesia from November to December 2021. Data on HbA1c levels and IDA were obtained from medical records. Data were analysed with the chi-Square test and significancy at $p<0.05$.

Results: In total, 43 men and 72 women with type 2 DM were included, with predominantly age over 45 years (89.6%), had DM for more than ten years (55.7%), had obesity I (53.9%), and with hypertension as the most common comorbidity (65.2%). Furthermore, the patients did not smoke (64.3%), had poor glycemic control ((76.5%) and had anemia (58.3%). There was a significant relationship between HbA1c levels and IDA ($p=0.003$).

Conclusion: This study shows a relationship between HbA1c and IDA in type 2 DM, therefore, DM patients with poor glycemic control need to be well monitored for iron deficiency anemia.

Keywords: HbA1c, iron deficiency anemia, type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is still an important global health problem.[1] The International Diabetes Federation (IDF) data 2021 shows that at least 537 million people aged 20–79 years worldwide suffer from DM, equivalent to a prevalence rate of 10.5% of the population in the same age range.[2] In 2019, Indonesia ranks seventh among the ten countries with the most DM cases, comprising 10.7 million.[3] Laboratory tests are used for diagnosing and monitoring DM, such as glycated hemoglobin (HbA1c), the predominant hemoglobin found in the HbA1 fraction, accounting for 5% of the total normal adult hemoglobin and attaining 15% in DM.[4] The HbA1c assay, used for determining blood glucose during the last 2–3 months, is also the best single test for the risk of tissue damage caused by high blood glucose.[5] HbA1c is currently the gold standard for the diagnosis of DM. The use of HbA1c for diagnosis and therapeutic monitoring in patients with type 2 DM who have anemia requires caution because anemia may give rise to falsely high or low HbA1c results that do not correspond to the patient's condition.[3]

Patients with type 2 DM are at risk of various comorbidities and complications, including iron deficiency anemia (IDA). The incidence rate of IDA in type 2 DM without nephropathy has reached around 40 to 55%.[6,7] The primary mechanism underlying the relationship of type 2 DM with IDA is still unclear, but it is thought due to low-grade inflammation. Various studies have shown that patients with type 2 DM have significantly increased serum concentrations of hepcidin, tumor necrosis factor, and interleukin-6.[8–12]

Anemia as a worldwide health issue negatively impacts the quality of life and utilization of medical facilities. Therefore, anemia in patients with DM must be managed immediately after diagnosis, as this may

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lead to the pathogenesis and development of severe cardiovascular disease and diabetic nephropathy.[13] Moreover, type 2 DM patients aged over 60 years are also more susceptible to anemia.[13] In addition, the prevalence of anemia is higher in uncontrolled DM.[14]

Studies conducted in India have reported that there is definitely an inverse relationship between IDA with HbA1c levels in type 2 DM.[14,15] In IDA, HbA1c increases concomitanly with reduced hemoglobin concentrations due to iron deficiency.[14] Conversely, other studies report that HbA1c concentrations are lower in DM with IDA.[16,17] Studies on the correlation of HbA1c with IDA in type 2 DM have shown controversies, while additionally, the prevalence of DM in Indonesia and throughout the world is steadily increasing. This study aimed to determine the correlation of HbA1c with IDA in type 2 DM.

Methods

This cross-sectional study based on medical records was conducted at Metropolitan Medical Center Hospital in South Jakarta from November to December 2021, involving 115 respondents (43 males and 72 females). Data collection was carried out using the simple random sampling method. Patients of this study were mainly from the middle to high socioeconomic class. The inclusion criteria in this study were age over 18 years, diagnosis as type 2 DM with or without IDA, and availability of complete data on the laboratory results for HbA1c, complete blood count, and iron status, i.e. serum iron (SI), total iron binding capacity (TIBC), transferrin saturation, ferritin. The exclusion criteria were incomplete medical records, pregnancy, chronic kidney disease (CKD), neuropathy, and diabetic nephropathy.

The HbA1c concentration was categorized into good glycemic control (<6.5%), and signifying poor glycemic control (≥6.5%).[18] The diagnosis of IDA was established from the criterion of microcytic hypochromic anemia based on the morphology of peripheral blood smears and using one of the following indicators; a) presence of 2 out of 3 of the following parameters: SI <50 mg/dL, TIBC >350 mg/dL, or transferrin saturation <15%; b) serum ferritin concentration <20 mg/L.[19] The data were presented descriptively using percentage, mean, standard deviation if the data had normal distributions; median and minimum–maximum range if the data had abnormal distributions. The analysis of the HbA1c concentrations as compared to IDA used the chi-Square test at $p<0.05$. This study was approved by the Ethical Clearance Committee, Faculty of Medicine, Universitas Trisakti, no. 72/KER-FK/IX/2021.

Results

The majority of subjects were females (62.6%), aged ≥45 years (89.6%) with BMI 25 kg/m^2 (53.9%), and duration of DM >10 years (55.7%). The most frequent comorbidity was hypertension (65.2%). Most of patients did not have smoking history (64.3%) (Table 1).

Laboratory data showed that the majority of the patients had HbA1c ≥6.5% with a mean of 8.06±2.1 (Table 2), indicating that 23.5% had controlled DM. There was a strong relationship (p=0.003) between HbA1c and iron deficiency anemia (Table 3). On the other hand, there was no significant relationship between BMI (p=0.236), duration of DM (p=0.624), hypertension (p=0.190), and iron deficiency anemia.

Table 1 Clinical Characteristics of Type 2 DM Patients in Metropolitan Medical Center Hospital, Jakarta, Year 2021 (n=115)

Clinical Characteristic	n (%)
Gender	
Male	43(37.4)
Female	72 (62.6)
Age (years); mean±SD	61.25±13.58
≥45	103 (89.6)
<45	12 (10.4)
BMI (kg/m^2); mean±SD	25.77±4.31
≥25	62 (53.9)
<25	53 (46.1)
Duration of DM (years); mean±SD	12.64±5.11
>10	64 (55.7)
≤10	51 (44.3)
Comorbidities	
None	17 (14.8)
Hypertension	75 (65.2)
Allergy	9 (7.8)
Dyslipidemia	9 (7.8)
Pulmonary tuberculosis	5 (4.3)
Smoking history	
Smoker	41 (35.7)
Non-smoker	74 (64.3)

Note: BMI= Body mass index; SD= Standard deviation

Table 2 Laboratory Data of Type 2 DM Patients in Metropolitan Medical Center Hospital, Jakarta, Year 2021

Variable	n(%)	Median (min.–max.)
HbA1c (%); mean ±SD	8.06±2.1	
<6.5	27 (23.5)	
≥6.5	88 (76.5)	
Hemoglobin (g/dL); mean ±SD	11.39±3.21	
No anemia	48 (41.7)	
Anemia	67 (58.3)	
Iron status *		
SI (mg/dL)		26 (9–138)
TIBC (mg/dL)		334 (99–494)
Transferrin (%)		9.4 (2.4–49.5)
Ferritin (mg/dL)		12.54 (1.34–557.8)

Note: SI: serum iron; TIBC: total iron binding capacity, *= examined only in patients with anemia (67 subjects). Anemia: Hb <13 g/dL in adult men; Hb <12 g/dL in adult non-pregnant women.[19]

Table 3 Relationship between HbA1c, BMI, Duration of DM, Hypertension and Iron Deficiency Anemia in Patients with Type 2 Diabetes Mellitus

Variable	Iron Deficiency Anemia (IDA)		p-value
	Present	Absent	
HbA1c (%)			0.003*
<6.5	9	18	
≥6.5	58	30	
BMI			0.236
25 kg/m^2	33	29	
< 25 kg/m^2	34	19	
Duration of DM (years)			0.624
>10 years	36	28	
10 years	31	20	
Hypertension			0.190
Present	47	28	
Absent	20	20	

Note: : *= p<0.05 significant difference (chi-Square); BMI= body mass index; DM= diabetes mellitus

Discussions

The results of the study showed that the majority subjects (76.5%) have poor glycemic control, similar to other study showing that patients with higher HbA1c concentrations (7.3±0.9%) have more IDA.[15] Reduced bone marrow reticulocytes production in IDA, which is counteracted by delayed clearance of older erythrocytes by reticuloendothelial cells, results in increased HbA1c concentrations as a consequence of a longer lifespan of the earlier forms of erythrocytes and an increased in the mean age of circulating erythrocytes.[5]

The study has shown a significant relationship between HbA1c concentrations and IDA in patients with type 2 DM (p=0.003), consistent with previous studies, where the HbA1c concentration is increased or uncontrolled in type 2 DM patients with IDA.[14,15] On the other hand, patients with IDA may have lower HbA1c concentrations due to the severity of IDA.[16] In Indian society, where IDA is a nutritional problem, and local community members are of low socioeconomic status, the effect of HbA1c concentrations may have different results from our study on IDA, although not significantly different. We conducted the study in a hospital with patients mainly from the middle to upper socioeconomic class.[16]

IDA is inversely correlated with HbA1c concentration.[14] This indicates that when the Hb concentrations decrease in response to the severity of iron deficiency in patients with anemia, HbA1c rises accordingly.[14,20]

The increased lifespan of the red blood cells, in conjunction with the increase in HbA1c concentrations and the reduction in ferritin concentrations is found in the majority of IDA cases. The HbA1c concentrations in patients with diabetes are generally increased when these patients have an iron deficiency compared to the controls with adequate iron. Body iron is mainly stored as ferritin, indicating the body's iron load status.[15]

This study showed the importance of periodic examinations for iron status and Hb in patients with type 2 DM because iron and Hb might affect HbA1c to evaluate glycemic control, before planning the management of these patients.[14,15,17] There is a need for IDA screening to correct disorders before determining the treatment goal as the optimal control of HbA1c, especially when these concentrations are at the diagnostic threshold.[14,17] The mechanism of the relationship between type 2 DM and IDA is not known with certainty. Several hypotheses related to this topic include a) the occurrence of chronic inflammation in type 2 DM is caused by the activation of proinflammatory cytokines such as interleukin 6, interleukin 8, tumor necrosis factor α, and interferon γ; b) abnormalities in the production and release of erythropoietin by the kidneys and increased hepcidin concentrations in the liver; c) anemia is caused by the direct effect of a reduction in red cell lifespan mediated by proinflammatory cytokines; d) iron deficiency in type 2 DM increases the concentration of angiogenic factors, resulting in anemia; e) iron and proinflammatory cytokines increase oxidative stress, causing endothelial dysfunction and abnormalities in angiogenic balance, resulting in anemia.[8–12]

In this study, most of the anemia cases had BMI<25 kg/m^2, but no relationship between BMI and IDA in type 2 DM (p=0.236), similar to other study.[21,22] However, obesity is associated with cytokines and hepcidin release that may interfere with the utilization of iron, thereby increasing the risk of anemia. Studies conducted in China and Colombia have reported that anemia is less common in overweight or obese patients.[23,24] Serum ferritin levels in the obese group, rather than being lower, are approximately similar to those in the healthy control group, makes this parameter unreliable to be used.[21] Another explanation is that obesity may also be due to higher intakes of iron, protein, and other micronutrients consumed to prevent IDA.[25]

In this study, most anemia cases have a DM duration of more than ten years, however, no correlation between the DM duration with IDA incidence in patients with type 2 DM (p=0.624) as also reported in other study.[22] DM cases of more than five years duration tend to have anemia because the more prolonged exposure to hyperglycemia causes an increase in inflammatory cytokines with anti-erythropoietin effects, resulting in a reduction in the circulating red cell count. However, this may not be related because the duration of DM depends on the speed of the patient's treatment.[13]

The majority of anemia cases suffered from hypertension, however, no correlation of hypertension with IDA in patients with type 2 DM (p=0.190), as shown in another study.[26] Interestingly, hypertension in DM patients increases the risk of renal impairment and the subsequent development of anemia.[26,27] However, another study has reported that hypertension is not essential in determining DM cases at risk of anemia, which may be due to modifications in food consumption affecting the parameters mentioned above.[25]

The limitation of this study is the incomplete data on the parameters SI, TIBC, transferrin saturation, and ferritin in patients without anemia. Therefore, these parameters cannot be analyzed further in connection with the HbA1c concentrations.

To conclude, there is a relationship between HbA1c and IDA in type 2 DM. It is recommended that patients with type 2 DM and IDA should be treated for IDA before using HbA1c as a guide for diagnosis and therapeutic monitoring. Further studies are needed on the mechanism of IDA in type 2 DM.

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