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Original Article

Serum iron is negatively correlated with the HbA1c level in children and adolescents with type 1 diabetes mellitus

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Highlights

- The prevalence of low serum iron level in T1DM children and adolescents was high (45.4%).
- There was a moderate negative correlation between the serum iron and HbA1c levels in children and adolescents with T1DM.

Abstract. Although mainly affected by the blood glucose levels, the level of HbA1c could be influenced by other important factors, such as an iron deficiency, which is commonly found in children with type 1 diabetes mellitus (T1DM). However, a clinical judgment could not be established, as previous studies still reported conflicting results and lack of data regarding Indonesia. We aimed to evaluate the correlation between the serum iron and HbA1c levels in children with T1DM. This single-center cross-sectional study was conducted from February to October 2020 at Sanglah Hospital, Bali, Indonesia. Patients aged 1–18 yr were included in this study. The HbA1c and serum iron levels were evaluated in the blood samples. Spearman and partial correlation analyses were used to analyze the correlations between variables. The statistical significance was set at $P < 0.05$. Thirty-three subjects were analyzed, with a mean age of 11.24 ± 3.76 yr. Low serum iron and poor glycemic index were found in 54.5% and 69.7% of the subjects, respectively. Spearman correlation analysis revealed a low negative correlation between the serum iron and HbA1c levels (Spearman's rho = –0.376, $P = 0.031$). A partial correlation showed a moderate negative correlation (r = –0.473, $P = 0.013$) after adjusting for confounding variables. This study found a moderate negative correlation between the serum iron and HbA1c level in children and adolescents with T1DM.

Key words: serum iron, HbA1c, type 1 diabetes mellitus, children, adolescent

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Introduction

Diabetes mellitus (DM) is a global health problem that negatively affects the health, society, and economy of both developed and developing countries (1). Type 1 diabetes mellitus (T1DM) is the most common chronic childhood disease (2), affecting approximately 0.028 per 100,000 people in Indonesia in 2020 (3).

The HbA1c test is currently the standard parameter for assessing the long-term glycemic control in patients with T1DM. The latest recommendations from the International Society of Pediatrics and Adolescent Diabetes (ISPAD) in 2018 state that the management of patients with T1DM must achieve a target HbA1c level of < 7.0% in children and adolescents who have access to comprehensive care (4). This parameter could be used to estimate the risk of developing complications and the quality of glycemic control (5). The HbA1c levels are mainly influenced by serum glucose levels, although recent studies have reported that other factors, such as anemia (iron deficiency and hemolysis), hemoglobinopathies, acute or chronic blood loss, pregnancy, hemoglobin glycation index (high or low glycators), and uremia, could interfere with the HbA1c measurement results (4, 6).

Iron deficiency is a major nutritional problem worldwide (7) and has been found to be higher in patients with T1DM than in the general population (8). It is postulated that chronic inflammatory processes and the risk of celiac disease, which have a negative effect on iron absorption, may play a role in the development of iron deficiency in children with T1DM. The effect of iron deficiency on the HbA1c levels was first investigated by Brooks *et al.*(9) and several studies have reported similar results (10–14). Therefore, the potential effect of iron deficiency on the HbA1c levels should be observed by clinicians; additionally, the status of iron levels in children with T1DM should be adequately assessed before interpreting the HbA1c results (15).

Although previous studies have suggested an association between the iron status and HbA1c levels in children with T1DM, the evidence regarding this association in the pediatric population is still limited. Moreover, some studies have reported conflicting results (6, 15), which urges cautious application in the general population. The absence of data or similar research conducted in Indonesia warrants further investigation of the correlation between the serum iron levels and HbA1c levels in children with T1DM in different geographical locations, socio-economic backgrounds, and the prevalence of anemia or iron deficiency.

Material and Methods

Study design and population

A single-center cross-sectional study from February 2020 to October 2020 was performed in the inpatient ward and pediatric endocrinology clinic of Sanglah Hospital, a tertiary health facility in Denpasar, Bali, Indonesia. Children and adolescents aged 1–18 yr and diagnosed with T1DM were included. The exclusion criteria included patients with malabsorption disease or symptoms, chronic kidney disease, patients taking drugs that affect the iron and HbA1c levels, patients with chronic bleeding, malignancy, chronic inflammatory diseases, history of hemolytic anemia, history of thalassemia, or if the parents/guardians did not consent to participate in the study.

The sample size was determined by using a correlation formula. The r value was set at 0.49 from a previous study by Silva *et al.* (16). Based on this calculation, the sample size in this study included 30 children with T1DM. All the eligible children with T1DM treated at Sanglah Hospital were included in the study.

Data collection

Complete information about the study was provided to each parent/guardian who were asked to consent to cooperate in this research by signing a research approval letter. After obtaining informed consent, the parent/guardian was interviewed to collect basic characteristics, such as the place of birth, age, sex, and address. At the time of the interview, the body weight and height of the subjects were measured accordingly. The age at diagnosis, duration of diabetes, and total daily dose of insulin were extracted from the medical records. Additionally, blood samples were collected from each patient for HbA1c and serum iron evaluation.

Definition of variables

The age of the patient was determined at the time of the interview; the age was expressed in years, and partial years were rounded off to the nearest year. The subjects' sex was determined by phenotype and categorized into males and females. The age at diagnosis was defined as the age at first diagnosis of T1DM established by clinical and laboratory investigations and expressed in years. The diabetes duration was calculated by subtracting the examination date from the time of diagnosis. The nutritional status was measured based on the actual weight of the subjects compared to the ideal body weight (based on the World Health Organization [WHO] curve) by Waterlow. This variable was divided into the categories of obese (more than 120%), overweight (110–120%), well-nourished (90–110%), mild malnutrition (80–90%), moderate malnutrition (70–80%), and severe malnutrition (< 70%). The HbA1c levels were obtained from the results of the blood tests in the laboratory using the immunoturbidimetric assay method, and the serum iron levels were obtained using the Ferrozine method. The serum iron levels were presented as numeric and categorical variables (low iron serum level < 50 µg/dL and normal ≥ 50 µg/dL) (17). HbA1c was also presented as numeric and categorical variables (optimal glycemic control < 7.5%, moderate control 7.5–9%, and poor control

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> 9%) (18). Hemoglobin and mean corpuscular volume (MCV) were obtained from the complete blood count (CBC) that was taken simultaneously with the serum iron and HbA1c measurements. MCV was presented as a numeric variable, whereas hemoglobin was presented in both numeric and categorical variables (anemia or non-anemia). Anemia was defined as a hemoglobin level below the standard value for age and sex, based on the WHO criteria (19).

Statistical analysis

All analyses were performed using SPSS for Windows version 25.0. The characteristic data were expressed as mean (standard deviation) or median (interquartile range) for normally distributed or skewed continuous variables and as frequency and percentage for categorical variables. The data distribution of the numerical variables was analyzed using the Shapiro–Wilk test. The Spearman's test was used to determine the correlation between serum iron and HbA1c, hemoglobin, MCV, and the total daily dose of insulin. The results are reported in the form of Spearman's rank correlation coefficient (ρ), which reflects the direction and strength of the correlation. Finally, a partial correlation was performed to obtain the correlation coefficient between serum iron and HbA1c by controlling for other confounding variables. The statistical significance was set at $P < 0.05$.

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Udayana University/Sanglah Hospital, Denpasar (2552/UN.14.2.2.VII.14/LP/2019), and the Indonesian Ministry of Health, Directorate General of Health Services Sanglah Hospital (LB.02.01/XIV.2.2.1/4240/2020).

Results

During the study period, a total of 35 patients with T1DM were eligible; however, only 33 subjects were finally analyzed due to two subjects being unwilling to participate (**Fig. 1**).

Most subjects were female (72.7%) and well nourished (72.7%). The detailed baseline characteristics, including sex, age, nutritional status, age at diagnosis, duration of diabetes, and hemoglobin levels are reported in **Table 1.** This study found that the median serum iron level was 54.1 (40.7–67.5) g/dL. Approximately half of the participants (45.5%) had low serum iron levels. The average HbA1c level was 10.5%, and the majority of the subjects had poor glycemic control (**Table 1**).

A positive correlation was observed between the serum iron and hemoglobin levels (Spearman's rank correlation coefficient (ρ) = 0.368 and P = 0.035) and MCV (ρ = 0.353 and P = 0.044, respectively) (**Fig. 2**). The Spearman's rank correlation test revealed a significantly low negative correlation between serum iron and HbA1c levels (ρ = –0.376, P = 0.031) (**Fig. 3**) and no significant correlation with the total daily dose of insulin (ρ = –0.3, P = 0.869).

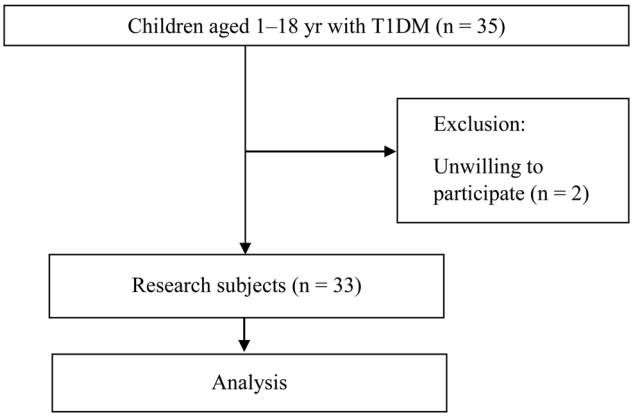

Fig. 1. Research scheme

After adjusting for confounding variables (age, sex, nutritional status, age at diagnosis, hemoglobin level, and duration of diabetes), a partial correlation analysis showed moderately negative serum iron and HbA1c levels (r = –0.473, P = 0.013) (**Table 2**).

Figure 4 shows that the mean HbA1c level in subjects with low serum iron and anemia was slightly higher than that in subjects with normal serum iron levels and non-anemia subjects. However, these differences were not statistically significant (P = 0.373 and P = 0.336, respectively).

Discussion

Our study revealed a moderately negative correlation between the serum iron and HbA1c levels after adjusting for other confounding variables. To our knowledge, this study is currently the first evidence of the correlation between the serum iron level and HbA1c in Indonesia and showcases the opportunity for further investigations of factors associated with glycemic control in children and adolescents with T1DM.

Based on the baseline characteristics, the female sex was predominant in our study (72.7%). This result was expected, as the epidemiological data show that T1DM is more prevalent in women in Indonesia (60%) (20). Contrasting results were reported by Rogers *et al.* (21) in the UK, who found that the incidence of diabetes mellitus was higher in males than females, with a ratio of 1.32 : 1. The main reason for the epidemiological differences between sexes is still unknown. These differences may be due to the differences in the population, race, and number of research subjects (22). Genetic influences on sex differences in T1DM were reported in a study sampled in the UK, USA, and Sardinia, which showed that diabetes mellitus was determined by the absence of the DR4 gene in HLA-DR3 positive patients. Moreover, they found an association between the Xp chromosome and the incidence of diabetes mellitus (23).

This study found that the average age of children diagnosed with T1DM was 9.06 ± 4.3 yr, and the

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Table 1. Characteristics of subjects

Variables	Total (n = 33)
Sex, n (%)	9 (27.3)
Male	24 (72.7)
Female	
Age, mean (SD) (yr)	11.24 (3.76)
Nutritional status, n (%)	24 (72.7)
Well-nourished	5 (15.1)
Mild malnutrition	2 (6.1)
Overweight	2 (6.1)
Obese	
Age at diagnosis, mean (SD) (yr)	9.06 (4.3)
< 5 yr, n (%)	6 (18.2)
5–10 yr, n (%)	12 (36.4)
> 10 yr, n (%)	15 (45.5)
Diabetes duration, median (interquartile range) (yr)	9 (6–13)
Insulin total daily dose, mean (SD) (unit/kg/d)	1.15 (0.18)
Hemoglobin, median (interquartile range) (gr/dL)	12.8 (12.1–13.3)
Anemia, n (%)	6 (18.2)
Non-anemia, n (%)	27 (81.8)
Mean corpuscle volume, mean (SD) (fL)	80.12 (7.3)
Iron serum level, median (interquartile range) (µg/dL)	54.1 (40.7–67.5)
Low, n (%)	15 (45.5)
Normal, n (%)	18 (54.5)
HbA1c level, mean (SD)	10.47 (2.4)
Moderate glycemic control, n (%)	10 (30.3)
Poor glycemic control, n (%)	23 (69.7)

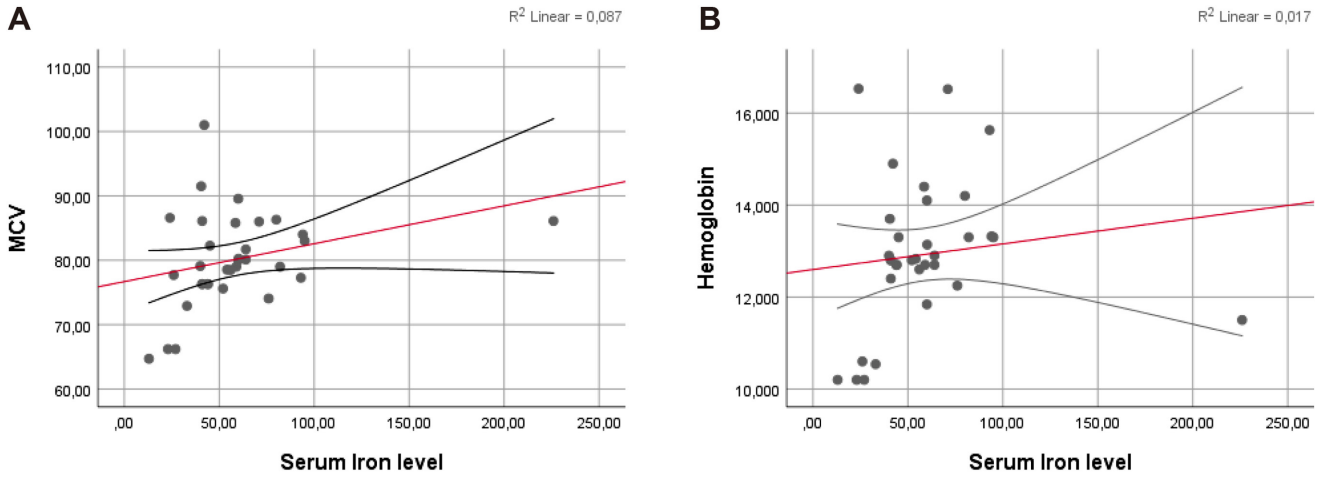

Fig. 2. Scatter plot shows the correlation between the serum iron level and hemoglobin (A) and MCV (B). Weak but significant correlations were found between the serum iron level and hemoglobin (The Spearman's rank correlation coefficient (ρ) was 0.368 and $P = 0.035$) and between the serum iron level and MCV (Spearman's rank correlation coefficient (ρ) was 0.353 and $P = 0.044$).

number of children diagnosed at the age of 5–10 yr was 12 subjects (36.4%) and the number of children aged over 10 yr was 15 subjects (45.5%). These results are in accordance with those of previous studies, which found that the peak incidence of T1DM occurred at the ages of 5–9 yr and 10–14 yr or puberty (24). The incidence of T1DM increases from birth to puberty, and subsequently decreases during the post-pubertal period (22). The increased incidence of T1DM at puberty is thought to be the result of metabolic and hormonal changes that affects insulin resistance in both men and women (25).

Glycemic control could be a challenge for long-term management, particularly in developing countries. The glycemic control of our subjects was predominately poor (69.7%). Similar results were reported by Taha *et al.* (26) in Sudan, in which more than three-quarters of children

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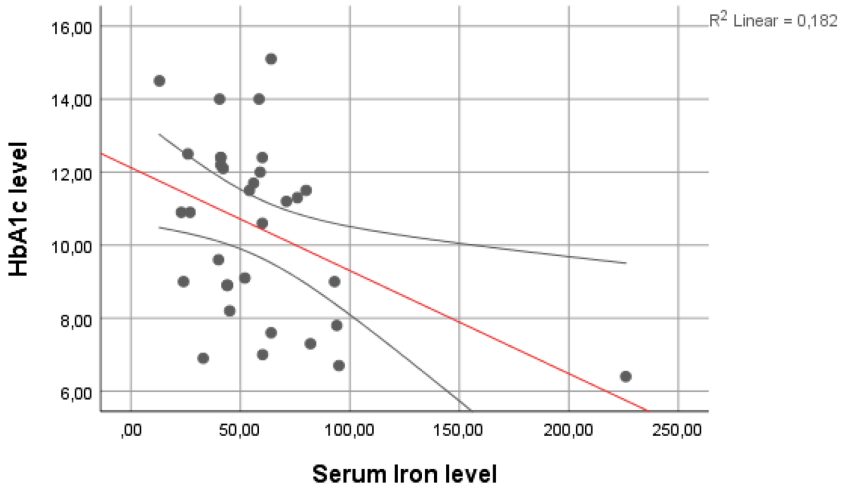

Fig. 3. The scatter plot shows a correlation between the serum iron and HbA1c levels. The Spearman's rank correlation coefficient (ρ) was –0.376 (weak negative correlation) with $P = 0.031$.

Table 2. Partial correlation between HbA1c and the iron serum level after adjusting the confounding variables

Adjusting	variables	r	*P* value
Age, sex, nutritional status, age at diagnosis, hemoglobin level, and duration of diabetes	Serum iron and HbA1c	–0.473	0.013*

r = correlation coefficient. * Significant < 0.05.

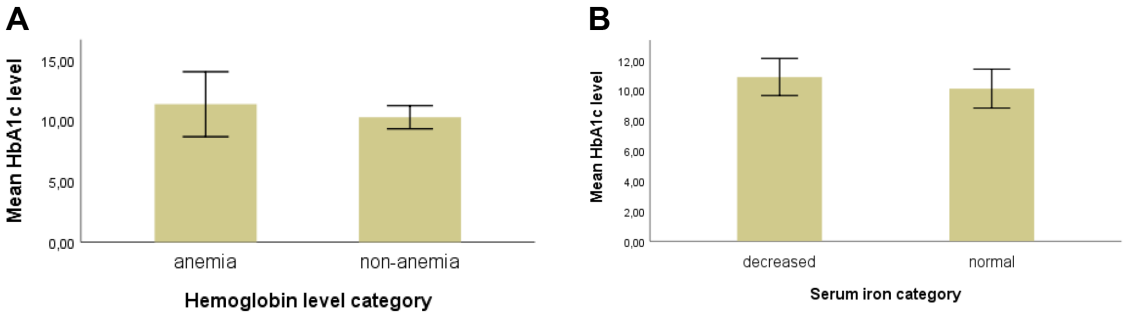

Fig. 4. The mean HbA1c level for each serum iron category (A) and hemoglobin category (B) subjects. The HbA1c level of the subjects with low serum iron were slightly higher (10.8 ± 2.2%) compared to normal (10.1 ± 2.6%). The HbA1c of anemia also higher compared to non-anemia subjects (11.3 ± 2.5% and 10.2 ± 2.4%, respectively). However, the differences were not significant ($P = 0.373$ and $P = 0.336$, respectively) (Error bars represent 95% confidence intervals).

and adolescents with T1DM exhibited poor glycemic control, and 80% had high blood glucose levels. The HbA1c targets for children and adolescents have continuously been developed. The latest ISPAD 2018 recommended a HbA1c value less than 7.0% for those who had access to insulin and regular blood glucose monitoring or use of CGM (4). However, individualized HbA1c targets are also emphasized in this recommendation, as several factors could be related, such as compliance, understanding symptoms, history of hypoglycemia, honeymoon phase, and hemoglobin glycation index (high or low glycators).

Fifteen subjects (45.5%) had low serum iron levels. This result is somewhat higher than that of previous studies that have shown a decrease in the iron levels in patients with T1DM. Tarim *et al.* (10) found that 11 of 37 (29.7%) children with T1DM had iron deficiency and the remaining 26 children (70.2%) had sufficient iron content. Salah *et al.*(11) screened 200 people with T1DM and found that 37.5% of the individuals with T1DM had anemia. The condition of anemia was dominated by iron deficiency, with 41 of 75 (54.7%) patients having T1DM, with a mean serum iron level of 57.0 ± 3.5 g/dL.

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El-Nezely *et al*. (12) found that 21 of 80 patients (26.3%), including children and adolescents with T1DM, had iron deficiency, and 73.7% had normal iron levels. Iron deficiency in children with T1DM can be caused by several factors (27). In patients with T1DM, there is a chronic inflammatory process characterized by an increase in the levels of proinflammatory cytokines, IL-6, and hepcidin. Hepcidin suppresses the flow of iron into the blood plasma by inhibiting the production of iron transporter proteins in macrophages, gut, and hepatocyte cells (28). The differences in some of these studies may be caused by demographic and socioeconomic differences in previous studies (8) and the high prevalence of children and adolescents suffering from anemia in Indonesia (29).

Serum iron is one of the parameters of systemic iron in the body, together with transferrin, total iron binding capacity, and ferritin. Ferritin is a recommended measurement that is highly specific for iron deficiency in the absence of other diseases. The serum iron alone could also describe the iron deficiency, and its level was reduced to less than 50 µg/dL under iron-deficient conditions (30). Our study found a significant positive correlation between the serum iron and hemoglobin levels and MCV. This means that lower serum iron levels result in a smaller MCV as a characteristic of iron deficiency anemia. Wojciak *et al*.(31) found that the lowest MCV value was observed in newly diagnosed T1DM patients compared to patients with a longer duration of disease. Concordantly, the lowest serum iron and highest HbA1c levels were also found in this patient group. This evidence supports the idea that serum iron levels could reflect iron deficiency in children and adolescents with T1DM.

We found a moderate negative correlation between the serum iron and HbA1c levels using the partial correlation test. Although various types of anemia can affect the HbA1c levels, iron deficiency is thought to be the main factor (32). So far, only small studies with similar objectives have been reported in child and adolescent populations. Research by El-Nezely *et al*. (12) in 80 children on insulin therapy in Egypt found a significant increase in the HbA1c levels in a group of patients with iron deficiency, even after HbA1c had been stratified for glycemic control. Similarly, Salah *et al*.(11) found that the HbA1c levels in the iron-deficiency group were significantly higher than those in the normal group. The HbA1c levels decreased significantly after iron supplementation in the iron-deficient group. Elngar *et al*.(13) reported a negative correlation between the HbA1c and serum iron levels ($r = -0.38$, $P = 0.00$) and ferritin levels ($r = -0.22$, $P = 0.04$). In contrast, Akkermans *et al*.(15), who conducted a prospective study on a group of 227 children and adolescents with type 1 diabetes mellitus, found no association between iron deficiency and HbA1c levels. They reported an HbA1c level of 65 ± 17 mmol/mol in the group of patients with reduced iron levels (both functional and absolute) compared to an HbA1c level of 65 ± 16 mmol/mol in the group without iron deficiency ($P = 0.815$). The differences in the results of this study may have been caused by demographic and research design differences. Akkermans *et al*. (15) divided decreased iron levels using different criteria from this study, namely, using the absolute and iron deficiency criteria from the WHO. Although our study found a significant moderate negative correlation between the HbA1c and serum iron levels, we failed to find a significant difference in the HbA1c levels between the anemia and low serum iron groups; however, the HbA1c levels in both the low serum iron and anemia groups were higher than those in the normal subjects. This may be due to the nature of this study to assess the correlation and the smaller sample size requirement. Therefore, further research is needed to characterize the iron deficiency and anemia using a single standard definition and requires larger samples from more than one study site for more representative data in Indonesia.

The total daily dose of insulin could reflect the economic status of the patient's family, as the socioeconomic status of families would influence the choice of management for children and adolescents with T1DM particularly, in areas that had no adequate reimbursement of devices by the national healthcare system or insurance companies (33). In our study, the total daily dose of insulin was not significantly correlated with the serum iron level. This was mainly because insulin therapy in Indonesia is covered by government national health insurance, and they are also routinely prescribed insulin that would be sufficient for one month. Therefore, the access to insulin therapy was considered adequate for each patient.

Although several studies have described the association between iron deficiency and HbA1c, the mechanism by which iron deficiency increases the HbA1c levels in children with T1DM cannot be explained clearly. One hypothesis claims that conditions of iron deficiency would decrease the production of red blood cells and subsequently increase the average age of the circulating red blood cells in the plasma. A longer mean age of erythrocytes tends to prolong the erythrocyte exposure to hyperglycemia and further increase the HbA1c levels (14). Another theory suggests that iron deficiency stimulates glycation of the terminal proline amino acid by modulating the structure of hemoglobin when the rate of red blood cell turnover decreases. Iron deficiency also stimulates hemoglobin glycation by peroxidation, wherein iron deficiency reduces the activity of iron-containing enzymes, which reduces the antioxidant capacity (34).

This study has some limitations that should be acknowledged. First, this study was only conducted at a single research location; therefore, generalization of the results obtained to the population of children and adolescents with T1DM should be performed cautiously. However, our site is a tertiary referral health facility; thus, the patients were representative of patients with T1DM in Bali, Indonesia. In addition, this limitation warrants further studies with larger sample sizes

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from several sites in Indonesia. Second, this study did not consider confounding factors, such as the dietary iron intake due to the difficulty in measuring the data precisely, especially in the extreme iron intake group (vegetarians). Third, we did not mention the possible effect of adherence to insulin administration, which may have affected the HbA1c levels. Apart from these limitations, our study could serve as the cornerstone of further research and suggests that much work needs to be done in the future.

Conclusion

This study found low serum iron levels and a poor glycemic index in 45.5% and 69.7% of children and adolescents with T1DM, respectively. A moderate negative correlation was observed between the serum iron levels and HbA1c in children and adolescents with T1DM after adjustment for age, sex, nutritional status, age at diagnosis, hemoglobin levels, and duration of diabetes.

Conflict of interests: The authors have nothing to declare.

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