Correlation of iron levels with glycemia and microvascular complications among type II diabetes mellitus patients in Najran university hospital

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ABSTRACT

Background: Diabetes is influenced by changes in the body's iron levels. Because iron deficiency anemia is common in diabetes, this study examines the link between iron, glycemic control, and complication in patients with type 2 diabetes mellitus (T2DM). Methods: The study is a cross-sectional study conducted from October 2019 to June 2020 at Najran university hospital in the Najran area, Saudi Arabia. All T2DM patients (N = 201) during the study were recruited by simple random sampling. A checklist was completed to extract the study variables from each patient's medical record. Results: There is a positive poor correlation between hemoglobin (Hb) and diabetic foot (r = 0.186, P < 0.05), but not with other diabetic microvascular complications (i.e., retinopathy, nephropathy, and peripheral neuropathy) or glycemic indicators fasting blood sugar, random blood sugar and hemoglobin A1C (i.e., FBS, RBS, and HbA1C). No link is found between ferritin and glycemic indicators or diabetic microvascular complications. Conclusion: The study suggests that particular attention be paid to regular monitoring of iron levels before modifying the treatment plans for type 2 diabetes mellitus (T2DM) patients. It raises critical inquiry about the reality of iron role in diabetes mellitus either in pathogenesis or treatment. It recommends accurately assessing body iron status with careful interpretation for better clinical judgment, encouraging large-scale and long-term epidemiological as well as interventional trials examining the effect of lowering iron in controlling glycemia.

Keywords: Glycemic control, Iron levels, Microvascular complications, Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common noncommunicable diseases globally. By 2045, the rate of diabetes is expected to affect 693 million people worldwide. Using epidemiological modeling, the prevalence of type two diabetes mellitus in Saudi Arabia is expected to reach 39.5% by 2022. Diabetic patients are at high risk to develop multiple complications, which may be acute or chronic. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs. This particularly includes the eyes, kidneys, nerves, heart, and blood vessels. Attaining and maintaining healthy glycemic control is the cornerstone of the prevention and management of diabetes. If clients control diabetes properly with medication and regular medical checkups, it is possible to maintain adequate glycemic control and thus reduce diabetic complications. Optimal monitoring of glycemic control involves fasting or random plasma glucose level and hemoglobin A1C measurement. Although hemoglobin A1C is the essential test for glycemic control.
careful considerations must be taken either in the measurement method or the interpretation of the results. HbA1c is not only altered by glucose levels, but also by other conditions such as anemia (nutritional/hemoglobinopathies), pregnancy, and chronic kidney diseases. A prospective study carried out over one year (January 2016–January 2017) showed that anemia is a common finding in T2DM patients when compared to the general population. Anemia in people with diabetes has significant adverse effects on their quality of life, and is associated with disease progression and the development of comorbidities. Most studies suggest that iron deficiency anemia (IDA) can have a significant impact on HbA1c with spuriously high HbA1c in IDA compared to other markers of glycemia. In fact, some studies suggest that in patients both with and without diabetes, IDA is associated with higher HbA1c. IDA can increase red blood cell turnover, which can then increase glycation of Hb, leading to higher HbA1c values. These higher values can be observed in blood loss, hemolysis, hemoglobinopathies, red cell disorders, and myelodysplastic disease. There is research to support that diabetes is influenced by changes in the body's iron levels. Lower levels of serum iron or serum ferritin have been linked to increased glycation of HbA1c; however, other studies have shown no correlation between markers of iron storage (ferritin) and increased HbA1c. Iron deficiency anemia is a widespread diagnosis in primary health care centers, and it is easy to detect and treat. Consequently, raising awareness among primary care physicians of the association of this diagnosis with complications of diabetes may enhance doctors’ attention to examine the presence of iron deficiency anemia and treat it, and know its impact on the accuracy of Hemoglobin A1c readings and complications in patients with T2DM. This study evaluates the correlation between iron, glycemic control, and complication in patients with T2DM in family practice clinics, Najran university hospital.

**Objectives**

1. Examine the correlation between hemoglobin (Hb) levels, glycemic indicators, and microvascular complications.
2. Examine the correlation between ferritin levels, glycemic indicators, and microvascular complications.

**Study design**

The study was cross-sectional, conducted from October 2019 to June 2020 at Najran university hospital in the Najran area, in the Southern region of Saudi Arabia. The Najran university hospital serves all university staff, students, and their families. The hospital served 41,048 patients in 2018.

All T2DM patients (N = 201) treated at the out-patient clinic during the study were recruited by simple random sampling. A checklist was completed to extract the study variables from each patient’s medical record.

The primary intended study variable was iron levels in the forms of Hb and ferritin. For ferritin, participants were classified into three groups: low (less than 30 µg/L), normal (30 µg/L to 400 µg/L), and high (greater than 400 µg/L). Regarding Hb levels, participants were classified into low (less than 13.5 g/dL), normal (13.5 g/dL to 17 g/dL), and high (greater than 17 g/dL).

The study’s dependent variables were indicators of glycemic status, hemoglobin A1C (HbA1c), preprandial capillary plasma glucose, and postprandial capillary plasma glucose. According to the American Diabetes Association’s (ADA) Standards of Care recommendations, participants were considered to have controlled diabetes if their HbA1c was less than 7%, preprandial capillary plasma glucose 80–130 mg/dL (4.4–7.2 mmol/L), and peak postprandial capillary plasma glucose <180 mg/dL (10.0 mmol/L). In addition, controlled diabetes excluded diagnosed microvascular complications (retinopathy, nephropathy, peripheral neuropathy, and diabetic foot).

The ethical committee of the faculty of medicine at Najran university along with Najran university hospital administration approved the study with the agreement that study’s researchers were committed to using the data for study purposes only and would self-fund all associated costs.

All statistical analyses were carried out using R Statistical Software (Version 3.6.0). The mode was estimated for each variable of interest. Spearman’s ρ was computed for variables of interest. An 0.10 ≤ ρ ≤ 0.20 was considered a poor correlation between pairs; an 0.3 ≤ ρ ≤ 0.50 was considered a fair correlation between pairs; a 0.6 ≤ ρ ≤ 0.70 was considered a moderate correlation between pairs; a 0.8 ≤ ρ ≤ 0.90 was considered a strong correlation; ρ = ±1 was considered a perfect positive or negative correlation between pairs. The level of statistical significance was set at 0.05. The listwise method was used for handling missing data. We did not use mode, or hot or cold deck imputation as they increase the chance of committing type I error. The effect size (ES) of differences for each variable of interest was estimated using Cohen’s d. The most promising correlation coefficients were then identified as those with moderate (0.3) or large (0.5) ES for each comparison of interest.

**Results**

The majority of the sample contained male participants (n = 121, 60.2%), mostly aged between 30 and 60 years (n = 131, 65.2%). Of the 201 patients, 63.7% (n = 128) received oral antiglycemic medications, followed by 29.4% (n = 59) who received a mixed treatment and 6% (n = 12) who received injections.

Table 1 shows a positive poor correlation between Hb and diabetic foot (ρ = 0.186, P < 0.05), but no correlation was
found for the other diabetic microvascular complications’ variables of interest (i.e., retinopathy, nephropathy, and peripheral neuropathy). Likewise, no correlation was observed between Hb and glycemic indicators (i.e., FBS, RBS, and HbA1c).

Table 2 shows no correlation between ferritin and glycemic indicators (i.e., FBS, RBS, and HbA1c). Likewise, there was no correlation between ferritin and diabetic microvascular complications (i.e., retinopathy, nephropathy, peripheral neuropathy, and diabetic foot).

Discussion

A number of recent studies have shown a relationship between changes in iron levels and the emergence of T2DM, and its complications.[8] The present study aimed to investigate this relationship more in-depth.

The majority of iron is contained in red blood cell Hb and circulating ferritin, and generally correlates with body iron stores.[21] While a proper state of glycemic control is assessed through glycemic indicators (e.g., HbA1C, FBS, and RBS), treatment usually targets lipid and renal profiles, as well as the occurrence of diabetic microvascular complications.

Many studies have established a clear contribution of iron in T2DM pathogenesis; however, the exact relationship is still not fully understood.[21-23] It appears that iron has multiple effects on beta cells, which can be either pro- or anti-diabetic. A certain level of iron is needed for metalation of proteins for glucose’s oxidation and sensing, but excess iron is also toxic.[21]

The current study showed a positive poor correlation between Hb and diabetic foot (r = 0.186, P < 0.05), but no correlation with other diabetic microvascular complications (i.e., retinopathy, nephropathy, and peripheral neuropathy). This finding is consistent with recent literature showing that in patients with diabetic foot ulceration, anemia is a common problem.[29] The present findings are in contrast with other cross-sectional studies, which have suggested that lower hemoglobin levels were associated with an increased risk of diabetic peripheral neuropathy (DPN).[28] Although recent studies have reported that DPN is commonly associated with a greater degree of anemia and have shown a significant correlation between a lower Hb and a decline in the GFR, these studies have identified diabetic patients with anemia as an at-risk group when requiring renal replacement therapy.[30]

This study did not find an association between HB and nephropathy in diabetes, nor did it find an association between low Hb and retinopathy among diabetics. This is in contrast to certain studies that reported that anemia contributes to diabetic retinopathy (DR), and that there is an association between the grades of anemia and severity of DR.[27,28] Another cross-sectional study with a large sample (N = 2123) conducted in Korea concluded that high Hb is significantly linked to a low risk of retinopathy.[29] This difference between the results of this study and previous studies can be explained by the fact that we relied on the information available in patients’ records. There may have been either undiagnosed or undocumented diabetic microvascular complications (i.e., retinopathy, nephropathy, and peripheral neuropathy).

Regarding a link between Hb and glycemic indicators (i.e., FBS, RBS, and HbA1c), the present study did not show any association.

### Table 1: Correlation coefficient between Hb, glycemic indicators, and microvascular complications

| Hb   | Retinopathy | Nephropathy | P. Neuropathy | D. Foot | FBS | RBS | HbA1c |
|------|-------------|-------------|---------------|---------|-----|-----|-------|
| Hb   | 1           | -0.011      | -0.069        | 0.186*  | -0.017 | 0.105 | 0.022 |
| Retinopathy | 1           | 0.321***    | 0.161*        | 0.052   | -0.073 | -0.050 | 0.014 |
| Nephropathy | 1           | 0.052       | 0.088         | 0.003   | -0.059 | -0.040 |       |
| P. Neuropathy | 1           | 0.172*      | -0.194*       | -0.122  | -0.164* |       |       |
| D. Foot | 1           | -0.005      | 0.148         | -0.051  |       |       |       |
| FBS   | 1           | 0.337***    | 0.366***      |       |       |       |       |
| RBS   | 1           | 0.377***    | 0.366***      |       |       |       |       |
| HbA1c | 1           |             |               |         |       |       |       |

NS=not significant (P>0.05), *P<0.05, **P<0.01, ***P<0.001

### Table 2: Correlation between ferritin, glycemic indicators, and microvascular complications

| Ferritin | Retinopathy | Nephropathy | P. Neuropathy | D. Foot | FBS | RBS | HbA1c |
|----------|-------------|-------------|---------------|---------|-----|-----|-------|
| Ferritin | 0.125       | -0.154      | -0.083        | 0.082   | -0.024 | 0.118 | 0.081 | 0.107 |
| Retinopathy | 1           | 0.321***    | 0.161*        | 0.052   | -0.073 | -0.050 | 0.014 |
| Nephropathy | 1           | 0.052       | 0.088         | 0.003   | -0.059 | -0.040 |       |
| P. Neuropathy | 1           | 0.172*      | -0.194*       | -0.122  | -0.164* |       |       |
| D. Foot | 1           | -0.005      | 0.148         | -0.051  |       |       |       |
| FBS   | 1           | 0.337***    | 0.366***      |       |       |       |       |
| RBS   | 1           | 0.377***    | 0.366***      |       |       |       |       |
| HbA1c | 1           |             |               |         |       |       |       |

NS=not significant (P>0.05), *P<0.05, **P<0.01, ***P<0.001
In contrast, one study suggested that low Hb plays a significant role in elevating A1C even with controlled blood glucose levels. These authors confirmed that Hb levels are positively correlated with insulin resistance and insulin secretion. However, a study conducted in Japan suggested that hemoglobin levels have a significantly negative effect on early-phase insulin secretion in nondiabetic males. The discrepancy between these findings can be explained by the different methods used, and/or by other physiological/analytical factors. If anemia is highly prevalent in diabetes, there might be an increase in microvascular complications. Thus, we suggest that particular attention be paid to regular monitoring of Hb, considering low Hb before modifying treatment plans, and reducing the occurrence and/or progression of diabetic microvascular complications.

Looking now to ferritin, this study observed no relationship between ferritin and blood sugar indicators, nor with microvascular complications. Similarly, in other studies, there was no association between ferritin and glycemic indices, where adjustment of metabolic syndrome components produced a null result; however, a systematic review and meta-analysis involving 185,462 participants found associations between body iron levels and diabetes. While decreased serum ferritin is a sensitive and specific test of low body iron stores, elevated serum ferritin is sensitive but very nonspecific. About 90% of causes of high ferritin are inflammation, infection, obesity, diabetes, metabolic syndrome (dysmetabolic hypersecretotena), alcohol, and malignancy.

A link between ferritin and nephropathy among diabetes has indeed been reported. The progression of diabetic nephropathy can be prevented either by an iron-deficient diet or by chelators. Conversely, one study suggested that iron plays no major role in the development of DR; however, it has been noted that iron overload appears to be the result of complex processes involved in DR. Despite the lack of consistent findings, hyperglycemia is still the primary pathogenic factor contributing to diabetic neuropathy. Also, several factors may contribute to diabetic neuropathy based on iron dysregulation. An in vitro study at a molecular model found an association between diabetic neuropathy and high iron under high-glucose concentration. In summary, considering the high number of contradictions in findings with similar studies, this study raises critical inquiry about the reality of iron role in diabetes mellitus either in pathogenesis or treatment.

Conclusion

The relationship between iron dysregulation, glycemia, and microvascular complications in diabetes is conflicted. Is there an established link? Is the relationship causal? If so, which might affect the other? To better understand this complex relationship, we recommend the following:

1. To develop better clinical judgment regarding iron, in terms of accurately assessing body iron status with careful interpretation.

2. To gain a deep understanding of the role of iron levels in diabetes, involving large-scale and long-term epidemiological studies of different age groups, genders, and ethnicities.

3. To increase the number of interventional trials examining the effect of lowering iron in controlling glycemia, and the prevention of microvascular complications among diabetes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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