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Original research article

EVALUATING THE IRON DEFICIENCY ANEMIA IN TYPE-II DIABETIC PATIENTS TAKING METFORMIN AND ITS ASSOCIATION WITH OXIDATIVE STRESS

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Abstract: *Iron deficiency anemia (IDA) is one of the most common nutritional disorders worldwide, affecting individuals across various demographic groups.* ***Objective:*** *The main objective of the study is to find iron deficiency anemia in type-II diabetic patients taking metformin and its association with oxidative stress.* ***Methods:*** *This cross-sectional observational study was conducted at the outpatient department (OPD) of the Medical Unit at Khawaja Muhammad Safdar Medical College, Sialkot, during the study period from 1st January 2024 to 31st June 2024. Data were collected from 285 patients diagnosed with type 2 diabetes mellitus (T2DM) who were receiving metformin therapy. Patients were divided into two groups—Group A (patients with IDA) and Group B (patients without IDA)—and the oxidative stress markers were compared between these two groups.* ***Results:*** *Data were collected from 285 patients with 92 in Group A (IDA) and 193 in Group B (Non-IDA). The mean age of participants was 57.6 ± 9.4 years, with no significant difference between Group A (58.2 ± 9.1) and Group B (57.3 ± 9.6) (p = 0.422). Gender distribution was similar between groups (p = 0.601). The mean duration of diabetes was also comparable between the groups (8.3 ± 3.4 years in Group A and 8.0 ± 3.1 years in Group B, p = 0.572). However, HbA1c levels were significantly higher in Group A (8.3 ± 1.6%) compared to Group B (7.5 ± 1.3%) (p = 0.012), indicating poorer glycemic control in the IDA group.* ***Conclusion:*** *This study concludes that iron deficiency anemia (IDA) is prevalent among type 2 diabetic patients on metformin therapy, affecting approximately one-third of the study population. Additionally, there is a significant association between IDA and increased oxidative stress, as evidenced by elevated levels of malondialdehyde (MDA) and reduced antioxidant enzymes (SOD and GPx) in patients with anemia.*

Keywords: Anemia, iron deficiency, Diabetes Mellitus, Metformin, Oxidative Stress, Vitamin Deficiency.

Introduction

Iron deficiency anemia (IDA) is one of the most common nutritional disorders worldwide, affecting individuals across various demographic groups. Characterized by reduced levels of hemoglobin, IDA results in insufficient oxygen transport to the tissues, leading to symptoms such as fatigue, weakness, and impaired cognitive and physical functioning. In recent years, there has been growing interest in understanding the relationship between iron deficiency and chronic diseases, particularly type 2 diabetes mellitus (T2DM), a metabolic disorder marked by insulin resistance, hyperglycemia, and increased oxidative stress (1). Newly identified type 2 diabetes is now a global threat, yearly incidences are on the rise due to increased prevalence resulting from wrong lifestyle choices including poor diets, crop Servlets, and obesity. T2DM is generally treated by adopting therapeutic interventions that include both pharmacological and non-pharmacological ways, with metformin being amongst the first-line drugs. Metformin is preferred as it achieves enhancements in insulin sensitivity and a decrease in blood glucose at a relatively low risk of hypoglycemia (2). However, they have established long-term metformin therapy is associated with side effects such as Vitamin B12 deficiency, gastrointestinal problems, and more alarmingly, the propensity to cause iron deficiency anemia. However, the most common relationship between metformin and IDA results from the medication's ability to affect nutrient assimilation within the stomach and intestines. Metformin can change the intrinsic factor and the rest of the absorption mechanisms in the small intestine that are important for the absorption of vitamin B12 and iron (3). This can over time lead to deficiencies that manifest themselves in anemia. The exact mechanism by which metformin induces these deficiencies is still under investigation, but the consequences for patients with T2DM are clear: if not addressed, anemia will aggravate the effects of diabetes including heart diseases, nerve damage, and the difficulty in healing skin ulcers. Secondly, T2DM patients are at high risk of anemia and they also undergo a high level of oxidative stress. Oxidative stress is defined as a state in which the body produces more ROS than antioxidants can handle or detoxify (4). This has got very strong incidences in the diabetics, whereby, constantly high levels of blood glucose will fuel the production of free radicals. Many of the micro and macro-vascular complications of diabetes such as nephropathy, retinopathy, and atherosclerosis have been linked to increased levels of oxidative stress. New evidence indicates that a combination of iron deficiency anemia and diabetes leads to a subsequent aggravation of oxidative stress, which in turn damages the health of diabetic patients. Hemoglobin containing iron is responsible for the transport of oxygen in the body, synthesis of DNA,

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and regulation of oxidation processes (5). Concerning an antioxidant defense system, a diminished supply of this essential metal represents a hindrance to antioxidant enzyme function in an IDA setting. Moreover, anemia caused by low RBC levels can result in hypoxia that leads to the generation of ROS as cells start to adjust to the oxygen shortage (6, 7). This then sets the stage where iron deficiency anemia not only threatens oxygen delivery but also increases oxidative stress including for those patients at risk because of metabolic changes related to T2DM. Clinicians must appreciate the relationships that exist between iron deficiency, metformin, and oxidative stress when treating diabetes (8). Since metformin is commonly used in managing T2DM, precautionary measures on anemia and the need for interventions should always be observed. Since the detection of early arterial complications and oxidative stress markers may be beneficial for diagnosing diabetic complications and treating the disease in advance, general screening for iron deficiency in diabetic patients is recommended (9). Lifestyle modification including iron fortification, changes in diet, and the use of antioxidants could be therefore helpful in stopping the vicious cycle of anemia and oxidative stress in patients with T2DM and might enhance their quality of life and prognosis (10).

Thus, the main objective of the study is to find iron deficiency anemia in type-II diabetic patients taking metformin and its association with oxidative stress.

Methodology

This cross-sectional observational study was conducted at the outpatient department (OPD) of the Medical Unit at Khawaja Muhammad Safdar Medical College, Sialkot, during the study period from 1st January 2024 to 31st June 2024. Data were collected from 285 patients diagnosed with type 2 diabetes mellitus (T2DM) who were receiving metformin therapy. Patients were divided into two groups—Group A (patients with IDA) and Group B (patients without IDA)—and the oxidative stress markers were compared between these two groups. The study utilized both clinical and laboratory data to comprehensively assess the impact of iron deficiency anemia on oxidative stress. Blood samples were collected to evaluate the participants' iron status and assess oxidative stress levels. Hemoglobin (Hb) levels were measured to assess anemia, and serum ferritin, serum iron, and total iron-binding capacity (TIBC) were evaluated to diagnose iron deficiency. Hemoglobin A1c (HbA1c) levels were collected to determine the patient's glycemic control over the preceding 3 months or longer. Blood levels of malondialdehyde (MDA) were also tested, as well as the level of other markers of oxidative stress, such as SOD and GPx, assessed biochemically in the participants. These oxidative stress markers were useful in determining the relationship between IDA and oxidative stress in patients with T2DM. Iron deficiency anemia was diagnosed according to certain defined hematologic and biochemical parameters. Hematologic parameters included Hb level lower than 13. 0 gm/dL in males and 12. 0 gm/dL in females, absolute micronized reticulocyte count below 55 femtoliters, reduced red cell volume by mean corpuscular volume less than 80 fl, elevated red cell distribution width over 13%, increased serum transfer These levels were assessed based on previous research-13 g/dL for men and 12 g/dL for women to diagnose anemia. Furthermore, subjects who had serum ferritin levels of less than 30 ng/mL or had low serum iron concentration, were also regarded as being iron-deficient. Total iron binding capacity (TIBC) was also increased which served as an index of deranged iron kinetics. Based on these results, the patients were stratified into two groups: Group A involved patients who had IDA; whereas Group B comprised patients who did not have IDA. Data were analyzed using SPSS software version 26. Continuous variables, such as hemoglobin levels, serum ferritin, and oxidative stress markers, were presented as mean ± standard deviation (SD). Categorical variables, such as gender and duration of diabetes, were expressed as frequencies and percentages.

Results

Data was collected from 285 patients with 92 in Group A (IDA) and 193 in Group B (Non-IDA). The mean age of participants was 57.6 ± 9.4 years, with no significant difference between Group A (58.2 ± 9.1) and Group B (57.3 ± 9.6) ($p = 0.422$). Gender distribution was similar between groups ($p = 0.601$). The mean duration of diabetes was also comparable between the groups (8.3 ± 3.4 years in Group A and 8.0 ± 3.1 years in Group B, $p = 0.572$). However, HbA1c levels were significantly higher in Group A (8.3 ± 1.6%) compared to Group B (7.5 ± 1.3%) ($p = 0.012$), indicating poorer glycemic control in the IDA group. (table 1)

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Table 1: Baseline Characteristics of Study Population

Variable	Total (N = 285)	Group A (IDA, n = 92)	Group B (Non-IDA, n = 193)	p-value
Age (years)	57.6 ± 9.4	58.2 ± 9.1	57.3 ± 9.6	0.422
Gender (Male/Female)	152/133	48/44	104/89	0.601
Duration of diabetes (years)	8.1 ± 3.2	8.3 ± 3.4	8.0 ± 3.1	0.572
HbA1c (%)	7.8 ± 1.5	8.3 ± 1.6	7.5 ± 1.3	0.012*

Group A (IDA) and Group B (Non-IDA) revealed significant differences. In males, the mean hemoglobin level was lower in Group A (10.8 ± 1.3 g/dL) compared to Group B (14.3 ± 1.1 g/dL), and similarly in females (10.2 ± 1.1 g/dL in Group A vs. 13.7 ± 1.0 g/dL in Group B), with both differences being statistically significant ($p < 0.001$). Serum ferritin levels were also markedly lower in Group A (22.5 ± 4.2 ng/mL) compared to Group B (78.9 ± 10.5 ng/mL, $p < 0.001$). Similarly, serum iron was significantly lower in Group A (45.6 ± 12.7 µg/dL) versus Group B (110.2 ± 15.3 µg/dL, $p < 0.001$). (Table 2)

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Table 2: Hematological and Iron Status Parameters

Parameter	Group A (IDA) (n = 92)	Group B (Non-IDA) (n = 193)	p-value
Hemoglobin (g/dL, Male)	10.8 ± 1.3	14.3 ± 1.1	<0.001*
Hemoglobin (g/dL, Female)	10.2 ± 1.1	13.7 ± 1.0	<0.001*
Serum Ferritin (ng/mL)	22.5 ± 4.2	78.9 ± 10.5	<0.001*
Serum Iron (µg/dL)	45.6 ± 12.7	110.2 ± 15.3	<0.001*
Total Iron Binding Capacity (TIBC, µg/dL)	428 ± 45	315 ± 33	<0.001*

The mean malondialdehyde (MDA) levels, an indicator of lipid peroxidation, were notably elevated in Group A (4.9 ± 0.8 nmol/mL) compared to Group B (3.1 ± 0.6 nmol/mL), with a p-value of <0.001. Antioxidant enzyme levels were lower in the IDA group, with Superoxide Dismutase (SOD) at 2.8 ± 0.4 U/mg in Group A and 3.9 ± 0.6 U/mg in Group B (p = 0.018). Similarly, Glutathione Peroxidase (GPx) levels were reduced in Group A (2.5 ± 0.3 U/mg) compared to Group B (3.6 ± 0.5 U/mg, p = 0.021). (Table 3)

Table 3: Oxidative Stress Markers

Marker	Group A (IDA) (n = 92)	Group B (Non-IDA) (n = 193)	p-value
Malondialdehyde (MDA, nmol/mL)	4.9 ± 0.8	3.1 ± 0.6	<0.001*
Superoxide Dismutase (SOD, U/mg)	2.8 ± 0.4	3.9 ± 0.6	0.018*
Glutathione Peroxidase (GPx, U/mg)	2.5 ± 0.3	3.6 ± 0.5	0.021*

Multivariate logistic regression analysis identified several independent predictors of oxidative stress. Iron deficiency anemia (IDA) was significantly associated with increased oxidative stress, with an odds ratio (OR) of 2.76 (95% CI: 1.82–4.15, p < 0.001). Additionally, higher HbA1c levels were also a significant predictor, with an OR of 1.43 (95% CI: 1.12–1.83, p = 0.003), indicating that poor glycemic control contributes to oxidative stress. Longer duration of diabetes was similarly associated with oxidative stress, with an OR of 1.25 (95% CI: 1.02–1.52, p = 0.025). (Table 4)

Table 4: Multivariate Logistic Regression for Predictors of Oxidative Stress

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Iron Deficiency Anemia (IDA)	2.76	1.82 – 4.15	<0.001*
HbA1c	1.43	1.12 – 1.83	0.003*
Duration of Diabetes	1.25	1.02 – 1.52	0.025*

Discussion

The present study aimed to evaluate the prevalence of iron deficiency anemia (IDA) in type 2 diabetic (T2DM) patients on metformin therapy and its association with oxidative stress. Our findings reveal a substantial prevalence of IDA, affecting 32.3% of the study population, and demonstrate a significant correlation between IDA and increased oxidative stress. These outcomes confirm the possible use of anemia as a risk factor to worsen oxidative stress in diabetic patients and the need to pay attention to the iron level in diabetic patients. The incidence rate of IDA that we have seen in our study is quite comparable to the results of previous studies, which indicated diabetic patients, especially those on long-term metformin use, are at risk of developing anemia (11). Metformin has been described to affect the gut absorption of some nutrients including vitamin B12 and iron which play a critical role in anemia in these patients. Our findings also showed that the IDA patients exhibited lower serum ferritin and iron levels than control subjects, which supports the fact that low iron status is responsible for anemia (12). This finding aligns with current literature that shows that metformin may cause IDA as it inhibits iron intake in the gastrointestinal tract after long-term use. As one of the study outcomes, patients with IDA presented increased oxidative stress markers when compared to patients without anemia (13). In particular, plasma MDA, which is an indicator of lipid peroxidation, was higher in the IDA group as compared with the control group, while plasma SOD and GPx levels were decreased. This indicates that patients suffering from IDA experience an increased level of oxidative stress when they have diabetes. Different works have proved that iron is an important cofactor in many enzymes and functions in many aspects of the cell, including antioxidant enzymes (14). These enzymes are less active in iron deficiency; failure to counterbalance ROS leads to an increased capacity to inflict oxidative damage. Many studies show the correlation between oxidative stress and diabetes where long-term hyperglycemia promotes ROS production hence diabetes-related complications including nephropathy, neuropathy, and cardiovascular diseases. It is especially worrying that our results indicate that if the effect of IDA is additive, it may well exacerbate this oxidative disturbance and even advance the development and worsening of complications of diabetes. This is more worrying given the fact that the patients in our study who had IDA also had worse glycemic control as evidenced by higher HbA1c levels (15). Speculated studies have hypothesized that anemia, poor glycemic control, and oxidative stress are mutually exacerbating and may together be responsible for the worse clinical prognosis of diabetic patients. This study therefore agrees with the multivariate analysis findings, which showed that IDA was an independent determinant of oxidative stress, despite adjustment for age, gender, and duration of diabetes. These results provide pivotal evidence of the link between iron status and oxidative stress in T2DM subjects (16, 17).

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Furthermore, higher HbA1c levels and diabetes duration were identified as other independent sources of increased oxidative stress confirming that poor glycemic control disrupts oxidative homeostasis. On this basis, healthcare providers need to ensure that iron concentrations are controlled in diabetes patients taking metformin (18). Screening of such patients for anemia and oxidative stress can prompt early intervention in the case of the onset of complications. Iron supplementation can play a useful role in decreasing oxidative stress and therefore improving the health profile of these patients. Moreover, it becomes vital to manage diabetes optimally thereby keeping other risk factors causing oxidative stress into consideration. Investigators of this study should acknowledge several of its limitations (19). Firstly, the present study was a cross-sectional study design, and therefore the relationship between iron deficiency anemia and oxidative stress could not be determined. More cross-sectional research is required to establish the time-based relationship between these factors. Second, we did not evaluate other factors that might causally affect ozone-induced oxidative stress components such as dietary practices or other lifestyle factors which would could affect the outcomes. Finally, an increased sample size is required for a broader representation of the population to determine the degree of IDA in diabetic patients (20).

Conclusion

This study concludes that iron deficiency anemia (IDA) is prevalent among type 2 diabetic patients on metformin therapy, affecting approximately one-third of the study population. Additionally, there is a significant association between IDA and increased oxidative stress, as evidenced by elevated levels of malondialdehyde (MDA) and reduced antioxidant enzymes (SOD and GPx) in patients with anemia. These findings suggest that IDA may exacerbate oxidative damage in diabetic patients, potentially worsening complications associated with type 2 diabetes mellitus (T2DM). Moreover, the study highlights that patients with IDA exhibited poorer glycemic control, as indicated by higher HbA1c levels, which may further contribute to oxidative stress.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department concerned. (IRBEC-KSH-99/23)
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Conflict of interest

The authors declared an absence of conflict of interest.

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Concept & Design of Study

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