Original Research

SERUM HEPCIDIN PROFILES IN TYPE 2 DIABETES MELLITUS: A COMPARISON OF METFORMIN MONOTHERAPY AND COMBINED ANTIDIABETIC TREATMENT

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Abstract

Objective: To assess how serum hepcidin and ferritin concentration is related to the pathogenesis and prognosis of Type 2 Diabetes Mellitus (T2DM) in patients taking metformin as monotherapy or in combination with other antidiabetic drugs.

Duration and place of study: This study was conducted at Sir Ganga Ram Hospital Lahore from September 2024 to September 2025

Methodology: The present observational case-control study involved 150 participants of both genders, each being divided into three equal categories; control group of healthy individuals with no diabetes, a group of patients with T2DM who were administered metformin in monotherapy, and a group of patients with T2DM who were treated with metformin in combination with other antidiabetic medications. Glucose oxidase-peroxidase was used to determine the fasting plasma glucose, and high-performance liquid chromatography was used to measure glycated haemoglobin. Standard enzymatic methods were used to measure parameters of lipid profiles. The serum ferritin, insulin, and hepcidin levels were determined through the enzyme-linked immunosorbent assays. The homeostasis model assessment of insulin resistance was used to calculate insulin resistance. Statistical analysis was done with a version of SPSS 26.

Results: Out of the 150 participants, there were equal representations of male and female members of all categories. Both diabetic groups had significantly high glycaemic parameters such as fasting plasma glucose and glycated haemoglobin compared to controls ($p<0.05$). The serum ferritin was found to be highly increased in patients with T2DM in comparison to the controls, with a significant difference in hepcidin levels among the treatment groups ($p<0.05$). There was a relatively lower level of hepcidin and ferritin in patients who were receiving metformin as a monotherapy compared to patients who were receiving combination therapy. Hepcidin had a significant negative relationship with glycated haemoglobin in the metformin-only group ($p<0.05$).

Conclusion: It seems that hepatocyte growth hormone (Hepcidin) and ferritin are closely associated with glycaemic control and iron metabolism in Type 2 Diabetes Mellitus. Metformin, especially as a monotherapy, can play a role in better regulation of these biomarkers, implying a possible role in addition to glucose lowering in T2DM pathophysiology and prognosis.

Keywords: Ferritin, Hepcidin, Insulin Resistance, Metformin, Combination Therapy, Type 2 Diabetes Mellitus.

INTRODUCTION

T2DM is a multifaceted pathophysiological condition of metabolic hyperglycaemia that follows the insulin resistance with subsequent progressive failure of pancreatic 8-cells. Its incidence has escalated horrendously in the past decades and has become one of the biggest contributors to cardiovascular disease, renal failure, blindness, and premature mortality in the world [1]. Although the classical perspective of T2DM has been based on the metabolism of glucose, of late, there is increasing awareness that the illness is closely correlated to chronic low-grade inflammation, oxidative stress, and iron homeostasis derangements [2].

Iron is a vital micronutrient that helps in the transportation of oxygen and in the respiration process of the mitochondria, and also in the synthesis of DNA. Nonetheless, iron overload may be toxic because it has the potential to catalyze the generation of reactive oxygen species by the Fenton reaction [3]. The major intracellular iron-storing protein, ferritin, indicates overall iron stores in the body, as well as acting as an acute-phase reactant. High serum ferritin concentration has always been linked with insulin resistance, obesity syndrome and predisposition to T2DM [4,5]. Some epidemiological studies have confirmed that more ferritin in individuals predisposes one to impaired glucose tolerance and diabetes, regardless of the relevant risk factors [6].

The interaction between iron overload and glucose dysregulation seems to be two-way. Excess iron causes oxidative stress on one hand, and this damages pancreatic cells and inhibits insulin secretion [7]. Conversely, hyperinsulinaemia and chronic inflammation could stimulate intestinal absorption of iron and ferritin production, which will result in additional accumulation of iron [8]. This forms a vicious circle where excess iron and insulin resistance enhance each other and thus lead to further disease.

The key controller of body iron is hepididin, a 25 amino-acid peptide hormone that is produced mainly in the hepatobiliary system. It regulates intestinal iron uptake and iron release by macrophages binding to the iron exporter ferroportin, and provoking its internalization and degradation [9]. In the healthy physiological state, hepcidin regulates iron homeostasis in reaction to body iron stores, erythropoietic need, as well as inflammatory cues. Hepcidin expression is highly stimulated by inflammatory cytokines especially interleukin-6, which results into decreased serum iron availability [10].

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The recent studies have given emphasis on the role of hepcidin in metabolic diseases such as T2DM. It is demonstrated that the diabetic patients exhibit altered levels of hepcidin, indicating that the disarmed iron homeostasis is involved in the metabolic and inflammatory environment of diabetes [11]. A number of studies have indicated lower level of hepcidin in insulin-resistant conditions, perhaps to augment iron availability, whilst some indicate inappropriately high hepcidin is present in the presence of inflammation [12]. These contradicting results suggest that the interaction between hepcidin and T2DM is complicated and can be dependent on the stage of the disease, glycaemic regulation, and treatment type.

Iron metabolism can also be altered by antidiabetic treatment. The initial pharmacological therapy of T2DM is metformin, which enhances insulin sensitivity by mainly activating the AMP-activated protein kinase and suppression of the hepatic gluconeogenesis process [13]. Metformin is also an anti-inflammatory and an antioxidant besides lowering levels of glucose. There is an emerging body of evidence that metformin could lower the level of serum ferritin and controls the expression of hepcidin which has the potential of alleviating iron-related oxidative stress [14].

During T2DM, most patients need to be combined with other oral hypoglycaemic agents or insulin. The effect of these regimens on the parameters of iron could be different than that of metformin monotherapy, but this field is under-researched. It is also crucial to understand the impact of different treatment methods on the levels of hepcidin and ferritin because the latter two biomarkers could be indicators of iron status as well as the inflammatory and metabolic burden of the disease [15].

The relationship between hepcidin, ferritin, and glycaemic control in metformin only and combined with other antidiabetic drugs might be an interesting journey that can give knowledge of the pathophysiology of T2DM. It can also assist in determining whether iron-related markers have the potential to be used as adjunctive outcomes of disease control and response to therapy. Thus, the current research was dedicated to the assessment of serum hepcidin and ferritin in patients with T2DM under various treatment options and determination of how these parameters affected insulin resistance and glycaemic condition.

METHODOLOGY

Ethical approval of the institutional ethics review committee was sought before the observational case control study was carried out. The sample size was estimated by calculated by the openEpi calculator

according to the 80% power of the test, 5 percent level of significant difference, and a 1:1 ratio between the two groups. The necessary sample size was estimated based on the mean hepcidin serums in previous researches. A consecutive sampling method was used in enrolling 150 participants.

Both genders aged 18 -70 years were included and divided into three equal groups healthy non-diabetic controls, patients with Type 2 Diabetes Mellitus taking metformin as monotherapy, and those taking metformin in combination with other antidiabetic agents. Healthy controls were also recruited through the general population and they were also matched with diabetic subjects in terms of age and gender. Fasting plasma glucose 126 mg/dl and Glycated haemoglobin 6.5 defined Type 2 Diabetes Mellitus. People whose plasma glucose was less than 100 mg/dL and did not have diabetes before were considered as controls.

The study excluded subjects who had acute or chronic hepatic disease, kidney dysfunction, acute infections, autoimmune disease, malignancy, pregnancy, Type 1 diabetes, pre-diabetes and haemochromatosis or were receiving glucocorticoids or iron supplementation. Demographic and clinical data were recorded with a structured, pre-designed proforma, such as age, gender, body mass index, length of diabetes, prescription history, and lifestyle after written informed consent had been obtained, and included the demographic and clinical data.

A venous blood sample was collected after 10-12 hours of starvation to determine the level of fasting plasma glucose, glycated haemoglobin, lipid profile, serum ferritin, serum insulin, and serum hepcidin. The glucose oxidaseperoxidase method was used to measure fasting plasma glucose and high-performance liquid chromatography was used to determine glycated haemoglobin. The cholesterol oxidase phenol 4-aminoantipyrine peroxidase method was used to estimate the total cholesterol, the glycerol phosphate oxidase phenol 4-aminoantipyrine peroxidase method was the triglycerides, the direct enzyme method was the high-density lipoprotein, and the low-density lipoprotein.

The serum ferritin and serum insulin were measured with the enzyme-linked immunosorbent assay kits as per the instructions of the manufacturer. Measurement of serum hepcidin concentration was made by use of Human Hepcidin-25 ELISA kit and absorbance was taken through a microplate reader that had been calibrated as per kit protocol. Homeostasis Model Assessment of Insulin Resistance index was used to estimate insulin resistance through the following formula: HOMA-IR = (insulin x Fasting glucose)/22.5.

The data were analysed with SPSS version 26. Continuous variables were given in mean standard deviation of normally distributed data and in median and interquartile range of non-normally distributed data. The ShapiroWilk test was used to check normality. The Kruskal Wallis test or one way analysis of variance was used to compare the parameters of the three groups in terms of biochemical parameters. Associations between hepcidin, ferritin, glycaemic indexes and insulin resistance were evaluated using Pearson or Spearman correlation analysis. The linear regression analysis was conducted to examine predictors of serum hepcidin levels. A p-value of a value lower than 0.05 was deemed to be of statistical significance.

RESULTS

A total of 150 participants were sampled in the study with 50 subjects per group. The general male to female distribution was similar in the three groups. There was no significant age difference between mean of controls and diabetic patients. Anthropometry revealed that the body mass index in the two groups with diabetes was far much higher than the control group ($p<0.05$).

Both groups of Type 2 Diabetes Mellitus patients indicated a significant level of fasting plasma glucose and glycated haemoglobin than healthy controls ($p<0.001$). The combination therapy showed a slightly increased level of HbA1c than the monotherapy of metformin, but this was not significant. The diabetic patients had higher insulin resistance levels shown by high HOMA-IR values and serum insulin levels compared to patients of the control group, thus revealing a significant increase in the values of serum insulin levels and HOMA-IR ($p<0.05$), highest values were recorded in the combination therapy group.

The lipid profile analysis revealed that the total cholesterol, triglycerides and low-density lipoprotein of the two diabetic groups were significantly higher than the controls ($p<0.05$), with the high-density lipoprotein level of the diabetic patients being significantly lower ($p<0.05$). The alterations were more significant in the patients who were under combination therapy.

The serum ferritin levels were found to be highly different between patients with Type 2 Diabetes Mellitus and controls ($p<0.001$). The subjects with diabetic patients on combination therapy had the greatest concentration in ferritin, compared to those on metformin treatment ($p<0.05$). The serum hepcidin levels varied significantly between the groups as well ($p<0.05$). The metformin mono-therapy patients showed relatively low levels of hepcidin in comparison to the metformin combination therapy, but both diabetic groups showed turned-around levels of hepcidin compared to controls.

It was found that serum ferritin and HOMA-IR showed a significant positive correlation with diabetic patients ($r=0.32$, $p<0.01$) which indicated the presence of a correlation between the insulin resistance and stores of iron. The level of serum hepcidin had a significant negative correlation with the glycated haemoglobin in the metformin monotherapy group ($r= 0.27$, $p=0.5$), and thus the lower the hepcidin level, the better were the glycaemic control in the patients under metformin monotherapy. There was no strong relationship between hepcidin and HbA1c in the combination therapy.Linear regression analysis revealed that the independent variables on serum hepcidin levels were serum ferritin and HOMA-IR when adjusted to age, sex and body mass index ($p<0.05$).

Table 1. Demographic and Anthropometric Characteristics of Study Participants

Parameter	Controls (n=50)	Metformin Only (n=50)	Metformin + Combination (n=50)	p-value
Age (years)	42.3 ± 8.1	44.1 ± 7.9	44.8 ± 8.2	0.28
Male, n (%)	24 (48%)	25 (50%)	26 (52%)	0.89
Female, n (%)	26 (52%)	25 (50%)	24 (48%)	0.89
BMI (kg/m²)	24.2 ± 3.1	27.6 ± 3.8	28.4 ± 4.0	<0.001

Table 2. Glycaemic and Insulin Resistance Parameters

Parameter	Controls (n=50)	Metformin Only (n=50)	Metformin + Combination (n=50)	p-value
Fasting Plasma Glucose (mg/dL)	91.5 ± 7.4	148.3 ± 22.6	152.7 ± 25.1	<0.001
HbA1c (%)	5.4 ± 0.3	7.8 ± 0.8	8.1 ± 0.9	<0.001
Fasting Insulin (µIU/mL)	7.8 ± 2.1	14.5 ± 4.3	16.2 ± 5.0	<0.001
HOMA-IR	1.8 ± 0.5	5.3 ± 1.6	5.8 ± 1.8	<0.001

Table 3. Lipid Profile and Iron Markers

Parameter	Controls (n=50)	Metformin Only (n=50)	Metformin + Combination (n=50)	p-value
Total Cholesterol (mg/dL)	178.4 ± 23.1	201.6 ± 28.7	208.3 ± 30.2	<0.001
Triglycerides (mg/dL)	115.7 ± 27.5	162.4 ± 35.1	168.9 ± 38.4	<0.001
LDL (mg/dL)	102.6 ± 19.3	126.5 ± 25.6	131.2 ± 28.1	<0.001
HDL (mg/dL)	54.2 ± 10.1	46.8 ± 9.5	45.5 ± 8.9	<0.001
Serum Ferritin (ng/mL)	78.5 ± 15.6	142.3 ± 28.7	158.6 ± 32.1	<0.001

DISCUSSION

We conducted an experiment to assess serum levels of hepcidin and ferritin in the patients with Type 2 Diabetes Mellitus (T2DM) on metformin monotherapy or metformin combined with other antidiabetic agents. We have shown that diabetic patients display a high level of changes in iron-related biomarkers and glycaemic parameters in comparison with healthy controls. Namely, the serum ferritin was increased in patients with T2DM whereas serum hepcidin was lower in the patients receiving metformin alone and higher in the ones receiving metformin combined therapy. These results indicate a complicated interaction between glucose metabolism, iron homeostasis, and antidiabetic therapy.

An increase in ferritin among diabetic patients is in line with the earlier works which had gauged hyperferritinemia as an indicator of insulin resistance and generalized inflammation [16,17]. The surplus iron may facilitate oxidative stress and dysfunction of pancreatic 5 -cells, which leads to inadequate glycaemic control [18]. Our study found elevated levels of ferritin in patients with combination therapy, perhaps due to more progressive disease, higher levels of inflammatory load, or effects of chronic hyperglycaemia. This is consistent with evidence that longer time of diabetes or greater stress on metabolism is associated with high iron stores in patients affected by diabetes [19]. The overriding regulator of systemic iron, hepididin showed a negative relationship with glycated haemoglobin in the metformin only group. This implies that the reduction in hepcidin levels can be linked to the improvement of glycaemic control. Metformin has demonstrated the ability to regulate hepcidin expression and decrease the production of inflammatory cytokines, and this could be to blame the relatively lower levels of hepcidin in such patients [20,21]. Conversely, patients undergoing combination therapy had elevated hepcidin levels, which might be explained by the vigor of inflammatory and immune reactions, the developmental level of insulin resistance, or other impact of the action of other antidiabetic medications [22].

Our results agree with the idea that the metabolism of iron is tightly associated with insulin resistance and glucose dysregulation in T2DM. The positive relations between ferritin and HOMA-IR in diabetic participants serve to support the notion that the increased iron storage can worsen insulin resistance and form a loop that increases the rate of the disease development [23]. The results of the hepcidin and ferritin levels in the treatment groups also indicate a possibility of antidiabetic therapy affecting iron-related pathways, where metformin could have a protective effect beyond its glycaemic effect [24,25].

These associations may be based on a number of mechanisms. Hyperglycaemia and chronic low grade inflammation in T2DM both provoke the production of hepcidin through interleukin-6 and other cytokines, which contributes to changes in the distribution of iron and decreased insulin sensitivity [26]. Activation of hepatic gluconeogenesis, inflammatory signaling mediated by Metformin can be reduced, and indirectly alter hepatic hepcidin and ferritin by activation of AMP-activated protein kinase [27]. The above effects can help in the enhancement of β-cells function and sensitivity to insulin as demonstrated by the negative correlation between hepcidin and HbA1c in our metformin only group.

We also found that there was a severe dyslipidaemia among diabetic patients, especially in patients taking combination therapy, as reported before where the insulin resistance and lipid abnormalities are interconnected in T2DM [28]. Dyslipidaemia can also interplay with the metabolism of iron and inflammatory processes, which underscores the multifactorial character of metabolic disturbances in diabetes [29].

The clinical implications of these findings are possible. The observation of hepcidin and ferritin in T2DM may give more information about the metabolic and inflammatory conditions of the patient and may assist in the development of personalized treatment plans. Additionally, the iron metabolism based interventions including dietary manipulation or pharmacological regulation can be used in addition to the usual antidiabetic treatment to enhance glycaemic control and to decrease complications [30].

To sum it up, we have shown that the association of serum hepcidin and ferritin with glycaemic control and insulin resistance in T2DM is close. It seems that metformin monotherapy regulating those biomarkers positively, but combination therapy can be an indicator of increased iron-related and inflammatory burden. These results support the significance of iron metabolism in the pathophysiology and treatment of T2DM, and the basis of future studies examining interventions of interest.

CONCLUSION

This paper indicates that serum hepcidin and ferritin are largely linked to glycaemic control and insulin resistance among Type 2 Diabetes Mellitus patients. The high ferritin levels indicate high iron stores and inflammatory load, and the hepcidin levels seem to depend on the type of antidiabetic treatment. The lower hepcidin and ferritin in metformin monotherapy indicated a possible modulatory mechanism of iron metabolism in addition to the lowered glucose. The patients on combination therapy reported better iron related biomarkers which may be indicative of more advanced disease. The

mentioned findings indicate the significance of iron metabolism tracking in T2DM and indicate a role of therapeutic interventions of hepcidin and ferritin.

Author Contributions

Madeeha Ashraf[1]: Study design and manuscript writing.
Urooj Mirza[2]: Data collection and manuscript review.
Vijay Kumar[3]: Data analysis and manuscript review.
Tazeem Hussain[4]: Literature review and data support.
Sana Arshad[5]: Manuscript editing and formatting.
Sobhya Karamullah[6]: Supervision and final approval of the manuscript.

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