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Influence of Ferritin Level and C-Reactive Protein on HbA1c in Type 2 Diabetes

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Abstract

There are complications of diabetes mellitus (DM) that have become a global public health concern. Moreover, there are numerous comorbidities that are associated with DM that have great potential to become a serious concern in the future. Thus, in order to obtain a diagnosis, a number of parameters that are related to the glycemic level have to be obtained. Recent studies have proven there is a connection regarding the level of blood sugar and also the level of ferritin and CRP in patients with type 2 diabetes mellitus (DM). Thus, there is a need to determine the relationship of Ferritin and CRP on HbA1c in Type 2 Diabetes Mellitus patients. A total of 50 type 2 diabetes patients participated in the study. After a 12 hour overnight fast, a 10 ml venous blood sample was taken to analyze the biochemical profile. The data was analyzed using SPSS 23. There was a positive association between the level of HbA1c and the level of C-reactive protein. However, the absence of a relationship between the two variables was due the high p-value of Ferritin that limited the findings.

Keywords

Type 2 diabetes, HbA1c levels, C-reactive protein, ferritin

Introduction

Diabetes is one of the most prevalent endocrine disorders, the estimates suggest we will reach 552 million affected individuals by 2030 [1;2]. Hence, the economic burden, and the risk of Chronic complication must be balanced by adequate early diagnosis, & control of the progression. Timely identification and control of these metabolic dysfunctions, especially T2DM with a focus on the obesity, are critical for reduction of related disturbances. [3; 4]. Despite ferritin being a well-documented as a body iron store, it has a dual role as a positive acute phase reactant protein. IL-6 mediated stimulation of hepcidin is a typical response, and leads to sequestration of iron within enterocytes & macrophages, reduced bioavailable iron, and increased circulating ferritin. This has been reviewed in detail [6]. T2DM has elevated ferritin that in correlation is more indicative of increased inflammatory

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response, than a positive iron imbalance. [5; 6].

Problems in the oxidative impact, mitochondria, and pancreatic beta cells' toxicity have implicated excess iron in the development of insulin resistance [7,8]. Elevated Ferritin and Insulin resistance and T2DM risk have been correlated in the past, especially in some epidemiological research [9,10]. Still, the data have been discordant in the various communities studied. In the current analysis, the lack of a strong relationship between serum ferritin and HbA1c indicates that, in isolation, ferritin may not serve as a good indicator of glycemic control.

Elevated ferritin is associated with complications - especially with poor glycemic control - in diabetes nephropathy, retinopathy, and the blood vessels, and many studies have documented this [11]. Chinese research has shown that HbA1c and Ferritin levels are strongly related. Freckmann et al. [12] claim that peripheral metabolism syndrome was developed by elevated levels of iron and that as serum ferritin levels decreased, insulin resistance improved. In this regard, these findings were consistent with those of Kaftan et al. [13]. It is important to highlight that consistent and limited research has not substantiated the potential role of ferritin with inflammatory markers like C-reactive protein (CRP) as an initial biomarker for T2DM.

Elevated blood sugar levels (hyperglycemia) cause the activation of several metabolic systems, some of which include the polyol pathway, protein kinase C activation, and advanced glycation end product (AGE) formation. All of these systems amplify oxidative stress and endothelial dysfunction, both of which are key components of inflammation related to diabetes [1,4].

AGEs and RAGE activate NF-κB, which in turn drives the synthesis of certain pro-inflammatory cytokines, namely IL-6, TNF-α, and IL-1β [14,15]. IL-6 is particularly important, as it directly triggers the liver to produce CRP. Thus, glycemic control, as evidenced by high levels of HbA1c, corresponds with increased CRP levels [16,17].

Elevated HbA1c levels are often seen in patients with poorly controlled diabetes, along with elevated CRP, because poorly controlled diabetes is linked to increased systemic inflammation [13]. HbA1c indicates the mean glucose levels in the blood over the last three months, which is why it is important in determining glycemic control. An HbA1c of 6-8% is found in healthy, non-diabetic individuals. This study aimed to examine the correlation between HbA1c and CRP and ferritin levels in patients with type 2 diabetes mellitus [18].

Methodology

The study was cross-sectional and focused on 50 patients with type 2 diabetes mellitus (T2DM). Participants were surveyed using a non-probability convenience sampling technique. All subjects were briefed about the study, and their participation was documented. The study took place over four months: November 2024 to February 2025 at Al-Sadr Teaching Hospital, Basra, Iraq.

Blood samples were collected from confirmed T2DM patients under standard venous aseptic procedures after an overnight fast. The hospital's routine laboratory analyzer (Roche Cobas e411) processed the automated chemiluminescent immunoassay to determine levels of serum ferritin and C-reactive protein (CRP). Standardized laboratory procedures, including high-performance liquid chromatography (HPLC), were used to analyze levels of glycated

hemoglobin (HbA1c). The hospital laboratory's standard operating procedures and manufacturer's guidelines were followed in the biochemistry tests to maintain analytical reliability and accuracy.

The diagnosis of the research participants must have included type 2 diabetes mellitus for more than two years. The exclusion criteria included pregnancy, obesity, renal disease, use of nutritional supplements, alcohol, and diuretic medications. Utilizing the pre-designed data collection form (Performa), the research team completed demographic details, personal information, and the medical history (current and past) of each participant.

The study considered the correlation of serum ferritin and CRP levels with HbA1c values, which are the three-month averages of the participant's glycemic levels. For biochemical analysis, overnight fasting participants provided approximately 10 mL of blood. The normal serum CRP level is <10 mg/L. The normal HbA1c value is <5.7%, and the normal serum ferritin levels are 12-300 ng/mL. The participant's blood pressure was recorded three times in the month before the study to rule out hypertension. Extensive urine analysis, blood urea, serum protein, and serum creatinine tests were performed to rule out nephropathy in addition to the regular tests.

The participants were given information about the study and were asked to share information on their diets and exercise. The study's methods and procedures were granted approval by the Ethics Committee of the College of Pharmacy, University of Basrah (approval number: EC17).

Statistical Analysis

Version 23.0 of the SPSS software was used for the statistical evaluations. Mean and standard deviation (SD) were used to explain continuous variables, and apply the Student's t-test and Pearson's correlation test when necessary. Descriptive statistics (at 95% confidence level) for the categorical variables were used. The p-value set for statistical significance was 0.05 or less.

Results

The study was conducted with 50 participants. Table 1 contains the demographic and clinical data of the participants who were diagnosed with diabetes mellitus (DM). Age data indicate that the majority of the participants were middle-aged. 52% of the participants were in the age range of 45 to 64 years, while 48% were in the range of 25 to 44. This data suggests that the diagnosis of diabetes is widespread among middle-aged and younger adults.

Concerning the distribution of the male-to-female ratio, the female participants were the majority with 60% of the total participants, while the males represented 40% of the total participants. Regarding the place of residence, a considerable proportion of the participants, 88% of the total participants, were dwellers of the urban regions.

Concerning the length of time with diabetes, almost half of the participants (48%) were diagnosed with the condition for under five years, while 36% of the participants were diagnosed within the 5-15 year timeframe. Only 16% of the participants stated that they had had the condition for over 15 years. This distribution could indicate that diabetes is being more readily diagnosed on the basis that screening and public awareness programs have improved in recent years.

In general, the majority of the participants in the study were urban, middle-aged females, and the majority of them had had a diagnosis of diabetes mellitus for a short period of time.

Patients' glycemic control is covered in Table 2. 34% of the study population achieved optimal glycemic control. Only three patients (6%) had acceptable control (HbA1c 7.0% - 8.0%). The remaining 30 patients (60%) had poor glycemic control (HbA1c 8.0% +). More than half of the population studied had inadequate diabetes control. High levels of HbA1c correspond to an increased risk of chronic complications such as neuropathy, nephropathy, and retinopathy, as well as cardiovascular disease.

Table 1. Sociodemographic and Clinical Characteristics of the Study Population.

Characteristic		**No (%)**
Age (years)	25-44 yrs	24 (48%)
	45-64 yrs	26(52%)
Gender	Male	20(40%)
	Female	30 (60%)
Residency	Urban	44 (88%)
	Rural	6 (12%)
Duration of DM (years)	< 5 yr	24 (48%)
	5 – 15 yr	18 (36%)
	> 15 yr	8 (16%)

Table 2. Glycemic Control Status Among Patients

Glycemic status	**Hb A1c (%)**	**No.**	**%**
Optimal control	< 6.5	17	34
Acceptable control	7.0 - 8.0	3	6
Poor control	> 8.0	30	60
Total	Total	50	100.0

Table 3 illustrates the pattern of serum ferritin levels in relation to HbA1c. The optimal control group has the lowest mean ferritin levels, while the acceptable control group has the highest. Furthermore, the P-value of 0.265 shows that the differences are not statistically significant and that glycemic control and ferritin levels do not correlate in the population examined.

Table 4 analyzes the link between inflammation and glycemic control, using the C-reactive protein (CRP) level as a reference point. In our research, the patients whose glycemic control is inadequate have considerably greater levels of CRP (mean:

2.8 mg/L) than those with optimal or acceptable control. The latter group's CRP levels are below 0.35 mg/L. The group in excess of 0.35 mg/L and the group below 0.35 mg/L constitute a significant difference with respect to CRP levels (P = 0.045, which is statistically significant as it is below 0.05).

The relationship between the three clinical parameters from the perspective of diabetic patients - CRP (C-reactive protein) and ferritin, and CRP and HbA1c, is presented in Table 5 alongside the correlations and relevant P-values.

Table 3. Association Between Glycemic Control (HbA1c) and Serum Ferritin Levels in Diabetic Patients.

Glycemic status	**Hb A1c(%)**	**No.**	**Ferritin (Mean)**	**P value**
Optimal control	< 6.5	17	93.5	0.265
Acceptable control	7.0 - 8.0	3	180	
Poor Control	> 8.0	30	127.5	
Total	Total	50		

Table 4. Association Between Glycemic Control (Hb A1c) and C-Reactive Protein (CRP) Levels in Diabetic Patients+

Glycemic status	**Hb A1c (%)**	**No.**	**CRP (Mean)**	**P value**
Optimal control	< 6.5	17	0.341	0.045
Acceptable control	7.0 - 8.0	3	0.306	
Poor control	> 8.0	30	2.8	
Total	Total	50		

Table 5. Correlation Between Inflammatory Marker (CRP), Ferritin, and Glycemic Control (HbA1c) in Diabetic Patients

Parameter		CRP (mg/dl)	Ferritin	HbA1c
CRP (mg/dl)	r	1	0.279	0.33
	P value		0.055	0.019
Ferritin	r	0.279	1	0.157
	P value	0.055		0.288
HbA1c	r	0.33	0.157	1
	P value	0.019	0.288	

There is no correlation between the serum level of ferritin and the level of HbA1c in diabetic persons ($p = 0.288$), and this correlation was not significant (with a p value of < 0.05 being significant).

CRP is an important sign of active inflammation in the body. Elevated CRP levels signal the presence of an infection in the body. In the backdrop of poor glycemic control or insulin resistance, there is an increased tendency for cellular inflammation. This explains the elevated levels of CRP in patients with diabetes. In the statistical assessment, CRP positively correlates with HbA1c levels (Pearson correlation, $p=0.019$). These findings highlight the significance of glycemic control in diabetes, not only from the metabolic perspective but also for reducing the inflammatory burden. These findings reinforce the importance of glycaemic control not just for metabolic management but also for reducing inflammatory burden.

Discussion

The link between body iron stores and the risk of diabetes has been studied globally; however, numerous studies have been unable to show a statistically significant association between diabetes and serum ferritin concentrations. Elimam et al. [4] documented significant positive correlations between HbA1c and C - reactive protein (CRP) levels, and between HbA1c and ferritin, which may suggest the role of inflammation in the dysregulation of glycemia.

In this study, we did not find a statistically significant correlation between serum levels of ferritin and HbA1c. However, several studies have shown that excess body iron stores correlate with greater levels of insulin resistance and hyperglycemia [9]. Although our study did not show a significant correlation, a plethora of studies have shown a significant correlation between serum ferritin levels and disturbances in glucose metabolism. Out of 9,486 subjects with diabetes in the United States, Ford et al. [11] found a larger number of them to have higher levels of serum ferritin. On the other hand, Liu et al. [19] reported a lack of significant correlation between ferritin and the risk of type 2 diabetes mellitus. Along the same lines, Wolide et al. [20] reported that Ethiopian patients with type 2 diabetes had higher levels of ferritin than other groups.

The current study findings continue to establish a relationship between systemic inflammation and the regulation of blood

sugar in individuals with type 2 diabetes mellitus. We noted a statistically significant difference in levels of C-reactive protein in relation to the differing levels of blood sugar control in the study participants. This goes hand in hand with studies that suggest that in patients with diabetes, C-reactive protein levels are higher than in non-diabetic patients. Additionally, studies by Wolide et al. and Rajpathak et al. show that the relationship between elevated levels of ferritin and metabolic dysregulation, that is, higher levels of body mass index and waist circumference, and C-reactive protein.

It can, therefore, be concluded that the findings of all these studies point to the fact that inflammation is a crucial constituent in the pathophysiology of type 2 diabetes mellitus. Even though ferritin is known to reflect the levels of iron and the level of inflammation, the fact that it is a marker of blood sugar control remains disputed, and therefore, it is worthwhile to conduct further studies to answer that question.

Conclusion

The relationship between HbA1c and serum ferritin was weak and statistically non-significant, while C-reactive protein showed a moderate and statistically significant correlation with glycemic control. This suggests that in patients with type 2 diabetes mellitus, systemic inflammation (excluding iron status) may influence the glycemic control mechanisms. Therefore, in patients with T2DM, CRP could be a valuable inflammatory marker for assessing glycemic control.

Conflict of Interest: The authors declare no conflict of interest.

Ethical Approval: The study protocol was reviewed and approved by the Ethics Committee of the College of Pharmacy, University of Basrah.

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تأثير مستوى الفيريتين والبروتين المتفاعل C على السكر التراكمي لدى مرضى داء السكري من النوع الثاني

صفا كفاخ قاسم

ماجستير كيمياء سريرية فرع العلوم المختبرية السريرية، كلية الصيدلة، جامعة البصرة، البصرة، العراق

الملخص

يُعد داء السكري من النوع الثاني من أكثر الأمراض الاستقلابية انتشارًا عالميًا، ويرتبط بزيادة خطر المضاعفات الصحية وتأثيرهما على مستوى C (CRP) والالتهابية. هدفت هذه الدراسة إلى تقييم العلاقة بين مستوى الفيريتين والبروتين المتفاعل لدى مرضى داء السكري من النوع الثاني.شملت الدراسة المقطعية خمسين مريضًا (HbA1c) .الهيموغلوبين السكري مشخصين بداء السكري من النوع الثاني، حيث جُمعت عينات دم وريدية بعد صيام ليلي كامل لتحليل المؤشرات الحيوية. تم قياس مستويات الفيريتين ب باستخدام الكروماتوغرافيا السائلة عالية الأداء الأداء. أُجري التحليل الإحصائي باستخدام برنامج SPCC Number 23

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الكلمات المفتاحية

داء السكري من النوع الثاني؛ الهيموغلوبينالسكريالفيريتين؛ البروتين المتفاعل