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# RAISED LEVELS OF HS-CRP AND FERRITIN IN PATIENTS WITH TYPE II DIABETES MELLITUS

**Dr. Anjum Zahra[1], Dr. Saad Muhammad[2], Dr. Muhammad Yaseen[3]**

[1] Ghazi Medical Collage DG Khan

[2] King Edward Medical University, Lahore

[3] Wah Medical College Wah Cantt

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**Abstract:**

***Aim:*** *To measure very sensitive blood levels of C-reactive protein and ferritin in the blood, and to assess its association with inflammation in people with type 2 diabetes.*

***Method:*** *Case control study was conducted at the Medicine Unit II of Nishter Hospital Multan for one year duration from February 2019 to February 2020, and included randomly selected patients and healthy controls. Fasting blood samples were analyzed to determine blood sugar, insulin, very sensitive C-reactive protein and iron status. SPSS 19 was used for statistical analysis.*

***Results:*** *Out of 210 originally selected patients, 99 (47%) were excluded from the study due to anemia. The study population is 111 (53%) with a total average age of 38.6 ± 1.56 years, and fasting blood sugar is 110.78 ± 3.795 mg / dl. In group 1, there were 44 (39.6%) healthy people and 67 (60.3%) diabetic patients in group 2. High serum ferritin (233.11 ± 43.84 ng / ml), insulin (29, 94 ± 2.19), insulin homeostasis pattern, resistance (10.23 ± 0.89) and very sensitive C-reactive protein (5.29 ± 0.80 mg / L) low serum iron levels (5.29 ± 0 , 80 mg / L) 1.07 ± 0.115 µg / dl) in group 2. The insulin resistance homeostasis model showed a positive correlation with fasting blood sugar (r = 0.596; p <0.009). There was a negative correlation with iron serum (r = -0.280; p <0.016) and transferrin saturation (r = -0.316; p <0.006).*

***Conclusion:*** *Increased ferritin levels without visible iron overload can affect glucose homeostasis and lead to insulin resistance with inflammatory changes, as seen at high levels of C-reactive protein.*

***Key words:*** *ferritin, hs-CRP, T2DM, insulin resistance.*

**Corresponding author:**

**Dr.Anjum Zahra,**

*Ghazi Medical Collage DG Khan*

QR code

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## INTRODUCTION:

Type 2 diabetes (DM2) is an important global lifestyle disorder. Asian countries make up over 60% of the world's diabetes population[1-3]. T2DM is a complex disease that requires the interaction of genetic and environmental factors. Patients with DM2 show defects in insulin resistance (IR) and defects in beta cells. Insulin defects after cooking are usually responsible for IR in DM2[4-6]. The relationship between DM2 and iron metabolism applies to both research and clinical practice. Scientific evidence has estimated the effect of high serum ferritin levels on IR and T2DM due to increased iron stores in the body or the effect of various inflammatory diseases[7-9]. Therefore, it is assumed that circulating ferritin levels, which are also an acute phase reagent, do not reflect iron stores in the body, but may cause other processes such as systemic inflammation.

The inflammatory process induces hepatic synthesis of various acute phase proteins, such as highly sensitive creative protein (hs-CRP) and serum ferritin, which are thought to play a role in cell-level IR. Given this model, the current study aimed to associate elevated iron levels and hs-CRP levels with diabetes, and assess ferritin-IR association.

## PATIENTS AND METHODS:

The case-control study was conducted at the Medicine Unit II of Nishter Hospital Multan for one year duration from February 2019 to February 2020, it included randomly selected patients and healthy controls. In order to achieve minimum 80% power with a 13.14% estimated prevalence of disease in project area and a two-sided 5% level of significance, the minimum sample size required, according to Power and Sample Size (PASS) version 11, was 42 for each group. After randomized individuals were excluded from the general population based on total blood count (CBC) indicating iron deficiency anemia. Other people were divided into two groups. They were healthy controls in group I and DM2 in group 2.

Clinically important concomitant diseases (iron deficiency anemia, cardiovascular disease, acute infectious disease or chronic inflammatory or debilitating disease), smoking and alcoholism, and drug use (multivitamins and iron supplements). The study protocol was approved by the corporate ethics committee. After obtaining written consent of all participants, 10 ml of blood was collected from each participant. Biomarkers were analyzed in serum samples. In addition, fasting blood sugar (FBS) levels for all subjects were estimated using the glucose-oxidase-phenol-aminophenone (GOD-PAP) method (Merck, France). The IR level was calculated by assessing the insulin resistance model (HOMA-IR) [fasting insulin (units per milliliter) x milligrams / fasting glucose decision inflammation / 405] homeostasis model. Serum iron and total iron binding capacity (TIBC) was determined by the Bio Merieux method (S.A. France) by an enzymatic colorimetric method. % Transferrin saturation was calculated at 100x serum iron / TIBC.

Data were analyzed using SPSS 19. Mann Whitney U test was used for comparison between groups. The mean ± standard deviation (SD) was calculated for quantitative variables. Spearman's correlation was applied to correlation variables, and $p < 0.05$ was considered significant.

## RESULTS:

99 (47%) of the 210 initially selected patients were excluded from the study due to anemia. The study population was 111 (53%) and the overall average age was 38.6 ± 1.56 years (range: 15-65 years), and fasting blood sugar was 110.78 ±. 3.795 mg / dl Group 1 had 44 (39.6%) healthy controls, and group 2 had 67 (60.3%) diabetic patients.

Mean blood glucose levels ($p < 0.001$), insulin ($p = 0.037$), IR ($p < 0.001$), ferritin ($p < 0.001$) and hs-CRP ($p < 0.05$) were significantly higher in DM2 as compared to Control. Together with this, serum iron was significantly lower in group 2 than in group 1 ($p < 0.001$) (Table 1).

**Table-1: Serum iron parameters, serum glycaemic, Anthropometric.**

| Parameters | Controls n= 44 | Diabetics n= 67 | P value |
|---|---|---|---|
| Age | 29.93±1.81 | 47.27±1.322** | < 0.001 |
| Weight | 62.52±1.87 | 76.30±2.74 | <0.001 |
| Fasting blood sugar (mg/dl) | 84.54±2.96 | 137.02±4.63** | < 0.001 |
| Serum Insulin (IU/ml) | 22.59±1.68 | 29.94±2.19* | 0.037 |
| Insulin resistance (HOMA-IR) | 4.61±0.46 | 10.23±0.89** | <0.001 |
| Serum iron (?g/dl) | 2.44±0.26 | 1.07±0.155** | <0.001 |
| Serum TIBC (?g/dl) | 1.91±0.21 | 2.98±0.14** | <0.001 |
| Serum transferrin saturation (%) | 306.63±142.57 | 65.51±18.14** | <0.001 |
| Serum ferritin (ng/ml) | 132.45±38.08 | 233.11±43.84** | <0.001 |
| hs-CRP (mg/L) | 2.49±0.66 | 5.29±0.80* | 0.002 |

There was a significant positive correlation with ferritin (r = 0.306) and TIBC (r = 0.302) in DM2. In group 2, a negative but significant correlation was found between IR and serum iron (r = -0.28) and serum transferrin saturation (r = -0.316) (Table-2).

**Table-2: Correlation of insulin resistance with iron parameters, FBS and CRP (n= 111).**

| Correlations of insulin resistance with: | Spearman's Correlation Coefficient | P value |
|---|---|---|
| Serum transferrin saturation | -0.316 | 0.006* |
| Serum ferritin | 0.306 | 0.008* |
| Serum iron | -0.28 | 0.016* |
| Serum total iron binding Capacity | 0.302 | 0.009** |
| Fating blood Glucose | 0.596 | 0.000** |
| hs-CRP | 0.089 | 0.45 |

## DISCUSSION:

According to modern understanding, IR has traditionally been considered a key step in the pathogenesis of DM2. Glucose, insulin and C-peptide levels are well known IR markers. An important feature of this disease is also subclinical inflammation with active cytokines[10-11]. Along with the production of cytokines, inflammation is accompanied by the production of acute phase proteins, mainly PCR. PCR impairs the ability of the insulin receptor to activate phosphatidylinositol 3-kinase and leads to IR development to induce serine phosphorylation at the insulin receptor. However, despite the high level of DM2 in our study, we could not find a significant relationship between hs-CRP and IR[12]. Our results showed a significant correlation between high serum ferritin and IR. This discovery is in line with earlier research on the peoples of China and Korea. High levels of ferritin have been recognized as a feature of DM2. The relationship between iron and DM2 levels is complex. Insulin stimulates ferritin synthesis and activates iron overload, and vice versa, iron interferes with insulin inhibiting hepatic glucose production. On the other hand, ferritin acts as an indicator of pancreatitis and is therefore known as an IR marker[13-14].

One study found 2.5-fold higher DM2 ferritin levels compared to healthy humans, but the percentage of transferrin receptors did not differ significantly, suggesting a link to elevated serum ferritin and negative iron levels. They can be caused by an inflammatory problem rather than an iron overload. Our results confirm the same hypothesis. Another study found that serum ferritin can be an indicator of systemic oil content and IR. Perhaps due to the selection bias, the possible relationship in our study group was not only related to diabetes[15].

The results are consolidated with an IR correlation with low iron, low transferrin saturation, high TIBC and high ferritin, resulting in high ferritin levels not induced by iron overload, which then leads to T2DM irrespective of sex. inflammatory changes. The effect of iron deficiency does not change the observation because ferritin levels are not clearly parallel to iron levels. Our study results did not show that sex is a discriminatory factor because inflammation in patients of any sex would be the same, but we still think the study has limitations.

## CONCLUSION:

High ferritin levels without iron overload can affect glucose homeostasis. This can lead to the development of IR with inflammatory changes observed at high levels of PCR.

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