# Serum Ferritin and Soluble Transferrin Receptors in Type II Diabetic Patients: Correlation with TNF-α as a Marker of Inflammation

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## ABSTRACT

*Over the past years cumulating evidence has confirmed interlinking pathways connecting type II diabetes mellitus (DM) with an underlying inflammatory process. Furthermore, iron overload states have also been directly linked to the development of insulin resistance and type II diabetes. Serum ferritin as well as most of the biochemical markers for iron are affected by the acute phase response rendering the assessment of iron status in patients with inflammatory conditions somewhat challenging. So, the present study aimed to determine circulating levels of ferritin and soluble transferring receptor (sTFR) in type II diabetic patients as well as TNF-α as an inflammatory marker in order to evaluate whether serum ferritin reflects iron body stores or inflammation in diabetic patients. Thirty diabetic patients and 15 healthy control subjects were included in the study. Serum ferritin, sTFR and TNF-α levels were measured by enzyme immunoassay. Serum iron and total iron binding capacity (TIBC) were determined by quantitative colorimetric determination. The results of the study showed that diabetic patients have significantly higher serum ferritin levels than control subjects. However, no differences in sTFR levels were observed between both groups. A significant negative correlation between ferritin and sTFR levels was detected in control subjects but not in diabetic patients. Moreover, a significant positive correlation was found between levels of TNF-α and ferritin but not with sTFR levels in diabetic patients.* ***Conclusion****: Serum ferritin levels are increased in type II diabetic patients in correlation with the inflammatory marker TNF-α and in the absence of a reciprocal decrease of sTFR. These findings suggest that the elevated ferritin levels in type II diabetes are mainly as a result of inflammatory mechanisms rather than iron overload.*

***Key words****: Ferritin, soluble transferrin receptor TNF-α, type II diabetes.*

## INTRODUCTION

Iron is a catalyst in the formation of hydroxyl radical; which are powerful prooxidants that attack cellular membrane lipids, proteins and nucleic acids[1-3]. It has been hypothesized that formation of hydroxyl radicals catalyzed by iron contributes initially to insulin resistance and subsequently to

decreased insulin secretion, and then to the development of type II diabetes[4-6].

Iron is an essential element for multiple metabolic processes, such as oxygen transport, DNA synthesis, and electron transport. However, it must be bound to proteins to prevent tissue damage from free radical formation[7]. In the steady state, circulating iron is bound to transferrin and is taken up from the blood by a high-affinity specific transferrin receptor (TFR). The iron-TFR complex is internalized by endocytosis and released into a non-acidic cellular compartment, where it can be used in the synthesis of essential cellular components. The synthesis of TFR and the iron storage protein ferritin is regulated reciprocally at the post-transcriptional level according to the cellular iron status[8]. As a result of the externalization of TFR during the endocytic cycle, a soluble form of TFR can be detected in serum. Circulating concentrations of TFR (sTFR) are proportional to cellular expression of the membrane-associated TFR[9]. Serum sTFR concentration is closely related to cellular iron demands and, in consequence, the higher the ferritin levels the lower the sTFR concentration. Indeed, as compared with normal values, sTFR levels are about 25% lower in patients with hemochromatosis and about 20% higher in non-anemic iron deficient subjects[10-12].

Serum ferritin, which generally reflects the size of iron stores, is regarded as a marker in the evaluation of iron status in the absence of inflammation. In inflammatory disorders, however, a cytokine-mediated pathway can activate the ferritin gene, causing the hyperferritinemia which commonly occurs in these disorders; and that mechanism is iron independent[13]. There is emerging evidence that suggests a major role of inflammation in the etiopathogenesis of type II diabetes[14]. Therefore, the high serum ferritin levels that have been reported in type II diabetic patients[5-18] could be due to the underlying inflammatory process rather than to an increase of iron stores. As sTFR concentratin is not influenced by the acute phase response[19], its measurement permits us to determine whether the enhancement of serum ferritin levels detected in type II diabetic patients reflects the iron stores or, by contrast, is more closely related to the inflammatory process. sTFR have been previously determined in type I diabetic patients in order to evaluate their usefulness in the diagnosis of iron deficiency in patients with atrophic gastritis[20]. **Hernandez et al.**[21] have measured for the first time sTFR in type II diabetic patients. They suggested that the level of ferritin may not be a reliable tool for evaluating iron deficiency anemia in type II diabetes, and recommended further studies analyzing the relationship between ferritin levels and markers of inflammation such as IL-6 and TNF-α. So, in the present study serum sTFR, ferritin levels, iron and TIBC were measured in order to clarify whether serum ferritin reflects iron overload or an underlying inflammatory process, and their correlation to TNF-α as one of the inflammatory markers.

## SUBJECTS & METHODS

**Patients:**

The study included 30 type II diabetic patients and 15 healthy subjects matched for age and gender.

The type II DM diagnosis (in groups 2 and 4) was assessed by a specialist in the Internal Medicine Department at Kasr El-Aini Hospital, and were selected by determining their fasting and 2 hours postprandial blood glucose and fasting insulin levels as well as HbA1c to determine the glycemic control. These patients had the adult onset form of DM with no history of ketoacidosis. All type II DM patients were being treated with a combination of diet and oral hypoglycemic drugs or insulin at the time of the study.

The exclusion criteria for the present study were: premenopausal women, clinical evidence of haemorrahge in the preceeding 6 months, treatment in the previous year with iron, alcohol consumption, concomitant infections, and other chronic diseases apart from diabetes.

**Laboratory Methods:**

Subjects were screened before study entry for medical history, physical examination, electrocardiogram, and laboratory tests. Peripheral venous blood samples were drawn from all patients after overnight fasting to analyze the lipid profile (plasma total cholesterol[22] and triacylglycerol[23]) and glucose levels (fasting and 2 hours postprandial)[24], HbA1c was measured using quantitative colorimetric determination of glycohemoglobin in whole blood by kit provided by Stanbio, Texas[25]. The level of serum ferritin was measured by enzyme immunoassay for quantitative determination of ferritin in human serum (Diamed Eurogen Ferritin Microtiterstrip ELIZA Kit, Belgium).

sTFR was measured by enzyme immunoassay for the quantitative determination of the soluble transferrin receptor (Diamd Eurogen sTFR Microtiterstrip ELIZA Kit, Belgium). Serum iron and total iron binding capacity (TIBC) were determined by quantitative colorimetric determination by kit provided by Stanbio, Texas. Transferrin saturation % was calculated as serum iron/TIBC X 100[26]. TNF-α was determined by enzyme immunoassay for quantitative measurement of human TNF-α (Biosource Europe SA, Belgium).

***Statistical Methods:***

Statistical package for social science (SPSS) program version 9.0 was used for analysis of data. Data was summarized as mean ± SD. Non-parametric (Mann-Whitney) test was used for analysis of 2 quantitative data. Pearson's correlation was used for detection of the relation between 2 variables. P-value is considered significant if $\leq 0.05$.

## RESULTS

The main clinical features and the iron status in type II diabetic patients and control subjects are shown in tables (1, 2, 3).

**Table (1)**: Main clinical features of subjects included in the study

| | ***Diabetic patients n=30*** | ***Control subjects n=15*** | ***P*** |
|---|---|---|---|
| Age (years) | 60±11 | 57±12 | 0.1 |
| Gender (male/female) | 10/20 | 5/10 | |
| BMI ($Kg/m^2$) | 27.5±4.2 | 22.2±3.2 | 0.03* |
| Duration of diabetes (years) | 10±7 | - | |
| Insulin treatment (%) | 40% | 82.58.7 | 0.0001* |

*Data are mean ± SD*

**Table (2)**: Serum lipid profile and glycemic state in subjects included in the study

| | ***Diabetic patients n=30*** | ***Control subjects n=15*** | ***P*** |
|---|---|---|---|
| Fasting blood glucose (mg/dl) | 144.8±46.9 | 82±58.7 | 0.0001* |
| Postprandial blood glucose (mg/dl) | 190.9±66.6 | 118.6±14.9 | 0.0001* |
| HbA1c (%) | 9.0±1.5 | 4.0±1 | 0.0001* |
| Total cholesterol (mg/dl) | 245±38 | 190±8 | 0.0001* |
| Triglycerides (mg/dl) | 116.3±64.9 | 58.6±7.5 | 0.0001* |

*Data are mean ± SD*

**Table (3)**: Serum ferritin, sTFR, iron, TIBC, Tsat% and TNF-α of subjects included in the study

| | ***Diabetic patients n=30*** | ***Control subjects n=15*** | ***P*** |
|---|---|---|---|
| Ferritin (ng/ml) | 87.3±20.6 | 15.7±4 | 0.0001* |
| sTFR (U/ml) | 429.4±77 | 395.4±51 | 0.1 |
| Iron (μg/dl) | 73.1±35.5 | 104.1±34 | 0.005* |
| TIBC (μg/ml) | 380.3±107.6 | 300.8±54.9 | 0.008* |
| Transferrin saturation (%) | 19.7±7.6 | 37.3±17 | 0.0001* |
| TNF-α (pg/ml) | 16.8±1.9 | 7.2±0.5 | 0.0001* |

*Data are mean ± SD*

The diabetic patients had higher serum ferritin levels than the control subjects (P=0.0001), however, no difference in sTFR concentrations was observed between diabetic patients and control subjects (P=0.1). Serum iron as well as transferrin saturation % were significantly lower in diabetic patients when compared to control subjects (P=0.005, P=0.008 respectively). The inflammatory marker TNF-α levels were found significantly higher in diabetic patients than in control subjects (P=0.0001).

As expected, a significant negative correlation between ferritin and sTFR levels was detected in control subjects (Fig. 2), but this was not the case in diabetic patients (Fig. 1).

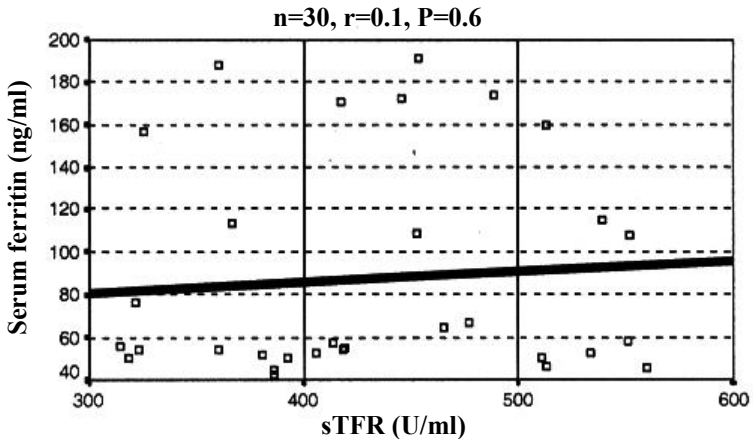


***Fig. (1): Correlation between serum ferritin and soluble transferrin receptor of diabetic patients included in the study***

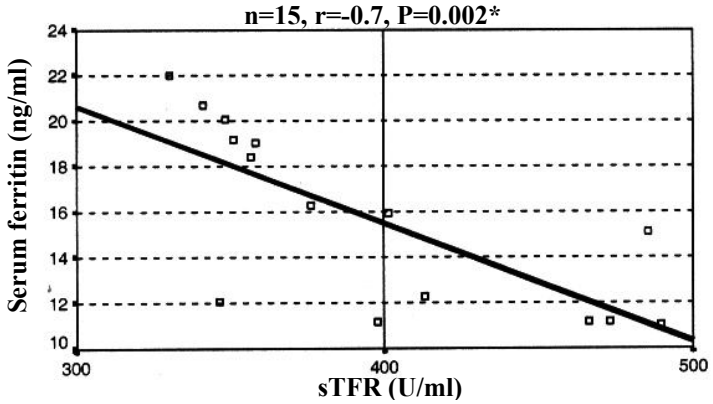


***Fig. (2): Correlation between serum ferritin and soluble transferrin receptor of controls included in the study***

In diabetic patients a significant positive correlation was found between ferritin and TNF-α levels (Fig. 3) whereas no correlation was detected between sTFR and TNF-α levels (Fig. 4).

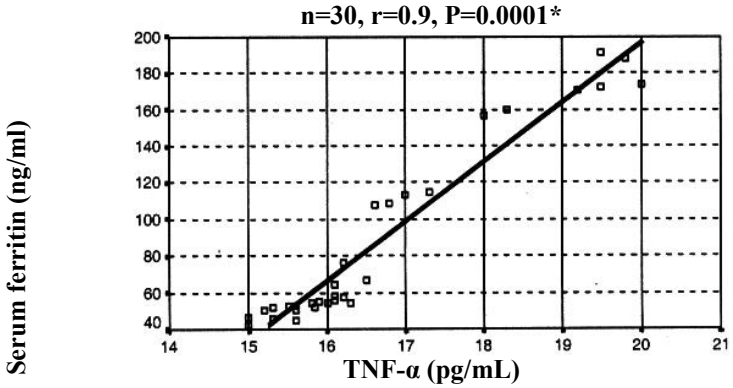


***Fig. (3): Correlation between serum ferritin and tumour necrosis factor in diabetic patients included in the study***

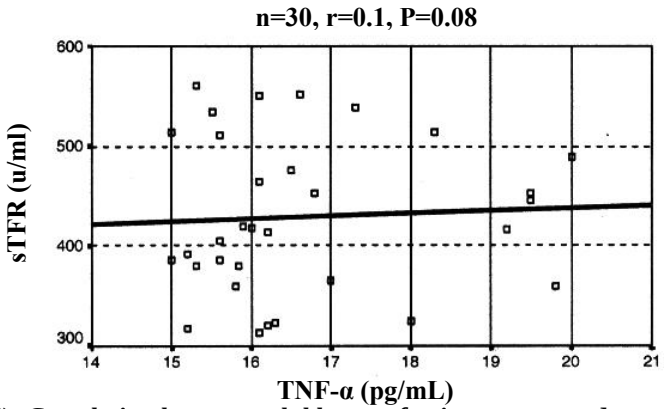


***Fig. (4): Correlation between soluble transferrin receptor and tumour necrosis factor in diabetic patients included in the study***

## DISCUSSION

The relationship between iron metabolism and type II DM are bidirectional: iron affects glucose metabolism and glucose metabolism impinges on several iron metabolic pathways, **Fernandez-Real et al.**[27] studied the contribution of sTFR and stated that insulin sensitivity and glucose tolerance status are significantly associated with sTFR concentrations although the latter did not significantly change during the

oral glucose tolerance test. They, also, noted a negative association between serum sTFR and serum ferritin (r=-0.16, P=0.02) which is one of the commonly used parameters in assessment of body iron stores.

Ferritin and transferrin were shown to independently predict hyperglycemia in a 3-year follow up study[28], also **Vari et al.**[29] stated that when both markers of iron metabolism are elevated, the incidence of metabolic syndrome is increased. In fact serum ferritin has been reported to correlate closely with body iron stores in healthy individuals[30]. However, serum ferritin levels can vary significantly overtime and may fluctuate in the presence of inflammation due to increase in its transcription via inflammatory cytokines[31]. This suggests that pathways related to stress and inflammation can impact ferritin regulation.

As reported in many researches[15-18], the present study detected high ferritin levels in type II diabetic patients when compared with non-diabetics as shown in table (3). However, this elevation reflects the total sum of body iron stores[32] and the production of acute-phase reactants which are increased in DM[33].

So measurement of circulating sTFR levels which are not influenced by acute phase response occurring in inflammatory processes enables the investigation of the source of ferritin increase.

In the present study, although there was increased ferritin levels in diabetic patients, a decrease of sTFR levels were not detected (Fig. 1). Furthermore, serum ferritin levels showed a significant negative correlation with serum iron levels (r=-0.4, P=0.02), also transferrin saturation index (Tsat%), which is considered to be one of the most reliable screening tests for iron overload[26], was found to be significantly lower in diabetic patients than in control subjects (P=0.0001) indicating that the high serum levels of ferritin are not attributed to iron overload in the tested population, and this supports the idea that inflammation is the main contributor to the high ferritin levels observed in diabetic patients[21,34].

Several recent studies analyzed the relationship between ferritin levels and some markers of inflammation such as C-reactive protein (CRP) and α1-acid glycoprotein (AGP), **Beard et al.**[35] found that serum ferritin-but not transferrin receptor, transferrin receptor index or serum iron-was related to acute phase proteins (APP) concentration, but poor predictive value was found (<72%), i.e. ferritin concentrations were poorly predicted by either elevated CRP or AGP. Also **Campenhout et al.**[33] found no relation between ferritin and CRP, a finding which argues in favour of elevated iron stores rather than a proinflammatory state as a source of serum ferritin in diabetic patients. On the other hand, **Vari et al.**[29] found that CRP was not correlated with ferritin but was correlated with transferrin in pre and post menopausal women with metabolic syndrome. The present work detected a significant positive correlation between serum ferritin and TNF-α, as an inflammatory marker (Fig. 3),

whereas no relation between serum sTFR and TNF-α was detected in diabetic population (Fig. 4), which confirms the role of inflammation as a major contributor to the high ferritin levels in diabetes, and on the other hand highlights the lack of influence of inflammation on sTFR levels. So, the present study's results suggest that the ferritin level may not be a reliable tool for evaluating iron deficiency anemia in type II diabetes, as diabetes is considered one of the inflammatory conditions[36] and most of the biomarkers for iron metabolism are affected by acute phase reaction, and since a significant negative correlation was found between iron and sTFR in both control subjects (r=-0.6, P=0.03) and diabetic patients (r=-0.5, P=0.003) (serum TFR levels rise with iron deficiency and fall with iron shores[29]), this study suggests that assessment of sTFR might be added to the measures used to investigate anemia in diabetic population. A finding that agrees with many studies[19,37,38] which demonstrated that sTFR is a sensitive marker in the differential diagnosis of anemia of chronic disorders and iron deficiency anemia. On the other hand, this finding contrast with other studies performed on patients with chronic inflammatory conditions; **Lee et al.**[39] and **Choi**[40] which stated that sTFR does not exceed the diagnostic value of low serum ferritin for evaluating iron deficiency. Also **Joosten et al.**[41] stated that serum ferritin level was a better marker than sTFR in assessment of iron status. As regards the relationship between insulin treatment and sTFR, no significant difference was found in sTFR levels between diabetics using insulin and those using oral hypoglycemic drugs (P>0.05), although **Davis et al.**[42] observed that insulin stimulates fat cell iron uptake. Also, **Tanner and Lienhard (1987)**[43] demonstrated that insulin elicits translocation of intracellular TFR to the microsomal membranes of cultured adipocytes. Also, **Clairmont and Czech**[44], demonstrated that insulin injection increase sTFR in rats. The present study's findings agree with those of **Hernandez et al.**[21] and **De Block et al.**[20], thus arguing with the possibility that hyperinsulinemia may contribute to the inappropriately high levels of sTFR detected in type II DM.

In summary, serum ferritin levels are increased in type II diabetic patients in absence of changes in sTFR levels and other parameters of iron overload. The inflammatory marker TNF-α was found to be significantly positively correlated with serum ferritin in diabetic patients whereas no correlation was found with serum sTFR, these findings suggest that elevated ferritin levels are mainly due to inflammatory mechanisms rather than iron overload. Also, the present study suggests that sTFR is a better marker than ferritin in assessment of iron status especially in inflammatory conditions associated with DM.

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# الفريتين ومستقبلات الترانسفرين الذائب فى مرضى البوال السكرى من النوع الثانى: العلاقة بعامل التنقرز الخلوى ألفا كأحد دلالات الإلتهاب

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أكدت أبحاث أجريت حديثاً أن حالات الإلتهاب المزمن تلعب دوراً فى إحداث مرض البوال السكرى من النوع الثانى وعواقبه بالإضافة إلى ذلك، أكدت عدة أبحاث أخرى دور زيادة نسبة الحديد بالجسم كمسببات للعديد من الأمراض منهم مرض البوال السكرى من النوع الثانى.

ولأن معظم المركبات المحتوية على الحديد مثل الفريتين قد يزداد تركيزها فى وجود إلتهاب بالجسم، فبذلك أصبحت غير دقيقة لتقدير نقص أو زيادة الحديد فى الجسم.

وقد إستهدف البحث قياس مستويات الفرتين ومستقبلات الترانسفرين الذائب وعامل التنقرز الخلوى ألفا فى مصل الدم لمرضى البوال السكرى النوع الثانى لتقييم ما إذا كان مستوى الفرتين بعكس نسبة الحديد بالجسم أم هذا الإرتفاع نتيجة الإلتهاب المصاحب للمرض.

وقد أجرى البحث على ٣٠ حالة من حالات البوال السكرى من النوع الثانى بالإضافة إلى ١٥ شخصاً غير مصاب بالمرض كمجموعة ضابطة. وقد تم قياس نسبة الحديد، الفرتين، مستقبلات الترانسفرين الذائب وعامل التنقرز الخلوى ألفا عند جميع الأفراد.

**النتائج:**

وقد إرتفاع ذو دلالة احصائية فى مستوى الفرتين فى مصل الدم لمرضى البوال السكرى مقارنة بالمجموعة الضابطة، فى حين لم يكن هناك فرق فى مستوى مستقبلات الترانسفرين الذائب بين المجموعتين.

وقد وجدت علاقة إرتباط سالبة وذات دلالة احصائية بين مستويات الفرتين ومستقبلات الترانسفرين الذائب فى المجموعة لاضابطة فقط وليس فى مرضى البوال السكرى. كما وجدت علاقة إرتباط موجبة ذات دلالة احصائية بين مستويات عامل التنقرز الخلوى ألفا والفرتين فقط وليس مع مستويات مستقبلات الترانسفرين الذائب فى مرضى البوال السكرى.

وقد أكدت نتائج البحث أن إرتفاع مستويات الفرتين فى مرضى البوال السكرى النوع الثانى تنتج عن وجود الإلتهاب المصاحب للمرض وليس بسبب زيادة نسبة الحديد فى الدم، مما يجعل قياس مستقبلات الترانسفرين الذائب أكثر دقة لتقدير نقص الحديد بالجسم فى مرضى البوال السكرى.