Journal of Pharmaceutical Research International

33(23A): 105-118, 2021; Article no.JPRI.66788
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Status of Transferrin Saturation in Diabetic Nephropathypatients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i23A31417
Editor(s):
(1) Dr. Farzaneh Mohamadpour, University of Sistan and Baluchestan, Iran.
Reviewers:
(1) João Cotas, Marine and Environmental Sciences Centre, University of Coimbra, Portugal.
(2) S. Vidyadhara, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/66788

Original Research Article

Received 25 January 2021
Accepted 01 April 2021
Published 15 April 2021

ABSTRACT

Serum transferrin saturation (TSAT%) ratio is a commonly used laboratory measure of iron deficiency and iron overload in clinical practice. It has become a first step in the routine screening of iron deficiency anaemia in patients with chronic kidney disease and for the detection of pathological iron overload in assessment for hemochromatosis. Used alone or in combination with other measures of iron metabolism, low levels of TSAT (typically<20%) reflect a state of iron deficiency whereas levels in excess of 50% indicate an excess of total body iron. In our study, transferring saturation levels was significantly high in diabetic Nephropathy (group I). Comparison of the parameters serum iron, Urine Albumin, TIBC, Trasferrin saturation, glycated hemoglobin (HbA1C), Fasting plasma glucose(FBS) between the 3 group was done using Student t test and was statistically significant.Pearson's coefficient correlation was done between transferrin saturation and serum iron, Urine microalbumin, TIBC, Trasferrin saturation, glycated hemoglobin (HbA1C), Fasting blood sugar (FBS) and found a positive correlation between them and had a statistical significance. This indicates that transferrin saturation levels increases with the extent of severity of diabetic Nephropathy. Positive correlation provides the information that transferrin saturation can be considered to reflect the iron depletion of an individual.

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Keywords: Serum transferrin saturation; urine albumin; glycated hemoglobin (HbA1C); Fasting plasma glucose (FBS).

1. INTRODUCTION

Iron stores in our body function as a component of proteins and enzymes. Approximately 2.5 grams of iron (i.e) two-thirds of iron in the body is found in hemoglobin. This hemoglobin which is a protein in red blood cells carries oxygen to tissues. Myoglobin of muscle tissue also contains hemoglobin whose major component is iron (15 percent). The body absorbs about approximately 1-2 mg of iron per day to compensate for the body's loses of iron (Non - menstruating). Transferrin saturation (TSAT) is measured as a percentage ratio of serum iron and total iron-binding capacity (TIBC). Transferrin, which is a transport protein transports iron from one organ to another. It then forms a complex with a highly specific transferring receptor (TfR). This TfR is located on surfaces of the plasma membrane. The major disorders of iron metabolism are iron deficiency and iron overload. Transferrin saturation ratio is an indicator of iron deficiency and iron overload [1,2]. TSAT is considered the first step in the screening of iron defiencyanaemia. High levels of dietary iron intake account for diabetes risk. Insulin resistance and β cell failure are the two major pathogenetic factors that occur due to deranged iron metabolism. Molecular mechanisms like modulation of adipokines, oxidative stress also take part in the risk of diabetes in the case of derangement of iron metabolism [3,4]. Fewer studies have stressed the association of transferrin saturation with mortality in the general population. Diabetes mellitus is a group of metabolic diseases and an ever-increasing worldwide health problem. The prevalence of Type 2 diabetes mellitus (T2DM) is 11.6% in the urban population and 2.4% in the rural population [5-9].

In the present study, the relationship between transferrin saturation in normal individuals and diabetic nephropathy patients are been studied. Elevation of TSAT in diabetic nephropathy patients is a pre-predictive factor for identifying early renal complications and thus reducing the complications (ie) progression of nephropathy to chronic renal failure (CKD).

2. MATERIALS AND METHODS

The study was conducted in the Department of Biochemistry, Sree Balaji Medical College and Hospital, Chromepet, Chennai during January 2015 – June 2016 among 35 Diabetic Nephropathy patients (group visiting the nephrology outpatient services of the Department of nephrology and 35 diabetic individuals without nephropathy (group 2) who came for a routine check-up in diabetic outpatient service, department of medicine and 30 nondiabetic controls (group 3). The groundwork for the study was started after getting clearance from the research committee and the Institutional human ethical committee (reference number for approval: 002/SBMC/IHEC/2015 -57) of Sree Balaji Medical College and Hospital, Chromepet, Chennai.

Age, gender, duration of type 2 Diabetes Mellitus, general history and medications and blood pressure were recorded. A routine clinical examination was done. The laboratory parameters that were measured include serum iron, Urine Albumin, TIBC, Trasferrin saturation, glycated hemoglobin (HbA1C), Fasting blood sugar (FBS) [10].

The study was explained to the participants and informed consent obtained from them before taking the blood sample. The blood samples were collected from subjects by venipuncture. Fasting (8hours of overnight fasting) samples were collected under aseptic precaution. Estimation of Fasting blood sugar (GOD/POD: enzymatic photometric Method), HbA1c by Ion Exchange Resin method, Total Iron Binding Capacity (TIBC), serum Iron, Microalbumin.

3. RESULTS AND DISCUSSION

Graph 1 shows that mean Fasting Blood Sugar values of Group I, Group II and Group III are 172.66±23.49, 167.40±22.48 and 98.63±11.97 respectively. The levels of blood sugar in diabetics (with and without complications) are higher than healthy controls and the difference is strongly significant ($P<0.001$).

Graph 2 shows that mean HbA1c values of Group I, Group II and Group III are 9.689 ±1.447, 8.803±1.325 and 4.980 ±0.675 respectively. The levelsin diabetics (with and without complications) are higher than healthy controls and the difference is strongly significant ($P<0.001$).

Table 1. Descriptive statistics: Cases (Group I)

Parameters	N	Mean	Std. Error of Mean	Std. Deviation
Fasting blood sugar (mg/dL)	35	172.65	3.97	23.49
HbA1C (%I)	35	9.68	0.24	1.44
Microalbuminuria (mg/dL)	35	48.94	1.60	9.46
Serum iron (mcg/dL)	35	258.23	2.75	16.28
Total iron binding capacity (µg of iron/dL)	35	466.34	1.96	11.62
Transferrin saturation (%)	35	55.37	0.55	3.27

Table 2. Descriptive statistics: Cases (GroupII)

Parameters	N	Mean	Std. Error of Mean	Std. Deviation
Fasting blood sugar (mg/dL)	35	167.4	3.80	22.48
HbA1C (%)	35	8.8	0.22	1.32
Microalbuminuria (mg/dL)	35	20.37	0.96	5.68
Serum iron (mcg/dL)	35	103.40	2.85	16.86
Total ironbinding capacity (µg of iron/dL)	35	308.74	7.38	43.70
Transferrin saturation (%)	35	33.92	1.07	6.35

Table 3. Descriptive statistics: Cases (GroupIII)

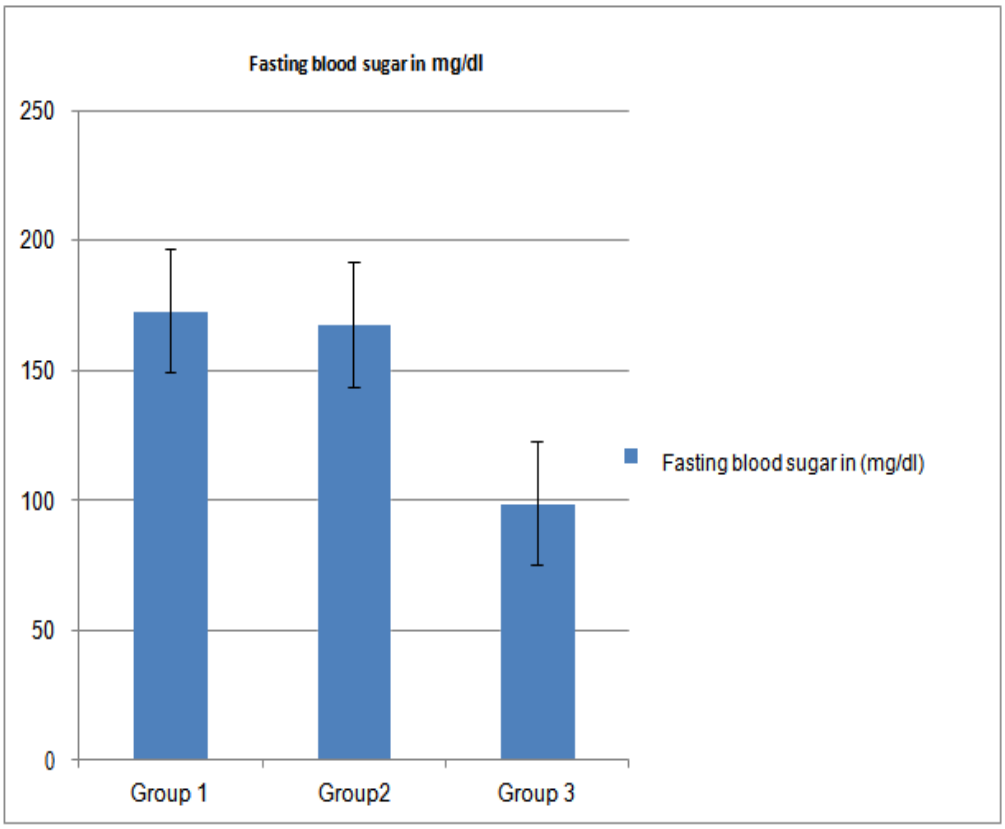
Parameters	N	Mean	Std. Error of Mean	Std. Deviation
Fasting blood sugar (mg/dL)	35	98.63	2.18	11.97
HbA1C (%)	35	4.98	0.12	0.67
Microalbuminuria (mg/dL)	35	18.87	0.82	4.50
Serum iron (mcg/dL)	35	100.70	2.61	14.32
Total ironbinding capacity (µg of iron/dL)	35	323.06	5.93	32.49
Transferrin saturation (%)	35	31.43	0.95	5.25

Graph 3 shows that mean urine micro albumin values of Group I, Group II and Group III 48.94±9.46,20.37±5.68and 18.87±4.50 are respectively. Comparison between group II and Group III shows that the p value is .0308 (t=1.0361) and this is not significant. Comparison between group I and Group II &between group I and Group III shows that the p values are .001 (t=14.7212) (significant) and .001(t=15.877) (significant)respectively.

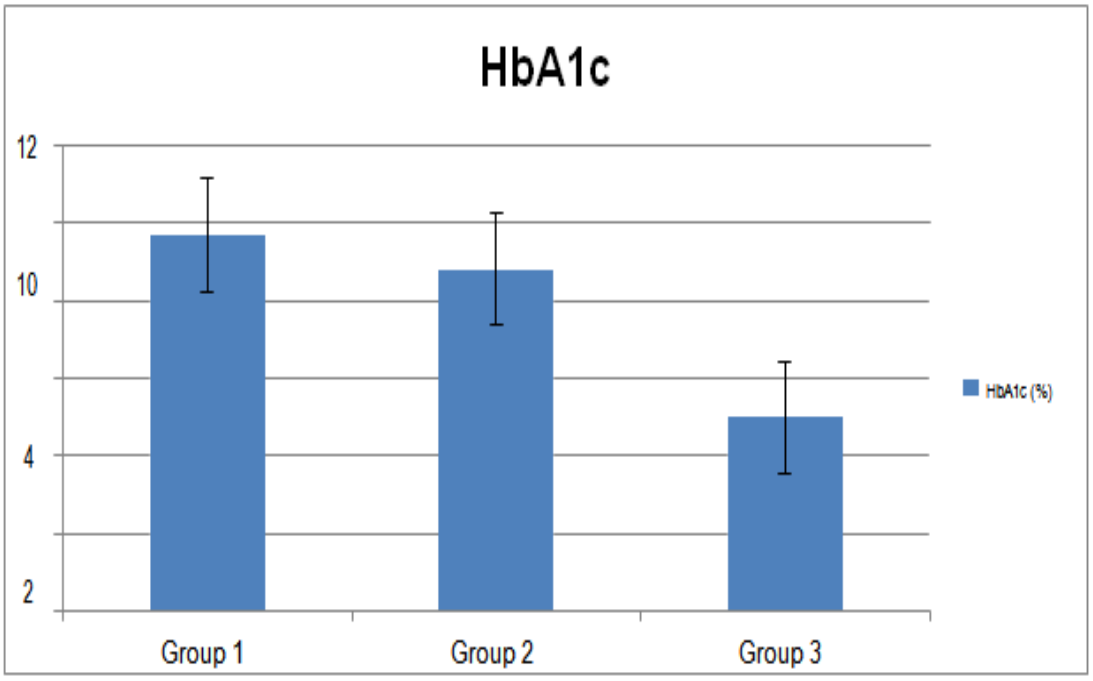
Graph 4 shows that mean S. Iron valuesofGroup I, GroupII and Group III are 258.23±16.28, 103.40±16.86 and 100.70±14.32 respectively. Comparison between group II andGroup III shows that the p value is 0.3555(t=0.9389) andthis is not significant. Comparison between group I and Group II &between group I and Group III shows that the p values are .001(t=41.3611) (significant) and .001 (t=37. 1006) (significant) respectively.

Graph 5 shows that mean TIBC values of Group I, Group II and Group III are 466.34±11.62, 308.74±43.71 and 323.07±32.49 respectively. Comparison between group II and Group III shows that the p value is 0606 (t=1.9525) and this is not significant. Comparison between group I and Group II &between group I and Group III shows that the p values are .001 (t=19.1806) (significant) and .001 (t=21.8391) (significant) respectively.

Graph 6 shows that mean TSAT values of Group I, Group II and Group III are55.374±3.278, 33.925±6.353and31.431±5.256 respectively. Comparison between group II and Group III shows that the p value is .0473 (t=2.0715) and this is not significant. Comparison between group I and Group II &between group I and Group III shows that the p values are 0.001 (t=17.5592) (significant) and 0.001 (t=20.9448) (significant) respectively.



Graph 1. Comparison of Fasting Blood Sugar (FBS) among Group I, Group II and GroupIII



Graph 2. Comparison of HbA1c among Group I, Group II and Group III

Table 4. Comparison of Fasting blood sugar (FBS) among Group I, Group II and Group III

Parameters	Group I (mean ±SD)	Group II (mean ± SD)	Group III (mean ± SD)	Significance
Fasting Blood Sugar(mg/dl)	172.66±23.49	167.40±22.48		t = 0.8140; P=0.4213 (between Group I and II)
		167.40±22.48	98.63±11.97	t = 14.3184; P<0.001 (between Group II and III)
	172.66±23.49		98.63±11.97	t = 15.9739; P<0.001 (between Group I and III)

The values are expressed in Mean± SD. Student t test (two tailed) has been used to find the significance. The FBS values in Group I, Group II and Group III are172.66±23.49, 167.40±22.48 and 98.63±11.97respectively.The levels of fasting blood sugar in diabetics (with and without complications) are higher than healthy controls and the difference is strongly significant(P<0.001)

Table 5. Comparison of glycated hemoglobin (HbA1c) among Group I, Group II and Group III

Parameters	Group I (mean ±SD)	Group II (mean ±SD)	Group III (mean ±SD)	Significance
HbA1c(%)	9.689±1.447	8.803±1.325		t = 2.2495; P=0.3 (between Group I and II)
		8.803±1.325	4.980±0.675	t =14.1320;P<0.001 (between Group II and III)
	9.689±1.447		4.980±0.675	t=17.8563; P<0.001 (between Group I and III)

The values are expressed in Mean± SD. Student t test (two tailed) has been used to find the significance. The HbA1c values in Group I, Group II and Group III are9.689±1.447, 8.803±1.325and4.980±0. 675 respectively. The levels of HbA1c (%) indiabetics (with and without complications) are higher than healthy controls and the difference is strongly significant(P<0.001)

Table 6. Comparison of urine microalbuminlevels among Group I, Group II and GroupIII

Parameters	Group I (mean ±SD)	Group II (mean ±SD)	Group III (mean ±SD)	Significance
Urine microalbumin (mg/l)	48.94±9.46	20.37±5.68		t=14.7212; P<0.001(between Group I and II)
		20.37±5.68	18.87±4.50	t= 1.0361; P=0.3087(betweenGroup II and III)
	48.94±9.46		18.87±4.50	t= 15.8773; P<0.001(between Group I andIII)

The values are expressed in Mean± SD. Student t test (two tailed) has been used to find the significance. The urine microalbumin values in Group I, Group II andGroup III are 48.94±9.46, 20.37±5.68, 18.87±4. 50respectively.The levels of Microalbinuria in diabetics (with and without complications) are higher than healthy controls and the difference is strongly significant (P<0.001)

Table 7. Comparison of serum iron among Group I, Group II and Group III

Parameters	Group I (mean ±SD)	Group II (mean ± SD)	Group III (mean ± SD)	Significance
S.Iron(µg/dl)	258.23±16.28	103.40±16.86		t = 41.3611; P<0.001 (between Group Iand II)
		103.40±16.86	100.70±14.32	t =0.9389; P=0.3555 (between Group IIand III)
	258.23±16.28		100.70±14.32	t = 37.1006; P<0.001 (between Group Iand III)

The values are expressed in Mean± SD. Student t test (two tailed) has been used to find the significance .The serumiron values in Group I, Group II and Group III are 258.23±16.28, 103.40±16.86 and100.70±14.32respectively. The levels of serum iron in diabetics (with and without complications) are higher than healthy controls and the difference is strongly significant (P<0.001)

Table 8. Comparison of Total Iron Binding Capacity (TIBC) among Group I, Group II and GroupIII

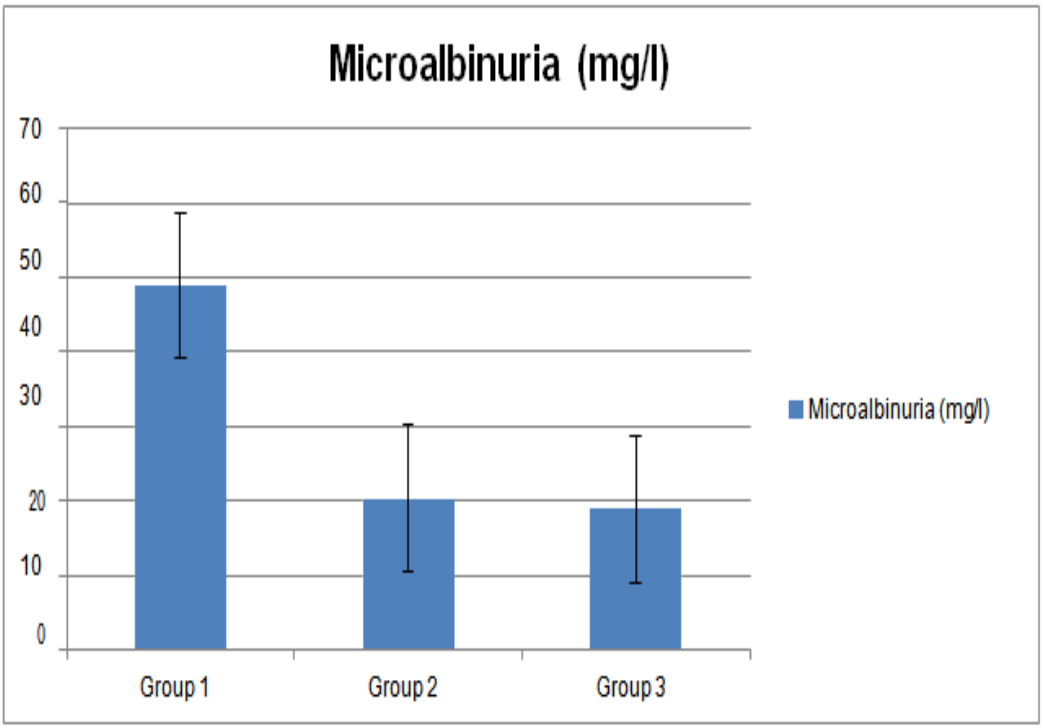
Parameters	Group I (mean ±SD)	Group II (mean ±SD)	Group III (mean ±SD)	Significance
TIBC (µg/dl)	466.34±11.62	308.74±43.71		t = 19.1806; P<0.001 (between Group I and II)
		308.74±43.71	323.07±32.49	t=1.9525 ; P= 0.0606(between Group II and III)
	466.34±11.62		323.07±32.49	t=21.8391 ;P<0.001 (between Group I and III)

The values are expressed in Mean± SD. Student t test (two tailed) has been used to find the significance. Total Iron Binding capacity (TIBC) values in Group I, Group II and Group III are 466.34±11.62, 308.74±43.71 and 323.07±32.49respectively. The levels of Total Iron Binding Capacity in diabetics (with and without complications) are higher than healthy controls and the difference is strongly significant(P<0.001)

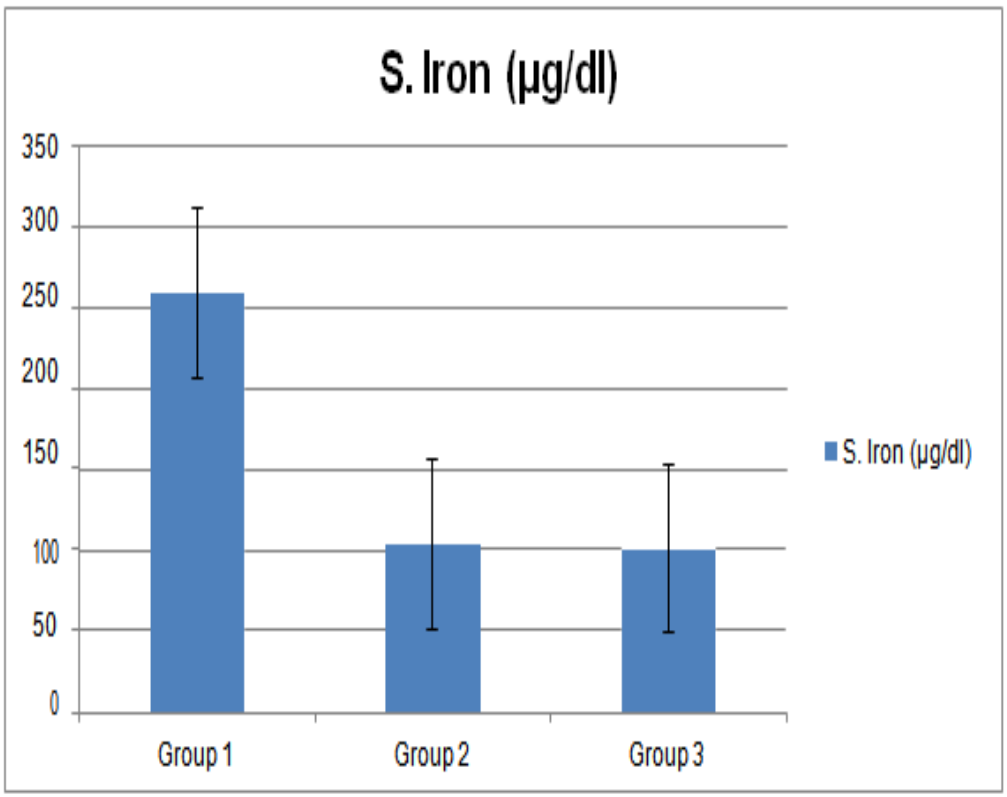
Table 9. Comparison of TSAT % among Group I, Group II and Group III

Parameters	Group I (mean ±SD)	Group II (mean ±SD)	Group III (mean ±SD)	Significance
TSAT(%)	55.374±3.278	33.925±6.353		t=17.5592; P<0.001(between Group I and II)
		33.925±6.353	31.431±5.256	t=2.0715; P=0.0473(between Group II and III)
	55.374±3.278		31.431±5.256	t = 20.9448; P<0.001 (between Group I and III)

The values are expressed in Mean± SD. Student t test (two tailed) has been used to find the significance. Total Transferrin Saturation (TSAT %) values in Group I, Group II and Group III are 55.374±3.278, 33.925±6.353 and31.431±5.256 respectively. The levels of Transferrin Saturation in diabetics (with and without complications) are higher than healthy controls and the difference is strongly significant (P<0.001)



Graph 3. Comparison of urine micro albumin levelsamong Group I, Group II and GroupIII



Graph 4. Comparison of serum iron among Group I, Group II and Group III

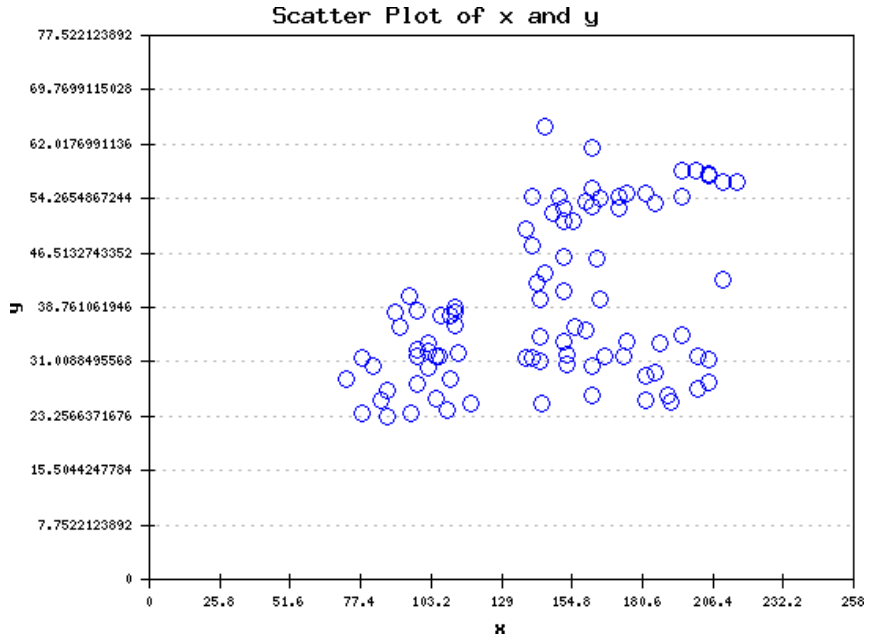


Fig. 1. Pearsons correlation between TSAT% and fasting blood sugar

Pearsons correlation between TSAT and HbA1c group I, group II, group III (r =0.528) p value =0.000, Correlationis significant at the 0.01 level (2-tailed).

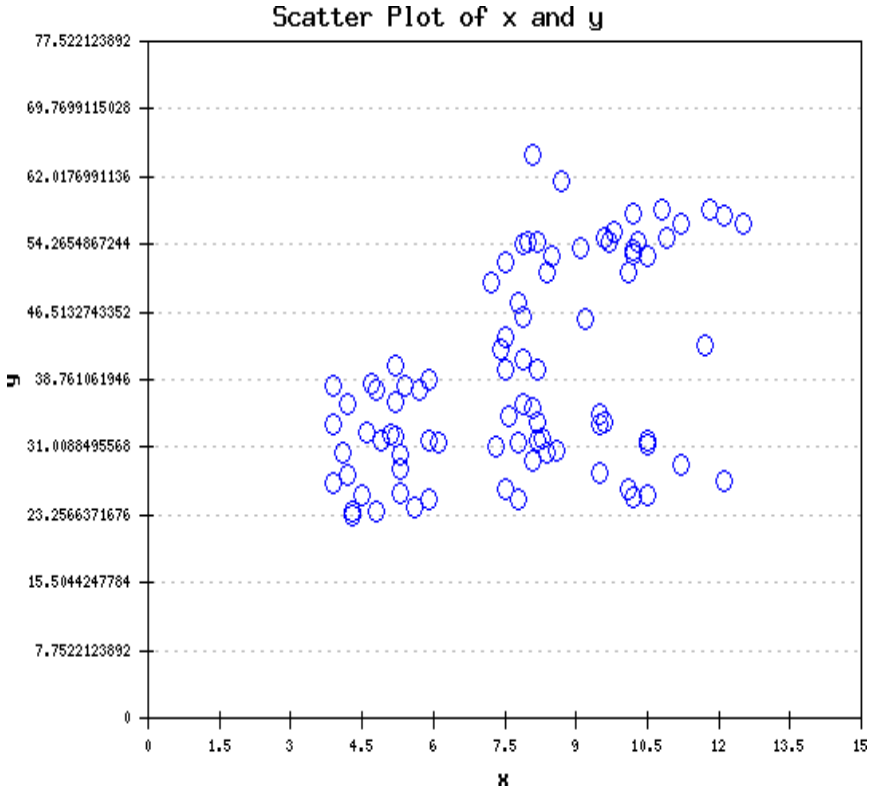


Fig. 2. Pearsons correlation between TSAT and HbA1c

Pearsons correlation between TSAT and Microalbumin group I, group II, group III (r = 0. 0.820) p value = 0.000, Correlation is significant at the 0.01 level (2-tailed).

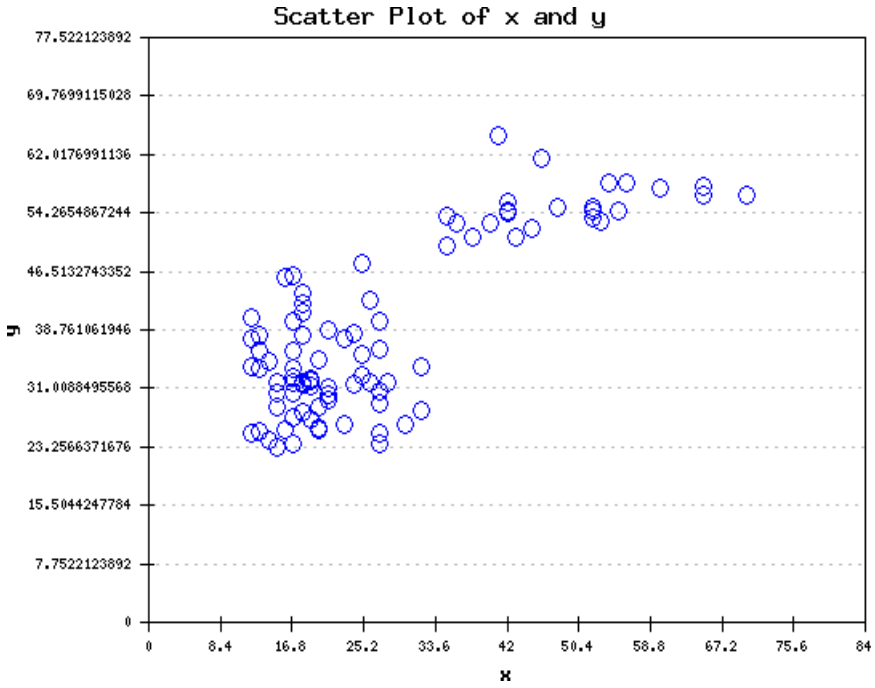


Fig. 3 Pearsons correlation between TSAT and microalbumin

1. Pearsons correlation between TSAT and S. Iron group I, group II, group III (r =0.950231) p value = 0.000, Correlation is significant at the 0.01 level (2-tailed).

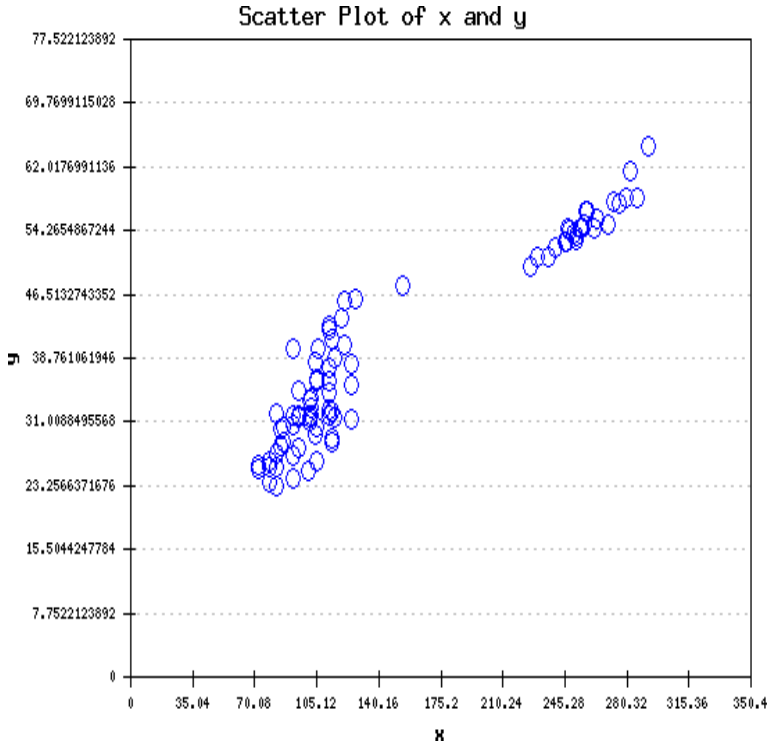


Fig. 4. Pearsons correlation between TSAT and S. Iron

2. Pearsons correlation between TSAT and TIBC group I, group II, group III (r = 0.741) p value = 0.000, Correlation is significant at the 0.01 level (2-tailed).

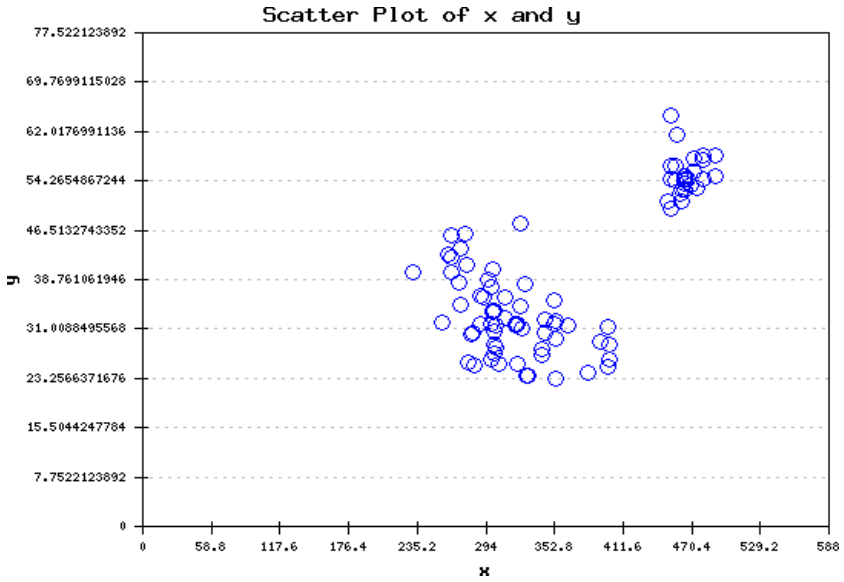
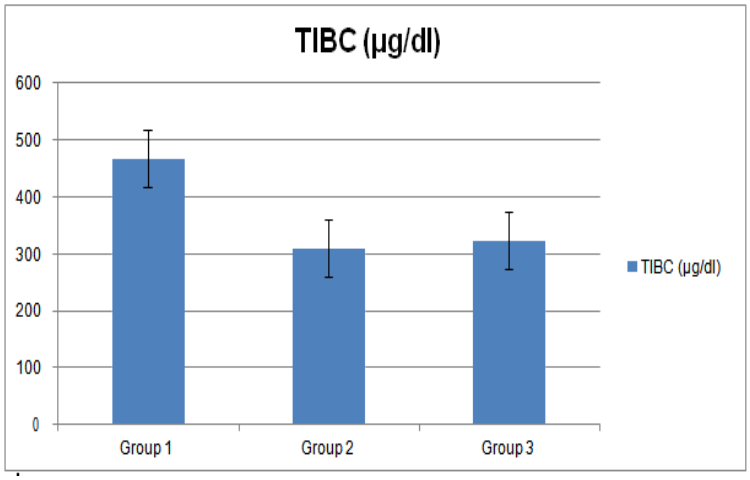
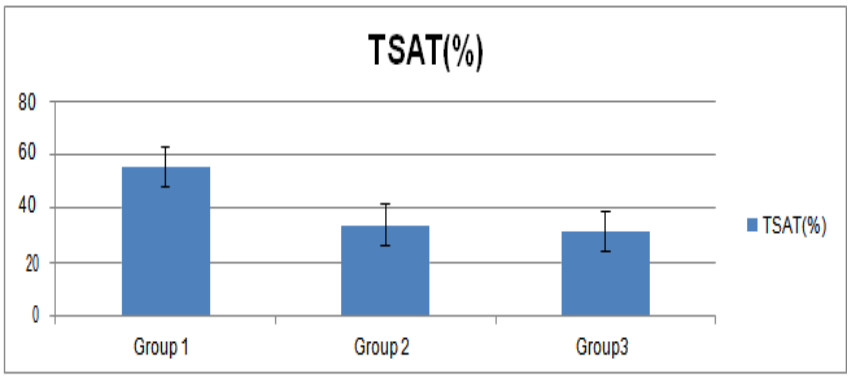


Fig. 5. Pearsons correlation between TSAT and TIBC



Graph 5. Comparison of Total Iron Binding Capacity (TIBC) among Group I, Group II and Group III



Graph 6. Comparison of TSAT % among Group I, Group II and Group III

3.1 Tests of Correlation (Pearsons Correlation)

Pearsons correlation between TSAT% and fasting blood sugar among groupI, groupII, groupIII (r=0.472) pvalue= 0.000, Correlation is significant at the 0.01 level (2 - tailed).

This study was done on "Status of transferrin saturation in Diabetic Nephropathy" Age, Sex matched diabetic individuals were taken as controls. Absolute iron deficiency is likely to be present in patients with end-stage renal diseasewheneitherthe percent transferrin saturation (plasma iron divided by total iron-binding capacity x 100, TSAT) falls below 20 percent the serum ferritin concentration is less than 100 ng/mL among predialysis and peritoneal dialysis patients or is less than 200 ng/mL among hemodialysis patients.

This difference in the serum ferritin level is based upon accumulating evidence in hemodialysis patients that the maintenance of ferritin levels above 200ng/mL is associated with decreased erythropoietin requirements. True iron deficiency is found in up to 40% of patients with diabetic nephropathy. However, it is not sufficient for patients with nephropathy to have "normal" iron stores. Patients require high iron availability tomaximize the use of endogenous erythropoietin and maintain satisfactory hematocrit.

Functional iron deficiency is characterized by the presence of adequate iron stores as defined by conventional criteria, but an inability to sufficiently mobilize this iron from the liver and other storage sites to adequately support erythropoiesis with the administration of erythrocyte stimulating agents (ESA) [11,12]. Typically, these patients have either normal or elevated serum ferritin levels but the transferrin saturation typically is about 20 percent or less.

The inflammatory block is also an important clinical distinction since it usually does not respond to iron. An inflammatory iron block occurs among patients with refractory anemia due largelytoanunderlying inflammatory state [13-15]. However, it should be emphasized that both functional deficiency and inflammatory block may be associated with TSAT≤ 20 percent and ferritin levels between 100 to 800 ng/mL or even higher.

The response to ESA and/or parenteral iron may help distinguish between these two possibilities: In patients with functional deficiency, increasing ESA doses may result in a decrease in ferritin levels while in patients with inflammatory block increased ferritin levels persist, due to persistent inflammation. Moreover, when inflammation is present and the cause is not addressed, the weekly administration of intravenous iron (50 to 125 mg) for up to 8 to 10 doses fails to result in increased erythropoiesis; instead, ferritin concentration progressively rises. By comparison, among patients with functional iron deficiency, additional intravenous iron (in association with an increase in EPO dose) can be effective in increasing Hgblevels, at least over the short term. This was best shown in theDRIVE study, in which 134 patients with anemia (hemoglobin levels less than 11 g/dL), elevated ferritin levels (500 to 1200ng/mL), low transferrin saturation levels (≤25 percent), and high erythropoietin requirements (≥ 225 international units/kg per week or ≥ 22,500 international units per week) were randomly assigned to ferric gluconate (125mg with eight consecutive dialysis sessions) or placebo [16].

Erythropoietin doses were increased in all patients by25 percent at the beginning of the study. At six weeks, hemoglobin levels had increased significantly more in the active therapy group (1.6 versus 1.1 g/dL). None of the iron parameters typically used in clinical practice, including percent transferrin saturation, ferritin, and reticulocyte hemoglobin content, were found to be particularly sensitive or specific for predicting a response to iron supplementation [17].

Two of the main concerns of this important study was that some patients who received both intravenous iron and the increase in EPO dose were more likely to have larger, more rapid increases in Hgb level, possibly resulting in adverse effects and that clinical outcomes beyond an increase in Hgblevel were not assessed. Nevertheless, the results of the DRIVE study raise the following question: Why nephrologists don't use more iron? A possible answer is that most of us are afraid of iron overload. Although this issue has not been clarified yet, it could well be that this fear is not justified. Feldmannetal showed that high ferritin, not cumulative iron dose is linked to increased mortality in hemodialysis patients. The use of traditional biochemical parameters for the evaluation of anemia in patients with Diabetic Nephropathyhas several limitations. Ferritin, a

complex of iron and protein is an acute-phase protein; Therefore, ferritin levels do not reflect accurately total iron stores. Serum iron levels fluctuate both during the day and from one day to the other, while transferrin saturation (Fe/total iron-binding capacity of transferrin) has good sensitivity but lacks specificity , due to fluctuations in serum transferrin levels.

Furthermore, the clinical utilityoftransferrin saturation is impaired by the absence of a diagnostic threshold. Nevertheless, and since the use of newer indices (derived from full blood count) has not yet become routine in everyday clinical practice, a combined approach based on iron, ferritin, and transferrin saturation (TSAT) can help in the diagnosis of absolute or functional iron depletion.

4. CONCLUSION

Our study shows Transferrin Saturation(%) increases in diabetic nephropathy patients. Also, serum levels of iron, total iron-binding capacity, increases with diabetic nephropathy. The correlations among serum levels of iron, total iron-binding capacity in patients with diabetic nephropathy are increased. Thus transferrin saturation plays a major role in diabetic nephropathy patients and assessment of transferrin saturation in diabetic patients without nephropathy is a prognostic factor for diagnosing diabetic nephropathy in an earlier state and finally preventing further complications like chronic kidney disease(CKD) and end-stage renal disease (ESRD).

CONSENT AND ETHICAL APPROVAL

The study was started after getting clearance from the research committee and the Institutional human ethical committee (reference number for approval: 002/SBMC/IHEC/2015-57) of Sree Balaji Medical College and Hospital, Chromepet, Chennai. The study was explained to the participants and informed consent obtained from them.

ACKNOWLEDGMENTS

The encouragement and support from Bharath University, Chennai is gratefully acknowledged. For provided the laboratory facilities to carry out the research work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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