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Correlation of Serum Ferritin with Glycated Haemoglobinin type 2 Diabetes Mellitus Patients.

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Abstract:

Background: Diabetes Mellitusis ametabolic disorder of multiple aetiology characterized by presence of hyper glycaemia with disturbances of carbohydrate, protein and lipid metabolism duetod efects in insulinse cretion, action or both.Increasing concentration of iron and ferritin incells could cause resistance to insulin and dysfunction of beta cells of pancreas. Early identification helps india gnosing grievous systemic manifestations and their prompt and appropriate treatment.

Aim:To find association and correlation of serum ferritin with glycated haemoglobin (HbA1c) inpatientswithtype2diabetesmellitus.

Methods: An observational study was carried out over a span of 1.5 years who were previously diagnosed case of type 2 Diabetes Mellitus attended Medicine department OPD and IPD between age group 35-70 years were included in study.Serum Ferritin, HbA1c,FBS,PPBS and other clinical features were noted based on history and clinical examination of thesepatients.

Results:A totalof 100 patients (53 males and 47 females;meanage years) oftype 2 Diabetes Mellitus were evaluated. Majority ofthe subjects were in age group 51-60 years (n=34) with (meanage years 51.38±11.52 years). Therewasastatisticallysignificantdifferencepresentin mean FBS level, mean PPBS leveland mean HbA1c level, when compared between subjects having high and normal serum ferritin level ($p=0.009$, $p=0.036$, $p<0.01$, respectively). We comparedserum ferritin with fasting blood sugar,post prandial blood sugar and HbA1c levels and coefficient of correlation among study subjects were +0.40, +0.45 and +0.51 respectivelywithpvalueof <0.01.

Limitation: First,it was only an observational study, so results could not be compared to those of normal control subjects with normal blood glucose levels; second, diabetic individuals did not receive any treatment; and third, since allthe subjects came froma single hospital,findingscouldnotbegeneralised.

Conclusion: The study highlights the importance of serum ferritin as a marker for early identification of type 2 Diabetes Mellitus patients and its role as a useful marker forglycaemiccontrol in diabeticpatients.

Introduction:

Diabetes Mellitus is a noncommunicable disease having predominant public health concern, affecting millions of people worldwide. Largest number of diabetic patients are found in India, and India is earning the distinction of 'diabetic capital of world'[1]. In practice, HbA1c reflects the mean blood glucose levels over the past three months, withan increased HbA1c value[2] (recommended ranges in non-diabetic individuals ≤6), indicating poor glycaemiccontrol.

The pathogenesis of type 2 diabetes mellitus (T2DM) is complex and shows both insulin resistance and beta cell defects[3]. Insulin stimulates cellular iron uptake through increased transferrin receptor externalization. Insulin resistance coupled with glycaemic control canalso increase serum ferritin levels. Iron affects the metabolism of glucose, and glucose metabolism impinges on several iron metabolic pathways. Iron is a catalyst in the formationof hydroxyl radicals, which may contribute initially to insulin resistance, subsequently to decreasedinsulinsecretion,and ultimatelytothedevelopmentoftype2diabetes[4].

The long-term hyperglycaemia status favours glycation reaction leading to formation of advanced glycated end products (AGE). This causes tissue damage by cross-linking of collagen.Increasing concentration of iron andferritin in cells could cause resistance to insulinand dysfunction ofβ cells ofpancreas. Hyperinsulinemia due to resistance to insulin may beresponsibleforincreasingserum ferritin.

Therefore, it is always better to have alternatives to HbA1c for measuring glycaemic control in diabeticsand ferritin can act as one such marker. Overall, there is paucity of literature hence this research was designed to enlighten this path and to examine the association and correlationbetween serumferritinandglycatedhaemoglobinlevelsin T-2DM.

Material&Methods:

An observational study was carried out over a span of 1.5 years, in the Department of General Medicine at SGT Medical College Hospital and Research Centre, Gurugram. Inclusion criteria: Clinically diagnosed type 2 diabetes mellitus patients with or without treatment in age group 35-70 years. Exclusion criteria: Type 1 diabetes mellitus, K/C/O Thalassaemia major, Haemochromatosis, Chronic alcoholics, Chronic inflammatory conditions like SLE, rheumatoid arthritis, hepatitis, overt thyroid dysfunction, CLD, CKD,chronicinfections,patientsoncorticosteroidtherapy.5ml(Teaspoonfull)of

fasting blood sample will be collected and centrifuged for serum/plasma separation. Sample will be then analysed for the measurement of plasma glucose by glucoseoxidase-peroxidase method. Whole blood will be taken in EDTA vial for HbA1c estimation by turbidimetric immunoassay. Serum ferritin assessment will be done by Chemiluminescence Immuno Assay (CLIA). Data were entered on MS office Exceland analysed by SPSS software version 24. The data were represented bycounts, percentage and mean± standard deviation. Statistical analysis of the biochemical parameters, FPG, HbA1c and serum ferritin was done. Student 't' test was used for comparison of variables.P–valueofp<0.05wasconsideredsignificant.

Results:

Mean of HBA1c was 9.27±1.99, Fasting blood sugar (FBS) was 234.86±93.87 and Postprandial blood sugar (PPBS) was 281.82±117.93. Hb was in range from 8.0-16.70 and meanwas11.94±2.045, RBC was inrange

from3.14-5.59 andmeanwas4.34±0.52,TLC was in rangefrom 4200-13800with mean in rangefrom 7401.0±2321.34, MCV was in range from68.90-106.0 and meanwas 84.48±7.95, MCH was inrange from 18.80-34.30 and mean was 28.21±3.79, MCHC was in range from26.66-37.10 and mean was 32.36±1.82 and HCT was in range from 25.10 -49.50 and mean was 38.27±6.29. Serum ferritin level was high in 58%subjectsand was normalin42%patients.

We compared Hb with HbA1c of our patients and the coefficient of correlation between Hb and HbA1c among study population was found to be +0.21 with p value of 0.034, which showed positive correlation with significant difference at 0.05 level of significance. This positive correlation suggests that as HbA1c increases, Hb rises too. We compared TLC with HbA1c of our patients and the coefficient of correlation between TLC and HbA1c among study population was found to be +0.03 with p value of 0.97, which showed positive correlation with insignificant difference at 0.05 levelofsignificance. There wasa statistically significant difference present in mean FBS level, mean PPBS level and mean HbA1c level, when compared between subjects having high and normal serum ferritin level (p=0.009, p=0.036, p<0.01, respectively).

In present study, Serum Ferritin level was in range from 0.20-3000.0 ng/ml and mean value was538.14±538.26ng/ml,TIBCwasinrangefrom80.0-466.20ug/dlandmeanvaluewas

260.0±101.03 ug/dl and Saturation of iron was in range from 7.30-60.97 % and mean value was 27.54±10.43 %.

We compared serum ferritin with FBS of our patients and the coefficient of correlation (r value) betweenserumferritinand FBS amongstudypopulationwas found tobe+0.40withp value of <0.01, which showed positive correlation with highly significant difference at 0.01 level of significance. This positive correlation suggests that as FBS increases, serum ferritin rises too.

We compared serum ferritin with HbA1c of our patients and the coefficient ofcorrelation(r value) between serum ferritin and HbA1c among study population was found to be +0.51withpvalueof<0.01,whichshowedpositivecorrelationwithhighlysignificantdifferenceat

0.01 level of significance. This positive correlation suggests that as HbA1c increases, serum ferritinrisestoo.

Figure1:CorrelationofserumferritinwithFBS

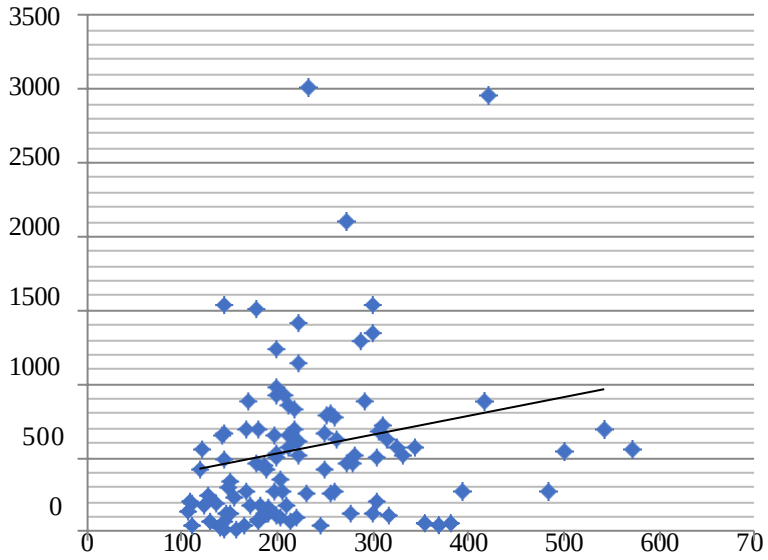
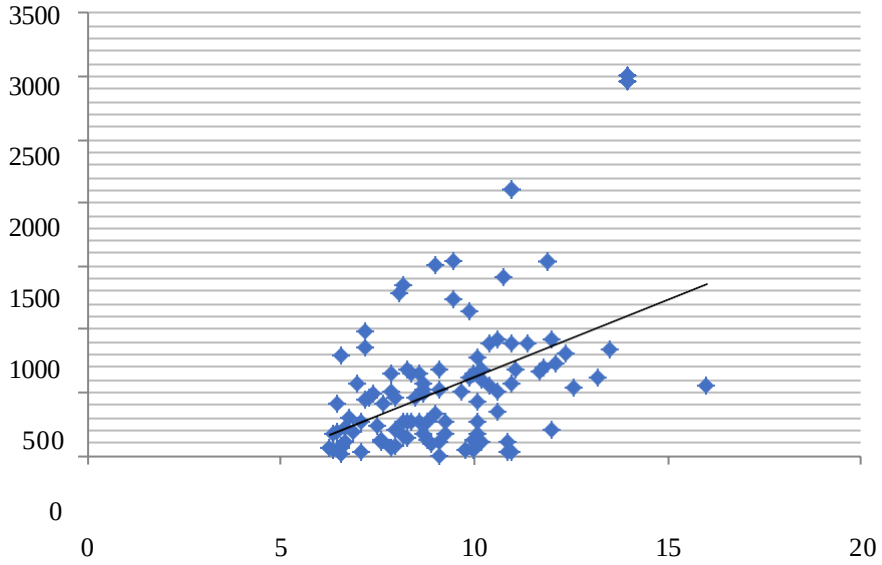


Figure2:CorrelationofserumferritinwithHbA1c



Discussion:

Type2DM is a chronic disease and its prevalence has been increasing everywhere around the globe. People livingwithtype 2 DM aremoreatriskofcomplicationsbothshortandlong term, which frequently result in their premature death[5].Oxidative stress mainly superoxide species has been implicated within the pathogenesis of the complications seen in T2DM[6].These species may then play a job within the generation of additional and more reactiveoxidants,including the highly reactive hydroxyl in which iron plays a catalytic role in an exceedingly complex reaction. This reaction is usually named the metal catalyzed Haber-Weiss reaction and fenton[7].Ironis a catalyst informationofhydroxylradicals, which are powerful pro-oxidants attack cellular membrane lipids, proteins and nucleic acids contributes to insulin resistance initially and subsequently to the development oftype 2 DM. The role of iron within the pathogenesis of diabetes is recommended by an increased incidence of type 2 diabetes in diverse causes of pathology and reversal or improvement in diabetes (glycaemic control) witha discount inironload achievedusingeitherphlebotomyor iron chelation therapy[8]. Thus, the present study was undertaken to establish the correlation between serum ferritinleveland type 2 DM.

In the present observationalstudy, 100 patients ofType 2 Diabetes Mellitus were taken from the OPD and IPD of the department of General Medicine, SGT medical college & research centre.In this study serum ferritin was compared with HbA1c,Fastingplasmaglucoseand

2 hours post prandial blood glucose levels in type 2 Diabetes Mellitus patients along with Other haematological parameters and clinical profile, eye and ECG finding samongsame individuals.

We compared serum ferritin levels with fasting blood sugar, post prandial blood sugar and with HbA1c among study subjects and found out that there was statistically significant difference present with linear positive correlation when compared between subjects having high and normal serum ferritin levels in type 2 Diabetes Mellitus patients.Thismay be due to abnormalities in ferritin metabolism following glycation ina hyperglycaemic state. Glycosylated ferritin has a longer serum half-life. Glycaemic control its elfinfluences serum ferritin concentration.

Our findings were significantly higher in diabetic patients and significantly increased with the duration ofdiabetes and HbA1c values. However, othersimilarstudies[9-14] differin parameters like number of subjects, geography of subjects, type of study, demographic profile, investigations performed, treatment like antidiabetic drugs received by the patients,cardiovascularrisk assessmentandfollowupdoneforsame patients.

The relationship of ferritin and glucose metabolism is bidirectional; iron affects glucose metabolism even in the absence of significant iron overload[15], and glucose metabolism impinges on several iron metabolic pathways. Glycation of haemoglobin contributes to substantial affinity for transitionalmetals and glycationofhaemoglobindecreases ability of transferring to bind ferrous iron. When concentrations of antioxidants are low, reducing potential and anaerobiosis progressively increases, thereby facilitating a rapid release of iron from ferritin.

Additionally, the ferroxidase activity of the heavy chain in apoferritin is also downregulated in this setting resulting in an increase in free iron as pro-oxidant agent. This alteration in iron induces oxidative stress and produce inflammatorycytokines that participate in regulating the signal transduction process of islets beta cells thereby affecting thesecretion of insulin andinterfering with the glucose metabolism process and also ironplays an important role inmitochondria,which will promote the production and synthesis of adenosine triphosphate and also it affects at insulin secretion level, ultimatelyleadingtoglucosemetabolismdisorder.

The blood sugar levels are closely related to the iron contents in beta islets cells.Elevated iron stores may induce diabetes through a variety of mechanisms, including oxidative damage to pancreatic beta cells, impairment of hepatic insulin extraction by liver, and interference with insulin's ability to suppress hepatic glucose production[16]. Increase in serum iron level contribute to comorbidities and complications as ironhas an adverse effect on endothelium and accelerates the development of atherosclerosis.During the course of plaque formation in atherosclerosis, ferritin gene expression increases. Hence, this studystated that serumferritinlevels could beusedasabiomarker in predictingthe risk ofdevelopingtype 2DM.

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