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Original Research

Correlation between serum uric acid, nitric oxide, ferrtin and HbA1c levels in Type II diabetic patients

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ABSTRACT

Objectives: To estimate fasting plasma glucose (FPG), serum ferritin, HbA1c, uric acid and serum nitric oxide levels in type 2 diabetes mellitus (T2DM) subjects and compare the parameters with healthy controls and also to assess the correlation analysis between the biochemical parameters in T2DM patients. **Materials and Methods:** A case control study is conducted with a total of 56 diagnosed T2DM subjects and 31 healthy controls. FPG, serum ferritin, HbA1c, uric acid and serum nitric oxide levels were measured in all individuals. **Results:** The mean levels (mean ± SD) of FPG, serum ferritin, HbA1c, serum uric acid and serum nitric oxide in control group were 98.06±7.28, 84.6±36.8, 5.46±0.84, 4.72±1.41 and 39.0±4.7 respectively. Similarly, in T2DM patients mean levels of 179.5±53.2, 457.9±402.2, 9.49±1.90, 8.57±2.38 and 100.9±26.5 were obtained for respective parameters. In T2DM subjects, mean values of serum ferritin, HbA1c, uric acid and serum nitric oxide were found to be significantly increased ($p<0.001$) when compared to controls. Moreover, Pearson coefficient analysis has shown that serum ferritin has positive correlation with HbA1c and serum nitric oxide in T2DM patients with $p<0.05$. **Conclusion:** The present study confirms the oxidative stress and iron over load among T2DM patients and they might be involved in the pathogenesis of T2DM.

KEY WORDS: Oxidative stress; diabetes mellitus; iron over load; serum ferritin; serum uric acid.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders that is characterized by hyperglycemia and insufficiency in production or action of insulin produced by the pancreas in the body. [1] Chronic hyperglycemia leads to a number of complications such as cardiovascular, renal, neurological, ocular and recurrent infections.[2]

Besides hyperglycemia, there are many other factors that play great role in pathogenesis of diabetes such as iron over load and oxidative stress leading to high risk of complications. It has been found that increased body iron stores are associated with the development of glucose intolerance, T2DM, gestational diabetes and insulin resistance. Reducing iron stores by frequent blood donation leads to improvement in both beta cell function and peripheral insulin action in diabetes. There is also a strong correlation between hyperferritinemia and diabetic complications.[3]

Studies have shown that an abnormality in the ferritin metabolism following glycation in chronic hyperglycemic state is a primary cause of hyperferritinemia in T2DM. Glycosylated ferritin has a longer serum half life and glycemic control itself governs serum ferritin concentration. [4] Elevated iron stores may induce diabetes and its complications through a series of mechanisms including oxidative damage to the pancreatic β cells, interference with insulin's ability to suppress hepatic glucose production and impairment of insulin extraction by liver .[5] Free iron is toxic to cells by inducing production of free radicals by Fenton reaction. Moreover, previous studies have shown positive correlation between serum ferritin and HbA1c levels.[6]

HbA1c is a glycated hemoglobin formed by a post translational non enzymatic, substrate concentration dependent combination of glucose and other hexose with the amino terminal valine in the beta chain of hemoglobin. The level of HbA1c in diabetes is used as a reliable index for glycemic control over the preceding 6 to 8 weeks.[7]

Nitric oxide (NO) is a potent vasodilator and also an endothelial relaxing factor. NO is a short lived free radical, involved in variety of physiological functions like smooth muscle relaxation, inhibition of platelet aggregation and non-noradrenergic-noncholinergic neurotransmission.[8] Uncoupling of endothelial nitric oxide synthase enzyme occurs in the blood vessels of diabetic subjects leading to endothelial dysfunction and excessive production of superoxide anion causing decreased NO bioavailability. [9] Studies have also shown that NO has influence on serum uric acid levels by interfering with action of xanthine oxidase enzyme. [10]

Serum uric acid is produced from purine by xanthine oxidase enzyme. It is a strong reducing agent in human; over half of the antioxidant capacity of blood comes from serum uric acid.Serum uric acid level is found to be increased

with increasing HbA_{1c} levels up to the category 6-6.9% and there after decreases with further increase in HbA_{1c} levels indicating bell shaped relation. However, hyperuricemia found to be associated with insulin resistance and metabolic syndrome. It is also a predictor of cardiovascular disease in type 2 diabetes.[11]

The aim of this study is to evaluate serum ferritin, HbA1c, serum uric acid and serum nitric oxide levels in cases of type 2 DM and compare it with healthy controls.

MATERIALS AND METHOD

A. Source of Data

Study was conducted in Bapuji Hospital and Chigateri General Hospital, Davangere, Karnataka, India from June 2012 to June 2013. A total of 87 participants were recruited for this study, of which 56 T2DM patients and 31 healthy individuals. T2DM patients were recruited from outpatient department of medicine and healthy controls from the general population. The study protocol was confirmed to the ethical guidelines of Declaration of Helsinki (Sixth revision, 2008). Approval from Institutional Ethical Committee was obtained from J.J.M Medical College, Davangere Karnataka, India before conducting the study. Patients and controls were voluntarily participated in the study and written informed consent was obtained from all the participants.

Inclusion criteria: Clinically diagnosed and known T2DM patients between the age group of 30-60 years of either sex with 5 years history of diabetes were included in the study. Healthy individuals of either sex between the age group of 30-60 years were enrolled as control group.

Exclusion criteria: Patients suffering from gestational diabetes mellitus, hemochromatosis, thalassemia and Hemosiderosis, type 1 diabetes mellitus patients, patients on iron therapy, diuretics, antioxidants and steroids, patients suffering from chronic infections and inflammation, neoplasia, renal disease, liver disease, alcoholics and smokers, critically ill patients in intensive care unit and pregnant women were excluded from this study.

B. Collection of blood sample

About 6 ml of venous blood was drawn from all the participants from large peripheral vein under aseptic precautions, using a sterile disposable syringe. Out of 6ml, 3 ml of blood was transferred to plain vaccutainer and remaining 3 ml into EDTA containing vaccutainer. 3 ml of plain vaccutainer blood was subjected to centrifugation and the serum was separated which was used for estimation of serum ferritin, nitric oxide and serum uric acid. 1 ml of anticoagulated whole blood was used to estimate HbA1c and remaining 2ml was used to separate plasma to estimate fasting plasma glucose.

C. Parameters measured

Fasting plasma glucose, HbA1c, serum ferritin and serum nitric oxide levels were measured in all the participants. Fasting plasma glucose was measured by glucose oxidase method.[12] Serum uric acid was measured by uricase method. [13] For HbA1c and serum ferritin estimation turbidimetric Immunoassay and Chemiluminescence Immunoassays were used respectively.[14]

RESULTS

Table 1 shows the demographic distribution of the participants. Among 56 T2DM patients, 24 were male and 32 were female. Similarly, in control group 19 were males and 12 were females. Mean ages for T2DM patients and healthy controls were 50.09±8.2 years and 45.64±12.1 years respectively. There is no significant difference between cases and controls with respect to age and sex of subject ($p > 0.05$).

All the biochemical parameters are expressed in mean ± SD. Table 2 shows levels of various biochemical parameters in T2DM and healthy individuals. The estimated mean levels of FPG, serum ferritin, HbA_{1c}, serum uric acid and serum nitric oxide in control group were 98.06±7.28, 84.6±36.8, 5.46±0.84, 4.72±1.41 and 39.0±4.7 respectively. Similarly, in T2DM patients mean levels of 179.5±53.2, 457.9±402.2, 9.49±1.90, 8.57±2.38 and 100.9±26.5 were obtained for respective parameters.

The statistical analysis by Unpaired 't'-test has shown that FPG, serum ferritin, HbA_{1c}, serum uric acid and serum nitric oxide levels are significantly increased in T2DM patients when compared to healthy controls with $p < 0.001$ (statistically highly significant).

The Pearson's correlation analysis was applied among the biochemical parameters of T2DM patients and showed

Table 1. Age and sex-wise distribution of control and T2DM patients.

	Cases	Controls	p value
No of subjects	56	31	
Age(years) mean ± SD	50.09±8.2	45.64±12.1	p=0.07 NS
Gender			
Male	24 (42.9%)	19(61.3%)	p=0.10 NS
Female	32 (57.1%)	12(38.7%)	

NS-Not Significant

Table 2. Levels of FPG, serum ferritin, serum nitric oxide, HbA_{1c} and uric acid in T2DM patients and healthy controls.

Variables		Cases	Controls	Control/Cases		
				Mean Diff	t value	p value
FPGmg/dl	mean±SD	179.5±53.2	98.06±7.28	83.44	11.36	<0.001**
	Range	97-288	78-106			
Serum Ferritin ng/ml	mean±SD	457.9±402.2	84.6±36.8	373.90	6.89	<0.001**
	Range	34.4-1745	12.3-162.2			
Serum Nitric Oxide µmol/l	mean±SD	100.9±26.5	39±4.7	61.90	17.03	<0.001**
	Range	38.4-146.0	30.1-45.8			
HbA_{1c}	mean±SD	9.49±1.90	5.46±0.84	4.03	13.64	<0.001**
	Range	4.80-13.51	4.10-6.40			
Serum uric acid mg/dl	mean±SD	8.57±2.38	4.72±1.41	3.86	9.49	<0.001**
	Range	3.92-17.50	1.96-6.6			

Unpaired 't' test ** Highly Significant.

statistically significant positive correlation between serum ferritin and HbA1c with r value of +0.49 and p <0.001. Serum nitric oxide and HbA1c parameters have showed statistically significant positive correlation with r value of +0.35 and p<0.05. Similarly, significant positive correlation was also found between serum nitric oxide and serum ferritin with r value of +0.34 and p value of <0.05.

Table 3. Showing the Pearson's correlation between biochemical parameters in T2DM patients

CORRELATION ANALYSIS		
Relationship between	**r value**	**p value**
Serum Ferritin and HbA_{1c}	0.49	<0.001**HS
Serum Nitric oxide and HbA_{1c}	0.35	0.009*S
Serum Uric acid and HbA_{1c}	0.25	0.07,NS
Serum Nitric Oxide and Serum Ferritin	0.34	0.01*S
Serum Ferritin and Serum Uric acid	0.21	0.13,NS

r-Pearson's correlation coefficient *S-Significant; **HS-Highly Significant;

NS- Not Significant

DISCUSSION

Diabetes mellitus (DM) is commonly associated with increased risk of cardiovascular diseases and also the principal causes of morbidity and mortality worldwide. [15,16]

Diabetic vascular complications such as macrovascular and microvascular complications are mainly dependents on hyperglycemia. [17,18] These vascular complications are due to generation of reactive oxygen species (ROS), through various pathways: (1) enhanced polyol activity, causing accumulation of sorbitol and fructose; (2) increased formation of advanced glycation end products (AGEs); (3) activation of protein kinase C (PKC) and (4) increased hexosamine pathway flux and hence ultimately leading to increased oxidative stress [19]. Inappropriate endogenous antioxidant defense mechanism can lead to ROS accumulation and activation of stress-induced intracellular signaling pathways that in turn promote cellular damage and contribute to the diabetic complications and disease progression [20].

In diabetes, hyperglycemia is caused by both overproduction and under utilization of glucose. There is also a relative excess of glucagon in DM. As a result, glucose is synthesized more rather than consumed by liver, muscles and adipose tissues leading to hyperglycemia. In this study the mean level of FPG in healthy controls and type 2 diabetic patients were 96.06±7.28 and 179.5±53.2 receptively. Unpaired student's t-test has shown that FPG level in T2DM patients was significantly increased when compared to controls ($p < 0.001$).

Serum Ferritin

It has been found that iron indirectly influences glucose metabolism by inhibiting internalization of insulin and its actions, resulting in hyperinsulinemia and insulin resistance. Thus, the increased oxidative stress and insulin resistance results in endothelial and tissue damage in DM.[21] Serum ferritin is a storage form of iron in most of the organs like liver cells, spleen, bone marrow, heart, pancreas and kidney. Physiologically human serum contains a small quantity of ferritin.[22] In our study serum ferritin levels were found to be significantly increased in type 2 diabetes mellitus patients (457.9±402.2) when compared to healthy controls (84.6±36.8). We also found statistically significant positive correlation between serum ferritin with serum nitric oxide, HbA1c, and serum uric acid. These findings are similar to the previous studies done by Sumeet Smotra, Wei Bao and N.G. Fourohi.[23]

Nitric oxide (NO)

Nitric oxide is inflammatory mediator and lipid soluble gas released from the vascular endothelium. It plays an

important role in regulation of vascular tone, inhibition of both platelet and leukocyte aggregation and adhesion, and inhibition of cell proliferation. The level of NO production by the endothelium may play a important role in the of vascular diseases.[24] NO is a potent inflammatory mediator because of its strong reactivity with oxygen, superoxide and iron-containing compounds.[25] NO is synthesized by the nitric oxide synthase (NOS) enzyme, using a molecular oxygen and the terminal guanidine nitrogen of the amino acid L-arginine, yielding L-citrulline as a co-product.

In this study, the serum NO levels were significantly increased ($p<0.001$) in type 2 diabetes mellitus patients (9.49 ± 1.90) as compared to healthy controls (5.46 ± 0.84). There is also positive correlation exists between serum nitric oxide with serum ferritin and HbA1c. These findings in accordance with previous studies of Dilshad Ahmed Khan and Katsuyuki Maejima.[26] Increased nitric oxide levels in T2DM is due to chronic hyperglycemia leading to overflow of the polyol pathway products along with depletion in the nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is an important cofactor for the enzymes in the metabolism of the reactive nitrogen species (RNS) and reactive oxygen species (ROS). Increased inflammation and endothelial injury in diabetes, large amounts of nitric oxide is synthesized through inducible nitric oxide synthase enzyme present in endothelium. This excess of nitric oxide could contribute to continuous and uncontrolled tissue damage especially after conversion into peroxynitrite radical ($ONOO^{\cdot}$).[27]

HbA1c

HbA1c is produced by glycation, the covalent binding of glucose to hemoglobin. The quantity of HbA1c formed is directly proportional to the average plasma glucose level that the red blood cell is exposed during its 120-day life span (6 to 8 weeks). Thus, in long term hyperglycemia, HbA1c forms a higher percentage of total hemoglobin than in normoglycemia.[28]

In this study HbA1c levels were significantly ($p<0.001$) increased in T2DM patients (9.49 ± 1.90) when compared to healthy controls (5.46 ± 0.84). Statistically significant positive correlation between HbA1c, serum ferritin, and serum nitric oxide levels were also found in this study. These findings are similar to the previous studies carried out by Sumeet Smotra, Elizabeth Selvin and H.K. Choi. [29, 30]

An elevated HbA1c level has been shown to be a predictor for the development and progression of microvascular complications in patients with T2DM. It is found that HbA1c levels ≥7.5% have a 2.5-5 fold increased risk of developing microvascular complications. Retinopathy, nephropathy and neuropathy have all been shown to correlate with the severity of hyperglycemia. However, achieving recommended blood glucose targets can substantially reduce the risk of microvascular complications, and possibly the macrovascular complications in DM.[31]

Acute glucose fluctuations above a mean value (HbA1c-7%, which is an estimated average glucose of 154 mg/dl) may trigger oxidative stress, which contributes to damage through oxidation of low-density lipoprotein, enhanced of endothelial dysfunction, and other proatherogenic mechanisms leading to the development and progression of vasculopathies.[32]

Diabetes control and complication trial (DCCT) has shown that 10% stable reduction in HbA1c results in 35% risk reduction for retinopathy, 25-44% risk reduction for nephropathy and 30% risk reduction for neuropathy. [32]

Uric acid

Uric acid is associated with inflammation, but it also functions as a strong endogenous antioxidant. This has led to contend that elevated uric acid could be protective by blocking lipid peroxidation. However, this concept is not supported by the evidence that increased uric acid levels are associated with worst outcomes. It is more likely that the increase in serum uric acid, rather than being protective, associated with increased oxidative stress. Hyperuricemia is also independently correlated with hypertension, insulin resistance, and cardiovascular diseases.

An increased purine biosynthesis which occurs due to an increased activity of the hexose monophosphate pathway shunt can be conceptually linked to insulin resistance and/or hyperinsulinemia. The increased flux of glucose-6-phosphate through the hexose monophosphate pathway shunt due to impairment of the glycolytic pathway, has been suggested as an explanation for the increased uric acid in impaired glucose tolerance in diabetics.[33]

It was found that elevated insulin levels due to insulin resistance in type 2 diabetes mellitus causes hyperuricemia due to enhanced renal reabsorption of uric acid by the insulin [34]. Hence, the thiazolidinediones, by improving insulin sensitivity and lowering insulin levels, also reduce the level of serum uric acid in diabetic patients.[35,36] Moreover, previous studies demonstrated that lowering uric acid by a xanthine oxidase inhibitor or a uricosuric agent improves insulin sensitivity as well as other features of metabolic syndrome, including hypertension, obesity, and hypertriglyceridemia. [37] Thus, uric acid may also have a role in the development of insulin resistance.

In this study mean serum uric acid levels of $8.57\ \pm2.38$ and $4.72\ \pm1.41$ were noted in T2DM and healthy controls respectively. This difference in mean values were found to be statistically significant with $p<0.05$ and the Pearson's correlation analysis between serum uric acid with HbA_{1c} and serum ferritin has shown a positive correlation with r value $+0.25$ and $+0.21$ respectively.

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