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A STUDY ON SERUM TOTAL BILIRUBIN AND URIC ACID IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS

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ABSTRACT: Background: Serum total bilirubin (SBT) and serum uric acid (SUA) have anti-oxidant properties. SBT and SUA may be potential biomarkers for type 2 diabetes mellitus (T2DM) and its complications. **Aim:** It is aimed to evaluate the level of STB and SUA in T2DM. **Materials and Methods:** In this case-control study, a total of 124 subjects (62 T2DM cases and 62 age and gender-matched controls) were recruited between the age group of 30-55 years. Fasting blood sugar (FBS), STB, SUA, Malondialdehyde (MDA), and Superoxide dismutase (SOD) were estimated. All the data were tested at a 5% level of significance. **Results:** The mean level of SUA was significantly higher in cases than controls (P=0.009). However, the mean level of STB was not found statistically significant in cases than controls (P=0.08). The mean level of MDA was found significantly elevated in cases than controls (P<0.001). In addition, the mean of SOD activity was found significantly low in cases than controls (P<0.001). A significant negative correlation was found between age and SOD activity (r= -0.327, P<0.05). However, a significant positive correlation was found between STB and MDA (r= 0.398, P<0.05). In addition, A significant negative correlation was found between MDA and SOD activity (r = -0.704, P<0.01). However, a positive correlation was found between STB and SUA, but not statistically significant (r= 0.071, P>0.05). **Conclusion:** Results showed that the SUA and MDA levels are elevated, and STB level and SOD activity are depleted in T2DM cases. These findings may give further insight into the pathogenesis and management of T2DM.

INTRODUCTION: Diabetes and its complications are the major cause of death worldwide. Type 2 diabetes mellitus (T2DM) is associated with dysfunction and failure of different organs, mainly the eyes, kidneys, nerves, heart, and blood vessels [1]. Hyperglycemia represents an independent risk factor for the disease of both micro and macrovascular system [2].

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With increasing incidence, T2DM is a leading cause of morbidity and mortality in the world [3]. According to the International Diabetes Federation (IDF), the current diabetic status worldwide was 425 million, which was estimated to increase by 629 million adults living with diabetes till 2045. In India, more than 72.9 million people living with diabetes and the prevalence of diabetes is more than 10.4%. In addition, 57.9% of people still have undiagnosed diabetes [4].

Serum total bilirubin (STB) is the final decom-position product of heme metabolism, belongs to important potent endogenous anti-oxidants [5]. It is characterized by chronic low-grade inflammation, which causes depletion in the anti-oxidant capacity

of the body [6]. Previously, it is suggested that STB is a cytotoxic waste product and has potential toxicity. However, recently it is considered that it has strong anti-oxidant, anti-inflammatory, and immunosuppressive properties [5-7]. Anti-oxidant capacity of serum bilirubin is believed to be beneficial in macrovascular diseases [8]. Since both T2DM and CVD are related to chronic inflammation [9]. Low STB levels in poorly controlled diabetic subjects were reported [10].

Serum uric acid (SUA) is the end product of purine catabolism and considered as metabolic waste, and excreted in the urine [11]. It is strongly associated with gout and urinary tract stones [12]. However, it is suggested that SUA plays an important role in anti-oxidation and can clear more than half the free radicals in human blood [7]. Its anti-oxidant capacity is much higher than vitamin C and vitamin E [13]. Insulin resistance causes an increase in SUA concentration by both reducing renal uric secretion [14] and accumulating substrates for uric acid production [15].

The present study was designed to evaluate the level of STB and SUA along with Malondi-aldehyde (MDA), and Superoxide dismutase (SOD) in T2DM and their association with disease complications.

MATERIALS AND METHODS:

Type of Study: Case-control
Duration of study: January 2019 to June 2019

Subject Selection: This study includes a total of 124 subjects (62 newly diagnosed T2DM cases and 62 age and gender-matched healthy controls). All subjects were aged between 30-55 years. Subjects were enrolled from the Out-Patient Department of Medicine & Diabetes Clinic, Medical College of the University.

Subjects were included as per the diabetes diagnostic criteria; Fasting blood sugar (FBS) ≥126mg/dL considered as diabetic and FBS <126mg/dL considered as control [16, 17].

Subjects with a history of impaired renal function, cardiac vascular diseases, liver diseases, hypertension, and gout were excluded. Subjects having any infectious disease were also excluded. A detailed medical and family history was taken from each subject. This was approved by the institutional ethical committee (IEC approval No. IEC/IIMS&R/2019/33), which strictly adhered to the Helsinki declaration and its later amendments [18]. Written informed consent was taken from each subject.

Laboratory Investigation: Total 05ml venous blood was collected in a plain vial from each subject under aseptic conditions and centrifuged it to separate serum after 1hr incubation at room temperature. Serum was used to analyze for STB and SUA by using the standard protocol on Erba Chem -7 semi auto-analyzer (Erba Diagnostics Mannheim GmbH, Germany) based on the bilirubin oxidase method and the Uricase-Peroxidase method, respectively [19]. FBS was estimated at Siemens Dimension RXL Max Integrated Chemistry System fully automated analyzer (Siemens Healthcare Private Limited, India) by commercially available kit. The plasma MDA levels were estimated by the thiobarbituric acid reactive substance (TBARS) method [20]. Plasma was deproteinized, and the precipitate is treated with thiobarbituric acid (TBA) at 90 ºC 1 hour. The pink color product formed at the end of the reaction, which was measured at 535 nm by UV -Visible double beam spectrophotometer (Systronics -2205, Systronic India Ltd. Gujarat, India). The SOD activity was estimated by the Nitroblue Tetrazolium (NBT) method [21]. The assay of SOD is based on the inhibition of the formation of NADH-phenazine methosulphate- nitroblue tetrazolium formazan. The color product formed at the end of the reaction, it was extracted into butanol and measured at 560 nm by UV-Visible double beam spectrophotometer (Systronics-2205, Systronic India Ltd. Gujarat, India).

Statistical Analysis: Statistical analysis was done using IBM SPSS software version 20.0 (Armonk, NY, USA). Results were represented as Mean ±SD (Standard Deviation). ANOVA with a Bonferroni post hoc test was used to analyze significant differences between cases and controls. Pearson correlation coefficient was calculated in T2DM cases. All the data were tested at a 5% level of significance.

RESULTS: In this case-control study, the mean age of case and control subjects were not found

statistically significant (P=0.14). The number of male and female subjects was also statistically, not significant. The mean level of FBS was found significantly higher in cases than controls (P<0.001). Similarly, the mean level of SUA was significantly higher in cases than controls (P=0.009). However, the mean level of STB was not found statistically significant in cases than controls (P=0.08). The mean of MDA was found significantly elevated in cases than controls (P<0.001). In addition, the mean of SOD activity was found significantly low in cases than controls (P<0.001), shown in **Table 1**.

A significant negative correlation was found between age and SOD activity (r= -0.327, P<0.05). However, a significant positive correlation was found between STB and MDA (r= 0.398, P<0.05). In addition, A significant negative correlation was found between MDA and SOD activity (r = -0.704, P<0.01). Although a positive correlation was found between STB and SUA, but not statistically significant (r= 0.071, P>0.05) among T2DM cases, shown in **Table 2**.

TABLE 1: CLINICAL CHARACTERISTICS OF CASE AND CONTROL SUBJECTS

Parameters	Case (n=62)	Control (n=62)	P-value
Age (years)	45.76±6.45	44.19±5.34	0.14
Gender (M/F)	17/45	17/45	1.00
FBS (mg/dL)	263.33±36.78	104.26±10.80	<0.001*
STB (mg/dL)	0.65±0.53	0.85±0.38	0.08
SUA (mg/dL)	5.60±2.10	4.49±1.0	0.009*
MDA (µM/L)	2.60±0.70	1.07±0.64	<0.001*
SOD (U/mg protein)	0.84±0.27	3.16±0.97	<0.001*

Data expressed as Mean ± SD (SD: Standard Deviation)
*P<0.05, considered as statistically significant
FBS: Fasting blood sugar, STB: Serum total bilirubin, SUA: Serum uric acid, MDA: Malondialdehyde, SOD: Superoxide dismutase

TABLE 2: CORRELATION BETWEEN CLINICAL PARAMETERS AMONG CASES

Parameters	Age (years)	FBS (mg/dL)	STB (mg/dL)	SUA (mg/dL)	MDA (µM/L)	SOD (U/mg protein)
Age (years)	1	0.034	-0.124	0.179	0.087	-0.327*
FBS (mg/dL)	-	1	-0.140	-0.202	-0.304	0.300
STB (mg/dL)	-	-	1	0.071	0.398*	-0.246
SUA (mg/dL)	-	-	-	1	0.144	-0.160
MDA (µM/L)	-	-	-	-	1	-0.704**
SOD (U/mg protein)	-	-	-	-	-	1

*P<0.05, Correlation is considered as statistically significant.
**P<0.01, Correlation is considered as statistically significant.
FBS: Fasting blood sugar, STB: Serum total bilirubin, SUA: Serum uric acid, MDA: Malondialdehyde, SOD: Superoxide dismutase.

DISCUSSION: The mean level of FBS was found significantly higher in T2DM cases than controls (P<0.001). Previous studies were reported that the mean level of FBS was found significantly higher in T2DM than controls [16, 22].

Similarly, the mean level of SUA was significantly higher in T2DM cases than controls (P=0.009). The study had reported that there is an increase in uric acid level in T2DM may be related to the inhibition of uric acid reabsorption in the proximal tubule by high glucose levels in diabetic cases [23]. Similarly, Rocic et al have found elevated uric acid levels in the diabetic population. He reported the evidence of the involvement and the role of uric acid on the alteration of the primary function of the beta cell and suggests the presence of an arginine residue combined with the critical site of the cell [24].

In addition, SUA levels have a positive correlation with insulin secretion and insulin resistance indexes in newly diagnosed T2DM patients [25].

Hyperuricemia is strongly associated with the development of diabetes and its complications. SUA mainly affects oxidative stress, inflammation, and endothelial dysfunction [26]. High concentrations of SUA were associated with tubular damage accompanied by the increase of urinary pro-inflammatory cytokines in patients with T2DM [27]. SUA levels are significantly associated with carotid atherosclerosis in patients with T2DM [28]. Kang *et al.* suggested that uric acid plays a dual role as pro- and anti-oxidant [29]. In addition, Sautin *et al.*, suggested that uric acid may function either as an anti-oxidant in plasma or pro-oxidant within the cell.

The study further recommended that uric acid has pro-oxidative effects and may be contributed to the pathogenesis of cardiovascular disease conditions [30]. However, Fabbrini *et al.*, reported that SUA is a major anti-oxidant and helps to protect against free-radical oxidative damage [31]. Chamorro *et al.*, reported that hyperglycemia induces oxidative stress by the increased production of reactive oxygen species (ROS) and depletion of local anti-oxidants like SOD, peroxides, and catalase. Formation of superoxide ions (free radicals) subsequently favors in anti-oxidant – pro-oxidant urate redox shuttle [32].

In the present study, the mean level of STB was not found statistically significant in cases than controls (P=0.08). Ndisang has reported that a low level of STB was found in diabetic cases [33]. Increased expression of Heme Oxygenase (HO), an enzyme used to breakdown the hemoglobin into bilirubin, is associated with enhanced insulin sensitivity and glucose metabolism [34]. STB has been regarded as a powerful endogenous anti-oxidant and has cytoprotective properties. The lower level of STB could probably be due to its action as it blocks the production of various free radicals that might hinder the inhibitory responses of the cell to take up the high glucose [35]. Similarly, an experimental study revealed that bilirubin regulates cholesterol metabolism, adipokines, and Peroxisome proliferator-activated receptor gamma (PPARγ) levels, which likely contribute to increased insulin sensitivity and glucose tolerance in diet-induced obesity (DIO) mice [36]. Kim *et al.*, reported that low levels of STB were significantly associated with arterial stiffness in Korean women with type 2 diabetes and further suggested that STB may protect against macrovascular disease in diabetic women [9]. Furthermore, lower physiological STB may be associated with the presence of diabetic nephropathy (DPN) due to its decreased anti-inflammatory and vascular protective effects [37]. A meta-analysis study indicates that STB may play a protective role in the occurrence of diabetic complications because a negative association has been reported between STB concentration and the risk of diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy [38]. In addition, an experimental study reported that hyperbilirubinemia is associated with a significant improvement of endothelial function in T2DM [39]. However, Yeh *et al.*, were not found an association between bilirubin levels and vascular reactivity in the macro- and microcirculation of individuals with diabetes. Therefore, STB has not been considered as a predictor of cardiovascular risk in the diabetic population [40].

The mean of MDA was found significantly elevated in cases than controls (P<0.001). In addition, the mean of SOD activity was found significantly low in cases than controls (P<0.001). Previous studies reported that the MDA level elevated and SOD activity depleted in T2DM cases [41, 42].

The present study indicated that STB and SUA might be used as biomarkers for T2DM and its complications along with MDA and SOD. But the molecular mechanism of STB and SUA in the association with oxidative stress, inflammation, insulin resistance needs to be explored.

CONCLUSION: Results show that the SUA and MDA levels are elevated, and STB level and SOD activity are depleted in T2DM cases. These findings may give further insight in the pathogenesis and management of T2DM. However, due to the limited scope of the present study further studies with a larger sample size are required to confirm the findings.

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ETHICAL APPROVAL: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IEC approval No. IEC/IIMS&R/2019/33) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT: Written informed consent was obtained from all individual participants included in the study.

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CONFLICTS OF INTEREST: Author M. Mishra, D. Tiwari, and M. M. Khan declare that they have no conflict of interest.

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