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Association of Serum Bilirubin and Serum Uric Acid with Glycemic Status in Type 2 Diabetes Mellitus

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Authors' contributions

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

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major public health problem affecting millions of people worldwide and its magnitude in developing countries including Bangladesh is rising rapidly. It is associated with multiple metabolic derangements that result in the excessive

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production of reactive oxygen species and oxidative stress. The major concern of health management in T2DM patients is to prevent diabetes-related complications which can only be achieved via strict glycemic control. Over the recent past it had been evident that serum bilirubin acts as a powerful antioxidant and upper limit of physiological ranges of serum bilirubin levels are beneficial and negatively associated with oxidative stress and glycemic status. Moreover, high serum uric acid plays an important role as an oxidative stress agent that is associated with poor glycemic control in diabetic subjects. Low serum bilirubin and high uric acid predicted a higher incidence for the development of T2DM and also had adverse impact on glycemic status. So, this study was designed to find out the association of serum bilirubin and uric acid with glycemic status among Type 2 diabetes mellitus subjects.

Objective: To evaluate the association of serum bilirubin and uric acid with glycemic status in Type 2 diabetes mellitus.

Materials and Methods: This cross-sectional analytical study was carried out in the department of Biochemistry, Sir Salimullah Medical College (SSMC), Dhaka from March, 2021 to February, 2022. A total number of 100 subjects were included in this study. Among them, 50 apparently healthy non-diabetic subjects age ranged from 30-59 years were considered as control group (Group A). Another 50 age and gender matched Type 2 diabetes mellitus patients without any complication were selected as study group (Group B). Ethical permission was taken from the Ethical Review Committee (ERC) of SSMC. All the study subjects were selected from the outpatient department of Medicine and Endocrinology, Sir Salimullah Medical College and Mitford Hospital, Dhaka. The study parameters were FPG, HbA1c, Serum bilirubin and serum uric acid. Estimation of study parameters were done in the Department of Biochemistry of SSMC, Dhaka. Statistical analysis was done by using SPSS version-22. Unpaired t test, Chi Square test, Pearson's correlation test and Binary logistic regression were performed to analyze the data as applicable.

Results: Serum bilirubin level was significantly lower and uric acid level was significantly higher among diabetic subjects in comparison to healthy controls. Comparison of glycemic status (FPG and HbA1c) in between different quartiles of serum bilirubin and uric acid in diabetic subjects were observed. FPG and HbA1c levels were significantly higher in Q1 & Q2 compared to Q3 & Q4 of serum bilirubin. However, FPG and HbA1c levels found high in Q3 & Q4 than Q1 & Q2 of uric acid. Pearson's correlation analysis showed significant negative correlation of serum bilirubin with FPG and HbA1c, whereas significant positive correlation of serum uric acid with FPG and HbA1c were observed in study subjects. Binary logistic regression was performed to show the association between several factors and diabetes which were expressed by the coefficients of logistic regression. The risk of diabetes for each factor was expressed as odds ratio (OR). Coefficient for serum bilirubin (showing inverse relation) was significant. In case of serum uric acid, coefficient showed significant positive relationship. Where serum uric acid was strongest predictor of diabetes with an odds ratio of 3.709.

Conclusion: Type 2 diabetic subjects have lower serum bilirubin and higher uric acid level than that of healthy subjects. Serum bilirubin has an inverse relationship with glycemic status (FPG and HbA1c), whereas uric acid shows positive correlation with glycemic status in diabetic subjects. Hyperuricemia appears to be a risk factor for development of Type 2 diabetes mellitus.

Keywords: Type 2 diabetes mellitus; Fasting plasma glucose (FPG); HbA1c; serum bilirubin; serum uric acid.

1. INTRODUCTION

"Type 2 diabetes mellitus is associated with dysfunction and failure of different organs, mainly the eyes, kidneys, nerves, heart, and blood vessels (American Diabetes Association, 2013). It is primarily involved with insulin secretory defects related to inflammation and metabolic stress along with other contributors, including genetic factors (American Diabetes Association, 2019). There is a strong link between hyperglycemia, hyperglycemia induced oxidative stress and inflammation with the development of complication of T2DM" (Oguntibeju, 2019).

"Serum Bilirubin has been shown to have strong anti-oxidant, anti-inflammatory and immunosuppressive properties" (Jangi et al., 2013). Abbasi et al. (2015) in their Mendelian Randomization Study reported that elevated bilirubin levels were associated with decreased risk of T2DM and diabetes related outcome.

"Antioxidant capacity of serum bilirubin has been considered to be protective against macrovascular and microvascular complications of diabetes mellitus" (Kim et al., 2014, Zhu et al., 2017). "Some authors elicited that serum bilirubin level in the upper limit of the physiological ranges are associated with protection from atherosclerosis, coronary artery disease and neurodegenerative diseases, whereas concentrations in the lower limit of the reference range might be regarded as an independent risk factor of coronary artery disease, diabetic nephropathy and diabetic retinopathy" (Erdogan et al., 2006, Ahn et al., 2017). "Serum bilirubin was reported to be lower among diabetic subjects with poor glycemic control compared to that of good glycemic control" Sridevi et al., 2013, Erkus et al., 2018).

"Serum uric acid acts as a powerful pro-oxidant in the intracellular environment (Roumeliotis et al., 2019). High serum uric acid has been reported to be a risk factor for the development of type 2 DM" (Bhole et al., 2010, Grover et al., 2019). Kawamoto et al. (2017) suggested high serum uric acid levels as oxidative stress agent and serum bilirubin at mildly elevated level as potent antioxidants (Kawamoto et al., 2017). "Several studies reported relationship of low serum bilirubin and high uric acid with glycemic status in Type 2 diabetes and its complications" (Fadhel and Yousif 2019, Rajendran et al., 2018).

Although there are a large number of studies conducted in abroad but there are few published data available regarding serum bilirubin and uric acid status among type 2 diabetic subjects in our country. Therefore, the proposed study was designed to evaluate the association of serum bilirubin and uric acid with Type 2 diabetes mellitus.

1.1 Objectives

General objective: To evaluate the association of serum bilirubin and serum uric acid with glycemic status in Type 2 diabetes mellitus.

Specific objectives:

1. To estimate fasting plasma glucose (FPG), glycated hemoglobin (HbA1C), serum bilirubin and serum uric acid in study subjects.
2. To compare all those biochemical variables between healthy control and type 2 diabetic subjects.
3. To observe the relationship of serum bilirubin and serum uric acid with glycemic status (FPG and HbA1c level) in study subjects.

2. METHODOLOGY

Study type: Cross-sectional analytical study.

Study place and period: Department of Biochemistry, Sir Salimullah Medical College, Dhaka, Bangladesh. The study was conducted during the period of 1st March, 2021 to 28th February, 2022.

Study population: Type 2 diabetes mellitus patients including age and gender matched healthy subjects.

Study methods: Study method used Fasting Plasma Glucose (FPG), Glucose Oxidase-Peroxidase (GOD-POD), HbA1c, Serum Bilirubin and Serum Uric Acid.

Selection Criteria:

- **Inclusion criteria: Inclusion criteria for study group were** Type 2 diabetes mellitus patients, age ranged from 30-59 years irrespective of gender and glycemic status. Age and gender matched healthy subjects were selected as control subjects.
- **Exclusion criteria for both groups:** Patients with type 1 DM, T2DM patients with complications like diabetic nephropathy, diabetic retinopathy or others, those with known history of hypertension, jaundice, liver disease, renal disease, gastrointestinal disease, cardiovascular diseases and gout, subjects with known history of infectious diseases, hemolytic diseases, myeloproliferative disorders and lymphoproliferative disorders, patients already on drugs that affects serum uric acid level and pregnant mothers were excluded from the study.

Grouping of study populations:

Study population was divided into 2 groups-

- Group A (control): Age and gender matched healthy subjects
- Group B (study group): Type 2 diabetic patients

Study procedure: A total number of 100 subjects were included in this study. 50 type 2 diabetic patients and 50 apparently healthy subjects were selected from the patients and accompanying attendants, attending the outpatient department of Medicine and Endocrinology, Sir Salimullah Medical College and Mitford Hospital, Dhaka. These subjects were recruited following history, physical examination and routine baseline biochemical investigations. Ethical permission was taken from the Ethical Review Committee (ERC) of this institute. After proper counseling aim, objectives, risk and procedure of the study were explained in details to all participants. Only voluntary candidates were recruited as research participants. They had the freedom to withdraw themselves from the study at any stage. Written informed consent was taken from all the respondents. Socio-demographic as well as other relevant data were taken and recorded in the data collection sheet with a prefixed questionnaire. Anthropometric variables were measured accordingly and blood samples were collected for biochemical variables to be measured.

Blood Sample Collection: Fasting blood samples were collected from all participants. They were allowed to fast overnight (10–12 hours). Precautions were taken to prevent hemolysis. Then plasma/serum were separated after centrifugation and were collected in labelled eppendorfs and stored for testing. For estimation of FPG plasma was stored in 2-8 ºC and test was done within 24 hours. For estimation of HbA1c whole blood sample was stored at 2-8 ºC and test was performed within 3 days. Sample for serum bilirubin was kept in the dark until laboratory analysis. Serum was preserved at -20 ºC for estimation of uric acid. Biochemical tests (FPG, HbA1c, serum bilirubin and uric acid) were done in the Biochemistry laboratory of Sir Salimullah medical college, Dhaka.

Statistical analysis: Data were analyzed with the help of software SPSS (Statistical Package for Social Sciences) version 22. Data were checked for normal distribution. Categorical variables were expressed as percentage and continuous data were expressed as mean $\pm$ SD. Chi square test was done to observe gender distribution. Unpaired t test was performed to show any significant difference between the mean values as applicable. Pearson's correlation test was performed to show the correlation between different variables. Binary logistic regression was performed to assess the factors determining diabetes. p- value of <0.05 was considered as statistically significant.

3. RESULTS

Table 1 showed gender distribution of study subjects among groups. It was observed that more than half of the participants were male in group A (56%) and group B (54%). There were no significant differences in terms of gender between healthy and Type 2 diabetic subjects.

Table 2. showed baseline characteristics of the study subjects. It was observed that there was no significant difference in respect of age, BMI and mean diastolic blood pressure but statistically significant (p<0.05) difference was observed in mean systolic blood pressure between two groups.

Table 1. Gender distribution of the study subjects (n=100)

Variables	Group A (n=50)	Group B (n=50)	p-value
Gender			
• Male	28 (56%)	27 (54%)	0.841
• Female	22 (44%)	23 (46%)	

Table 2. Baseline characteristics of the study subjects (n=100)

Variables	Group A (n=50) Mean ± SD	Group B (n=50) Mean ± SD	p-value
Age (years)	50.38 ± 4.07	51.68 ± 3.76	0.098
BMI (kg/m2)	24.74 ± 1.18	24.92 ± 0.95	0.426
Systolic BP (mmHg)	122.90 ± 8.81	126.60 ± 7.66	**<0.05**
Diastolic BP (mmHg)	76.70 ± 6.59	78.50 ± 5.08	0.129

Group A – Control subjects
Group B – Type 2 diabetic subjects
Unpaired t test was done to measure the level of significance

Table 3 showed the biochemical parameters of the study subjects. FPG, HbA1c, Serum uric acid was significantly (p<0.001) higher in Type 2 DM group than control subjects, whereas serum bilirubin was significantly (p<0.001) lower in diabetic subjects than the healthy subjects.

Table 4 showed comparison of glycemic status (FPG and HbA1c) in between different quartiles of serum bilirubin in Type 2 diabetes mellitus subjects. FPG and HbA1c levels were significantly (p<0.001) higher in <0.60 (Q1 & Q2) group in comparison to ≥0.60 (Q3 & Q4) group of serum bilirubin.

Table 5 shows comparison of glycemic status (FPG and HbA1c) in between different quartiles of serum uric acid in Type 2 diabetic subjects. FPG and HbA1c levels were significantly (p<0.001) higher in ≥6.94 (Q3 & Q4) group in comparison to <6.94 (Q1 & Q2) group of serum uric acid.

Table 6 showed correlation of serum bilirubin with glycemic status in group A and group B. Serum bilirubin had significant negative correlation with FPG and HbA1c in both groups of study subjects.

Table 7 demonstrated correlation of serum uric acid with glycemic status in group A and group B. There was significant positive correlation of serum uric acid with FPG and HbA1c in both groups of study subjects.

Table 8 demonstrated serum bilirubin and serum uric acid level at different HbA1c status in Type 2 diabetic subjects. Serum bilirubin was significantly lower (p<0.001) in poor glycemic control in comparison to that of good glycemic control group. However, serum uric acid was significantly higher (p<0.001) in poor glycemic control compared to that of good glycemic control group.

Table 3. Biochemical parameters of the study subjects (n=100)

Variables	Group A (n=50) Mean ± SD	Group B (n=50) Mean ± SD	p-value
FPG (mmol/L)	4.84 ± 0.84	8.26 ± 1.56	**<0.001**
HbA1c (%)	4.64 ± 0.73	7.21 ± 1.43	**<0.001**
Serum bilirubin (mg/dl)	0.90 ± 0.13	0.62 ± 0.23	**<0.001**
Serum uric acid (mg/dl)	5.14 ± 0.80	6.77 ± 1.15	**<0.001**

Unpaired t test was done to measure the level of significance

Table 4. Comparison of glycemic status in between different quartiles of serum bilirubin in Type 2 diabetic subjects (n=50)

Variables	Serum bilirubin (mg/dl)		p-value
Q1 & Q2 (<0.60)		**Q3 & Q4 (≥0.60)**	
FPG (mmol/L)	9.45 ± 1.37	5.58 ± 1.27	**<0.001**
HbA1c (%)	8.36 ± 1.13	5.11 ± 0.91	**<0.001**

Data were expressed as mean ± SD
Unpaired t test was done to measure the level of significance

Table 5. Comparison of glycemic status in between different quartiles of serum uric acid in Type 2 diabetic subjects (n=50)

Variables	Serum uric acid (mg/dl)		p-value
Q1 & Q2 (<6.94)		**Q3 & Q4 (≥6.94)**	
FPG (mmol/L)	5.65 ± 1.41	9.23 ± 1.54	**<0.001**
HbA1c (%)	5.21 ± 1.15	8.04 ± 1.33	**<0.001**

Data were expressed as mean ± SD
Unpaired t test was done to measure the level of significance

Table 6. Correlation of serum bilirubin with glycemic status (n=100)

Variables	Group A (n=50)		Group B (n=50)	
	r	p-value	r	p-value
FPG (mmol/L)	-0.776	<0.001	-0.805	**<0.001**
HbA1c (%)	-0.772	<0.001	-0.822	**<0.001**

Correlations were determined by Pearson's correlation coefficient test

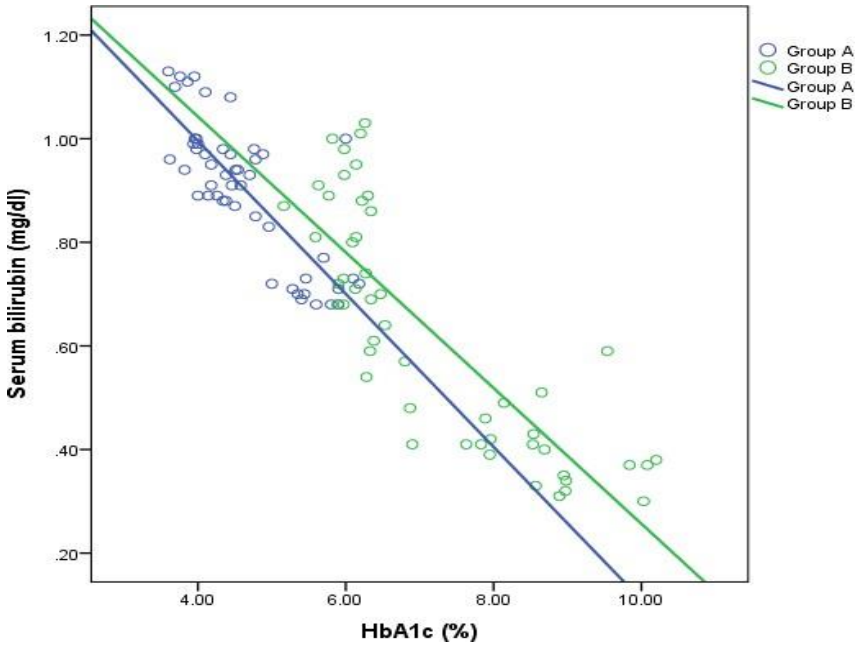

Fig. 1. Scattered diagram showing significant negative correlation of serum bilirubin with HbA1c in group A (r= -0.772; p=<0.001) and group B (r= -0.822; p=<0.001)

Table 7. Correlation of serum uric acid with glycemic status (n=100)

Variables	Group A (n=50)		Group B (n=50)	
	r	p-value	r	p-value
FPG (mmol/L)	0.627	<0.001	0.745	**<0.001**
HbA1c (%)	0.606	<0.001	0.736	**<0.001**

Correlations were determined by Pearson's correlation coefficient test

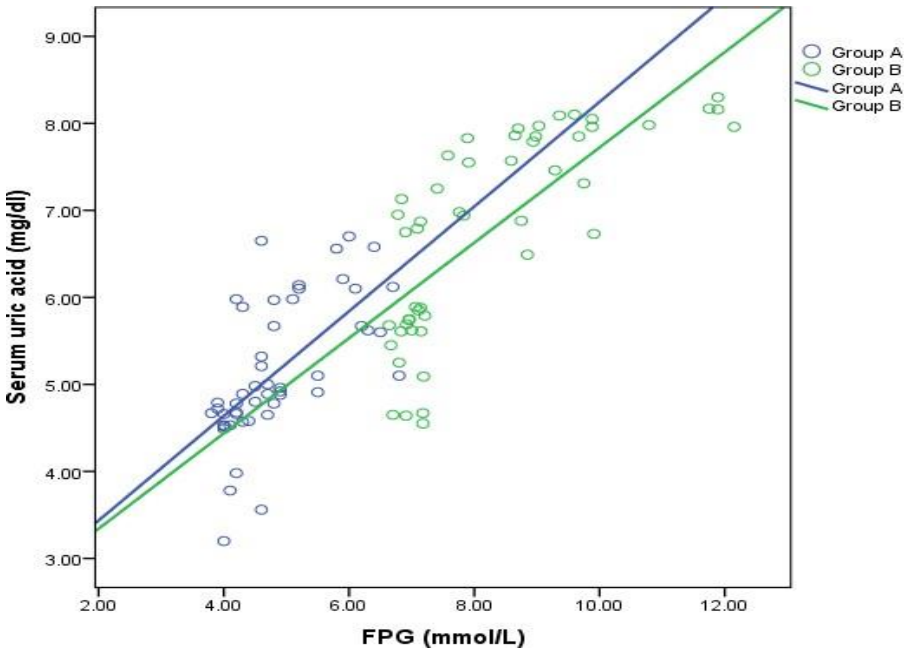

Fig. 2. Scattered diagram showing significant positive correlation of serum uric acid with FPG in group A (r= 0.627; p=<0.001) and group B (r= 0.745; p=<0.001)

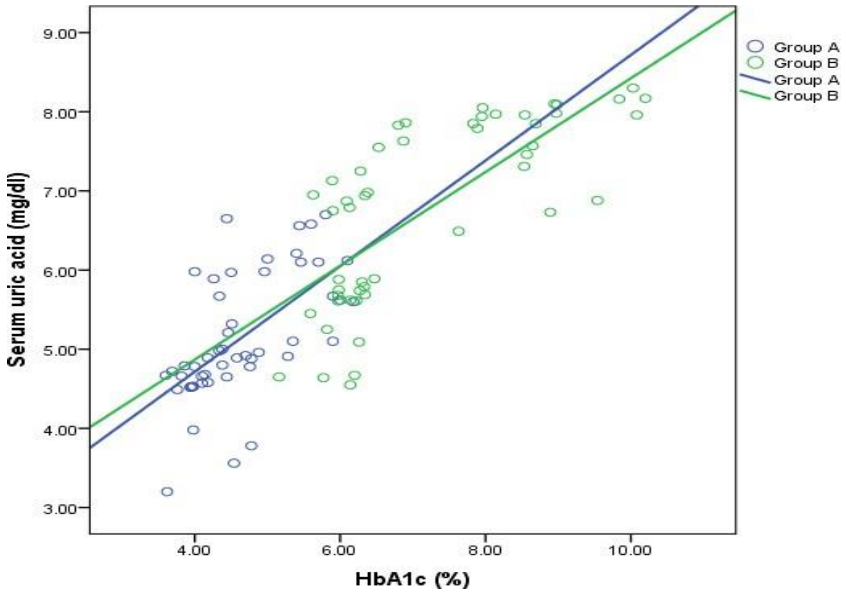

Fig. 3. Scattered diagram showing significant positive correlation of serum uric acid with HbA1c in group A (r= 0.606; p=<0.001) and group B (r= 0.736; p=<0.001)

Table 8. Serum bilirubin and serum uric acid level at different HbA1c status in Type 2 diabetic subjects (n=50)

Variables	HbA1c (%)		p-value
	<7 (n=30)	≥7 (n=20)	
Serum bilirubin (mg/dl)	0.77 ± 0.16	0.40 ± 0.07	**<0.001**
Serum uric acid (mg/dl)	6.13 ± 1.00	7.73 ± 0.51	**<0.001**

HbA1c < 7% as good glycemic control
HbA1c ≥ 7% as poor glycemic control
Unpaired t test was done to measure the level of significance

Table 9. Binary logistic regression to determine factors associated with diabetes (n=100).

Variables				95% CI for OR	
	B	p-value	OR	Lower	Upper
Age	.632	.136	1.405	.331	1.670
Gender	-.735	.231	.265	.083	2.214
BMI	.351	.497	1.309	.524	3.109
SBP	.051	.425	1.023	.816	1.207
DBP	.083	.248	1.092	.921	1.332
Serum bilirubin	-3.529	**<0.05**	.087	.031	.793
Serum uric acid	1.254	**<0.01**	3.709	1.216	6.972

Table 9 demonstrated a binary logistic regression model. Association between several factors and diabetes were expressed by the coefficients of logistic regression (B). The risk of diabetes for each factor was expressed as odds ratio (OR). Coefficient for serum bilirubin (showing inverse relation) was significant (p<0.05). In case of serum uric acid, coefficient showed significant (p<0.01**)** positive relationship. However, coefficients for age, gender, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were not significant. Where serum uric acid was the strongest predictor of diabetes with an odds ratio of 3.709.

4. DISCUSSION

The mean serum bilirubin level was in normal range but it was significantly lower among the diabetic subjects than control (Table 3). This observation was in accordance with the studies conducted by Rajendran et al., (2018) and Baker

et al., (2020). Low serum bilirubin 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 (Chen et al., 2008). Other studies also found low serum bilirubin in newly diagnosed diabetics than healthy subjects but the difference was not statistically significant (Mishra et al., 2020). However, Mathur et al. (2018) reported higher serum bilirubin level among the diabetic subjects as compared to healthy controls but they also found deranged thyroid function in diabetes subjects (Mathur et al., 2018). Variation of study subjects, method of estimation, geographical differences or sample size might also be responsible for this discrepancy.

This study also showed that subjects with diabetes mellitus had significantly higher mean serum uric acid level than non-diabetic subjects (Table 3). This finding was consistent with the studies of other researchers (Fadhel and Yousif, 2019, Mishra et al., 2020). Guarda et al., (2019) reported that high concentrations of uric acid were associated with tubular damage accompanied by the increase urinary proinflammatory cytokines in patients with T2DM (Guarda et al., 2019). In contrast, Pavani, Mohanty and Dharwadkar (2018) found significantly low mean serum uric acid level in diabetic subjects as compared to control and also hypothesized that low uric acid levels in diabetics are probably due to inhibition of uric acid reabsorption in the proximal convoluted tubule of kidney by glucose (Pavani et al., 2018).

Quartiles were made according to the increasing level of serum bilirubin for comparison of glycemic status in between different quartiles of serum bilirubin in diabetic subjects (Table 4). FPG and HbA1c levels were found high in Q1 & Q2 than Q3 & Q4. Therefore, FPG and HbA1c levels were intended to decrease significantly from lowest to highest quartiles of serum bilirubin among diabetic subjects. This finding was in accordance with other studies where they also observed inverse relation of serum bilirubin quartiles with glycemic status. It was also suggested that high serum bilirubin within physiological range might serve as a protective factor in T2DM development that supported the antioxidant nature of bilirubin which signifies the above statement (Jung et al., 2014, Kwon et al., 2017, Yang et al., 2019).

A significant negative correlation was observed between serum bilirubin with FPG and HbA1c level among study subjects in the present study (Table 6). This finding was in consistent with the studies of Farasat et al., 2017 and Erkus et al., 2018. Similar finding was also evident in binary logistic regression analysis of this study. Another study shown from their binary logistic regression analysis suggested that serum bilirubin was an independent prognostic factor of diabetes. They also suggested that higher bilirubin (within the physiological range) might prevent the development of T2DM among general population by inhibiting oxidative stress and inflammation (Zhong et al., 2019). However, some other researchers reported a negative correlation of serum bilirubin with FPG and positive correlation of bilirubin with HbA1c among diabetic subjects but those were not statistically significant (Mishra et al., 2020, Baker et al., 2020).

Serum uric acid quartiles were made according to the increasing level, for comparison of glycemic status in between different quartiles of uric acid in diabetic subjects (Table 5). FPG and HbA1c levels were found high in Q3 & Q4 than Q1 & Q2. Therefore, FPG and HbA1c levels were intended to increase significantly from lowest to highest quartiles of uric acid among diabetic subjects. Nearly similar finding was observed in the studies conducted by Wang et al., (2011) and Bai et al., (2015). Hyperinsulinemia as a consequence of insulin resistance causes an increased serum uric acid concentration by reducing renal uric acid secretion and accumulating substrates for uric acid production as suggested by Hu et al., 2021. But these findings were not consistent with the study of Amerian et al. (2020) whom suggested that the exact mechanism of the effect of uric acid on the amount of glucose is unknown, but speculation is being made in this area (Amerian et al., 2020).

It was evident from the present study that FPG and HbA1c showed a strong positive correlation with serum uric acid among the study subjects (Table 7). Similar finding was also evident in binary logistic regression analysis of this study (Table 9). This observation was in agreement with other researchers who reported a strong positive correlation of serum uric acid with FPG and HbA1c among diabetic subjects (Moinuddin and Awanti 2016, Khaire and Wattamwar 2020). Serum uric acid has an adverse impact on glycemic status as stated by Babikr et al. (2016) and Fadhel and Yusif (2019) which is in favour of the present study findings (Babikr et al., 2016). However, observation of this study was not

consistent with Wei et al. (2016) who reported an inverse relationship of uric acid with HbA1c and FPG in diabetic patients. They explained that reverse transporting of uric acid and glucose in renal tubules might be accounted for these associations (Wei et al., 2016).

It was also evident that serum bilirubin was significantly lower in poor glycemic control group in comparison to that of good glycemic control. However, serum uric acid was significantly higher in poor glycemic control compared to that of good glycemic control subjects (Table 8) which were in accordance with the findings of other researchers (Erkus et al., 2018, Kocak et al., 2019). According to Erkus et al. (2018), bilirubin might play an important role in preventing glycation of protein which supports the association of low serum bilirubin with worst glycemic control (Erkus et al., 2018).

The risk of diabetes for each factor was expressed as odds ratio (OR) by binary logistic regression analysis (Table 9). It was evident that serum uric acid was strongest predictor of diabetes with an odds ratio of 3.709. These findings were almost in accordance with Bai et al. (2015) whom reported uric acid as a possible predictor which was significantly associated with diabetes (Hu et al., 2021).

According to Duman et al. (2018) and Ren et al. (2018), diabetic complications were associated with poor glycemic control and co-presence of both high serum uric acid and low serum bilirubin had a synergistic effect to increase the risk of microvascular disease in T2DM. Therefore, association of serum bilirubin and uric acid with HbA1c is obvious. Observation of the study suggests the beneficial role of evaluating serum bilirubin and uric acid in addition to HbA1c assay to predict the risk of developing T2DM.

5. CONCLUSION

From the present study, it can be concluded that, Type 2 diabetic subjects have lower serum bilirubin and higher uric acid level than that of healthy subjects. Serum bilirubin has an inverse relationship with glycemic status (FPG and HbA1c) whereas uric acid shows positive correlation with glycemic status in diabetic subjects. Hyperuricemia appears to be a risk factor for development of Type 2 diabetes mellitus.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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