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The Association between Serum Uric Acid in Patients of Impaired Fasting Glucose and Type 2 Diabetes Mellitus

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Abstract: ***Aims: To study the association between serum uric acid in patients of impaired fasting glucose and Type 2 Diabetes mellitus. Methods and Material: Hospital based observational prospective study. The study was conducted on patients attending the Internal Medicine OPD of Acharya Shri Chander College of Medical Science and Hospital, Jammu over a period of one year from November 2021 to October 2022. The total number of 100 patients were taken. This study was approved by the Institutional Ethics Committee of the hospital. Written informed consent was taken from all the subjects, who were included in the study after explaining to them the nature and purpose of the study. Definite inclusion criteria and exclusion criteria was set with all required investigations. Statistical analysis: The data was collected and recorded on Microsoft excel data sheets and was analyzed using statistical package for social science (SPSS) software and appropriate statistical analytical tests. Conclusions: This observational study observed that the level of serum uric acid is an independent and positive factor associated with the diabetes. It was concluded that the serum uric acid level was significantly associated with the diabetic status of the patients, therefore, uric acid can be a useful biomarker of blood glucose in patients.***

Keywords: Impaired fasting glucose, Biomarker, HbA1c. Uric acid

1. Introduction

"Health is the greatest gift, contentment the greatest wealth, faithfulness the best relationship. " — Buddha.

Uric acid, metabolic end product of the purine nucleotides, is a weak acid with pK as of 5.75 and 10.3 and more soluble in urine than in water, possibly because of the presence of urea, proteins and mucopolysaccharides. The levels of Serum Uric Acid (SUA) are genetically determined, but are influenced by multiple environmental factors

The uric acid is produced by three mechanisms, i. e. PPribose - P - amidotransferases (PPRP amidotransferase), hypoxanthine guanine phosphoribosyl transferase (HGPRT) and xanthine oxidase. It is the most highly oxidized member of the purine class. In case of diabetes mellitus, serum uric acid level falls and continues to decrease with increasing duration of the disease. And various researchers observed that in hyperglycemic state, the increased glucose reabsorption leads to impairment in the tubular reabsorption of uric acid, as both glucose as well as filtered uric acid are reabsorbed through proximal convoluted tubule **(Haridas S, 2018).**

Chen L, et al. (2007) reported that the prevalence of hyperuricemia is increased globally about 10 - 25% (**Chen L *et al.*, 2007).** The serum uric acid is associated with various diseases such as cardiovascular diseases, metabolic syndrome, diabetes mellitus, etc **(Remedios C*et al.*, 2012 [(1)], Glantzounis G*et al.*, 2005 [(2)] & N Ali *et al.*, 2018).**

It was reported that uric acid worsen the insulin resistance by inhibiting the bioavailability of nitric oxide, which is essential for insulin - stimulated glucose uptake. The positive association was suggested between serum uric acid and fasting plasma glucose and impaired fasting glucose. The increased serum uric acid is the risk factor of developing type 2 diabetes mellitus (**Wen - Chih Wu*et al.*, 2020) [(3).]**

The increased serum uric acid levels in the blood leads to the expression of interleukin - 1β (IL - 1β), interleukin - 6 (IL - 6), tumor necrosis factor - α (TNF - α) and CRP production which leads to decreased insulin sensitivity and also increases the reactive oxygen species (ROS) production, which leads to inflammation and dysfunction in the vessel. The oxidative stress affects the expression of insulin gene, causing a decrease in insulin secretion. The serum uric acid levels are independently associated with endothelial dysfunction as well as it directly inhibits the trigger of insulin signalling pathway by an ectonucleotidepyrophosphatase/phosphodiesterase 1 (ENPP1) recruitment at the receptor level **(Qing X *et al.*, 2019).**

The various studies reported that elevated serum uric acid is associated with glucose metabolic disorders, i. e. impaired fasting glucose, elevated glycated hemoglobin ($HbA1_c$),

hyperinsulinemia and insulin resistance and diabetes **(Ren Y *et al.*, 2019).**

The European Prospective Investigation into Cancer and Nutrition - Netherlands study suggested that high serum uric acid concentrations are associated with increased diabetes risk. Similarly, **Wu W - C*et al.*, 2020** [4] determined that the serum uric acid was positively associated with hyperinsulinemia and insulin resistance in prediabetes patients. Further it was observed that the serum uric acid is related to the early stages of the development of type 2 diabetes.

The uric acid act as a potent anti - oxidant and free radical which is necessary to protect the cells from oxidative damage related to diabetes and its vascular complications. Moreover, it was reported that serum uric acid decreases in patients with type 2 diabetes and chronic smokers, which can lead to increased susceptibility to oxidative damage and account for the excessive free radical production. A therapeutic potential of uric acid was observed in patients with ischemic stroke who were treated with intravenous thrombolytic therapy, intravenous infusion of uric acid in the early period as reduced markers of oxidative stress **(Haridas S, 2018).**

In a patient with high BMI, the amount of NEFA, glycerol, hormones, cytokines, proinflammatory substances, and other substances that are involved in the development of insulin resistance are increased **(Al - Goblan AS*et al.*, 2014)** [5].

The type 2 diabetes mellitus and obesity leads to insulin resistance and the patients who have high BMI become insulin resist. The non - esterified fatty acids are secreted by adipose tissues which lead to insulin resistance and beta cell dysfunction **(Kahn *et al.*, 2006)** [6].

It was observed that the patients with chronic diabetes develops the complications like, neuropathies, cardiovascular disease, retinopathy, metabolic syndrome, etc. studies suggest that the metabolic syndrome is associated with hyperuricemia which reflects the problems in insulin action on the renal tubular reabsorption of uric acid (**C. Arjuna, 2020).**

The previous data suggests that there was a positive association between the serum uric acid and type 2 diabetes mellitus. Thus, the present study was undertaken to analyze the levels of serum uric acid in patients of impaired fasting glucose and type 2 DM.

Aim and Objective

To study the association between serum uric acid in patients of impaired fasting glucose and Type 2 Diabetes mellitus.

2. Material and Methods

Study Design: Hospital based observational prospective study

The study was conducted on patients attending the Internal Medicine OPD ofAcharya Shri Chander College of Medical Science and Hospital, Jammu over aperiod of one year from November 2021 to October 2022. The total number of 100patients were taken. This study was approved by the Institutional Ethics Committee of the hospital. Written informed consent was taken from all the subjects, who were included in the study after explaining to them the nature and purpose of the study. The data for the purpose of the study was collected in a predesigned and pretested proforma which include various socio- economic parameters like age, sex, occupation, religion etc. About 100 cases were selected on the basis of the simple random sampling method.

Inclusion Criteria:

- Impaired fasting glucose (IFG): Fasting plasma glucose between 100 - 125 mg/dl.
- T2DM: Symptoms of diabetes plus RBS: ≥200 mg/dl

Or

- Fasting plasma glucose: ≥126 mg/dl

Or

- Two hour plasma glucose: ≥ 200 mg/dl

Exclusion Criteria:

- Pregnancy
- Age < 15 years
- Patients suffering from any kidney disease
- Patients of Chronic alcoholism and smoking
- Patients taking drugs like salicylate (>2gm/day), diuretic, alcohol, levodopa, Ethambutol, pyrazinamide, Nicotinic acid, cyclosporine, losartan.
- Patient suffering from any haematological malignancy/ haemolytic diseases.
- Patients having history or sign/ symptom suggesting acidosis, beryliosis, sarcoidosis, hypothyroidism, hyperparathyroidism, diabetes insipidus.
- Patient not giving consent for being part of the study.

Investigations:

1) Serum Uric Acid Levels.
2) Fasting Blood Glucose.
3) Two hour PPBG (Post Prandial Blood Glucose) and Oral Glucose Tolerance Test.
4) Serum Urea and Creatinine.
5) HbA1c %

Biochemical analysis was carried out with the help of Department of Biochemistry, ASCOMS & Hospital, Jammu.

After making the subject to sit comfortably on a couch near a table, a tourniquet was applied about 2 - 3 cms above the elbow. The punctured site was cleaned with methylated spirit swab. The needle of disposable syringe was inserted in anti - cubital vein after the spirit has dried. Venous blood sample was taken. Then under all aseptic precautions, about 10ml of blood samples was collected from each subject in a clean vacutainer tube.

Blood was allowed to clot for at least 30 minutes. It was centrifuged for 20 - 30 minutes at 2500rpm. Supernatant Serum was collected with the help of a pipette and transferred to another container and stored in deep freezer whose temperature was maintained at - 20 C. in frozen form.

For plasma needed for our investigation, blood was drawn into a clean test tube containing heparin. The plasma was separated by centrifugation and stored in refrigerator. (Up to one week or stored frozen).

Following biochemical investigations were done and values recorded for each subject:

Fasting Plasma Glucose (FPG).
Venous blood sample was obtained and quantitative determination of Plasma Glucose was done by Hexokinase method. It was measured by using fully automated analyser.

Serum Uric Acid
Venous blood samples were taken in the morning with the subjects fasting for minimum 8 hours. The uric acid was measured by the uricase method.

Statistical Analysis
The data was collected and recorded on Microsoft excel data sheets and was analyzed using statistical package for social science (SPSS) software and appropriate statistical analytical tests.

3. Results and Observations

Statistical Analysis
The statistical analysis was done using SPSS (Statistical Package for the Social Sciences, SPSS Inc., v.16). The descriptive statistics were calculated as mean and standard deviation. Comparison of study parameters between participants with IFG and T2DM was done using Independent t - test. The level of significance for the present study was fixed at a P - value of less than 0.05.

Results

Gender Distribution

Table 4.1: Gender - wise distribution of study participants

		Group		
		IFG	T2DM	Total
Sex	Male	36	26	62
	Female	14	24	38
Total		50	50	100

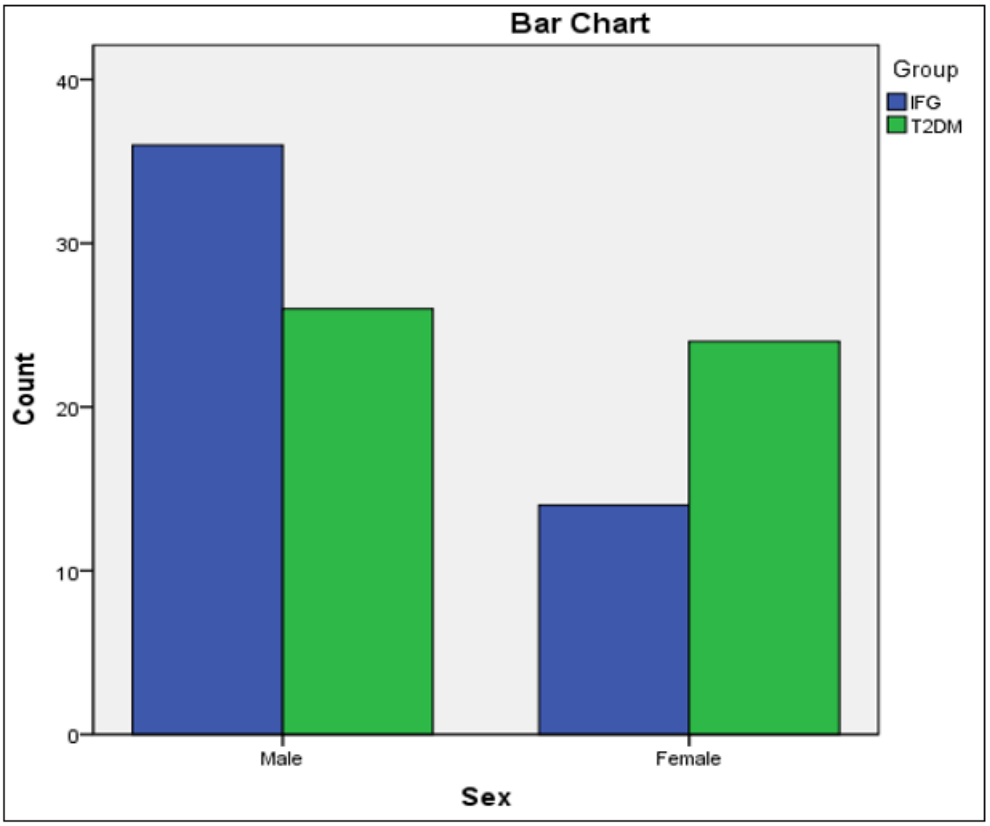

Figure 4.1: Gender - wise distribution of study participants

Age Distribution

Table 4.2: Age distribution of study participants

	Group	N	Mean	Std. Deviation	Std. Error Mean
Age	IFG	50	55.9000	13.85236	1.95902
	T2DM	50	58.0400	13.62914	1.92745

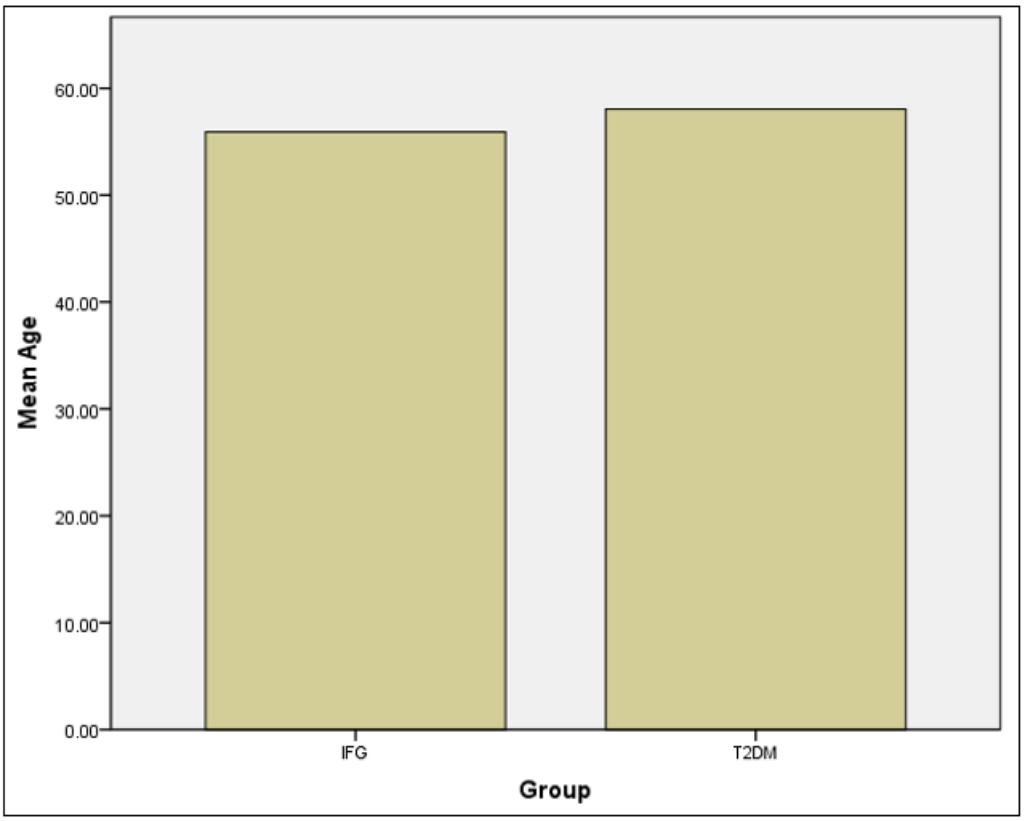

Figure 4.2: Age distribution of study participants

Serum Uric Acid

Table 3 shows the comparison of serum uric acid between the study groups. Statistical analysis showed that there was a statistically significant difference in mean serum uric acid concentration between IFG and T2DM (P=0.016).

Table 4.3: Comparison of serum uric acid

	Group	N	Mean	Std. Deviation	P value
Serum Uric Acid	IFG	50	6.0960	1.62355	0.016*
	T2DM	50	6.9720	1.93960	

*Statistically significant (P<0.05, Independent t - test)

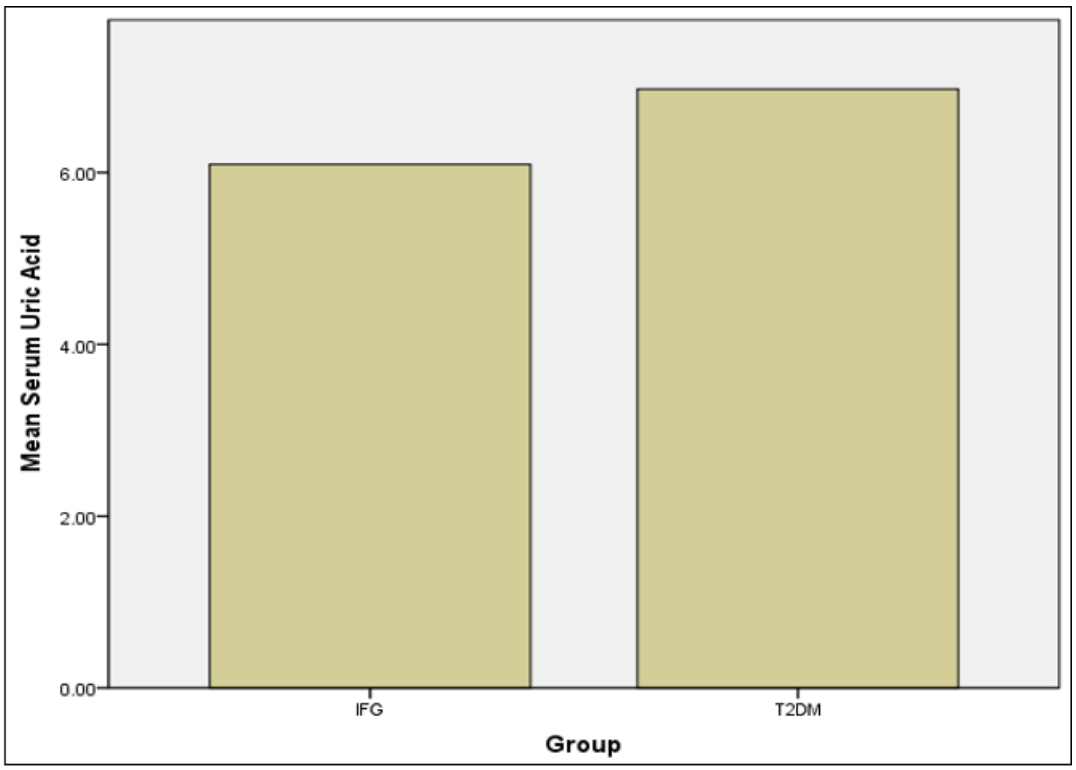

Figure 4.3: Comparison of serum uric acid

FBG

Table 4 shows the comparison of fasting blood glucose between the study groups. Statistical analysis showed that there was a statistically significant difference in mean fasting blood glucose concentration between IFG and T2DM (P<0.001).

Table 4.4: Comparison of FBG

	Group	N	Mean	Std. Deviation	P value
FBG	IFG	50	113.9200	8.91648	<0.001*
	T2DM	50	172.2800	39.93211	

*Statistically significant (P<0.05, Independent t - test)

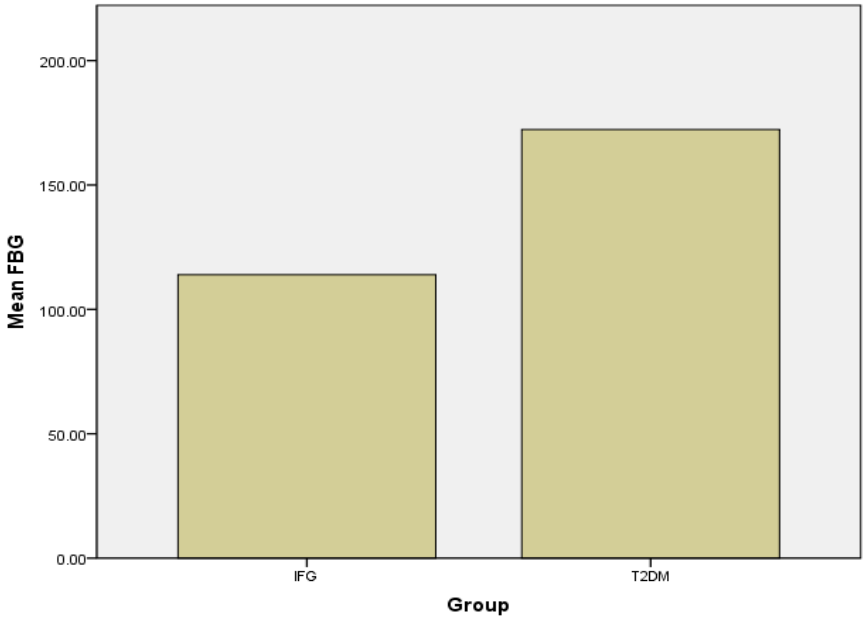

Figure 4.4: Comparison of FBG

Two Hour PPB Glucose

Table 5 shows the comparison of 2 hour PPBS between the study groups. Statistical analysis showed that there was a statistically significant difference in mean 2 hour PPBG levels between IFG and T2DM (P<0.001).

Table 4.5: Comparison of 2 Hr PPBS

	Group	N	Mean	Std. Deviation	P value
2 Hr PPBG	IFG	50	186.0800	15.41777	<0.001*
	T2DM	50	287.6400	90.18502	

*Statistically significant (P<0.05, Independent t - test)

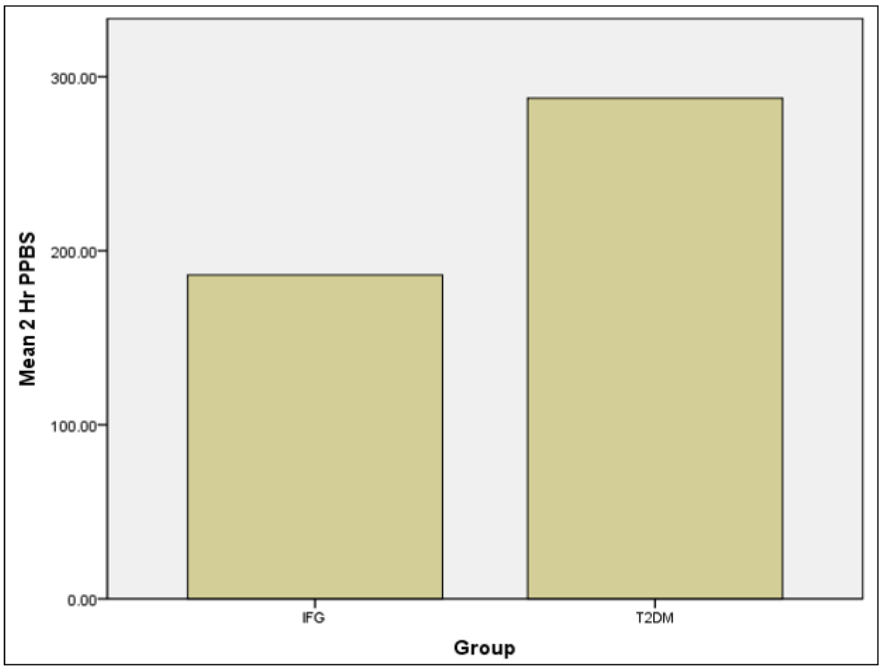

Figure 4.5: Comparison of 2 Hr PPBS

Serum Urea

Table 6 shows the comparison of serum urea between the study groups. Statistical analysis showed that there was a statistically significant difference in mean serum urea concentration between IFG and T2DM (P=0.002).

Table 4.6: Comparison of serum urea

	Group	N	Mean	Std. Deviation	Std. Error Mean
Serum Urea	IFG	50	45.7600	23.10187	3.26710
	T2DM	50	60.4000	23.93784	3.38532

*Statistically significant (P<0.05, Independent t - test)

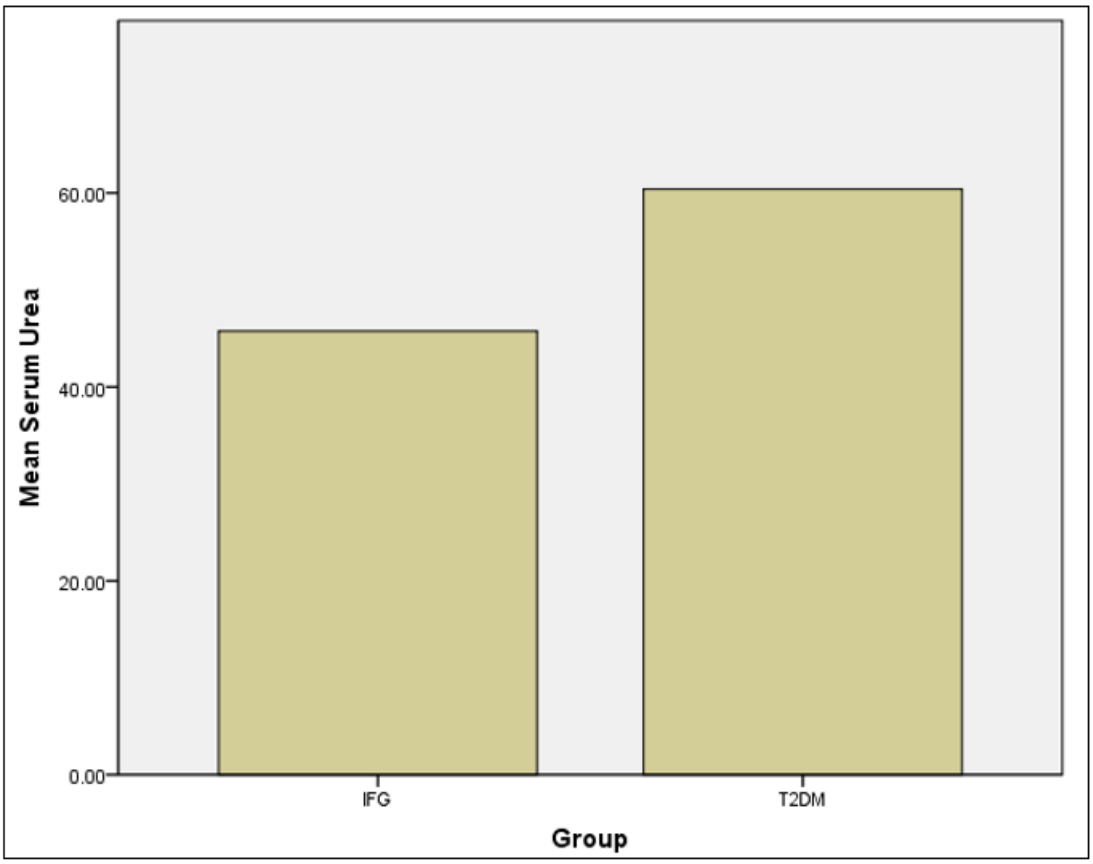

Figure 4.6: Comparison of serum urea

Serum Creatinine

Table 7 shows the comparison of serum creatinine between the study groups. Statistical analysis showed that there was a statistically significant difference in mean serum creatinine concentration between IFG and T2DM (P<0.001).

Table 4.7: Comparison of serum creatinine

	Group	N	Mean	Std. Deviation	P value
Serum Creatinine	IFG	50	.9760	.36397	<0.001*
	T2DM	50	1.4620	.81614	

*Statistically significant (P<0.05, Independent t - test)

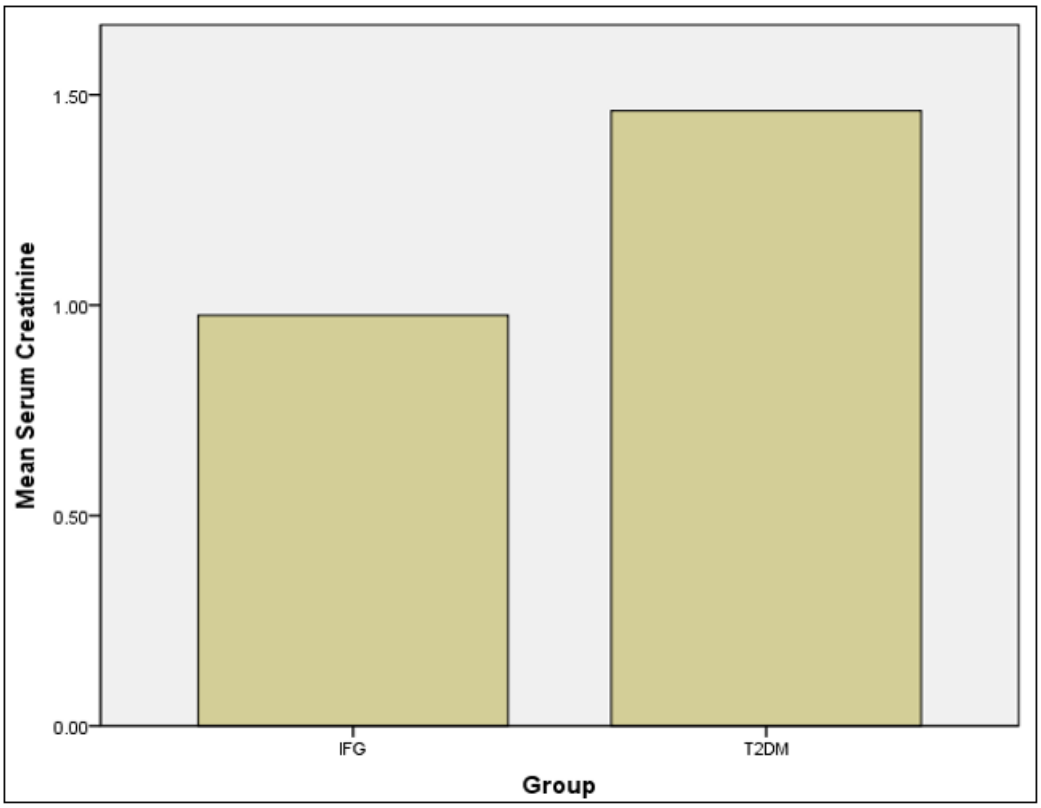

Figure 4.7: Comparison of serum creatinine

HbA1C%

Table 8 shows the comparison of HbA1C% between the study groups. Statistical analysis showed that there was a statistically significant difference in mean HbA1C% between IFG and T2DM (P<0.001).

Table 4.8. Comparison of HbA1C%

	Group	N	Mean	Std. Deviation	Std. Error Mean
HbA1C%	IFG	50	5.9480	.43903	.06209
	T2DM	50	8.0320	1.20787	.17082

*Statistically significant (P<0.05, Independent t - test)

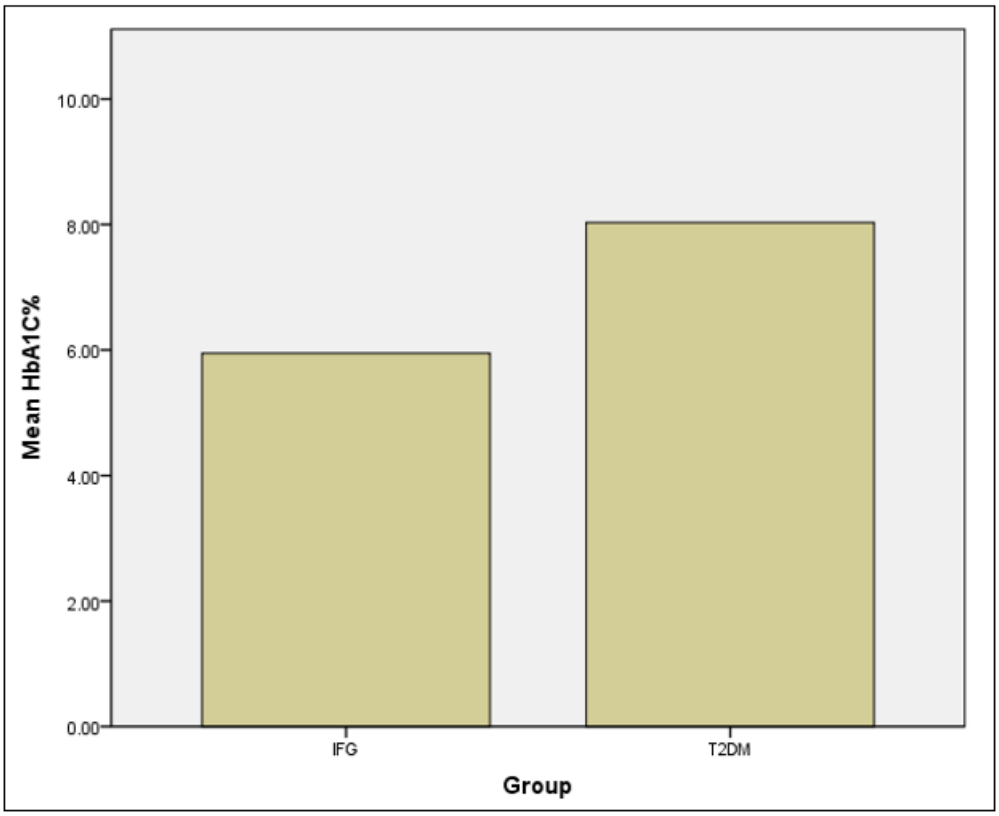

Figure 4.8: Comparison of HbA1C%

4. Discussion

The uric acid is an end product of human purine metabolism and generated during nucleotide and adenosine triphosphate metabolism. Various studies showed that a significant increase of serum level of uric acid is associated with increased risk of type 2 diabetes mellitus independently of other risk factors.

Several studies show that there was significant association between the diabetes mellitus and serum uric acid level. The present study was undertaken to observe the association between serum uric acid levels in patients of impaired fasting glucose and type 2 diabetes mellitus.

In our study the mean age of patient in impaired fasting glucose group was 55.9000±13.85236 years and mean age of patient with T2 DM group was 58.0400±13.62914 years. The majority of the patients were males (62%), followed by females (38%). The findings of present study were correlated with the study conducted by Kramer **CK, *et al.* (2009)** [7], found that the mean age of the study participants was 63.3 ± 8.6 years. In another study conducted by **Shirsath A, et al. (2019)** [8], observed that the mean age of the study participants was 59.04±13.47 years, majority of the study participants were males. Similarly, a retrospective cross sectional study conducted by **Nugraha R, *et al.* (2018)** [9], the mean age of the patient was 57±11.1 years and female patients was 57±7.2 years.

The comparison of serum uric acid between the study groups showed that there was a statistically significant difference in mean serum uric acid concentration between impaired fasting glucose and T2DM (P=0.016). The result was consistent with the study conducted by **Aboud AS, et al. (2022)** [10], reported the statistically significant association between HbA1c and serum uric acid. Serum uric acid played a significant role in disturbance of glucose metabolism. Similarly, **Solanki HK, *et al.* (2021),** found the positive correlation between serum uric acid and duration of type 2 diabetes. **Wu WC, *et al.* (2020)** [11], they also stated that increased serum uric acid results in significant increase in development of diabetes mellitus in the patients. In another study conducted by **Wu Y, *et al.* (2019)** [12], found a positive association between serum uric acid and insulin resistance in prediabetic patients.

On comparison of fasting blood glucose between the study groups a statistically significant difference was observed in mean fasting blood glucose concentration between impaired fasting glucose and T2DM (P<0.001) and a statistically significant difference was found in mean 2 hour post prandial blood levels between impaired fasting glucose and T2DM (P<0.001). The findings are similar to the study conducted by **M Sudhindra R, *et al.* (2012),** found the significant difference between mean diabetic and non - diabetic patients. In another study conducted by **ShirsathA, *et al.* (2019),** *reported a* statistically significant difference between the mean fasting blood glucose concentration between impaired fasting glucose, mean postprandial blood glucose, HbA1c level and T2DM.

The present study observed a statistically significant difference in mean serum urea concentration between IFG and T2DM (P=0.002). The results of present study are in accordance with the study conducted by **Nakanishi N, *et al.* (2003)** [13], found a strong positive association between the serum uric acidlevel and risk for impaired fasting glucose or Type 2 diabetes mellitus. **Satoru Kodama, *et al.*, (2009),** reported that level of serum uric acid was positively associated with the development of type 2 diabetes regardless

of various study characteristics.

Kramer CK, *et al. (*2009), observed that 1mg/dl serum uric acid increases the 60% risk of diabetes. Thus, the uric acid is a good predictor of type 2 diabetes. In another study conducted by **Meisinger C, *et al.* (2012),** found that the serum uric acid was significantly associated with impaired glucose regulation. **Qin Lv, et al 2013,** stated that the level of serum uric acid is an risk factor of developing type 2 diabetes in middle - aged and older people.
In another meta analysis conducted by **Jia Z, *et al. (*2013)** [14], reported the pooled multivariate - adjusted relative risk (RR) (95%CI) of impaired fasting glucose and T2DM for the highest vs. lowest level of serum uric acid was 1.54 (1.41–1.68), I^2 = 42.2%. The association was consistent and significant across subgroup analysis. It was concluded that serum uric acid level was positively associated with type 2 diabetes mellitus and impaired fasting glucose. Similarly **Khare S, *et al. (*2015), revealed** that mean serum uric acid was higher in diabetic patients.

In our study a statistically significant difference was observed in mean serum creatinine concentration between impaired fasting glucose and T2DM (P<0.001). The findings are correlated with a *observational, descriptive cross sectional study* conducted by **Shirsath A, *et al. (2019),** *observed* mean fasting blood sugar was 186.10±77.53mg/dl, mean postprandial blood sugar was 274.94±108.66mg/dl, HbA1c level was 8.15±1.7, the mean uric acid was 9.53±4.38, mean blood urea was 46.91±15.13 and serum creatinine was 1.44±0.29. It was stated that the patients with diabetes mellitus with elevated uric acid levels also had elevated serum creatinine and microalbuminuria. Similarly, **Bhole V, *et al., (*2010)** [15], a statistically significant difference in mean serum creatinine concentration between impaired glucose levels and T2DM. It was observed by **TerMaaten JC *et al., (*1992) and Muscelli E *et al., (*1992)** that elevated serum acid levels may reflect prediabetes status, particularly at the renal level, although our observed association was independent of fasting glucose, triglycerides, and serum creatinine.[1, 2]

The literature suggests that increased insulin levels associated with prediabetes can reduce renal excretion of uric acid, [3, 4] as insulin can stimulate the urate - anion exchanger and/or the Na+ - dependent anion co - transporter in brush border membranes of the renal proximal tubule and increase renal urate reabsorption.[1, 2]

The present study found a statistically significant difference in mean HbA1C% in impaired fasting blood glucose and T2DM (P<0.001). The findings are consistent with the study conducted by **Deb N, *et al. (*2019),** found a statistically significant difference in mean HbA1C% in impaired fasting glucose and T2DM. Similarly**Abound AS, *et al. (*2022),** observed a statistically significant difference in mean HbA1C% in diabetic patients.

5. Summary and Conclusion

The present prospective observational study was conducted patients attending the Internal Medicine OPD of Acharya Shri Chander College of Medical Science and Hospital, Jammu over a period of one year from November 2021 to October 2022 to determine the association between serum uric acid and impaired fasting glucose. The total number of 100 patients were included in the study.

After obtaining the ethical permission from Institutional EthicsCommittee of the hospital and written informed consent from participants, a detailed history was taken and data was collected.

Following key observations was obtained:

1) In the present study in impaired fasting glucose group 36% were males and 14% were females. In T2DM group, 26% were males and 24% were females.
2) The observed mean age of the patients in impaired fasting group was 55.9000±13.85236 years and mean age of patient with T2DM group was 58.0400±13.62914 years.
3) The data showed a statistically significant difference in mean serum uric acid concentration between IFG and T2DM, between the mean fasting blood glucose concentration between IFG and T2DM and between mean 2 hour PPBG levels between IFG and T2DM.
4) The present study found a statistically significant difference in mean serum urea concentration between IFG and T2DM (P=0.002) as the mean serum urea in impaired fasting group was 45.7600±23.10187 and serum urea in patient with T2 DM group was 60.4000±23.93784.
5) In our study a statistically significant difference was observed in mean serum creatinine concentration between IFG and T2DM. The mean serum creatinine in impaired fasting group was.9760±.36397 and serum creatinine in patient with T2 DM group was 1.4620±.81614.
6) A statistically significant difference in mean HbA1C% between IFG and T2DM (P<0.001) was observed. The mean HbA1C% in impaired fasting group was 5.9480±.43903 and HbA1C% in patient with T2 DM group was 8.0320±1.20787.

Conclusion

This observational study observed that the level of serum uric acid is an independent and positive factor associated with the diabetes. It was concluded that the serum uric acid level was significantly associated with the diabetic status of the patients, therefore, uric acid can be a useful biomarker of blood glucose in patients

Prior publication : NIL
Support : NIL
Conflicts of interest: NIL
Permissions : NIL

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