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Original Research Article

Association between elevated serum uric acid levels and islet beta cell function indices in newly diagnosed type 2 diabetes mellitus-a one year cross sectional study at tertiary care center

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ABSTRACT

Background: Serum uric acid (SUA) has been reported as a risk factor for type 2 diabetes mellitus (T2DM). Even though various studies concluded that SUA plays an essential role in DM onset, association between SUA and pancreatic islet β cell function and the effect of gender and body mass index (BMI) on it in is still unclear.
Methods: A hospital based one-year cross-sectional study was conducted and required data was collected from 76 patient who were newly diagnosed T2DM. All patients were investigated for SUA, and homeostasis model assessment-insulin resistance (HOMA-IR) was calculated using the HOMA2 calculator.
Results: Mean SUA level among the males was 4.65±1.81 mg/dl and among the females was 4.31±1.94 mg/dl. β pancreatic cell function index was estimated using HOMA-IR. Mean HOMA-IR level among the male study population was 5.01±7.44 and 5.02±4.63 among the females. A positive and significant correlation was observed between SUA and HOMA-IR (r=0.2283, p=0.0489) at 5% level, and was more pronounced among the female population (r=0.5127, p=0.0175). Correlation between HOMA-IR and BMI was found to be positive and significant (r=0.4948, p=0.0001). On plotting multiple regression analysis, coefficient of determination (R^2) was 0.8374 ($p<0.05$), indicating significant contribution of all variables when combined towards HOMA-IR.
Conclusions: Present study demonstrates that SUA harbours a positive and significant correlation with pancreatic islet β cell function index among newly diagnosed T2DM patients and is influenced by gender and BMI.

Keywords: Newly diagnosed T2DM, SUA, Pancreatic islet β cell function, HOMA-IR

INTRODUCTION

Type 2 diabetes mellitus (T2DM), a chronic metabolic disorder, with its dramatically rising prevalence over the past 2-3 decades, has evolved into a silent epidemic as well as a substantial universal health burden. India occupies the top 5 ranking in the prevalence of DM, with approximately 77 million population living with DM as of 2019 according to the latest survey done by international diabetes federation (IDF). [1]

Even with better comprehension of its pathophysiology, recognising which of the patients are at utmost risk of developing critical complications related to DM is an unceasing challenge.[2]

Therefore, keeping in mind the ubiquity of T2DM, and the multiple micro as well as macrovascular complications it gives rise to, it is crucial to diagnose it as promptly as possible to maintain accurate glycemic control and defer the development of complications.[3]

The pathology of DM can range from severe insulin resistance (IR) with relative insulin deficiency to severe insulin deficiency with IR. The initial stage of diabetes is characterized by the stage of compensation i.e., increased insulin secretion in order to keep up normoglycemia when there is IR along with reducing mass of the β-cells.[4,5]

Based on this, SUA is unfolding as a possible marker of DM risk. Uric acid (UA), which is a breakdown product of metabolism of purine, is majorly excreted from the body via kidneys, where the glomeruli filter it and the proximal tubules excretes it.[6,7]

The levels of SUA in a person are a blended result of genetics as well as multiple life style factors including eating habits, exercise, type of work etc. Hence Indian population by virtue of different food practices, lifestyle along with genetic constitutions compared to other populations in world, will have varying levels of SUA.[8]

Past studies have revealed that SUA is a risk factor for multiple chronic diseases, including cardiovascular disorders, hypertension, as well as kidney diseases.[9,10]

Lately it's been hypothesised that high SUA may be potential precursor for the development of DM rather than just consequence of IR, i.e., causal role of SUA.[11,12]

Even though various animal as well as clinical studies concluded that SUA plays an essential role in the onset of DM by virtue of inflammatory processes along with oxidative stresses, the association between SUA and pancreatic islet β cell function is still unclear.[13]

Thus, this hospital based cross sectional study aims to associate SUA levels to pancreatic islet function index (by calculating IR using HOMA-IR) in cases of newly diagnosed T2DM as well as to examine whether SUA levels in T2DM are affected by gender, age and BMI.

Objectives

The objectives were to study the association between elevated SUA levels and pancreatic islet β cell function index in newly diagnosed T2DM.

METHODS

Hospital based cross-sectional study was conducted in department of medicine, KLES Dr. Prabhakar Kore hospital and MRC, Belagavi for duration of 1 year from month of January to December 2019. Total of 76 subjects fulfilling inclusion and exclusion criteria were enrolled in this study after obtaining approval of institutional ethics committee, Jawaharlal Nehru medical college, Belagavi and written informed consent from patients.

Study included patients ≥18 years of age who were newly diagnosed T2DM using ADA criteria. Exclusion criteria included patients with diabetic micro and macro-vascular complications, thyroid disease, Cushing syndrome, liver cirrhosis, pheochromocytoma, renal failure, malignant tumors and those who were taking UA-lowering therapy.

The selected patients were interviewed for complete medical history along with demographic data. Following this detailed clinical as well as systemic examination was carried out. Patients were evaluated for BMI, blood pressure and fundus examination. Preformulated proforma was constructed and all the relevant data was noted.

Investigations done on the study population included fasting and post prandial blood sugars, SUA, fasting C peptide or fasting serum insulin level, glycosylated haemoglobin (HbA1C) and serum creatinine. All parameters were analyzed by available standardized enzymatic methods.

Islet β cell function index

HOMA-IR was calculated in order to assess IR, and thus the pancreatic islet β cell function. Values of fasting blood glucose and either fasting C-peptide or fasting serum insulin levels were entered in the HOMA 2 calculator and values of HOMA-IR were obtained.

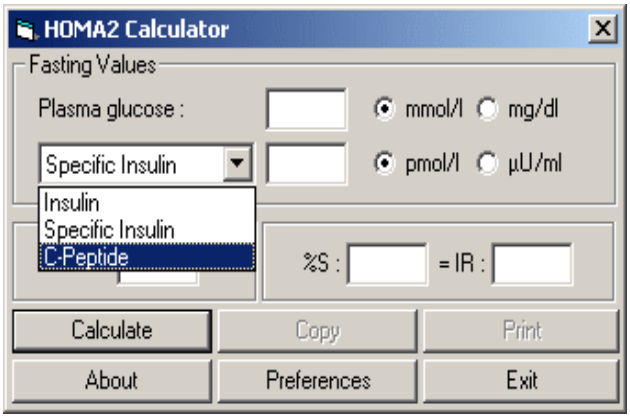

Figure 1: HOMA-IR calculator.

Statistical methods

The data obtained was coded and entered into Microsoft excel spreadsheet and data was analysed using SPSS version 21. The categorical data was expressed in terms of rates, ratios and percentages and the continuous data was expressed in terms of mean ± standard deviation. The association between the clinical and demographic characteristics were tested using chi square test whereas t test and one way ANOVA test were applied for group-comparison of the skewed data. Correlation of SUA with islet β cell function was determined using Karl Pearson's correlation coefficient method. At 95% confidence interval, a probability $p \leq 0.050$ considered as statistically significant. Multiple linear regression analysis of HOMA-IR scores by other variables was carried out.

RESULTS

There was a male preponderance with 72.4% of the study population being male, and 27.6% female, with male to female ratio of 2.62:1. Majority of the patients were more than 60 years of age (32.89%), and the mean age was 53.76±13.33 years. The prevalence of hypertension among the study population was 48.7%. The most common habit among the study population was tobacco consumption (55.3%). Family history of DM was observed in 46.1% of the patients. Most of the patients were obese (75%), i.e., BMI≥25 kg/m^2 and the mean BMI was 27.19±3.23 kg/m^2 and 48.7% of the patients had signs of insulin resistance on physical examination. The clinical profile and parameters of study population based on gender stratification is shown in Table 1 and 2.

The mean SUA levels among the male study population were 4.65±1.81 mg/dl and among the females, it was 4.31±1.94 mg/dl. The β pancreatic cell function index was estimated using HOMA-IR. The mean HOMA-IR level among the male study population was 5.01±7.44 and 5.02±4.63 among the female study population.

A positive and significant correlation was observed between SUA and HOMA-IR (r=0.2283, p=0.0489) at 5% level, when SUA was modelled as a continuous variable. On further gender wise stratification, in female population SUA and HOMA-IR had a positive and significant correlation (r=0.5127, p=0.0175) at 5% level, where as in male population the correlation was positive, but not significant (r=0.0549, p=0.6933) at 5 percentages level.

Table 1: Comparison of the gender groups with clinical profile.

Variables	Male		Female		Total		χ^2	P value
	N	%	N	%	N	%		
Age groups (years)								
≤40	9	16.36	3	14.29	12	15.79	5.2473	0.1546
41-50	15	27.27	3	14.29	18	23.68		
51-60	17	30.91	4	19.05	21	27.63		
≥61	14	25.45	11	52.38	25	32.89		
BMI (kg/m^2)								
Normal	5	9.09	2	9.52	7	9.21	5.2473	0.1546
Overweight	11	20.00	1	4.76	12	15.79		
Obese	39	70.91	18	85.71	57	75.00		
Status of signs of IR								
Absent	31	56.36	8	38.10	39	51.32	2.0302	0.1542
Present	24	43.64	13	61.90	37	48.68		
Habits								
None	7	12.73	14	66.67	21	27.63	23.4909	0.0001*
Alcohol	9	16.36	0	0.00	9	11.84		
Tobacco	35	63.64	7	33.33	42	55.26		
Both	4	7.27	0	0.00	4	5.26		
Family history								
None	31	56.36	10	47.62	41	53.95	2.7279	0.4355
Father	6	10.91	5	23.81	11	14.47		
Mother	16	29.09	6	28.57	22	28.95		
Siblings	2	3.64	0	0.00	2	2.63		
Hypertension								
Absent	31	56.36	8	38.10	39	51.32	2.0302	0.1542
Present	24	43.64	13	61.90	37	48.68		
Total	55	100	21	100	76	100		

*p<0.05

Table 2: Comparison of the gender groups with clinical parameters by t test.

Parameters	Male		Female		T value	P value
	Mean	SD	Mean	SD		
FBS	234.93	67.52	222.43	64.21	0.7312	0.4670
HBA1C	9.88	2.67	9.17	2.98	1.0046	0.3184
SUA	4.65	1.81	4.31	1.94	0.7117	0.4789
Fasting c peptide	3.73	2.55	4.26	2.36	-0.8154	0.4175
HOMA-IR	5.01	7.44	5.02	4.63	-0.0058	0.9954
Creatinine	0.86	0.20	0.74	0.32	2.1052	0.0387

Table 3: Correlation between SUA levels and HOMA-IR by Karl Pearson's correlation coefficient method.

Samples	Parameters	Correlation between SUA with		
		R value	T value	P value
Total	HOMA-IR	0.2283	2.0033	0.0489*
Males	HOMA-IR	0.0549	0.3965	0.6933
Females	HOMA-IR	0.5127	2.6031	0.0175*

*p<0.05

Table 4: Correlation between BMI and HOMA-IR levels by Karl Pearson's correlation coefficient method.

Parameters	Correlation between BMI with		
	R value	T value	P value
HOMA-IR	0.4948	4.8644	0.0001*

*p<0.05.

Table 5: Correlation between HOMA-IR with all parameters by Karl Pearson's correlation coefficient method.

Parameters	Correlation between HOMA-IR with		
	R value	T value	P value
Age (years)	0.1560	1.3403	0.1844
BMI (Kg/m^2)	0.4948	4.8644	0.0001*
FBS	0.2152	1.8702	0.0655
HbA1c	-0.2354	-2.0556	0.0435*
SUA	0.2283	2.0033	0.0489*
Fasting c peptide	0.8174	12.0397	0.0001*
Creatinine	0.1989	1.7220	0.0894

*p<0.05.

Table 6: Multiple linear regression analysis of HOMA-IR scores by other variables.

Independent variable	Estimate	SE of estimate	T value	P level
Intercept	-4.6605	1.7599	-2.6481	0.0101*
Age (years)	0.0120	0.0134	0.9003	0.3712
BMI (Kg/m^2)	-0.0554	0.0642	-0.8625	0.3915
FBS	0.0216	0.0033	6.5578	0.0001*
HbA1c	-0.0425	0.0690	-0.6159	0.5401
SUA	0.1644	0.1223	1.3443	0.1835
Fasting c peptide/ insulin	1.2364	0.0864	14.3031	0.0001*
Creatinine	-0.2674	0.8258	-0.3238	0.7471

R=0.9151, R²=0.8374, F (7.66)=48.590 p<0.05, S Std. error of estimate: 1.4252. *p<0.05.

Similarly, a positive and significant correlation was found between body mass index and HOMA-IR (r=0.4948, p=0.0001) at 5 percentages level as shown in Table 4 and Figure 4.

On correlating HOMA-IR with multiple variables as shown in the Table 5, a significant correlation was observed with body mass index (p=0.0001), HbA1C (p=0.0435), SUA levels (p=0.0489) and fasting C peptide values (p=0.0001) at 5 percentages level, but not with age (p=0.1844) as well as the serum creatinine (p=0.0894).

On plotting multiple regression analysis, coefficient of determination (R^2) was 0.8374 (p<0.05), indicating significant contribution of all variables when combined towards HOMA-IR, shown in the Table 6.

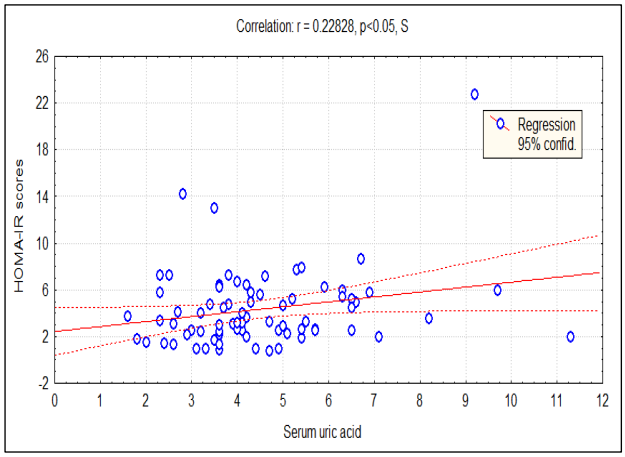

Figure 2: Correlation between SUA levels and HOMA-IR in total study population.

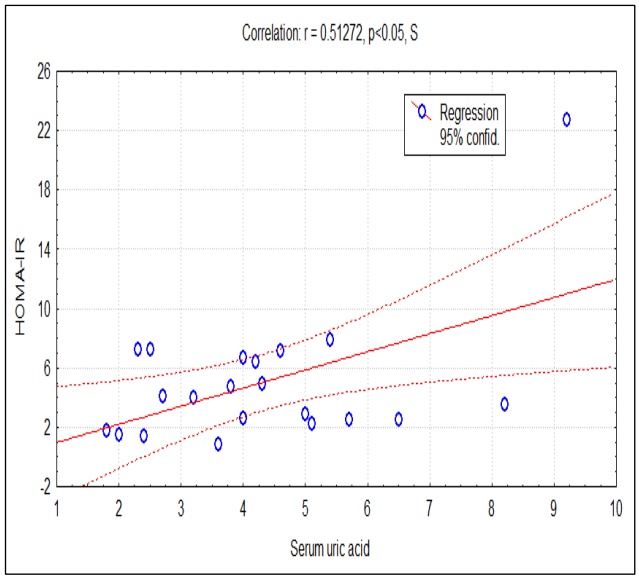

Figure 3: Correlation between SUA levels and HOMA-IR in female study population.

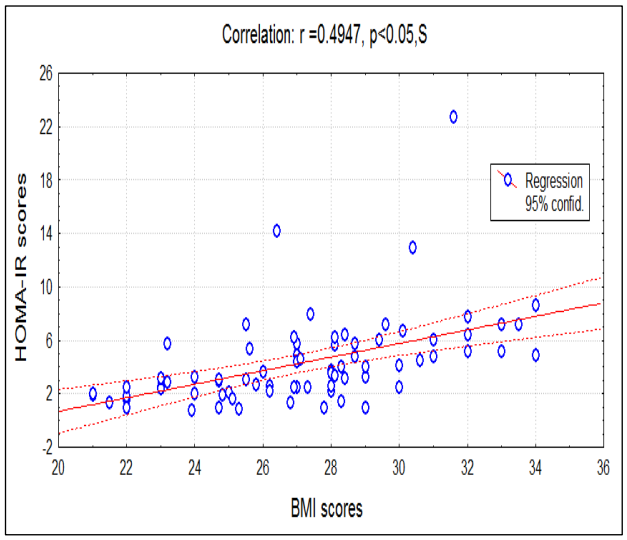

Figure 4: Correlation between BMI and HOMA-IR levels.

DISCUSSION

One of the important components in pathogenesis of T2DM is the reduction in the mass of β pancreatic cells along with increasing IR. This is compensated with increased insulin secretion in the initial phases of DM. Theoretically, this elevated insulin secretion might possibly compensate for IR to maintain normoglycemia for as long as 10 years prior to the onset of overt DM.[14]

Past studies have proved that increasing SUA is potential risk factor for development of various cardiovascular as well as renal disorders. Of late, the causal role of SUA in incident T2DM is being studied. The oxidative stress and inflammation of adipocytes caused by UA by multiple pathways contributes to IR, leading to development of T2DM.[15]

In the present hospital based cross-sectional study in newly diagnosed T2DM patients, a male preponderance was noted. 72.4% of the study population was male, and 27.6% female, with male to female ratio of 2.62:1. This sex distribution pattern of the study was consistent with a single centre, retrospective, observational study by Kivity et al to study the association between SUA and incident T2DM on the basis of gender distribution, where 72% of the study population was male and 28 % female.[16]

In this present study, the age of the study population ranged between 20 to 84 years. Most of the patients were more than 60 years of age (32.89%), whereas the mean age was 53.76±13.33 years. Hu et al in their single centre, cross-sectional, observational study reported mean age of 50.21±13.34 years (range-20-85 years).[17]

In the present study, majority of the study population was obese (75 %), i.e., BMI≥25 kg/m^2 and the mean BMI was 27.19±3.23 kg/m^2. Among the male patients, mean BMI was 26.97±3.27 kg/m^2, whereas among the female patients, it was 27.79±3.13 kg/m^2. The maximum BMI was seen in the age group of ≥61 years, with a mean BMI of 28.75±2.76 kg/m^2. On rest of the physical examination, 48.7% of the patients had signs of insulin resistance. Kivity et al observed that among the incident DM cases, the mean BMI among the male population was 28.7±3.6 kg/m^2 whereas among the female population, it was 27.9±4.3 kg/m^2.

On studying clinical characteristics of the present study, the mean SUA levels among the male study population were 4.65±1.81 mg/dl and among the females, it was 4.31±1.94 mg/dl. This was similar to a study done by Hu et al where the SUA concentration among the male patients was 5.57 mg/dl and 4.5 mg/dl among the females. Similarly, the mean HbA1c was 9.88±2.67% among males and 9.17±2.98% among females. In the study done by Tang et al similar values were noted, i.e., 9.18±2.45% in females and 9.49±2.47% in males.[18]

The β pancreatic cell function in the present study was estimated using HOMA-IR, which was calculated using FBS and either fasting C peptide levels or fasting serum insulin levels using the HOMA2 calculator. The mean HOMA-IR level among the male study population was 5.01±7.44 and 5.02±4.63 among the female study population. In a similar study done by Hu et al the average HOMA-IR levels were 3.36 and 3.31 in males and females respectively, and Juraschek et al in their study reported an average HOMA-IR value of the 4.4±3.0. [19]

As already discussed above, elevated SUA has been regarded as an independent risk factor for cerebrovascular disease, and it is also a powerful and optimal predictor for cardiovascular events in diabetic patients. Still, an

independent relationship between SUA and islet dysfunction has never been confirmed. Our study showed that IR increased with rising SUA levels. In the present study, a positive and significant correlation was observed between SUA and HOMA-IR (r=0.2283, p=0.0489) at 5% level, when SUA was modelled as a continuous variable. Similar results were noted in the study done by Juraschek et al where SUA when modelled as continuous variable remained significantly associated with HOMA-IR (p=0.03).

On further gender-wise stratification, in the female population SUA and HOMA-IR had a positive and significant correlation (r=0.5127, p=0.0175) at 5% level, where as in the male population the correlation was positive, but not significant (r=0.0549, p=0.6933) at 5% level. These findings were in concordance with the study done by Hu et al in which the female population had a positive and significant correlation between SUA and HOMA-IR (r=0.22, p<0.01), whereas in the male population, the correlation was not significant (r=0.09, p=0.14) at 5% level.

Furthermore, correlation between HOMA-IR and BMI was found to be positive and significant (r=0.4948, p=0.0001), which was also observed in the study by Hu et al (p<0.05). This finding supports the fact that weight loss can reduce insulin resistance. Similarly, a positive correlation was also noted between SUA and BMI (r=0.1943, p=0.0925) which was in agreement with the aforementioned study.

On correlating HOMA-IR with multiple variables, a significant correlation was observed with BMI (p=0.0001), HbA1C (p=0.0435), SUA levels (p=0.0489) and fasting C peptide values (p=0.0001), but not with age (p=0.1844) and serum creatinine (p=0.0894). Using these variables, when multiple regression analysis was carried out (to identify confounding factors influencing β cell functions), coefficient of determination (R^2) was 0.8374 (p<0.05), indicating significant contribution of all variables when combined towards HOMA-IR, which was consistent with the study done by Hu et al.

Thus, our study suggests that SUA level is associated with the development of T2DM. Hence SUA can be a potential predictor of T2DM development especially in primary care medical practice. Further research can be focussed to investigate whether SUA would be useful with respect to the prevention of type 2 diabetes.

CONCLUSION

This study demonstrated that SUA harboured a positive and significant correlation with pancreatic islet β cell function indices among patients of T2DM who were newly diagnosed and this was influenced by gender and BMI. Thus, SUA may be considered as a predictor for islet β cell function in clinical practice.

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