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Urate levels in relation to CVD markers in diabetic-duration-wise sub-grouped t2 dm patients

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Abstract

Introduction: Diabetes mellitus has been long recognised as a principle biochemical predisposing event of atherogenicity as well as Cardio Vascular Diseases.(CVD) Uric acid, the end product of purine metabolism , has been shown elevated in diabetes mellitus and its complications.

Objectives: The present study is planned to evaluate the significance of urate levels in t2 dm patients in assessing cardiac involment in this patients. The t2dm patients attending medical outpatient department (OPD) of Subbaiah Institute of Medical Sciences (SuIMS), Shivamogga and its affiliated hospitals, above the age group of 30 years were randomly selected. The study consists of a total number of 160 subjects with 80 normal control subjects and 80 t2dm patients. The selected t2 dm patients were sub-grouped – Age wise and diabetic-duration-wise.

Methods: A fasting heparinised blood sample was collected and plasma samples were employed for the estimation of Uric acid (UA)Fasting Plasma Glucose,(FPG) total cholesterol,(TC) triglyceride (TG) and HDL cholesterol.(HDLC) VLDL cholesterol, (VLDLC) LDL cholesterol, (LDLC) Atherogenic Index of Plasma(AIP) Atherogenic Coefficient (AC) and Cardiac Risk Ratio,(CRR) were calculated using standard relations.

Results: The results show that the levels of FPG ,TC, TG,LDLC,VLDLC, AC CRR and UA are significantly elevated ($p>0.001$) in t2 dm patients whereas the levels of HDLC and AIP are significantly lowered and a proportionate rise in UA levels along with CVD marker AIP, AC and CRR suggesting that there is a close relationship between CVD markers and plasma uric acid levels in t2 dm patients. Further it is clear from the results that proportionate rice in uric acid levels in relation to diabetic duration in the studied t2 dm patients. The rise observed in uric acid in t2dm patients is proportional to the duration of diabetic disease.

Conclusion: It is clear from the present study that plasma uric acid may be a strong marker for CVD risk in t2dm patients and the CVD risk is proportional to the diabetic duration as the rise in uric acid is proportional to diabetic duration

Keywords: t2 dm,dislipidemia , CVD markers , Uric Acid, Diabetic Duration.

Introduction

Poor glycemic control results in consistent hyperglycaemia which may lead to life threatening micro and macro vascular complications in t2dm patients. The mortality rate due to non- communicable diseases specifically diabetes mellitus and Coronary Heart Diseases are rapidly increasing across the globe and in India nearly causing about 5.8 million deaths annually (1,2). Dyslipidaemia has been long recognised as a principle biochemical predisposing event of atherogenicity as well as Cardio Vascular Diseases (3).(CVD) Many lipid profile parameters derived cardiac markers helps to assess the Cardiac-Vascular complications in t2dm patients. Uric acid the end product of purine catabolism has been claimed elevated in Prediabetics (4), diabetics (5-14) as well as in diabetic complications (15, 16). Thus suggesting a close relationship between type-2 diabetes mellitus and urate metabolism .The studies regarding the significance of urate levels and lipid profile derived CVD markers in t2dm is scanty. Hence a study has been planned to assess the plasma urate levels in t2dm patients and to correlate the levels with lipid profile parameters derived cardiac markers to evaluate the significance of urate levels in assessing the cardiac involvement in t2dm patients.

Aim: The present study is planned to evaluate the significance of urate levels in t2 dm patients in assessing cardiac involment in this patients.

Objectives

1. To assess urate levels in t2dm patients.
2. To assess lipid profile parameters in t2dm patients.
3. To correlate lipid profile parameters derived CVD markers with urate levels.

Materials & Methods

Normal control subjects: Normal control subjects above the age of 30 years were taken from the employees of Su IMS and its affiliated hospitals, Shivamogga.

T2 DM Patients: The t2dm patients attending medical outpatient department (OPD) of Subbaiah Institute of Medical Sciences (SuIMS), Shivamogga and its affiliated hospitals, above the age group of 30 years were randomly selected. A detailed history regarding the illness was collected from these patients. Diabetic patients below the age of 30 years and those with psychiatric disorders as well as the patients receiving hormone therapy were excluded from the study.

Grouping

The study consists of a total number of 160 subjects with 80 normal control subjects and 80 t2dm patients. The selected t2 dm patients were sub-grouped – Age wise (30-40 years, 41-50 years, 51 – 60 years and above 61 years)and diabetic-duration-wise (0-3 years , 3.1-6 years , 6.1-10 years and above 10 years). The subjects were selected in such a way that each sub-group in normal controls as well as in t2 dm patients must have minimum 20 subjects (this was concluded after discussion with statistician). The sub group division as well as number of patients included is elaborated in chart-1.

Chart 1: Chart showing the sub-grouping of T2-DM patients age-wise as well as duration –wise and the number of subjects included in each group.

Group	Description	Number of Subjects
GROUP - N	Normal, Nondiabetic Group	80
GROUP – D	T2 DM PATIENTS	80
GROUP – D1	T2 DM – 31-40 Years	20
GROUP – D2	T2 DM – 41-50 Years	20
GROUP – D3	T2 DM – 51-60 Years	20
GROUP – D4	T2 DM – Above 61 Years	20
GROUP – D5	T2 DM – Diabetic Duration-0-3 Years	20
GROUP – D6	T2 DM-Diabetic Duration 3.1- 6Years	20
GROUP – D7	T2 DM –Diabetic Duration- 6.1-10 Years	20
GROUP – D8	T2 DM –Diabetic Duration- above 10 Years	20

Study Period: The present work was undertaken at Research and Development Department, SuIMS during the period of December 2020 to July 2021. Ethical clearance was procured from Institutional Ethics Committee (IEC) after successful presentation.

Sample Collection: A fasting blood sample (5-6 ml) was collected from both t2dm patients and from normal control subjects after obtaining a written Informed Consent from each one of them. The samples were centrifuged at 3000 rpm for 6-8 min and the separated serum was employed for the estimation of Uric acid (UA) (17) Fasting Plasma Glucose (FPG) (18), total cholesterol (TC), triglyceride (TAG) and HDL cholesterol (HDLC) levels (19-21). VLDL cholesterol (VLDLC), LDL cholesterol (LDLC), Cardiac Risk Ratio (CRR), Atherogenic Index of Plasma (AIP) and Atherogenic Coefficient (AC) were calculated using the following relations (22-25).

VLDLC = (TAG/5)

LDLC = (TC-HDLC-VLDLC) CRR = (TC/HDLC)

AIP = log (TAG/HDLC) AC = (TC-HDLC/HDLC)

Statistical analysis: The data obtained was statistically analysed using SPSS version 16 Software. Student:" t" test was used to ascertain the significance and the level $p < 0.05$ was considered significant. Group D is compared with Group N and the t2 dm sub-groups compared among each other to evaluate significance.

Result

The results obtained in the present study are depicted in Table1, Table2, and Table3 and in Graphs 1, 2, and 3. Table 1 shows plasma levels of fasting plasma glucose (FPG),Total Cholesterol (TC), Triglyceride (TG), HDL Cholesterol (HDLC) LDL Cholesterol (LDLC), VLDL Cholesterol (VLDLC), Atherogenic Index Plasma (AIP), Atherogenic Coefficient (AC), Cardiac Risk Ratio (CRR), and Uric Acid (UA) in normal non diabetic subjects (group-N) and in t2 dm patients (group-D) . it is evident from the table that the levels of FPG ,TC, TG,LDLC,VLDLC, AC CRR and UA are significantly elevated ($p>0.001$) in t2 dm patients (group D) as compared to normal non diabetic subjects (group- N)

whereas the levels of HDLC and AIP are significantly lowered (p>001) in group D as compare to group N. Further it is evident from the table that there is a proportionate elevation in plasma uric acid levels along with CVD markers in group D as compared to group N indicating there is a close relationship between uric acid and CVD risk in t2 dm patients.

Table 1: Table showing plasma levels of fasting glucose (FPG),Total Cholesterol (TC), Triglyceride (TG), HDL Cholesterol (HDLC) LDL Cholesterol (LDLC), VLDL Cholesterol (VLDLC), Atherogenic Index Plasma (AIP), Athrogenic Coefficient (AC), Cardiac Risk Ratio (CRR), and Uric Acid (UA) in normal non diabetic subjects (group-N) and in t2 dm patients (group-D).

Analyte	Group – N (80)	Group –D (80)
FPG mg/dl	78.60±16.40	213.09 ± 20.18***
TC mg/dl	161.84 ± 31.82	224.62 ± 26.60***
TG mg/dl	114.64 ± 32.21	187.15 ± 12.14***
HDLC mg/dl	50.27 ± 8.62	33.09 ± 11.20**
LDLC mg/dl	104.86 ± 20.28	169.0 ± 2.26***
VLDLC mg/dl	28.35 ± 9.08	45.43 ± 8.80***
AIP	0.513 ± 0.041	0.74 ± 0.08***
AC	1.78 ± 0.32	5.58 ± 1.21***
CRR	2.78 ± 0.13	6.48 ± 0.42***
UA mg/dl	3.73 ± 1.06	8.22 ± 0.80***

Note:

1. The values are expressed as their Mean±SD.
2. The number in parentheses indicates the number of subjects.
3. Probability * p>0.05, **p>0.01 and ***p>0.001.

Table 2 gives the plasma levels of FPG , TC, TG, HDLC, LDLC, VLDLC, AIP, AC, CRR, and UA levels in age wise sub-grouped (D1 – 31-40 years, group D2-41-50 years, group D3 51-60 years and group D4- above 61 years) t2 dm patients. Group D1 is compared with Group D2 , D3 and D4, group D2 is compared with group D3 and group D4 whereas group D3 is compared with group D4. It is seen from the table that there is a proportionate rise in UA levels along with CVD marker AIP, AC and CRR suggesting that there is a close relationship between CVD markers and plasma uric acid levels in t2 dm patients.

Table 2: Table showing plasma levels of FPG, TLC, TG, HDLC, LDLC, VLDLC, AIP, AC), CRR, UA in age wise sub grouped t2 dm patients (group-D1, group-D2, group-$_{D3,}$ group-D4)

Analyte	Group – D1 (20)	Group –D2 (20)	Group –D3 (20)	Group –D4 (20)
FPG mg/dl	181.9±18.80	188.9 ± 18.30	183.46 ± 10.38	147.05±10.20
TC mg/dl	178.03 ± 16.60	195.03 ± 16.60	170.19 ± 11.50	172.00±8.68
TG mg/dl	158.75±21.20	171.72 ± 12.36	150.59 ± 8.32 αα	170.12±6.86
HDLC mg/dl	48.85 ± 9.80	31.35 ± 8.12**	31.27 ±3.86***	28.50±8.20***
LDLC mg/dl	111.47 ± 12.20	130.65 ± 11.24	106.34±10.50	111.37±16.20
VLDLC	31.74 ± 9.66	35.34 ± 8.22	31.12± 9.40	34.02±9.20

AIP	0.584 ± 0.052	0.730 ± 0.030**	0.687 ± 0.026*	0.805±0.021***, β β
AC	4.59 ± 0.72	6.35 ± 0.66**	5.48. ± 0.72	6.18±0.86**
CRR	1.37 ± 0.08	1.56 ± 0.06***	1.46 ± 0.06*	1.64±0.05***
UA mg/dl	6.40 ± 1.26	7.72 ± 0.**	8.29 ±0.88*** αα	8.30±0.46*** α β

Note:

1. The values are expressed as their Mean±SD.
2. The number in parentheses indicates the number of subjects.
3. Probability */ α / β p>0.05, **/ αα/ β β p>0.01 and ***/ ααα / β β β p>0.001.
4. Comparison of group D1 with D2, D3 and D4- represented by *
5. Comparison of group D2 with D3, D3 and D4- represented by α
6. Comparison of group D3 with D4- represented by β

Table 3 narrates the plasma levels of FPG , TC, TG, HDLC, LDLC, VLDLC, AIP, AC, CRR, and UA levels in diabetic duration wise sub-grouped – group D5 – diabetic duration 0-3 years, group D6- diabetic duration 3.1-6 years, group D7 diabetic duration 6.1-10 years and group D8- above 10 years. Group D5 is compared with group D6 , D7 and D8, group D6 is compared with group D7 and group D8 whereas group D7 is compared with group D8. It is evident from the table that there is a proportionate rise in uric acid levels along with CVD markers in group D5, D6, D7 and D8 in duration -wise sub grouped t2 dm patients. Further it is clear from the table that proportionate rice in uric acid levels in relation to diabetic duration in the studied t2 dm patients.

Table 3: Table showing plasma levels of FPG, TLC, TG, HDLC, LDLC, VLDLC, AIP, AC), CRR, UA in duration-wise sub grouped t2 dm patients (group-D5, group-D6, group-D7, group-D8),

Analyte	Group – D5 (20)	Group –D6 (20)	Group –D7 (20)	Group –D8 (20)
FPG mg/dl	232.39±22.8	151.34±19.60	206.74±18.60	252.33 ±25.80
TC mg/dl	179.93±18.8	212.67±24.60	171.24±10.60	193.98±22.30
TG mg/dl	175.07±14.2	211.7±16.80	138.29±13.20** αα	160.90±15.50
HDLC mg/dl	35.44±11.80	35.50±12.20	31.50±10.60	28.40±10.20
LDLC mg/dl	139.50±12.80	134.84±13.60	112.66±10.90*	128.90±11.60
VLDLC mg/dl	36.99±9.20	42.34±8.40	29.67±8.20 αα	32.18±7.90
AIP	0.776±0.030	0.675±0.020**	0.662±0.031**	0.742±0.028 αα
AC	4.36±0.82	5.07±0.96	4.45±0.68	6.32±0.72**, β β
CRR	5.39±0.96	6.07±1.01	4.47±0.62 αα	7.19±0.88**, β β β
UA mg/dl	6.54±0.88	7.30±0.76	8.63±0.64**	9.35±0.42*** ααα, β β

Note:

1. The values are expressed as their Mean±SD.
2. The number in parentheses indicates the number of subjects.
3. Probability */ α / β p>0.05, **/ αα/ β β p>0.01 and ***/ ααα / β β β p>0.001.
4. Comparison of group D5 with D6, D7 and D8- represented by *
5. Comparison of group D6 with D7 and D8- represented by
6. Comparison of group D7 with D8- represented by β

Figure 1, 2 and 3 gives the variation of uric acid (UA) and CVD markers (AC, CRR, AIP) in normal non Diabetic subjects (Group-N), T-2 DM subjects (Group-D) as well as in T-2 DM subgroups. Figure 1 gives comparative bar graph of UA in group N and D (Figure 1a) and Figure 2 gives comparative bar graphs of CVD markers – AIP, AC and CRR along with UA in T2 DM sub groups – D5, D6, D7 and D8. It is evident from the graphs that UA and other CVD markers are significantly elevated in T2 DM subjects as compared to normal non-diabetic subjects. It is also clear from the graph (Figure 2) that there is a proportionate increase in UA as well as CVD markers in group D5, D6, D7, D8 T2 DM sub group subjects indicating a direct relationship between UA and CVD markers in Diabetic-Duration-Wise sub grouped T2DM subjects.

Figure 1: Graph showing the comparison of plasma UA levels, AC, CRR and AIP levels in group-N and in group – D.

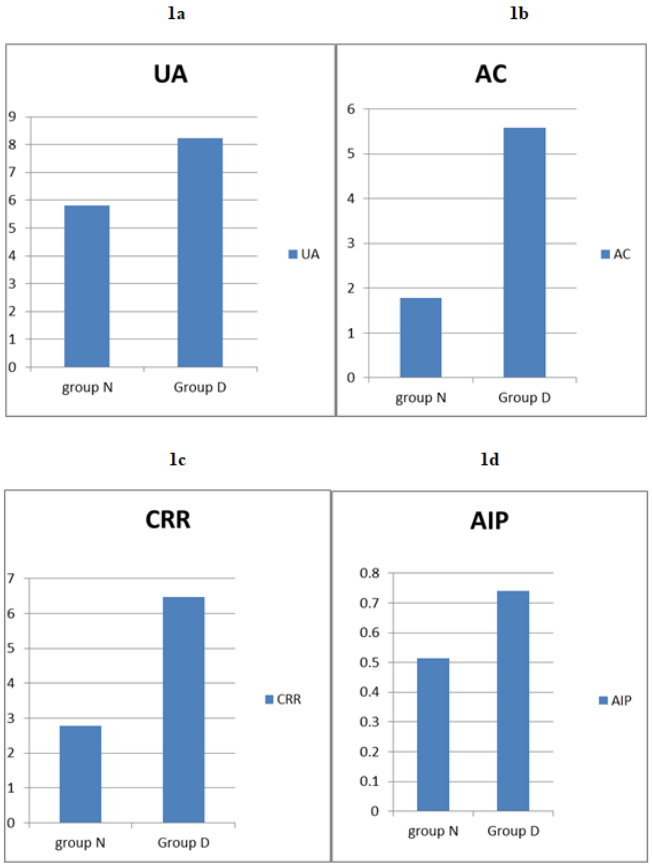


Figure 2: Graph showing the comparison of plasma UA levels in Group-D5, Group-D6, and Group-D7 and in Group-D8.

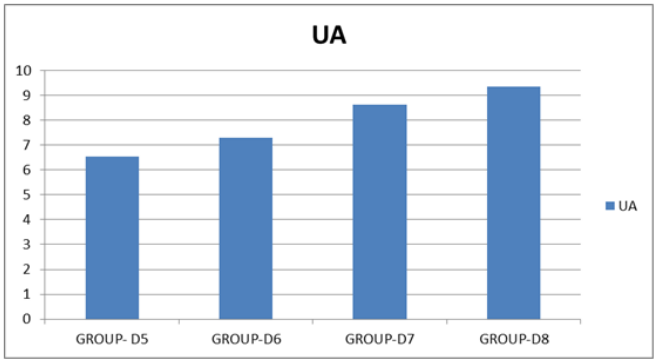
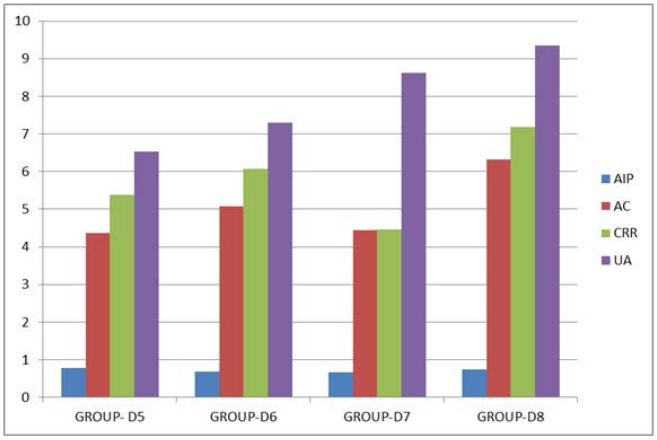


Figure 3: Graph showing the comparison of AIP, AC, CRR and UA levels in Group-D5, Group D6, Group D7 and in Group D8



Discussion

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycaemia followed by glucosuria and disturbances in carbohydrate, fat, and protein metabolism in general and glucose metabolism in particular due to defects in insulin secretion, action or both (26). Consistent hyperglycaemia results in dyslipidaemia leading to elevation/ disturbances in body lipid turn over resulting in hyperlipidaemia. This diabetes induced hyperlipidaemia, characterised by increased plasma lipid parameters, is the primary cause for cardio-vascular complications in diabetes mellitus (27). The results given in table 1 clearly indicates that lipid parameters like TC, TG, LDLC, VLDLC are elevated in t2dm patients and this rise is proportional to diabetic duration (Refer table 3). Further these lipid parameters derived CVD risk indicates- AIP, AC and CRR are elevated in group-D in contrast to group-N suggesting that t2dm patients are prone to CVD risk due to underlying dyslipidemia. Further the elevation in CVD marker proportional to the diabetic duration as indicated and the results of the studies shown in table 3 and figure 3. Uric acid, the end as well as an excretory product of purine metabolism in humans, has been claimed by many researchers as rised in t2dm patients (5-14) and it has been confirmed in earlier works (28) that a proportional rise in uric acid with total cholesterol in t2dm patients. Also few earlier works (29, 30) claimed uric acid is elevated in diabetic complications including cardio-vascular diseases as uric acid generates amino carbonil radicals which are pro-inflammatory and subsequently may result in cardio-vascular complications (31, 32). The present study with t2dm patients has clearly establishes that uric acid is elevated in t2dm patients (Refer table 1, figure 1) and its elevation is directly proportional to the rise in CVD markers in these patients. Thus confirming that uric acid rise in these patients is proportional to the rise in CVD markers. Further the rise in uric acid is highly significant with respect to rise in CRR levels in these patients. The rise observed in t2dm patients, specifically the group D5, D6, D7 and D8 patients indicates the rise in the uric acid is proportional to the duration of diabetic disease (Refer table 3, figure 3).

Conclusion

It is clear from the present study that plasma uric acid may be a strong marker for CVD risk in t2dm patients. The rise in UA in t2 dm patients is proportional to the diabetic duration as well as to CVD risk in these patients. (Ref fig.3).

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