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Serum Uric Acid in Prediabetes

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Abstract: ***Background: The association between hyperuricemia and diabetes has been proved to be strongly associated with the risk of cardiovascular diseases, but it is not clear whether hyperuricemia is related to the early stage of diabetes. Method: Uric acid level was measured by Uricase-PAP methodology in patients with pre-diabetes (n=150)/Control groups (n=150). Uric acid levels in the above two groups were compared based on age, sex and other factors which can affect uric acid level. Results: The mean serum uric acid level was lower in control group (3.84mg/dl), rose in pre-diabetics (5.31mg/dl), P value comparing control and pre diabetes was 0.0001,i.e significant. Conclusion: Hyperuricemia seems to be associated with pre-diabetes. It can be used as a biomarker of deterioration of glucose metabolism.***

Keywords: Hyperuricemia, Prediabetes,uric acid

1. Introduction

422 million people worldwide have Diabetes Mellitus in 2014.[1] In 2012 an estimated 1.5 million people died from consequences of high blood sugar.(WHO diabetes fact sheet 2012).[2] 79 million people in United States have prediabetes.(American Diabetes Association jan 26 2011).[3]

In India prevalence of diabetes and prediabetes in 2011 was 62.4 and 77.2 million respectively. The weighted prevalence of diabetes mellitus (both known and newly diagnosed) was 10.4 in Tamil Nadu, 8.4 in Maharashtra, 5.3 in Jharkhand, and 13.6 in Chandigarh. The prevalences of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) were 8.3 in Tamil Nadu,12.8 in Maharashtra,8.1 in Jharkhand and 14.6 in Chandigarh.[4] WHO criteria for diagnosing pre diabetes states fasting blood glucose level is between 110mg/dl and 125mg/dl Or Two hour plasma glucose levels after 75gm oral glucose load (OGTT) is between 140 to 199mg/dl.[5]

Prediabetes or impaired fasting glycemia or impaired fasting glucose (IFG) refers to a condition in which the fasting blood glucose is elevated above what is considered normal levels but is not high enough to be classified as diabetes mellitus.

It is considered a prediabetic state, associated with insulin resistance and increased risk of cardiovascular pathology, although of a lesser risk than impaired glucose tolerance (IGT). Effects of disease can be macrovascular, as seen in cardiovascular system, or microvascular, as seen with retinopathy, neuropathy and nephropathy. IFG sometimes progresses to type 2 diabetes mellitus. There is a 50% risk over 10 years of progressing to overt diabetes. A recent study cited the average time for progression as less than 3 years.[6]

Now a days, several studies had shown the association of uric acid as a risk factor for transforming prediabetes to diabetes type 2. Serum uric acid is formed by the breakdown of purines and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine.[7] Serum urate levels vary with age and sex. Most children have serum urate concentraions of 180 to 240 mu mol[3 to 4mg/dl]levels begin to rise in males during puberty but low in females until menopause.[8] With increasing numbers of people with diabetes or prediabetes, as an important component of the primary prevention in diabetes, it becomes more and more important to find the risk factors associated with abnormal glucose metabolism. Previous studies showed that in adults elevated Serum Uric Acid is associated with diabetes.[9]

2. Material

This study was carried out in Acharya Vinoba Bhave Rural Hospital (AVBRH,a tertiary care hospital] attached to Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharashtra. Cases were prediabetics as per WHO criteria. The controls were age and sex match asymptomatic individuals. Patients with history of diabetes, myocardial infarction, stroke, patient having cancer,nephropathy, renal calculi, gout and those on thiazide diuretics were excluded from study. Sample size were calculated on the basis of prevalence of prediabetes 40% and level of significance at 5% with error of margin to be 0.08.

Sample Size

$$n = \frac{Z\alpha/2^2 P(1-P)}{d^2}$$

P = Prevalence of Pre Diabetes = 40%
Z∝ = level of Significance = 5% = 1.96
d = Error of Margin = 0.08

$$n = \frac{1.96 \times 0.40\ (1-0.40)}{0.08 \times 0.08}$$

= 144.0
n ⇉ 150
Cases-150, Controls-150

3. Methods

The patients who were diagnosed as prediabetes as per the WHO criteria as impaired fasting blood glucose and/or impaired glucose tolerance test by glucose oxidase method were taken for study.

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Patients underwent detailed history and clinical examination and were subjected to following :

1) **BMI:**
Body mass index or Quetelet index,is a value derived from the mass [weight] and height of an individual. It is defined as body mass divided by square of body height in metres, it is expressed in units of kg/m^2.[10]
2) **Blood pressure:**
We measured blood pressure by auscultatory method using stethoscope and sphygmomanometer, which comprises of Riva-Rocci cuff placed around the upper arm at roughly the same vertical height as the heart, attached to mercury manometer, which measures the height of a column of mercury giving an absolute result.
3) **Waist Circumference:**
The WHO STEPS protocol for measuring waist circumference instructs that the measurement be made at the approximate midpoint between the margin of the last palpable rib and the top of the iliac crest.[11]
4) **Hip Circumference:**
Hip circumference should be taken around the widest portion of the buttocks.[11]
5) **Waist/Hip Ratio:**
It is measured by dividing the waist circumference by hip circumference.

We used stretch resistant tape that is wrapped snugly around the subject,but not to the point that the tape is constricting. We kept the tape level and parallel to the floor at the point of measurement. We ensured that the subject is standing upright during the measurement, with arms relaxed at the side, feet evenly spread apart and body weight evenly distributed.[11]

World Health Organisaton cut off points[11]
Waist circumference= >90 cm[MALES],>80cm[FEMALES]-Increased
Hip circumference= >102cm[MALES],>88cm[FEMALES]-Substantially increased.
Waist hip ratio= >0.90[MALES],>0.85[FEMALES]-Substantially increased.

BIOCHEMICAL PARAMETER ESTIMATION

Estimation of Glucose in Plasma:
Fasting plasma glucose was estimated by GOD/POD method by the machine Robonic Semiautomatic Chemical Analyzer

Estimation Of Serum Total Cholesterol
Serum total cholesterol was estimated using Liquid Stable CHOD – PAP method by machine Robonic Semiautomatic Chemical Analyzer.

Estimation Of Serum Triglyceride
Serum triglycerides were estimated using LIQUID STABLE GPO – PAP method by machine Robonic Semiautomatic Chemical Analyzer.

Estimation of Serum HDL
Direct Enzymatic Method estimated serum HDL by machine Robonic Semiautomatic Chemical Analyzer.

4. Stastical Analysis

Statistical analysis was done by using descriptive and inferential statistics using Chisquare test and Student's unpaired t test and software used in the analysis were SPSS 22.0 version and GraphPad Prism 6.0 version and $p<0.05$ is considered as level of significance.

5. Observations

Table 1: General Characteristics

General features	*Prediabetes [n=150]*	*Controls [n=150]*	*P value*
Age	49.88±14.86	47.52±15.89	0.14,NS
Sex ratio:Male	88(58.67%)	90(60%)	
Female	62(41.33%)	60(40%)	0.81,NS
BMI	24.06±2.12	21.40±2.07	**0.0001,S**
Waist hip ratio:male	0.88±0.06	0.83±0.06	**0.0001,S**
Waist hip ratio:female	0.83±0.07	0.74±0.06	**0.0007,S**
SBP	130.70±12.03	126.26±11.63	**0.013,S**
DBP	82.03±7.54	81.36±7.34	0.35,NS
Serum uric acid	5.31±0.87	3.84±0.63	**0.0001,S**
Total cholesterol	176.09±26.34	158.92±18.47	**0.0001,S**
HDL	43.87±15.24	51.38±12.18	**0.0001,S**
VLDL	35.89±11.26	39.60±6.13	**0.0001,S**
LDL	96.69±25.46	67.94±19.17	**0.0001,S**
TG	133.18±29.13	127.92±23.41	0.086,NS

Table 2: Age Distribution in Prediabetes & Controls

Age Group (yrs)	Prediabetes [n=150]	Controls [n=150]	$\chi 2$-value	P value
21-30 yrs	18(12%)	25(16.67%)		
31-40 yrs	20(13.33%)	36(24%)	9.58	P=0.14,NS
41-50 yrs	44(29.33%)	30(20%)		
51-60 yrs	29(19.33%)	22(14.67%)		
61-70 yrs	28(18.67%)	28(18.67%)		
71-80 yrs	8(5.33%)	7(4.67%)		
>80 yrs	3(2%)	2(1.33%)		
Total	150(100%)	150(100%)		
Mean ±SD	49.88±14.86 (21-85 years	47.52±15.89 (21-85 years)		

Table 3: Distribution of Prediabetes & Controls According to BMI(kg/m^2)

BMI(kg/m2)	Prediabetes (n=150)	Controls (n=150)	$\chi 2$-value	P value
<18.5(Underweight)	0(0%)	14(9.33%)	65.92	0.0001,S
18.5-22.9(Normal)	46(30.67%)	96(64%)		
23-24.9(Overweight)	64(42.67%)	34(22.67%)		
≥25(Obese)	40(26.67%)	6(4%)		
Total	150(100%)	150(100%)		
Mean ±SD	24.06±2.12 (20.40-30.11)	21.406±2.07 (18-25.80)		

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Table 4.1: Distribution of Prediabetes & Controls According to Waist Hip Ratio [Males]

Waist Hip Ratio	Prediabetes [n=88]	Controls [n=90]	P Value	$\chi 2$-value
Waist Hip Ratio <0.9	50[56.82%]	80[88.89%]	0.0001,S	23.24
Waist Hip Ratio > 0.9	38[43.18%]	10[11.11%]		
Total	88	90		
Mean ±SD	0.88±0.06 (0.72-1.05)	0.83±0.06 (0.70-1.02)		

Table 4.2: Distribution of Prediabetes & Controls According To Waist Hip Ratio [Females]

Waist Hip Ratio	Prediabetes [n=62]	Controls [60]	P Value	$\chi 2$-value
Waist Hip Ratio <0.85	34[54.84%]	50[83.33%]	0.0007,S	11.54
Waist Hip Ratio > 0.85	28[45.16%]	10[16.67%]		
Total	62	60		
Mean ±SD	0.83±0.07 (0.70-1.04)	0.74±0.06 (0.69-0.92)		

Table 5: Distribution of Prediabetes & Controls According to Blood Pressure

Blood Pressure	Prediabetes (n=150)	Controls (n=150)	$\chi 2$-value	P value
SBP≤140	128(85.33%)	141(94%)		
SBP>140	22(14.67%)	9(6%)	6.08	0.013,S
DBP≤90	146(97.33%)	143(95.33%)		
DBP>90	4(2.67%)	7(4.67%)	0.84	0.35,NS
Mean ±SD SBP	130.70±12.03	126.26±11.63		
DBP	82.03±7.54	81.36±7.34		

Table 6: Distribution of Prediabetes & Controls According to Lipid Profile

Lipid Profile	Prediabetes (n=150)	Controls(n=150)	t-value	p-value
TC	176.09±26.34	158.92±18.47	6.53	0.0001,S
LDL	96.69±25.46	67.94±19.17	11.04	0.0001,S
VLDL	35.89±11.26	39.60±6.13	3.53	0.0001,S
TG	133.18±29.13	127.92±23.41	1.72	0.086,NS
HDL	43.87±15.24	51.38±12.18	4.71	0.0001,S

Table 7: Distribution of Prediabetes & Controls According to Serum Uric Acid

Sr. Uric Acid Level	Prediabetes (n=150)	Controls (n=150)	t-value	p-value
Mean	5.31±0.87	3.84±0.63	16.64	0.0001,S

6. Result

Maximum number of cases were in the age group of 41-50 i.e. 44[29.33%] with mean age of 49.88±14.86. Maximum number of controls were in the age group of 31-40 i.e 36[24%] with mean age of 47.52±15.89. Chi square value is 9.58 and p value is 0.14 which is non-significant.Both cases and controls were comparable[Table 2]. 88 (58.67%) cases were males and 62(41.33%) were females.90(60%) controls were males and 60 (40%) were females.Chi-square value was 0.05 and p-value was 0.81 (p >0.05) i.e. not significant. 64 (42.67%) cases were overweight and 40(26.67%) cases were obese .Mean BMI for cases was 24.06±2.12.34 (22.67%) controls were overweight and 6(4%) controls were obese. Mean BMI for controls was 21.406±2.07.Chi-square value was 65.92 and p-value was 0.0001 (p < 0.05), which was statistically significant[Table 3]. 38 (43.18%) male cases were having W/H Ratio > 0.90.Mean W/H ratio for male cases was 0.88±0.06. 10 (11.11%) male controls were having W/H Ratio > 0.90.Mean W/H ratio for male controls was 0.83±0.06.Mean W/H ratio for male cases was more than male controls. Chi-square value was 23.24, and p-value was 0.0001 (p < 0.05) i.e. statistically significant. 28(45.16 %) female cases were having W/H Ratio > 0.85. Mean W/H ratio for female cases was 0.83±0.07. 10 (16.67%) female controls were having W/H Ratio > 0.85.Mean W/H ratio for female controls was 0.74±0.06.Mean W/H ratio for female cases was more than female controls.Chi-square value was 11.54; p-value was 0.0007 (p <0.05) i.e. Significant[Table 4.1,4.2]. 22 (14.67%) cases and 9 (6%) controls were having systolic blood pressure more than 140 mmHg.In cases mean systolic blood pressure was 130.70±12.03.In controls mean systolic blood pressure was 126.26±11.63. Mean systolic blood pressure in cases was more than controls, which was statistically significant.Chi-square value was 6.08, p- value was 0.013 (p <0.05) i.e. Significant.4 (2.67%) cases and 7 (4.67%) controls were having diastolic blood pressure more than 90 mmHg.In cases mean diastolic blood pressure was 82.03±7.54.In controls mean diastolic blood pressure was 81.36±7.34.Chi-square value was 0.84, p-value was 0.35 (p < 0.05) i.e. Non Significant[Table 5]. Mean value of total cholesterol for cases was 176.09±26.34.Meanvalue of total cholesterol for controls was 158.92±18.47. Mean total cholesterol for cases was more than controls, which was statistically significant. Independent student t test[t value] was 6.53, and p-value was 0.0001 (p < 0.05) i.e. Significant. Mean value of low-density lipoprotein for cases was 96.69±25.46.Mean value of low-density lipoprotein for controls was 67.94±19.17.Mean low-density lipoprotein for cases was more than controls, which was statistically significant.Independent student t test [t value] was 11.04, and p-value was 0.0001(p < 0.05) i.e. Significant. Mean value of very low-density lipoprotein for cases was 35.89±11.26.Mean value of very low-density lipoprotein for controls was 39.60±6.13.Mean very low-density lipoprotein for cases was more than controls, which was statistically significant.p-value was 0.0001(p < 0.05) i.e. significant. Mean value of triglyceride for cases was 133.18±29.13.Mean value of triglyceride for controls was 127.92±23.41 p-value was 0.086(p<0.05) i.e. Non significant. Mean value of high-density lipoprotein for cases was 43.87±15.24.Mean value of high-density lipoprotein for controls was 51.38±12.18.Mean high-density lipoprotein for cases was lower than controls. Independent student t test[t value] was 4.71,p-value was 0.0001 (p < 0.05) i.e. significant[Table 6]. Mean serum uric acid in cases was 5.31±0.87.Mean serum uric acid in controls was 3.84±0.63.Mean serum uric acid in cases was higher than controls.Independent student test[tvalue] was 16.64,p value was 0.0001(<.05)i.e. significant[Table 7].

7. Discussion

Maximum number of cases were in the age group of 41-50 i.e. 44[29.33%] with mean age of 49.88±14.86.Maximum number of controls were in the age group of 31-40 i.e. 36[24%] with mean age of 47.52±15.89.There was no

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significant age difference between both the groups as ($p > 0.05$, NS). Similarly, Kelly J. Hunt et al (2003), reported mean age of cases(n=66)was 48.4 years and of controls (n=1127) was48.9 years with no statistical significant difference($p > 0.05$, NS).[12]

In our study, in cases 88(58.67%) were males and 62(41.33%)were females whereas in control group, 90(60%) were males and 60(40%) were females. There was no statistical significant difference found in gender of subjects in both the groups ($p > 0.05$, NS). Also, Xiaolong Zhao et al (2012) observed that out of 143 prediabetics 65(45.45%) were males,78(54.46%) were females,in control group 394(50.51%) were females,374(49.49%) were males.p value was 0.39 with no statistical significant difference.[13]

In our study, 64(42.67%) cases and 34 (22.67%) controls were overweight (BMI 23–24.9). Also, 40 (26.67%) cases were obese (BMI ≥ 25). Mean BMI for cases was 24.06±2.12. Mean BMI for controls was 21.406±2.07. The difference in the two groups was statistically significant ($p < 0.05$, S). Also,David Faeh et al(2007) found BMI was higher in prediabetics (n=73) in comparison to controls (n=316). Mean BMI of prediabetics was 29.0 ± 0.5 kg/m^2 and controls was 26.0 ± 0.2 kg/m^2 ($p < 0.01$,S).[14]

In our study, 38 (43.18%) male cases out of 88 and 10 (11.11%) male controls out of 90 were obese (W/H Ratio ≥ 0.90). Mean W/H ratio for male cases was 0.88±0.06. Mean W/H ratio for male controls was 0.83±0.06. The difference in the two groups was found to be statistically significant ($p < 0.05$,S) and 28(45.16) female cases out of 62 and 10 (16.67%) female controls out of 60 were obese (W/H Ratio ≥ 0.85). Mean W/H ratio for female cases was 0.83±0.07. Mean W/H ratio for female controls was 0.74±0.06. The difference in the two groups was found to be statistically significant. ($p< 0.05$, S). Similarly Esayas Hargot Hilawe et al(2016) reported mean waist hip ratio in prediabetics (n=782) was 0.93± 0.07 and mean waist hip ratio in controls (n=752) was 0.92 ± 0.08.p value was <0.0001,hence significant.[15]

In our study, 22(14.67%) cases and 9 (6%) controls were having systolic blood pressure more than 140 mmHg. Mean systolic blood pressure for cases was 130.70±12.03 and mean systolic blood pressure for controls was 126.26±11.63. The difference in the two groups was found to be 0.013 i.e. statistically significant. ($p< 0.05$, S). Similarly, Kelly J Hunt et al(2003) observed that the mean systolic blood pressure of the prediabetics (n=66) was higher than the controls(n=1127). Mean systolic blood pressure in prediabetics was 122 ± 4 mmHg and controls was 114 ± 1 mmHg. This difference in the mean systolic blood pressure was statistically significant ($p < 0.05$, S).[12]

In our study, 4(2.67%) cases and 7 (4.67%) controls were having diastolic blood pressure more than 90 mmHg. Mean diastolic blood pressure for cases was 82.03±7.54 and mean diastolic blood pressure for controls was 81.36±7.34 . The difference in the two groups was found to be 0.35 i.e statistically non significant. On the contrary Kelly J Hunt et al (2003) reported that the mean diastolic blood pressure of the prediabetics (n=66)was 74.80 ± 2.40 mmHg which was higher than the controls (n=1127) which was 70.20 ± 0.50 mmHg.[12] This difference in the mean diastolic blood pressure was statistically significant($p < 0.05$). This difference in diastolic blood pressure levels in above mentioned studies can be due to the difference in study population.

In our study, mean value of total cholesterol for cases was 176.09±26. Mean total cholesterol for controls was 158.92±18.47. Mean value of total cholestrol of cases was more than controls.The difference in the two groups was found to be statistically significant. ($p< 0.05$, S). Also, Hulya Parildar et al (2013) reportedthat mean total cholesterol was 235.1 ± 22.3 mg/dl in prediabetes(n=110) and 213.7 ± 50.6 mg/dl in controls(n=76). They concluded that total cholesterol was higher in prediabetes than controls and was stastically significant.[16]

In our study, Mean value of low-density lipoprotein for cases was 96.69±25.46. Mean value of low-density lipoprotein for controls was 67.94±19.17. Mean of low-density lipoprotein for cases was more than controls. The difference in the two groups was found to be statistically significant ($p < 0.05$, S). Similarly,David Faeh et al(2007) observed that LDL cholesterol (mmol/l) was higher in prediabetes (n=73)than controls (n=316), where mean LDL in prebiabetes was 3.82 ± 0.10 and in control group was 3.43 ± 0.04 ($p< 0.01$, S).[14]

In our study, mean value of very low-density lipoprotein for cases was 35.89±11.26. Mean value of very low density lipoprotein for controls was 39.60±6.13. Mean value of very low-density lipoprotein for controls was more than cases. The difference in the two groups was found to be statistically significant ($p < 0.05$).However, we did not find any study suggesting direct relationship between very low-density lipoprotein and prediabetes in the literature.

In our study,mean value of triglyceride for cases was 133.18±29.13. Mean value of triglyceride for controls was 127.92±23.41. Mean triglyceride for cases was more than controls. The difference in the two groups was found to be statistically significant ($p <0.05$, s). Similarly,Kelly J Hunt et al (2003) reported that median triglyceride of 1st and 2nd quartile was 247 mg/dL (211, 282) in prediabetes (n=66) and 98 mg/dL (190, 207) in controls (n=1127) ($p <.05$, S).[12]

In our study, mean value of high-density lipoprotein of cases was 43.87±15.24.Mean value of high density lipoprotein of controls was 51.38±12.18. Mean high-density lipoprotein for cases was lower than controls. The difference in the two groups was found to be statistically significant. ($p< 0.05$, S). Similarly, Kelly J Hunt et al (2003) reported that HDL was less in prediabetes group (n=66) in comparison to control group (n=1127). Median HDL cholesterol was 29.2 mg/dL (27.0, 31.5) in prediabetes group and was 32.8 mg/dL (32.3, 33.4) in control group (1st and 2nd quartile) ($p<. 05$, S).[12]

In our study, Mean serum uric acid of cases was 5.31±0.87.Mean serum uric acid of controls was 3.84±0.63.Mean serum uric acid of cases was more than controls and it was found to be statistically significant ($p <0.05$, s). Also, Abhay S Tirkey et al (2014) reported mean

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serum uric acid in prediabetics (n=12) i.e. 4.88±0.79 was more than controls (n=34)i.e. 3.84±0.88 and was statistically significant.[17]

8. Conclusion

Body mass index and waist hip ratio was significantly higher in prediabetes as compared to controls.Systolic blood pressure was significantly higher in prediabetes as compared to controls.There was non significant relation between diastolic blood pressure between cases and controls.Total cholesterol, low-density lipoprotein (LDL), triglyceride (TG), were significantly higher in prediabetes and High-density lipoprotein (HDL) was significantly lower in prediabetes as compared to controls.Very low density lipoprotein was lower in cases as compared to controls.Serum uric acid was higher in prediabetes in comparison to controls.

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