SERUM URIC ACID LEVEL IN PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE AS COMPARED TO SUBJECTS WITH NORMAL GLUCOSE TOLERANCE

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ABSTRACT

Objective: To determine serum uric acid level in patients with impaired glucose tolerance as compared to subjects with normal glucose tolerance.

Study Design: Case control study.

Place and Duration of Study: Department of Chemical Pathology and Endocrinology, CMH Lahore, from Jun 2016 to Nov 2016.

Methodology: Upon the referral from outdoor clinicians, approx. 300 patients were included in the study. Oral glucose tolerance test was carried out with 75 g glucose load in patients with impaired fasting glucose. Serum uric acid level was determined in both cases (impaired glucose tolerance) and control (normal glucose tolerance) groups. Serum uric acid and glucose level were performed on fully automated chemistry analyzer Selectra XL ensuring Internal and External quality Control procedures. Data was entered and analyzed on SPSS 21.

Results: Hyperuricemia was present in 84 (56%) patients who had impaired glucose tolerance. Analysis of association between cases and control groups with hyperuricemia and non hyperuricemia was done which gave *p*-value of <0.001 with odds ratio of 7.4.

Conclusion: Significant proportion of patients with impaired glucose tolerance had hyperuricemia in comparison to patients with normal glucose tolerance. So hyperuricemia should be considered a red flag in these patients and should alert the clinician to strive to utilize a global risk reduction program in a team effort to reduce the complications secondary to high serum uric acid level in prediabetes.

Keywords: Diabetes mellitus (DM), Impaired fasting glucose, (IFG), Impaired glucose tolerance (IGT), Normal glucose tolerance (NGT), Oral glucose tolerance test (OGTT), Serum uric acid level (SUA).

INTRODUCTION

Diabetes mellitus is a heterogeneous group of disorders characterized by hyperglycemia due to an absolute or relative deficiency in insulin production or action[1].Diabetic population has risen from 108 million in 1980 to 422 million in 2014; The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014[2]. In Pakistan, 38 million cases of pre diabetes are reported in 2011, in which 20.5% are women and 15.9% cases are men. It is estimated that Pakistan became the 7th largest country in terms of diabetic population and it will be the 4th largest by the year 2030[3].

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Poorly managed diabetes can damage many organs of the body like kidneys, heart, eyes, blood vessels, and nerves. Diabetes causes one death every 6second, and the number of deaths caused by diabetes is 5 million which is much higher than those caused by HIV (1.5 million), tuberculosis (1.5 million), and malaria (0.6 million) combined[4]. Much of this excessive mortality is attributed to cardio vascular diseases. Risk of ischemic heart disease and stroke is 2-4 times higher in diabetes as compared to normal population. Cardiovascular disease in woman with diabetes is23% more prevalent than woman with non-diabetes. In 2014 mortality rate due to diabetes mellitus in adult population of Pakistan (20-79 years) was 87,548[5]. Prediabetes is an intermediate metabolic state between normoglycaemia and diabetes and includes those with impaired glucose tolerance (IGT), impaired fasting

glucose (IFG) or raised HbA1c[6]. Prediabetes causes increased risk of developing type 2 diabetes mellitus (T2DM), and there are risks inherent to the prediabetes state, including microvascular and macrovascular diseases especially cardiovascular problems[7].

The prevalence of hyperuricemia in the world population has steadily increased over the past 40 years[8]. Uric acid is formed by the breakdown of purine and by direct synthesis from 5–phosphoribosyl pyrophosphate and glutamine[9]. Serum urate level vary with age and sex. Most children have serum urate concentration of 180 to 240 umol/L. Levels begin to rise in males during puberty but remain low in females until menopause. Mean serum urate value of adult men and post-menopausal women are 415 and 360 umol/L respectively. After menopause, value for women increases to approximate those of men[10]. In adulthood, concentration rise steadily over time and vary with height, body weight, blood pressure, renal function, and alcohol intake[10]. Many epide-miological studies showed that hyperuricemia is major contributor to the development of medical conditions which are similar to those which are associated with diabetes and pre diabetes, including cardiovascular diseases, kidney diseases, endothelial dysfunction, insulin resistance and chronic inflammation[11].

The SR Meena in his 2015 study gave reference of Daniel flag *et al* study which concluded that hyperuricemia was present in 40-60% of patients with impaired glucose tolerance[12]. Hong *et al*, reported that hyperuricemia was significantly associated with impaired glucose tolerance(17.2%), normal glucose tolerance (12.3%) and as a risk factor for development of type 2 diabetes[13,14]. Hong has also shown that 59.5 umol/L increase in serum uric acid level signaled a 60% higher risk of type 2 diabetes[13]. Perticon *et al*, showed that hyperuricemia is strongly associated with 1– hour post glucose levels inentire hypertensive population whether having normal glucose tolerance, impaired glucose tolerance or diabetes mellitus[15]. The same study showed hyperuricemia and 2 hour post glucose association was stronger in women than in men[16]. These studies indicated that serum uric acid was a major determinant of 2 hour post glucose in patients with prediabetes, suggesting the crucial role of serum uric acid in the deterioration of glucose metabolism. The rationale of this study was to highlight the importance of hyperuricemia in deterioration of glucose metabolism in pre-diabetes patients who are prone to develop diabetes or its complication in near future and secondly, provision of awareness to health care practitioner regarding hyperuricemia in these patients so that physicians give importance to control of hyperuricemia which leads to more health related issues in presence of impaired glucose metabolism in this group of patients.

METHODOLOGY

This study was a case control study which was conducted at Department of Chemical Pathology and Endocrinology, CMH Lahore from June 2016 to November 2016. The sample size of 300 cases (150 in each group) was calculated by WHO calculator with 80% power of test, 5% level of significance and expected percentage of hyperuricemia in both groups i.e. 40% in IGT group (cases) and 12.3% in NGT group (control). The sampling was non probability consecutive sampling. In this study cases were patientshaving Impaired glucose tolerance and controls were those who have Normal glucose tolerance. The study population age varies from (25 to 55) years including both gender. The patients having pregnancy, diabetes mellitus, kidney disorders, hyperlipidaemia, hypertension, usinganti-hypertensive drugs, anti-TB drugs like (ethambutol and pyrazinamide), allopurinol and oral contraceptive pills were excluded.

After approval from College of Physicians and Surgeons of Pakistan and CMH Lahore research ethics committee, all patients fulfilling the inclusion criteria were appraised about the study to obtain their informed consent. Brief medical history and physical examination were

carried out before specimen collection. Laboratory investigations of all patients were done at CMH Lahore. During the procedure of oral glucose tolerance test, 75 gram glucose dissolved in 250-300 ml of water was given to patients and exactly after 2 hours blood was drawn for plasma glucose determination. Control group included those patients whose Fasting Plasma Glucose was less than 5.6 mmol/L and 2 hour OGTT result were less than 7.8mmol/Land case group included those patients whose 2 hour OGTT plasma glucose value was in range of 7.8-11.1 mmol/L. Plasma glucose estimation was performed by glucose oxidase method and serum uric acid determined in both cases and controls by enzymatic uricase method. Patients were labelled as hyperuricemic in both groups according to criteria mentioned in operational definition. All tests were run on Selectra XL (fully automated chemistry analyzer) after ensuring internal quality control by running two levels of Randox controls for all analytes.

External Quality control was ensured by results of National External Quality Assurance Program Pakistan(NEQAPP).

Data was entered and analyzed on SPSS-21. Mean ± SD was calculated for quantitative variables in both cases and controls.

Independent sample t-test was applied for the comparison of oral glucose tolerance, serum uric acid level and body mass index with respect to study groups (cases and control), gender groups (male, female), BMI groups (two categories on the basis of cut off value of 30kg/m^2) and hyperuricemia (two categories who had high and low uric acid level). Chi square test applied to see association of gender groups (male, female), BMI (both categories), cases and controls groups with hyperuricemia. The *p*-value and Odds ratio were calculated. The *p*-value ≤0.05 and odds ratio >1 is considered as significant[22,2].

Table-I: Characteristics of case and control groups.

Total no of patients	**Cases**	**Control**	***p*-value**
	150	150	
Sex distribution in groups	M=95 (63.3%) F=55 (36.7%)	M=86 (57.3%) F=64 (42.7%)	
Mean age	46.52 ± 7.43	39.47 ± 8.37	<0.001
Mean serum uric acid level	377.22 ± 80.01 umol/L	292.58 ± 86.29 umol/L	<0.001
Mean body mass index	27.56 ± 2.67	26.14 ± 2.45	<0.001
Mean 2 hours OGTT test value	9.117 ± 0.97 mmol/L	6.69 ± 0.56 mmol/L	<0.001

Table-II: Stratification of hyperuricemia in cases and control with respect to gender groups.

Gender of Patient		**Hyperuricaemia**		***p*-value**	**Chi-square Odds Ratio**
		Yes	**No**		
Male	Cases	52	43	<0.001	5.92
	Control	16	70		
Female	Cases	32	23	<0.001	13.45
	Control	06	58		

Table-III: Analysis of association between cases and controls groups with hyperuricemia and non-hyperuricemia.

Study Group	**Hyperuricemia**		***p*-value**	**Odds ratio with 95% CI**
	Yes	**No**		
Cases	84 (56%)	66 (44%)	<0.001	7.4
Controls	22 (14.6%)	128 (85.4%)		

RESULTS

The case group had 95male and 55 female subjects while there were 86 male and 64 female in control group. The mean age of all studied patients in both cases and control groups was 43 ± 8.6 (table-I). The mean serum uric acid level in males of both groups was 367 ± 85umol/L and

mean serum uric acid level in females of both groups was 285 ± 82umol/L.

Similarly, the mean serum uric acid level of males and females in each individual group was calculated which showed that male patients had high serum uric acid level as compared to females in cases as well as in control group (table-II).

Regarding Body Mass Indexit was also observed that the mean serum uric acid level in patients with BMI greater than 30 was 416 ± 47 while, it was 323 ± 92 in patients with BMI lesser than 30. The frequency of Hyperuricemia in case (IGT) group was 56% as compared to control group in which only 14.6% had Hyperuricemia (table-III). Analysis of association between cases and control groups with hyperuricemia and non hyperuricemia was done with *p*-value of <0.001 and odds ratio of 7.4.

DISCUSSION

Our study concluded that approximately 56% patients of IGT and 15% patients of NGT had hyperuricemia. The descriptive findings of our studywere comparable to results of other studies like Meena *et al* (2016) andFeig *et al* (2008) who claimed that 40-60%subjects with IGT had hyperuricemia[12,3].

Current study illustrated that mean serum uric acid levels of 401.22 ± 78.74 and 335.76 ± 64.09 in IGT case group were significantly higher than 329.87 ± 76.37 and 242.67 ± 72.76 in control group in males and females, respectively. This finding was supported by the observations of the research conducted by MS Rao and Sahayo BJ (2012) who reported thatthatserum uric acid levels were significantly elevated in patients with pre diabetes[10].

Gender based analysis of serum uric acid levels in our case and control groups resulted that males have higher serum uric acid levels than females. The same was analogous with the description of the study done by Meena R and Meena SR (2016) study[12]. It was also consistent with Abdel Rahman TT (2014) who reported that 21% elderly males and 15.1% elderly females with metabolic syndrome had hyperuricaemia[7].

Body Mass Index (BMI) is influencing factor in development of diabetic conditions. Present study divulged that the mean serum uric acid level in patients with BMI greater than 30 was 416±47 while was 323 ± 92 in patients with BMI lesser than 30. This indicated that the patients with high BMI bear high uric acid levels which might further be referring to pre-diabetic conditions; as described by Abdel Rahman TT (2014)[13].

This study alongwith with previous research findings, like by Fan Hong Qi *et al*, who concluded that elevated serum uric acid levels were significantly associated with 2-hour OGTT plasma glucose levels and risk of type 2 DM, hold up the conclusion that there was significant association between raised levels of hyperuricaemia and impaired glucose tolerance[17-18]. However, keeping in mind the confounding variables and limitation of our study,we suggest further studies to clarify the role of hyperinsulinaemia, purine diet consumption and insulin resistance especially in relation to impaired glucose tolerance and hyperuricaemia.

LIMITATION OF STUDY

The study population only represented entitled patients reporting to Combined Military Hospital Lahore. Genetic studies require to clarify the gender differences in serum uric acid concentration in relation to impaired glucose tolerance, urinary uric acid clearance and details on purine diet consumption were not available, limiting exploration of roles of these factors in the association of serum uric acid with impaired glucose tolerance.

CONCLUSION

Serum uric acid levels were significantly elevated in individuals with Impaired Glucose Tolerance.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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