ORIGINAL ARTICLE

Prevalence of Hyperuricemia in Indian Subjects attending Hyperuricemia Screening Programs-A Retrospective Study

Gauri Billa[1], Ramesh Dargad[2], Ashwani Mehta[3]

Abstract

Objectives: To determine the prevalence of hyperuricemia (HU) in patients with hypertension (HTN) and type 2 diabetes mellitus (T2DM) in the Indian setting.

Methods: A retrospective analysis of patients undergoing screening for HU in health clinics across India between April to May 2017 was carried out. Data regarding demographics, history of T2DM and HTN and uric acid levels (easy touch uric acid monitoring system) were recorded during the program.

Results: Data from 3044 screening programs was analysed. The mean age of the study population was 47.9 years; about two-thirds of the subjects were males. Of the 29391 subjects screened, 25.8% were found to have HU. The proportion of diabetics, hypertensives and diabetic hypertensives who had HU was 33.6%, 35.1%, and 34.4% respectively. A trend towards increased prevalence of HU was seen with increasing age and increased duration of diseases like HTN and diabetes.

Conclusion: High prevalence of HU was observed in T2DM and HTN and in patients with both co-morbidities. Age-wise analysis revealed an increasing trend of HU with age. Further, the prevalence of HU also increased with increasing duration of T2DM and HTN.

Introduction

Hyperuricemia (HU) is characterized by elevated levels of serum uric acid (SUA); the levels are increased due to either overproduction or under-excretion of uric acid (UA) (a final oxidation product of purine metabolism in humans). On the physiochemical basis, HU is defined as SUA levels > 7 mg/dL.[1] HU can be classified as primary or secondary depending upon its occurrence as a consequence of another coexisting disease or drug.[2] The dietary intake of purine-rich foods (red meat, seafood, beans) or high fat dairy product/alcohol/sweetened soft drink or under-excretion of UA due to renal dysfunction and use of thiazide and loop diuretics or extreme levels of physical activity are the main causes for increased production of SUA.[3]

The level of SUA depends upon the balance between its hepatic production and renal excretion. The high levels may trigger oxidative stress, production of urate (due to xanthine oxidoreductase) and plasma triglycerides, endothelial dysfunction, thereby leading to an impact on smooth muscle proliferation, oxidative metabolism and platelet aggregation. High levels of SUA have been evident throughout all regions of the world, including Philippines and Seychelles: 25%, USA: 21-22%, Japan: 20-26%, Indonesia: 18%, Russia and Nigeria: 17%, Brazil: 13%, Turkey: 12%, Taiwan: 10-52%, Thailand: 9-11%, Mexico: 11%, Sweden: 10-16%, Italy 9-12%, Iran and Saudi Arabia: 8%, China: 6-25%, Spain: 5-11% and South Korea: 5%.[4]

Elevated levels of SUA have been associated with an increased risk for not only type 2 diabetes mellitus (T2DM) and hypertension (HTN) but also for dyslipidemia, metabolic syndrome, hyperinsulinemia, gout, stroke, atherosclerosis, chronic kidney disease, congestive heart failure, obesity, coronary artery disease and stroke.[1,5-7] Similar results have been reported from India where patients with T2DM (25.35%), metabolic syndrome (47.1%), obesity (44.6%), and HTN (37.33%) have a higher prevalence of HU in comparison to healthy individuals.[8-10] In a study, hypertensive patients with coexisting HU were reported to be at a greater risk of uncontrolled HTN, in spite of good compliance with their antihypertensive treatment.[1]

Considering the growing incidence of HTN and DM in developing and developed countries and having the potential link between high SUA levels and impaired renal function and cardiovascular complications, it was important to know whether emphasis should be laid on early screening of SUA levels. This would help in early detection, prevention, and management of complications of T2DM and HTN (two major public health problems). Indicators that are easy to assess and have a high predictive value (like Easy touch uric acid monitoring system) may help in providing an accurate UA levels.[11]

There is a paucity of available information regarding the burden of HU in the Indian population and about its association with age, gender and comorbidities like T2DM and HTN. Hence, the present retrospective, cross-sectional study was planned to determine the prevalence of HU in subjects attending multiple HU screening programs across India.

Methods

Study design

Abbott Healthcare Private Limited has been conducting HU screening programs across India since 2017. In these HU screening programs, subjects identified as having risk factors for HU are referred for UA test. UA levels are

[1]Abbott Healthcare Private Limited, Mumbai, Maharashtra; [2]Jeevan Building, Mukund Nagar, Mumbai, Maharashtra; [3]Dr. Mehta's Clinic, Delhi

Received: 24.01.2018; Accepted: 18.02.2018

Table 1: Proportion of subjects with hyperuricemia by underlying conditions, age categories and gender

Parameters	Total Number of subjects	Number (%) of subjects with HU	P-value
By underlying conditions			
Diabetes	5823	1958 (33.6)	
Hypertension	7351	2581 (35.1)	
Diabetes and hypertension	2782	957 (34.4)	
By age			
≤ 30 years	3581	612 (17.1)	0.02[1]
31-50 years	13740	3069 (23.3)	< 0.0001[2]
>50	12070	3900 (32.3)	< 0.0001[3]
By gender			
Females	9630	2148 (22.3)	< 0.0001[4]
Males	19761	5432 (27.5)	

[1]age category ≤ 30 years vs. 31-50 years; p = 0.02;
[2]age category 31-50 years vs >50 years, p < 0.0001;
[3]age category ≤ 30 years vs >50 years, p < 0.0001;
[4]Males vs females, p < 0.0001.

tested by Easy touch UA monitoring system.

This study was designed as a non-interventional, retrospective study. Data was analyzed from 3044 HU screening programs conducted by Abbott across India between April and May 2017. All the subject records for which UA level was performed and results were available were included in the study while the subject records with incomplete information were excluded from the study. Patients with SUA levels > 7 mg/dL were considered as hyperuricaemic in this study.

The final protocol was approved by respective institutional ethics committee. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization of Good Clinical Practice guidelines, Indian Council of Medical Research, Indian GCP guidelines and approved protocol.

Data collection

The data pertaining to demographics (age, gender), duration of HTN and/or T2DM and SUA levels were collected from subject records by the third-party firm, RxPont India Limited after taking the subject consent. Subject's confidentiality was maintained during data entry and analysis process.

Study objectives

The primary study objective was to determine the overall prevalence of HU in the population and by underlying conditions (T2DM, HTN and subjects having both T2DM and HTN). The secondary study objectives were to determine the 1) demographic characteristics (age and gender) and clinical profile of HU subjects attending HU screening programs, 2) relationship between HU and age categories (≤ 30 years, 31-50 years and ≥ 50 years); gender (men and women), underlying condition (T2DM, HTN and both T2DM and HTN) and duration of disease (≤ 2 years, 2-5 and > 5 years).

Statistical analysis

No formal sample size calculation was done as this was a retrospective and non-interventional study. All the subject records collected during HU screening programs conducted between April and May 2017 were analysed in this study. The statistical analysis was done using Statistical Analysis System® version 9.3 software. The continuous variables were summarized descriptively by mean, standard deviation, median and range. The categorical variables were described by frequencies and percentages. No missing data imputation was carried out. All the statistical analyses were done using chi-square test at alpha level = 0.05. Chi Square test was used to evaluate the significance of the association between different categories.

Results

Subject population

A total of 29391 individuals attended the HU screening programs across India during the study period. The data of all the subjects were analysed in the study. No subject data was excluded from the analyses. Of all the subjects attending the HU screening programs, 19761 (67.2%) were males and 9630 (32.8%) were females. Based on the age categories, 3581 (12.2%) had age ≤ 30 years, 13740 (46.7%) had age 31-50 years and 12070 (41.1%) subjects had age > 50 years. The mean age of the overall population was 47.9 years (range: 10 to 97 years). A total of 5823 (19.8%) subjects were diabetic, 7351 (25.0%) were hypertensive, 2782 (9.5%) subjects were both diabetic and hypertensive and the remaining 13435 subjects had unknown disease.

Prevalence of hyperuricemia by underlying conditions, gender and age

Approximately 25.8% (7580/29391) of the overall subjects had HU. Table 1 provides the proportion of HU subjects in diabetic, hypertensive and diabetic + HTN conditions.

Gender-wise, a slightly higher proportion of males experienced HU than females (27.5% versus 22.3%). Age-wise, a higher proportion of subjects with age > 50 years were found to have increased UA levels as compared to subjects with age ≤ 30 years (32.3% versus 17.1%) and 31-50 years (32.3% versus 22.3%). In the age category of 31-50 years as well, a higher proportion of subjects reported HU in comparison to subjects with age ≤ 30 years (22.3% versus 17.1%).

There was a statistically significant association between gender (male vs. female; p < 0.0001) and different age categories (≤ 30 years vs. 31-50 years; p = 0.02, 31-50 years vs. > 0 years; p < 0.0001, ≤ 30 years and > 50 years; p < 0.0001; chi square test) with respect to prevalence of HU in the overall population (Table 1).

Relationship between Hyperuricemia and Age, Gender, and Duration of Disease in subjects with type 2 diabetes and hypertension

Age

With progression in age, elevated UA levels were reported in higher proportion of diabetics aged > 50 years than diabetics aged 31-50 years and ≤ 30 years (37.7% vs 29.4% vs 22.3%, respectively). Similarly, a higher proportion (29.4%) of diabetics with age 31-50 years reported HU than the diabetics with age ≤ 30 years (22.3%). In hypertensive subjects, there was a small increase in the proportion of HU subjects when the age increased from < 30 years to > 50 years (29.1% to 31%) (Table 2).

Gender

The proportion of males and females having HU was comparable in subjects with T2DM or hypertension (Table 3).

Duration of Disease

With an increase in the duration of disease (from the period of < 2 years to > 5 years), the proportion of HU subjects steadily increased from 34 % to 38.4% in subjects with T2DM and from 36.7% to 42.2% in hypertensive subjects (Table 4).

Relationship between Hyperuricemia and Age and Gender in Subjects with T2DM and Hypertension

The elevated UA levels were reported

Table 2: Relationship between hyperuricemia and age in subjects with type 2 diabetes mellitus and hypertension

Age Groups	Total number of subjects	Number (%) of subjects with HU
Type 2 diabetes mellitus		
≤ 30 years	256	57 (22.3)
31-50 years	2344	688 (29.4)
>50 years	3226	1216 (37.7)
Hypertension		
≤ 30 years	299	84 (29.1)
31-50 years	2947	915 (31.0)
>50 years	5108	1585 (31.0)

Table 3: Relationship between hyperuricemia and gender in subjects with type 2 diabetes mellitus and hypertension

Gender	Total number of subjects	Number (%) of subjects with HU
Type 2 diabetes mellitus		
Males	4607	1536 (33.3)
Females	1218	424 (34.8)
Hypertension		
Males	4905	1740 (35.5)
Females	2448	843 (34.4)

in a higher proportion of subjects with age >50 years (38.4%) against patients of other age categories (≤ 30 years [30.3%] and 31-50 years [17.3%]). Similar results were observed when subjects with age 31-50 years were compared against ≤ 30 years (30.3% vs 17.3%). Comparing by gender, high UA levels were reported in a higher proportion of females than males (38.4% vs 33.3%) (Table 5).

There was a statistically significant association between gender (male vs. female; p = 0.02) and different age categories (≤ 30 years vs. 31-50 years; p = 0.0075, 31-50 years vs. > 50 years; p < 0.0001, ≤ 30 years and > 50 years; p < 0.0001) with respect to prevalence of HU in subjects with both T2DM and HTN (Table 5).

Discussion

Diabetes and HTN have emerged as a major public health issue worldwide and have been important risk factors for coronary artery disease, heart failure and cerebrovascular disease, resulting in increased morbidity and mortality, decreased quality of life and high economic loss. It is estimated that by 2025, the number of diabetic and hypertensive adults would rise up to 300 million and 1.56 billion worldwide, respectively.[12,13] Subjects with both DM and HTN are at increased risk of developing atherosclerosis,

Table 4: Relationship between Hyperuricemia and duration of type 2 diabetes and hypertension in diabetics and hypertensive subjects

Duration of	Total number of subjects	Number (%) of subjects with HU
Type 2 diabetes mellitus		
< 2 years	535	182 (34.0)
2-5 years	1601	596 (37.2)
> 5 years	1043	400 (38.4)
Unknown	2648	784 (29.6)
Hypertension		
< 2 years	626	230 (36.7)
2-5 years	1248	477 (38.2)
> 5 years	1172	494 (42.2)
Unknown	3618	1139 (31.5)

retinopathy, renal failure, and nontraumatic amputation and CVD.[14] Since, both diabetes and HTN impose a huge burden in India, there should be strategies for early diagnosis of these disorders by improving monitoring and management of risk factors.[15]

Various studies have reported HU to be an independent risk factor for T2DM and HTN and by lowering the SUA levels, the risk of these disease may be lowered. Elevated SUA levels induce endothelial dysfunction, which lead to reduced insulin-stimulated nitric oxide-induced vasodilatation in skeletal muscle, resulting in reduced glucose uptake in skeletal muscles. Hence, screening of SUA levels at regular periods may serve as a good, fast, reliable, cheap and a minimally invasive procedure to circumvent the onset or progression of diabetes and HTN.[16] In 2005, Dai et al evaluated the accuracy of Easy Touch UA monitoring system by evaluating 177 Easy Touch readings and reported this monitoring system to be an acceptable diagnostic device in terms of providing accurate UA measurements.[11] In the present study as well, Easy touch UA monitoring system was used to assess SUA levels.

Cardiovascular risk factors like HTN, obesity, dyslipidaemia have found to be more prevalent in T2DM than in subjects without T2DM.[17] DM and HTN are known to coexist together in ~40-60% of T2DM patients.[18] In our study as well, approximately half of the subjects with T2DM were associated with HTN.

We report the overall prevalence rate of HU as 25.8%, with higher proportion of males having elevated

Table 5: Relationship between hyperuricemia and age categories and gender in subjects with type 2 diabetes mellitus and hypertension

Parameters	Total number of subjects	Number (%) of subjects with HU	P-value
Age groups			
≤ 30 years	104	18 (17.3)	0.0075[1]
31-50 years	1112	337 (30.3)	< 0.0001[2]
>50 years	1566	602 (38.4)	< 0.0001[3]
Gender			0.02[4]
Males	2207	736 (33.3)	
Females	575	221 (38.4)	

[1]age category ≤ 30 years vs. 31-50 years; p = 0.0075; [2]age category 31-50 years vs >50 years, p < 0.0001; [3]age category ≤ 30 years vs >50 years, p < 0.0001; [4]Males vs females, p = 0.02.

SUA compared to females. Similar prevalence of HU was documented in previous studies from different population.[19-20] Additionally, we found that >30% of the subjects with T2DM with or without HTN had HU. The proportion of diabetic subjects with HU (~33.6%) was much higher in our study as compared to previous published literature where around 25% of T2DM patients were reported to have elevated SUA levels.[8,19] This may be due to variation in genetic and geographical factors since our's was a PAN-INDIA study.

Furthermore, around 35.1% of hypertensive subjects had HU. Our results were in concordance to the earlier study where HU was reported in 26-33% of patients with essential HTN.[21] In 2016, Shrivastav et al in a cross-sectional, case control study, conducted among 125 subjects (with age of 20-50 years), reported 37.3% of the subjects with essential HTN to have HU. In addition, significant higher mean SUA levels were reported in newly diagnosed cases of essential HTN than healthy normotensive subjects (6.56 ± 0.76 mg/dl versus 4.91 ± 0.97 mg/dl, p < 0.001).[10]

The prevalence of HU varies with age and gender. In the previous literature, SUA levels were reported to increase with advancing age.[22,23] In the US study conducted from 1959 to 1960, the SUA values in males rose rapidly to a peak level at 20-24 years followed by a slight decline and a rise at 55 to 59 years. In females, the SUA levels rose to a minor peak at 15-19 years followed by a decline and levelling at approximately 40 years and reached peak levels at

50-54 years and 60-64 years, due to a decline in the production of estrogen due to menopausal conditions.[22] In 1999, Culleton et al, in the Framingham Heart Study, also reported that there is a gradual increase in SUA levels in females from the fourth to the seventh decades of life.[23] In our study as well, the proportion of HU subjects increased with progression in age; maximum subjects were evident in the age category of > 50 years followed by 31-50 years and ≤ 30 years. Similar results were reported in T2DM subjects with and without HTN. In hypertensive subjects, there was a slight increase in proportion of HU subjects as the age progressed from ≤ 30 years to 31-50 years (29.1% to 31%). Our findings were contrary to the earlier reported results where the highest prevalence of HU was reported in 20-39 years of age category, with a subsequent decline in the proportion of HU subjects with age in cases of essential HTN.[24]

Various studies have reported higher SUA levels in males than females.[8, 9] This may be due to the presence of estrogen in premenopausal females, which enhances renal urate clearance or excretion by inhibition of renal urate reabsorption via organic ion transporter, resulting in low SUA levels. The results of our study were in concordance with the earlier published data. We also observed a higher proportion of males to have HU than females (27.5% versus 22.3%). However, when the data was split by T2DM and HTN alone, a higher proportion of females had HU than males (38.4% versus 33.3%), this may be due to more severe condition of the patient or low estrogen production, leading to a decrease in tubular excretion of UA.

Duration of disease plays an important role in increasing the SUA levels. In our study as well, a trend in increase in the proportion of HU subjects was reported with an increase in the duration of T2DM and HTN.

Our study has few limitations. First, it was not a prospective study, but a retrospective analysis of data collected from ongoing healthcare clinics. Hence, the scope of finding the association between the SUA levels and different patient characteristics, including weight or BMI, antihypertensive or antidiabetic or other medications, systolic and diastolic BP, diet, smoking status, alcohol consumption, different stages of HTN, other comorbidities etc was limited. Second, there was no healthy control group, which limited the ability to compare the SUA levels between patients of different comorbidities and healthy individuals.

In conclusion, the overall prevalence of HU in patients attending the screening programs was 25.8%. More than 30% of patients with T2DM, HTN and both comorbidities had elevated SUA levels. There was an increasing trend in the prevalence of HU with age and progressing years of duration of T2DM and HTN. Thus, there is a need to do prospective case control studies in Indian population to corroborate the results of the current study and to determine if early screening of SUA levels may help to reduce the risk of comorbidities and its further complications.

Funding

The study was fully funded by Abbott Healthcare India Pvt. Limited.

Conflict of Interest

This work was supported by Abbott Healthcare Private Limited. Dr. Gauri Billa authored this article in the capacity as an employee of Abbott Healthcare Pvt Limited. All other authors have declared and confirmed that there is no conflict of interest with respect to the authored article.

Acknowledgment

We thank RxPont India Limited for assisting in overall conduct of the study, and GCE Solutions for the overall preparation of manuscript.

References

1. Yamanaka H. Japanese Society of Gout and Nucleic Acid Metabolism. Japanese guideline for the management of hyperuricemia and gout: Second edition. *Nucleosides Nucleotides Nucleic Acids* 2011; 30:1018-29.
2. Making AD. Approach to a Case of Hyperuricemia. *Ind J Aerospace Med* 2010; 54:1.
3. Schlesinger N. Hyperuricemia, Gout, and Diet. In: Coleman L.A. (eds) Nutrition and Rheumatic Disease. Nutrition and Health. Humana Press 2008.
4. Smith E, March L. Global Prevalence of Hyperuricemia: A Systematic Review of Population-Based Epidemiological Studies [abstract]. *Arthritis Rheumatol* **2015**;67 (suppl 10). Accessed April 28, 2017.
5. Chen JH, Chuang SY, Chen HJ, Yeh WT, Pan WH. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. *Arthritis Rheum* 2009; 61:225-32.
6. Chang HY, Tung CW, Lee PH, et al. Hyperuricemia as an independent risk factor of chronic kidney disease in middle-aged and elderly population. *Am J Med Sci* 2010; 339:509-15.
7. Raina S, Raina RK, Raina SK. Hyperuricemia: A risk factor beyond gout. *J Obes Metab Res* 2015; 2:228-33.
8. Mundhe SA, Mhasde DR. The study of prevalence of hyperuricemia and metabolic syndrome in type 2 diabetes mellitus. *Int J Adv Med* 2016; 3:241-49.
9. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese. *Obes Surg* 2012; 22:945-48.
10. Shrivastav C, Kaur M, Suhalka ML, Sharma S, Basu A. Hyperuricaemia- Potential Indicator to Diagnose the Risk of Essential Hypertension. *J Clin Diagn Res* 2016; 10:CC01-3.
11. Dai KS, Tai DY, Ho P, et al. An evaluation of clinical accuracy of the EasyTouch blood uric acid self-monitoring system. *Clin Biochem* 2005; 38:278-81.
12. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998; 21:1414-31.
13. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365:217-23.
14. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. *Diabetes Care* 1993; 16:434-44.
15. Swami SS, Swami SC, Patil VW, Kanhere AM. Hypertension and diabetes in India: a review. *Int J Clin Biochem Res* 2015; 2:54-8.
16. Fouad M, Fathy H, Zidan A. Serum uric acid and its association with hypertension, early nephropathy and chronic kidney disease in type 2 diabetic patients. *J Bras Nefrol* 2016; 38:403-10.
17. Wang CC, Reusch JE. Diabetes and cardiovascular disease: changing the focus from glycemic control to improving long-term survival. *Am J Cardiol* 2012; 110:58B-68B.
18. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. *Diabetes Care* 2002; 25:134-47.
19. Ogbera AO, Azenabor AO. Hyperuricaemia and the metabolic syndrome in type 2 DM. *Diabetol Metab Syndr* 2010; 2:24.
20. Tuomilehto J, Zimmet P, Wolf E, Taylor R, Ram P, King H. Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. *Am J Epidemiol* 1988; 127:321-36.
21. Kahn HA, Medalie JH, Neufeld HN, Riss E, Goldbourt U. The incidence of hypertension and associated factors. The Israeli ischemic heart disease study. *Am Heart J* 1971; 84:171-82.
22. Mikkeksen WM, Dodge HJ, Valkenburg H. The distribution of serum uric acid values in a population unselected as to gout or hyperuricemia. Tecumseh, Michigan, 1959-1960. *Am J Med* 1965; 39:242-51.
23. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999; 131:7-13.
24. Lin CS, Lee WL, Hung YJ, et al. Prevalence of hyperuricemia and its association with antihypertensive treatment in hypertensive patients in Taiwan. *Int J Cardiol* 2012; 156:41-6.