Research article

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Burden of hyperuricemia among ambulatory patients with Type 2 diabetes at Kenyatta National Hospital diabetes outpatient clinic

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Abstract

Background: The prevalence of hyperuricemia has been increasing around the world accompanied by a rapid increase in obesity and diabetes. Hyperuricemia has been positively associated with hyperglycemia. This study was carried out to determine the prevalence especially in Kenya where there is limited data on prevalence of hyperuricemia in diabetes.
Objective: To determine the prevalence of hyperuricemia among ambulatory patients with Type 2 diabetes at Kenyatta National Hospital.
Methods: This was a descriptive cross-sectional study. Simple random sampling was employed to recruit eligible participants. Height, weight and blood pressure was taken from participants, and 6-8mls of peripheral blood was drawn to determine serum uric acid and HbA1c levels.
Results: A total of 150 participants were recruited, with 66% females, 34% males, and a mean (SD) age of 56.4 years. The mean (SD) duration of follow-up for diabetes was 10.3 years. Hypertension was a comorbidity in 65.3% of the participants, and obesity in 36%. The mean (SD) HbA1c levels were 7.76% and 42.7% had good glycemic control. Prevalence of hyperuricemia is at 19.3% in the study. The mean (SD) serum uric acid levels were 5.02mg/dl (299µmol/L).No correlation was found between hyperuricemia and duration of diabetes and glycemic control. Relationship between hyperuricemia and the variables of age, BMI and hypertension did not achieve statistical significance. Female gender achieved significance with a P value of 0.046.
Conclusion: There is a high prevalence of hyperuricemia at 19.3% in this study population especially in the females above the age of 40 years. Patients were on long-term follow-up for diabetes, the glycemic control was average to good. This forms a basis for regularly screening patients for serum uric acid levels in the clinics. Further studies with larger number of patients with diabetes are needed to explore the relationship of hyperuricemia to other clinical and laboratory parameters.

Key words: Serum uric acid, Type 2 diabetes

Introduction

Uric acid is a product of the metabolic breakdown of purine nucleotides, and it is a normal component of urine. Hyperuricemia is defined as a serum urate level of 6.8 mg/dl (404µmol per liter) or more[1]. The rising incidence and prevalence of hyperuricemia are probably related to the increased life expectancy of the population, increasing levels of obesity, sedentary lifestyles and change in dietary habits[2].

Type 2 diabetes mellitus consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of insulin resistance, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Type 2 diabetes mellitus is less common in Non-Western countries where the diet contains fewer calories and daily caloric expenditure is higher. However, as people in these countries adopt Western lifestyles, weight gain and Type 2 diabetes mellitus are becoming virtually epidemic. Prevalence of diabetes is increasing worldwide. The International Diabetes Federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2030[3].

It has been shown that serum uric acid is positively associated with serum glucose levels in healthy subjects[4]. Recent studies have demonstrated that uric acid levels are higher in subjects with Type 2 diabetes than in healthy controls[5-8]. Furthermore, an elevated serum uric acid level was found to increase the chances and predispose to developing Type 2 diabetes in individuals with impaired glucose tolerance[9]. Hyperuricemia has also been added to the set of metabolic abnormalities associated with insulin resistance and/or increased insulin

secretion in metabolic syndrome[10]. An elevated uric acid levels, as reported, often precedes the development of obesity, hyperinsulinemia, and diabetes[11].

Potential clinical consequences of hyperuricemia include gout, urate crystal deposition disorders, chronic kidney disease, nephrolithiasis and non-crystal deposition disorders such as hypertension and coronary artery disease.

The morbidity and mortality of diabetes is increased by hyperuricemia. It confers a poor prognosis on the diabetic complications. There is increased prevalence of diabetic peripheral neuropathy and it shows a significant correlation with increased UA levels[12]. UA concentration has been shown to be associated with an increased severity of diabetic retinopathy in a study done over a three-year period in patients with T2DM[13]. Hyperuricemia is also associated with accelerated disease progression in the early stage of diabetic nephropathy[14].

Significance of the study: Hyperuricemia is a serious yet forgotten test to be screened for and has been implicated in Type 2 diabetes. It is associated with poor glycemic control and diabetes-related complications including retinopathy, foot ulcers and deterioration in renal function. There is paucity of data on the prevalence of hyperuricemia amongst patients with Type 2 diabetes in Kenya which can be used in formulating local guidelines.

Objective: To determine the prevalence of hyperuricemia among ambulatory Type 2 diabetes patients at KNH and to correlate with duration of disease and glycemic control, and their clinical and demographic characteristics (age, sex, BMI and hypertension).

Materials and methods

This was a descriptive cross-sectional study conducted in the diabetes out-patient clinics at KNH. Patients aged 18 years and above were included, with a documented diagnosis of Type 2 diabetes, with normal kidney function tests and no dyslipidemias, who gave written informed consent. Patients on long-term diuretics (Thiazide diuretics as they are known to cause hyperuricemia) and steroids, on antimetabolite and chemotherapy drugs, pregnancy and lactating mothers, on uricosuric drugs and urate lowering agents were excluded. The sample size was calculated using the Daniel's formula and a minimum sample size of 150 was achieved.

Patients were recruited by simple random sampling. Data collection was done using a structured data collection tool and anthropometric measurements taken. Blood samples for serum uric acid and HbA1c levels were drawn and analysed in the KNH Biochemistry Laboratory using an automatic biochemistry analyser (COBAS INTEGRA 400/400 PLUS/800).

Study variables:

- ✓ Serum uric acid levels
- o Hyperuricemia was defined as serum uric acid levels greater than 7.2mg/dl (>428µmol/L)
- ✓ Glycemic control - This was assessed by measuring glycated haemoglobin (HbA1c). HbA1c less than or equal to 7% was considered as good control, HbA1c between 7% to 8% was considered as moderate control and HbA1c greater than 8% as poor control.

Data analysis: Pearson product moment correlation was used to evaluate for any relationship between hyperuricemia and duration of diabetes and glycemic control. Pearson Chi-Square and Fischer exact tests was used for the different patient characteristics.

This study was carried out after a written approval had been issued by the Department of Clinical Medicine and Therapeutics, University of Nairobi, and KNH/UON Ethics and Review committee based at KNH.

Results

Table 1 shows the demographic characteristics of the 150 diabetic patients recruited into the study. The study population had a mean (SD) age of 56.47 ± 13.43 years and a median of 57 years with majority between the ages of 46 – 65 years at 52%. The population was predominantly females at 66% and most had attained primary school education at 45.3 years.

Table 1: Demographic information of the patients (N=150)

Characteristic	Frequency n (%)
Age group (years)	
18 – 25	1 (0.7)
26 – 35	7 (4.7)
36 – 45	26 (17.3)
46 – 55	36 (24.0)
56 – 65	42 (28.0)
66 – 75	26 (17.3)
76+	12 (8.0)
Sex	
Male	51 (34.0)
Female	99 (66.0)
Marital status	
Single	7 (4.7)
Married	122 (81.3)
Separated/Divorced	3 (2.0)
Widowed	18 (12.0)
Education level	
None	6 (4.0)
Primary	68 (45.3)
Secondary	54 (36.0)
Tertiary	22 (14.7)

Table 2 shows the clinical and anthropometric characteristics of the 150 study participants. The mean duration since diagnosis of diabetes was 10.3 years with majority having been on follow up for 1-10 years. The most common mode of treatment was oral hypoglycemic agents only in 47.3%.

The study population had comorbidities of hypertension at 65.3% whose mean blood pressure was at 140/78mmHg (±20.8mmHg) and obesity at 36%.

Table 3 shows the laboratory characteristics of the study population. Hyperuricemia prevalence is at 19.3% in the study participants. The mean (SD) serum uric acid level was 5.02 mg/dl (299µmol/L). Glycemic control was good as the mean (SD) HbA1c was 7.76% with 42.7% having a HbA1c below 7%.

Table 4 shows the relationship between serum uric acid levels and demographic data. Results show that there are no statistical differences between hyperuricemia in respect to age (p = 0.067), BMI (p = 0.100), and history of hypertension (p = 0.315). Female sex is a risk factor for hyperuricemia in the study (p = 0.046). Serum uric acid levels had no correlation with duration of diabetes, r = 0.019, p = 0.816 and glycemic control p = 0.013.

Table 2: Clinical and anthropometric characteristics of the study population

Clinical characteristics	All study participants	
	N	(%)
Duration since diagnosis of DM (years)	Mean (SD)	Median
	10.3 ±7.8 years	10.0 years
Duration of diabetes (years)		
1-10	87	58
11-20	51	34
21-30	7	4.7
31-40	5	3.3
History of hypertension		
Yes	98	65.3
No	52	34.7
Current diabetic medication		
Insulin injections	23	15.2
Insulin and oral hypoglycemics	55	36.7
Oral hypoglycemic agents only	71	47.3
None	1	0.7
BMI category		
Normal	37	24.7
Overweight	59	39.3
Obese	54	36.0

Table 3: Laboratory characteristics of the study population

Laboratory parameter	Mean±SD (n = 150)	Median
HBA1c	7.76% ± 2.3	
Serum uric acid levels	5.02 ± 1.84 mg/dl (299µmol/L)	4.60 mg/dl (274µmol/L)
Categories of parameters	N	(%)
HBA1c category		
Good (< 7%)	64	42.7
Moderate (7 to 8 %)	32	21.3
Poor (> 8 %)	54	36.0
Serum uric acid level category		
Low (< 3.4 MG/DL / <202µmol/L)	16	10.7
Normal (3.4 – 7.2 MG/DL / 202 - 428µmol/L)	105	70.0
High (> 7.2 MG/DL / >428µmol/L)	29	19.3

Table 4: Correlation of selected characteristics with serum uric acid levels among the study participants

	Frequency n (%)			Total n (%)	P value
	Hypouricemia	Normouricemia	Hyperuricemia		
Age (years)					
18 – 25	1 (6.2)	0 (0.0)	0 (0.0)	1 (0.7)	0.067
26 – 35	0 (0.0)	7 (6.7)	0 (0.0)	7 (4.7)	
36 – 45	4 (25.0)	20 (19.0)	2 (6.9)	26 (17.3)	
46 – 55	5 (31.2)	21 (20.0)	10 (34.5)	36 (24.0)	
56 – 65	1 (6.2)	33 (31.4)	8 (27.6)	42 (28.0)	
66 – 75	3 (18.8)	18 (17.1)	5 (17.2)	26 (17.3)	
76+	2 (12.5)	6 (5.7)	4 (13.8)	12 (8.0)	
Sex					
Male	1 (6.2)	39 (37.1)	11 (37.9)	51 (34.0)	0.046
Female	15 (93.8)	66 (62.9)	18 (62.1)	99 (66.0)	
BMI					
Normal	6 (37.5)	28 (26.7)	3 (10.3)	37 (24.7)	0.100
Overweight	6 (37.5)	43 (41.0)	10 (34.5)	59 (39.3)	
Obese	4 (25.0)	34 (32.4)	16 (55.2)	54 (36.0)	
History of hypertension					
Yes	8 (50.0)	69 (65.7)	21 (72.4)	98 (65.3)	0.315
No	8 (50.0)	36 (34.3)	8 (27.6)	52 (34.7)	

Discussion

The study established that 1 in 5 patients with diabetes (19.3%) had hyperuricemia. Hyperuricemia was predominantly seen in females at 62.1% and obese study participants at 55.2%. Studies done in different countries give a prevalence ranging from 11.4 – 32% in Type 2 DM patients. The prevalence in our study is lower in comparison to what is reported in studies conducted in Egypt, Ethiopia and Nigeria but has a similar prevalence to the study done locally in Kenya[6-8,15].

The variation in prevalence can be attributed to differences in population profiles such as different dietary habits and choices, as well as geographical / environmental and genetic differences. Some of the differences observed in prevalence of hyperuricemia across in the above studies[6-8] are attributable to the difference in sample sizes and cut off value for defining hyperuricemia used by the authors. Our study excluded patients with deranged renal function tests based on calculating eGFR, dyslipidemias and any drug, that would potentially influence serum uric acid levels. These exclusion criteria may have contributed to our low prevalence. In our study, hyperuricemia is defined as serum uric acid levels above 7.2mg/dl (428µmol/l). The mean (SD) age of our study population was 56.47 years (±13.4 years) and the mean (SD) duration of DM was 10.3 ± 7.8 years.

Ogbera *et al*[8] used a cut off point of 7.0mg/dl for hyperuricemia, did not exclude dyslipidemias and used a large sample size of 601 patients. It has been shown that serum uric acid is positively associated with serum triglycerides and total cholesterol. Fouad *et al*[7] also found a high prevalence, however he did not exclude patients with deranged renal function tests and used a large sample size of 986 patients. Patients with low eGFR tend to have hyperuricemia due to poor excretion[16]. Woyesa *et al*[6] also found a high prevalence rate of hyperuricemia at 33.8%, however his sample size was larger than our study. Majority of his sample population were obese and he did not exclude dyslipidemia. Rao *et al*[17] found a low prevalence as he had a small sample size of 70 patients. Locally Sylvia *et al*[15] found hyperuricemia in 44% of hypertensive patients attending Moi Teaching and Referral Hospital. She further looked into those with diabetes and found a prevalence of 18.2%. She had similar findings to our study as her diabetic patients with hyperuricemia were predominantly female, obese and in similar age bracket.

Obesity has been found to contribute to hyperuricemia[18]. BMI is highly dependent on the individual's genetic composition, dietary habits and level of physical activity. Majority of our population were obese and overweight at 75.3%. In the hyperuricemia group 89.7% were in the overweight and obese group. The mean (SD) BMI among the patients with hyperuricemia was 29.2 kg/m². This is similar to majority of the studies. Ogbera *et al*[8] found a mean (SD) BMI of 28.9 kg/m² and Fouad *et al*[7] found a mean (SD) BMI of 30 kg/m² in the patients with hyperuricemia. Locally Sylvia *et al*[15] found a mean (SD) BMI of 30.2 kg/m² in the hyperuricemia patients and achieved statistical significance. Rao *et al*[17] found a low prevalence, his study had lower number of obese participants. In our study we did not reach a statistical significance between serum uric acid levels and BMI, p = 0.100. Though we did not entirely screen for metabolic syndrome in our study, it seems like most of our patients would fall in this category; considering that the prevalence of obesity and metabolic syndrome is rapidly increasing in developing countries due to urbanization, unhealthy food options and physical

inactivity. Metabolic syndrome causes insulin resistance which enhances renal urate reabsorption via stimulation of urate-anion exchanger and/or the sodium dependent anion co-transporter in brush border membranes of the renal proximal tubule. Our population also needs to be screened for fructose consumption habits. The epidemic trend of obesity in recent years has also coincided with the increasing use of fructose especially in beverages. Fructose intake contributes to insulin resistance, impaired glucose tolerance, and hyperinsulinemia predisposing to hyperuricemia by increasing ATP degradation to AMP, a uric acid precursor and also de novo purine synthesis is accelerated[19].

Hyperuricemia has been strongly associated with male gender[6,7]. There was a female preponderance in the hyperuricemia group, 37.9% were males and 62.1% females, with a gender ratio of 1:1.6. This goes against what is known that gout is largely a male dominated disease. The difference can be explained by the possible reason that more females were recruited as they have a better health seeking behavior than the males. More females have diabetes in our setup, also proven by other studies looking into diabetes[20]. The age of women was significantly higher as most of them were older than 50 years, and may have been menopausal losing the protective effect of estrogen, and majority were in the overweight and obese group. The same has been shown in the study done by Sylvia *et al*[15] in Eldoret,who also had a female preponderance at 66% and hyperuricemia was seen in 71.1% of the females and is explained by the same possible reason of older age, and most being obese. Our study achieved a statistical significance between female gender and serum uric acid levels at p = 0.046.

Our study shows that majority of the patients with hyperuricemia were in the older age group, between the age of 46 and 65 years at 62.1% and is comparable to the other studies. All the other studies achieved a statistical significance between old age and hyperuricemia confirming that the prevalence of hyperuricemia is more with advancing age. Though our study did not achieve a statistical significance, p = 0.067. This is in keeping with the study done locally by Sylvia *et al*[15] who found a mean (SD) age of 54 years and also did not achieve a statistical significance. The mean (SD) age of the overall population in our study was 56.47 ± 13.4 years. It is comparable to the age obtained by Ogbera *et al*[8] in Nigeria who recorded a mean (SD) age of 59.9 years. However, Woyesa *et al*[6] in Ethiopia reported a lower mean (SD) age of 49.8 years and Fouad *et al*[7] in Egypt recorded a mean (SD) age of 47.9 years.

Hyperuricemia has been found to be prevalent in hypertension[15]. In our study, 65.3% had a documented diagnosis of hypertension with 72.4% being hypertensive in the hyperuricemia group. Only 34% of the patients had adequate BP control. It is also quite evident that diabetes and hypertension do co-exist in many of our patients. Diabetic patients with hypertension are more vulnerable to both cardiovascular and renal complications compared to diabetic non-hypertensive patients; hence, BP control is paramount in this patient population. We excluded patients on Losartan due to its urate lowering effects and thiazide diuretics which increase serum uric acid levels. Our study did not achieve statistical significance between serum uric acid and hypertension, p = 0.315.

The mean (SD) duration of DM in our study is 10.3 ± 7.8 years. This is higher in comparison to the other studies. Ogbera *et al*[8] reported a mean (SD) duration of 6.9 years and Woyesa *et al*[6] reported a mean (SD) of 7.2 years. Longer duration of disease predisposes to a higher likelihood of diabetic complications predisposing to hyperuricemia and also requiring intensified treatment, such as use of injectable as a viable treatment option to achieve good glycemic control, this has been shown in the study that 53% were on insulin based therapy either as monotherapy or in combination with the oral drugs. The relationship of hyperuricemia with duration of diabetes needs more studies as the other studies done have found different results. Woyesa *et al*[6] reported patients with duration of diabetes with less than 10 years had more hyperuricemia as compared to patients with a diagnosis of a longer duration. Fouad *et al*[7] found the converse where patients with a diagnosis of 10 years and more had more hyperuricemia. Most of the patients with hyperuricemia in our study had a mean (SD) duration of more than 10 years. There was no correlation between serum uric acid levels and duration of diabetes P = 0.816.

Glycemic control was generally good at 42.7% having HbA1c below 7% based on the ADA criteria[3]. This shows improvement to other studies done, Omari *et al* (KNH 2013) found 29.2% with HbA1c below 7%; and Otieno *et al* (KNH 1998) found 39.5% of patients with HbA1c less than 8%. Patients with poor glycemic control are more likely to have hyperuricemia as compared to those with good glycemic control and this was found to be statistically significant in the other studies. We did not achieve a statistical significance in our study (p = 0.013) as the glycemic control was largely good and the population sample size was small. Poor glycemic control is associated with hyperinsulinemia that enhances uric acid reabsorption in the kidneys[21].

Conclusion

(i) We found a relatively high prevalence of hyperuricemia at 19.3% in our study population.
(ii) Females have been shown to have a higher prevalence and those in the age group of 40 – 60 years should be routinely screened.
(iii) Hyperuricemia has no correlation with duration of diabetes and glycemic control in the study.
(iv) Hyperuricemia has no relationship with the variables of age, BMI and hypertension in the study. Only female gender achieved significance.

Study limitations

(i) This was a cross-sectional study hence no causal inference or temporal association could be drawn. It would have been ideal to compare the serum uric acid levels obtained in our study with those generated from the local population; however, there is lack of locally generated data on serum uric acid levels.
(ii) We were unable to investigate for other causes of hyperuricemia among our diabetic patients due to limited resources. Our study did not factor in genetics, which significantly affect the serum uric acid levels.
(iii) This was a single center study with a relatively small sample size so these results may not be generalizable to the entire population of patients with Type 2 diabetes in Kenya.
(iv) Patients included in the study are not representative of all the patients with Type 2 diabetes as confounding factors like deranged renal functions and dyslipidemias were excluded and the lack of a control group to compare with serum uric acid levels in the general population.

Recommendations

(i) Studies should be conducted to determine serum uric acid levels in the normal population. This will show the prevalence of hyperuricemia, as well as give normal population values in the local population.
(ii) Regular screening for serum uric acid levels in the patients on follow up in the diabetic clinic especially female patients in the age of 45 to 60 years.

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