

High Prevalence of Hyperuricemia and Gout in North American Patients with IgA Nephropathy

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Abstract

Objectives: To determine the prevalence of hyperuricemia (HU) and gout in 153 adult IgAN patients in North America (NA) and to compare this with the prevalence in the USA general population and with IgAN patients in Asia and Europe.

Methods: Serum creatinine and serum uric acid (SUA) concentrations were measured in a central laboratory. Estimated glomerular filtration rates (eGFR) were determined in 109 of the patients and the prevalence of HU (SUA>7 mg/dl in men; >5.7 mg/dl in women) was correlated with chronic kidney disease (CKD) Stages 1 (eGFR \geq 90 ml/min/1.73m²), 2 (eGFR 60-89 ml/min/1.73m²), 3 (eGFR 30-59 ml/min/1.73m²), and 4 (eGFR<30ml/min/1.73m²).

Results: Seven patients (all males with a median age 50 years, range 33-63 years), who had been diagnosed with gout, were receiving allopurinol. The SUA levels in these patients were not used in defining the prevalence of HU. They all had reduced eGFRs (30-90 ml/min/1.73m²). HU was detected in 96 (65.8%) of the other 146 patients. SUA was >9mg/dl in 30 of these patients. HU was present in 43.2% of CKD1 patients; 67.6% of CKD2 patients, 85.7% of CKD3 patients, and both of the two CKD4 patients.

Conclusions: Persistent HU and gout occur more frequently in IgAN patients in NA compared with the general population and with IgAN patients in other parts of the world.

Keywords: IgA Nephropathy; Hyperuricemia; Gout

Introduction

The relationship between hyperuricemia (HU) and chronic kidney disease (CKD) has been a topic of great interest in recent years [1-4] and some studies have shown that lowering serum uric acid (SUA) levels may slow the rate of progression of CKD [5-6]. Reports describing HU in adult patients with IgA nephropathy (IgAN) have been especially prominent [7-25] and have increased rapidly since 2010 [14-25]. However, none of the reports has involved patients in North America (NA). Surprisingly, little attention has been paid to the prevalence of gout in IgAN patients with HU. HU has also been incriminated as an independent risk factor for cardiovascular and cerebrovascular events [1,26-29]. In this study, we report SUA levels in 153 IgAN patients aged \geq 20 years of age from Canada and the United States (USA) who were enrolled in two multicenter trials [30,31]. We also define the correlation between SUA and CKD categories, as determined by two formulas [32,33] in non-gout IgAN patients, and describe the features of 7 gout patients within this cohort.

Subjects and Methods

Inclusion criteria for this post-hoc study

1. Patient age \geq 20 years
2. Renal biopsy diagnostic for IgAN
3. Measurements of SUA and serum creatinine

Exclusion criteria

1. Systemic lupus erythematosus

2. Henoch-Schönlein purpura
3. Chronic liver disease or hepatitis
4. History of other major organ system disease or malignancy.

Objectives of the study

- A. To compare prevalence data for HU in our non-gout patients versus the USA general population and versus IgAN patients in other parts of the world.
- B. To describe the prevalence of HU in different CKD categories.
- C. To describe a series of gout patients who have IgAN.

Laboratory Evaluations

SUA and serum creatinine (SCr) concentrations were measured on the Roche Modular Chemistry Analyzer in a central laboratory (Laboratory Corporation of America). eGFR was calculated using both the Cockcroft-Gault (CG) and CKD-EPI equations [32,33].

Definitions

There is no standard definition for HU in men or women. This is exemplified by published reports of HU in IgAN patients from around the world, wherein at least 9 different definitions have been used [7,9,10,13-15,17-19]. We define HU as SUA>7 mg/dl in men, >5.7 mg/dl in women.

Statistics

Summary statistics are reported as count (%). Pearson correlation coefficients were calculated to estimate the linear relationship between

continuous variables. The criterion for statistical significance was set at $\alpha=0.05$, two-tailed. SPSS version 22 (IBM, Armonk, NY) was used for analyses.

Results

Prevalence of HU in non-gout IgAN patients

The overall prevalence of HU in 146 non-gout IgAN patients aged 20-63 years was 65.8% (96/146). The prevalence of HU in the 145 non-gout IgAN patients aged 20-59 years is compared with the general US population in Table 1 [34]. One non-gout patient was 63 years old and is not included here. The data are categorized according to a) sex and b) age group. Severe HU (>9 mg/dl) in both men and women was present in 30 (20.5%) of the patients. Evidence of the persistence of severe HU in 18 of these patients, who had 3-4 SUA levels at monthly intervals (but were not treated), is depicted in Figure 1.

Prevalence of HU in non-gout IgAN patients in different CKD categories

Figure 2 shows the relationship between eGFR (based on both the CG equation and the CKD-EPI equation) and SUA levels. The correlation was stronger when the eGFR was estimated using the CKD-EPI equation, which will therefore be used below to define the CKD categories. HU was present in 43.2% of the patients who were categorized as CKD1 (eGFR ≥ 90 ml/min/1.73m²); 67.6% of the patients categorized as CKD2 (eGFR 60-89 ml/min/1.73m²); and 85.7% of the patients categorized as CKD3 (eGFR 30-59 ml/min/1.73m²). Both of the two CKD4 patients (eGFR <30 ml/min/1.73m²) had HU.

Prevalence of gout in IgAN patients

Seven male gout patients, 33-63 years of age (10% of 70 males in this age range), had SUA levels ranging from 5.9 to 9.5 mg/dl despite receiving allopurinol for gout. Clinical features, laboratory results and medications in the 7 patients, and in a 26-year-old male patient who had a SUA 11.4 mg/dl and then developed gout 6 months later, are shown in (Table 2). The eGFR was below the normal range in all 8 patients. Although the 7 gout patients were receiving allopurinol, SUA levels had been reduced to the desired range (<6 mg/dl) in only one of them (5.9 mg/dl). Also shown in Table 2 are the body mass indices (BMI), which ranged from 24.9 to 30.6

Prevalence of HU (SUA>7 mg/dl in males; >5.7 mg/dl in females)	IgAN Patients in NA	US Population
Overall (n=145)	67%	21.4%
Males (n=86)	66%	21.2%
Females (n=59)	66%	21.6%
20-29 years (n=47)	55%	18.6%
30-39 years (n=70)	73%	15.3%
40-49 years (n=18)	59%	17.9%
50-59 years (n=10)	80%	22.6%

Table 1: Prevalence of HU in non-gout IgAN patients in North America* versus the general US population (NHANES 2007-2008) [34].

*This table excludes 8 patients who were >59 years of age and/or were being treated with allopurinol.

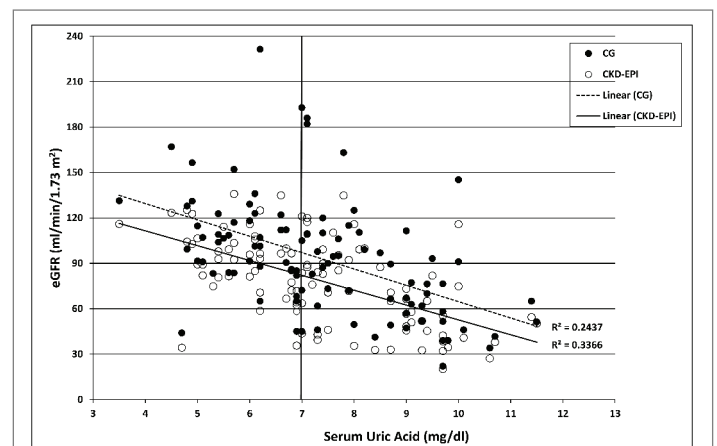


Figure 2: Inverse correlation between serum uric acid and estimated GFR (based on both CG and CKD-EPI equations) in 101 adult non-gout IgAN patients aged 20-59 years.

kg/m² in all but one patient who had a BMI of 44 kg/m². Most of the gout patients would therefore be classified as “overweight” or “mildly” obese (BMI >30 kg/m²).

Discussion

The main conclusion that can be drawn from this study is that the prevalence of HU is very high in North American IgAN patients. This includes patients who have a relatively well preserved GFR (i.e. HU was present in 55% of patients with CKD stages 1 and 2 (eGFR ≥ 60 ml/min/1.73m²). Our study also suggests that severe HU (SUA >9 mg/dl) and gout are relatively common in NA males with IgAN, especially those over 39 years of age, and that management of elevated SUA levels in such patients is sub-optimal since none of the asymptomatic HU patients were being treated and the SUA was <6 mg/dl in only one of the gout patients.

The prognostic importance of HU in IgAN patients has been examined in previous reports by two major approaches: a) correlation with renal histopathology and b) correlation with progressive deterioration of renal function. At least 9 reports, from 5 countries, have shown more severe histologic lesions in adult IgAN patients with HU when compared to patients with normal SUA levels [10-12,14-16,22,23,25]. The first large study evaluating the relationship between SUA and renal pathology in IgAN patients was reported by Ohno et al. in 2001 [10]. They found that HU correlated positively with tubulo-interstitial damage in a study involving 748 IgAN patients. This correlation was confirmed by Myllymaki in 2005 [11]. In 2011, Ghani et al. found that higher SUA levels were associated with Hass classes III to V [16]. Cheng et al. [22] in 2013,

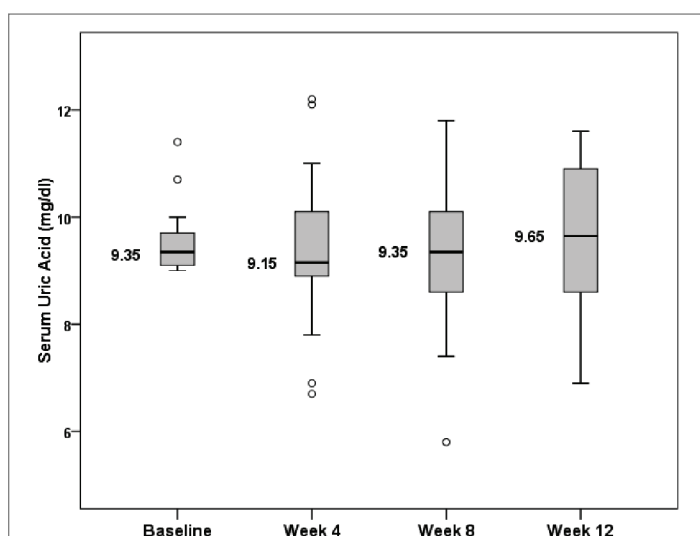


Figure 1: Serial (3-4) monthly SUA measurements in 18 adult IgAN patients who presented with SUA ≥ 9 mg/dl. N=18 for all time points except Week 4 where n=14.

ID#	Ht cm	Weight kg	BMI kg/m ²	Age yrs	BP mmHg	UP/C (mg/dl)	S Creat (mg/dl)	eGFR (ml/min/1.73m ²)		SUA μ mol/L (mg/dl)	Medications
								CKD-EPI	CG		
49	175	85	27.8	33	124/80	0.9	1.4	66	77	9.5	ALL, ARB, FO
69	183	86	25.7	53 ^②	135/79	2.3	2.2	33	39	8.9	ALL, ACE, ASA
87	179	98	30.6	41	103/61	0.8	1.4	62	76	6.2	ALL, ACE, ARB, FO, STAT
103	175	92	30.0	57 ^②	142/98	2.9	1.1	74	79	5.9	ALL, ACE, ASA, COL, TH
139	188	145	41.0	39	138/92	1.9	1.7	50	75	8.2	ALL, ACE, COL
165	178	79	24.9	50	130/80	0.3	2.3	32	38	6.1	ALL, ACE, FO, STAT
183	173	90	30.1	63 ^②	112/75	2.1	1.5	49	54	6.8	ALL, ARB, CCB, STAT
97 ^①	175	79	25.8	26	116/80	1.6	1.7	54	65	11.4	ACE, ARB, CCB, FO, FU

Table 2: Patients with IgA nephropathy and gout

BMI: Body mass index; UP/C: Urine protein + urine creatinine; ALL: Allopurinol (dosage ranged from 100 mg to 300 mg per day); ACE: Acetyl salicylic acid; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; COL: Colchicine; FO: Fish Oil; FU: Furosemide; STAT: Statin; TH: Thiazide diuretic

①Patient #97 was not diagnosed with gout and was not receiving ALL at the time of the initial evaluation. He developed podagra 10 months into the study. He was then treated with ALL and COL. His SUA then fell from (11.2 to 6.9 mg/dl).

②The three patients > 50 years of age had all been treated with ALL for 4-6 years before these measurements were obtained.

Country	Author/Year (Reference)	Number of patients	Definition of HU	Prevalence of HU ^①	
				A.	B.
Japan	Hosoya et al. 1989 [7]	357	M>7 mg/dl F>7 mg/dl	26%	52%
	Ohno et al. 2001[10]	204	M \geq 7 mg/dl F \geq 7 mg/dl	24%	54%
Finland	Syrjanen et al. 2000 [9]	189	M>7.5 mg/dl F>5.7 mg/dl	29.6%	57%
Korea	Kim et al. 2012 [19]	193	M \geq 7.3 mg/dl F \geq 5.3 mg/dl	25.9%	64%
Poland	Sulikowska et al. 2008 [13]	50	M \geq 7.8 mg/dl F \geq 6 mg/dl	40%	53%
China	Cui et al. 2011 [15]	148	M>7 mg/dl F>5.8 mg/dl	28%	68%
	Shi et al. 2012 [18]	353	M>7 mg/dl F>6 mg/dl	31.7%	67%
	Cheng et al. 2013 [22]	348	M>7 mg/dl F>6 mg/dl	19%	67%
	Zhou et al. 2014 [23]	623	M>7 mg/dl F>6 mg/dl	51%	67%

Table 3: Global prevalence of HU in Adult IgAN patients

①Column A = Prevalence of HU described in these individual reports from Asia and Europe. Column B = Prevalence of HU in NA patients described in the current paper using the same criteria for HU.

noted increased severity of glomerulosclerosis, tubulo-interstitial disease and vascular injury in 66 IgAN patients with HU (SUA>7 mg/dl in men; > 6 mg/dl in women) compared to 282 patients with normal SUA levels (p<0.05). In 2014, Zhou et al. [23] found a significant correlation between SUA and tubulo-interstitial fibrosis/tubular atrophy at an early stage of disease in 623 IgAN patients [23]. In a further study in 2014, Moriyama et al. [24] reported that HU was associated with global sclerosis in patients with IgAN, specifically patients with CKD Stage 3A [25].

Ten studies over the past 15 years have shown that HU is an independent risk factor for progressive renal insufficiency in IgAN patients [7,9,10,17-20,22,24,25]. Four of the studies from China, which involved a total of 2,868 patients, showed that HU was an independent risk factor by multivariate analysis [17,18,22,24]. Similar findings were reported in 2 studies from Japan that involved 1,238 patients [7,10]. Other reports from Finland, Hungary and Korea involved fewer patients [9,19,20], but came to the same conclusions.

The prevalence of HU and gout in our patients appears to be considerably higher than reported elsewhere—even when different definitions for HU are employed (Table 3). For example, in Japan, where HU is defined as

SUA>7 mg/dl in both men and women, the average prevalence of HU was 25% of 561 patients [7,10] compared to 52% of our patients using the same definition. In China, where HU is defined as SUA >7 mg/dl in men and >6 mg/dl in women, the average prevalence of HU in 4 reports describing 1472 patients [15,18,22,23] was 41% compared to 67% of our patients using the same criteria.

Why is HU so prevalent in IgAN patients in NA? The answer to this question is probably multifactorial. It is clear that the prevalence of HU in the USA population as a whole is on the increase [34]. It is likely that changes in diet, which include a higher intake of fructose, may play a significant role in this phenomenon [35]. In addition to these dietary considerations, recent studies have raised the possibility that the association of HU with IgAN may have a genetic component. Gharavi et al. [36] demonstrated linkage of IgAN to chromosome 6q22-23 in 60% of 30 IgAN kindreds and Nath et al. [37] demonstrated that a major focus for control of SUA was also present in chromosome 6q22-23 in 644 participants in the San Antonio Family Heart Study. Nath et al. [37] suggested that one or more genes in this genetic region may influence SUA levels and be associated with IgAN.

Our study has also documented a high prevalence of gout in NA patients with IgAN (10% of 70 males aged 30-63 years). The most striking statistic in our study was seen in men aged 41-63 years. Five (19.2%) of 26 men in this age group were receiving allopurinol for gout when IgAN was diagnosed. Surprisingly, the prevalence of gout in IgAN patients has only been addressed in 3 previous publications. Hosoya et al. [7] described gout in 2 of 357 patients; Shi et al. [18] in 2 of 353 patients, and Syrjänen et al. [9] in 2 of 223 patients. However, Syrjänen et al. [9] reported that gout developed subsequently in 11 of their patients during a prolonged follow-up (median 10 years). It is worth noting that the patient cohort reported by Syrjänen et al. [9] was older (median age 41 years at the time of renal biopsy) than most series in the literature.

The results of our post hoc analysis indicate that many adult IgAN patients in NA have persistent levels of SUA that have been shown to be associated with increased rates of cardiovascular events [26-29], as well as progressive CKD. The lack of specific guidelines regarding the management of HU in NA patients with IgAN, or other forms of CKD, has resulted in most patients with severe HU being untreated (as exemplified by patients with persistent levels of SUA ≥ 9 mg/dl in the present study). In contrast, recent Japanese guidelines, published by Yamanaka, recommend that drug therapy to reduce SUA levels should be considered in patients with asymptomatic HU when the SUA reaches 8 mg/dl if the patients have renal disease or hypertension [38]. If the Japanese guidelines were adopted for patients in this study, uric acid lowering therapies would be considered in at least 31% of the patients (40% of the male patients). Hopefully, future clinical trials will define the risk/benefit of therapeutic approaches designed to lower SUA levels in patients with IgAN and HU, especially those with SUA levels ≥ 9 mg/dl, despite the challenges associated with such a trial as detailed by Badve et al. [39].

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