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Hyperuricemia and Obesity in North American and European Children with IgA Nephropathy

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Abstract

Background: Hyperuricemia and obesity are associated with more severe renal pathology and more progressive disease in adults with IgA nephropathy (IgAN). However, only one study has described the prevalence of hyperuricemia and none has described obesity in pediatric patients with IgAN.

Methods: The prevalence of hyperuricemia and obesity in IgAN patients 7 to 18 years of age was compared between multiple centers in the USA and Canada (USA/CAN group) and 2 centers in the Czech Republic and Germany (CZE/GER group). Serum uric acid (SUA) and estimated glomerular filtration rate were measured in 79 USA/CAN patients and 48 CZE/GER patients. Body mass index percentiles (BMI percentiles) were compared between 51 of the 79 USA/CAN patients and all 48 CZE/GER patients.

Results: The prevalence's of both hyperuricemia and obesity were higher in the USA/CAN patients than the CZE/GER patients: 35.4% versus 16.7%; p=0.026, and 35.3% versus 4.2%, p<0.001, respectively. The BMI percentile in the combined populations was significantly higher in hyperuricemic patients (78.9 ± 21.6 versus 60.2 ± 31.0), p=0.003.

Conclusions: There is a much higher prevalence of hyperuricemia and obesity in pediatric IgAN patients in the USA/CAN compared to CZE/GER. These abnormalities may have serious long-term consequences for the USA/CAN patients.

Keywords: BMI percentile; Hyperuricemia; IgA Nephropathy; Obesity

Introduction

Hyperuricemia (HU) is considered by some investigators to be an independent risk factor for both cardiovascular and cerebrovascular events and for progressive disease in patients with chronic kidney disease (CKD), and is also associated with obesity, metabolic syndrome, albuminuria and essential hypertension, even in children [1-6]. In studies conducted around the world, HU has been detected in up to 51.5% of adult patients with IgA nephropathy (IgAN). This combination is often associated with more severe renal histopathology and a poor prognosis [7-10]. Only one report from Seeman et al. [11] has described the prevalence of HU in children and adolescents with IgAN. They reported a low prevalence of HU (14%) in their patients. Obesity has also been incriminated as a risk factor in adult patients with IgAN [12,13]. Although there are no reports of obesity in children with IgAN, severe obesity was shown recently to be associated with an increased prevalence of cardio metabolic risk factors in children and adolescents 3-19 years of age in the USA [14].

In this observational study, we compare serum uric acid (SUA) levels in 79 IgAN patients ≥ 7 to ≤ 18 years of age in the USA and Canada (USA/CAN) with 48 patients of comparable age in the Czech Republic and Germany (CZE/GER). Some of the CZE/GER patients were included in the previous report referenced above [11]. We also compare the prevalence rates of HU in patients of comparable age based on samples drawn up to 20 years apart in each of the locations. In addition, we compare the prevalence of overweight and obesity (based on body mass index percentiles (BMI percentiles)) in the USA/CAN and CZE/GER patients. Finally, we examine the correlations between SUA and CKD Stage (1 versus 2), obesity, blood pressure levels, and proteinuria.

Methods

Objectives of the study

1) To compare the prevalence of HU in children and adolescents with IgAN and relatively well preserved renal function (eGFR ≥ 60 ml/min/1.73 m^2) in the USA/CAN with those in CZE/GER; 2) to correlate these SUA measurements with CKD Stage 1 versus 2; and 3) compare the prevalence of obesity in the USA/CAN versus CZE/GER and evaluate the relationship between HU and obesity in the two populations.

Inclusion criteria: 1) age ≥ 7 to ≤ 18 years; 2) renal biopsy diagnostic for IgAN; 3) SUA and serum creatinine drawn simultaneously on at least one occasion, and 4) CKD Stages 1 (eGFR ≥ 90 ml/min/1.73m^2) or 2 (eGFR ≥ 60-89 ml/min/1.73 m^2).

Exclusion criteria: 1) systemic lupus erythematosus, 2) Henoch-Schönlein purpura (HSP), 3) chronic liver disease or hepatitis, 4) CKD stages 3-5, 5) use of allopurinol or other medications that were given to reduce SUA levels.

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Clinical Evaluations

Height, weight and blood pressure (BP) were measured and BMI percentiles were determined using the Centers for Disease Control and Prevention (CDC) on-line Calculator (http://nccd.cdc.gov/dnpabmi/Calculator.aspx).

Laboratory Evaluations

In the USA/CAN patients, SUA and serum creatinine (SCr) measurements were obtained as part of studies performed to determine eligibility for one of two prospective randomized clinical trials. Measurements in the CZE/GER patients were carried out as part of routine nephrologic studies in the clinical laboratories of the participating institutions. SUA concentrations were measured using an enzymatic colorimetric test. SCr was measured with a kinetic colorimetric assay (Jaffé method). SCr levels were used to calculate eGFR and CKD Stages according to the K/DOQI guidelines described in [15].

Definitions

For consistency, we will use the definitions for HU that were used previously by Seeman et al. [11], i.e. HU= SUA>5.88 mg/dl (>350 μmol/L) in all girls and in boys less than 15 years of age; and >7.06 mg/dl (>420 μ mol/L) in boys 15-18 years of age. Prevalence of HU was determined a) in 2 time periods; b) in boys and girls; and c) in two age categories: <15 years of age and 15-18 years of age. Persistent HU is defined as consistent elevation of SUA measurements (≥ 2 in each patient), which were available in most of the patients. Obesity is defined as BMI ≥ 95th percentile; overweight is defined as BMI ≥ 85 < 95th percentile [14].

Concomitant medications taken by patients when SUA levels were drawn

The medication class that was most frequently given to patients in both populations was an angiotensin-converting enzyme inhibitor (ACEi) (USA/CAN group: 39 of 78 patients (50%); CZE/GER group: 17 of 47 patients (36.2%); overall: 56 of 125 patients (44.8%); ACEi status was missing in 2 patients. The indications for starting an ACEi varied, i.e. hypertension versus proteinuria. Hence, we cannot conclude that patients on ACEi were hypertensive when the ACEi was started. Less than 10% of the patients were on other medications: fish oil: 7 patients, corticosteroids: 6 patients, thiazides: 5 patients, and angiotensin receptor blockers: 5 patients.

Statistics

Data were abstracted from clinical and study records and imported into SPSS ver. 22 (IBM Corp, Armonk NY). Continuous data are reported as means (SD); categorical data as counts (%). Analysis of variance or Students t-tests were used to analyze continuous data; chi-square analysis or Fisher's exact tests were used for categorical data. Pearson correlation coefficients were used to estimate the strength of the relationship between variables. An alpha of 0.05, two-tailed, was set as the criterion for statistical significance.

Results

Patient population

One hundred and twenty-seven patients fulfilled the eligibility criteria (79 from USA/CAN and 48 from CZE/GER). Clinical and laboratory features are shown in table 1. There were no differences in age, sex, height, serum creatinine or BP between the two groups. The mean body weight, BMI and BMI percentiles in the USA/CAN patients were significantly greater than those in the CZE/GER patients (p<0.001 for both). The mean eGFR and percentage of CKD 1 patients were lower in the CZE/GER patients but the majority of both populations had CKD 1.

SUA levels and HU

Whereas the initial SUA levels in the USA/CAN and CZE/GER patients were not statistically different (p=0.068), the percentage of patients with HU based on these initial blood samples was significantly greater in the USA/CAN group than in the CZE/GER group (35.4% versus 16.7%), p=0.026) and serial SUA measurements were considerably higher in the USA/CAN patients. Overall, 2 or 3 SUA measurements were obtained in 61 USA/CAN patients and 25 CZE/GER patients. Persistent HU was present in 42.6% of the USA/CAN patients and 12% of the CZE/GER patients. The mean SUA based on 2-3 measurements was 6.01 ± 1.88 mg/dl in the USA/CAN group and 4.80 ± 1.40 mg/dl in the CZE/GER group, p=0.005 (Table 1).

Subsequent analyses in the 2 patient populations showed that the prevalence of HU in children and adolescents varied according to sex, location and time period (Table 2). In period 1, the prevalence of HU in the USA/CAN group (1996-1999) versus the CZE/GER group was not significantly different (28.9% versus 15.8%, p=0.353). However, in period 2 (2003-2006), the prevalence of HU was greater in the USA/CAN group than the CZE/GER group (2003-2014) (44.1% versus 16.1%, p=0.030), and also when the two time periods were combined (35.4% versus 16.3%, p=0.026).The increase in SUA from period 1 to period 2 was similar in the 2 locations (USA/CAN: +0.59 (5.18 up to 5.77) mg/dl., CZE/GER: +0.67 (4.81 up to 5.48) mg/dl.).

Prevalence of obesity and overweight

There was a very high prevalence of obesity (35.3%) and overweight (21.6%) in the 51 USA/CAN patients (prevalence of obesity and overweight combined was 56.9%). The prevalence of obesity and overweight in the CZE/GER patients was 4.1% and 14.6% respectively (18.7% combined). Hence, there was an 8.6 fold higher prevalence of obesity and a 3 fold higher prevalence of obesity/overweight combined in the USA/CAN patients, p<0.001. There was no significant difference in the prevalence of obesity in the USA/CAN group over time, but in the CZE/GER patients, there was a higher prevalence of obesity and overweight combined in the second period (29%) compared to the first period (0%), when the highest BMI percentile among the 18 patients was only 74%.

Relationship between BMI percentile and SUA levels

The BMI percentile was significantly greater in the 30 hyperuricemic patients (78.9 ± 21.6) than the 69 normouricemic patients (60.2 ± 31.0, p=0.001) when the USA/CAN and CZE/GER patients were combined. The correlation between BMI percentile and SUA was statistically significant, r=0.245, p=0.014. The overall prevalence of HU was significantly greater in the obese/overweight children than in the non-overweight/non-obese children, i.e. 43.2% (16/37) versus 21.0% (13/62), p=0.015.The mean SUA was significantly higher in obese/overweight children versus non-overweight/non-obese children 6.10 ± 1.38 versus 5.35 ± 1.58, p=0.018.

When data from the 2 locations were evaluated separately, HU was present in 12.5% of the CZE/GER patients with BMI% < 85 versus 33.3% of the patients with BMI percentile ≥ 85; HU was seen in 36.4% of the USA/CAN patients with BMI percentile < 85 versus 48.3% of those with BMI percentile ≥ 85.

Relationship between CKD stages and SUA levels

CKD Stage 1 was present in 73/79 USA/CAN patients and 39/48 CZE/GER patients. CKD Stage 2 was present in 6 USA/CAN patients and 9 CZE/GER patients. The overall prevalence of CKD Stage 1 in the two populations was therefore 112 of 127 (88.1%) and CKD Stage 2, 11.9%. The prevalence of HU in CKD Stage 1 patients (27.0%) did not differ from that of CKD Stage 2 patients (31.3%), p=0.767.

	USA/CAN Patients (n=79)	CZE/GER Patients (n=48)	p-value
Period 1/2 (%)[a]	57.0%/43.0%	40%/60%	0.043
Age (%<15 yr)	13.86 ± 2.89 yr (51.9%)	14.35 ± 3.04 (43.8%)	0.365 (0.373)
Sex (%male)	68.4%	72.9%	0.586
Weight (Kg)	63.8 ± 22.6[b]	54.6 ± 15.6	0.014
Height (cm)	163.1 ± 14.0[b]	162.7 ± 17.7	0.911
BMI	25.4 ± 5.9[b]	20.2 ± 3.1	<0.001
BMI percentile (%obese/overweight)	78.1 ± 25.2[b] (35.3%/21.6%)	52.6 ± 28.9 (4.2%/14.6%)	<0.001 (<0.001/0.368)
Serum creatinine (mg/dl)	0.75 ± 0.28	0.73 ± 0.18	0.774
eGFR (min/min/1.73m²)	146.1 ± 43.2	120.0 ± 38.5	0.001
CKD Stage 1/2	92.3%/7.7%	81.3%/18.8%	0.063
BP (mm Hg)	120.9 ± 12.7/71.6 ± 10.81	122.4 ± 13.1/71.4 ± 9.2	0.592/0.868
SUA 1 (mg/dl)	5.63 ± 1.65	5.21 ± 1.42	0.151
HU (%) based on SUA 1	35.4%	16.7%	0.026
SUA 2 (mg/dl)	5.92 ± 1.85 n=61	4.80 ± 1.39 n=24	0.009
SUA 3 (mg/dl)	6.15 ± 2.01 n=62	4.55 ± 1.41 n=20	0.001
Mean SUA (mg/dl)[c]	6.01 ± 1.88 n=65	4.80 ± 1.40 n=24	0.005
ACEi	50.0% n=78	36.2% n=47	0.132
UP/C (mg/mg)[d]	1.89 ± 1.44	1.28 ± 1.61	0.032

Table 1: Clinical and laboratory features in patients with IgAN from USA/CAN and CZE/GER
[a]Period 1 = pre 2003; period 2 = 2003 and beyond
[b]Height, BMI and BMI percentile available in only 51 of the USA/CAN patients. Body weight was 62.2 ± 20.5 kg and serum creatinine was 0.76 ± 0.25 mg/dl in the 51 patients.
[c]Mean SUA based on 2 or 3 measurements of SUA in each patient .
[d]UP/C (=urine protein to creatinine) ratios calculated from first morning or 24-hour urines. Urine creatinines in CZE/GER patients were divided by 88.4 to convert the results from mg/mmol to mg/dl.

Age Groups	USA/CAN Period 1 (1996-1999)	USA/CAN Period 2 (2003-2006)	Combined results from both periods in USA/CAN pts.	CZE/GER Period 1 (1994-2000)	CZE/GER Period 2 (2003-2014)	Combined results from both periods in CZE/GER pts.
Boys ≥ 7<15 years	7/23 (30.4%)	3/5 (60.0%)	10/28 (35.7%)	0/7 (0.0%)	1/7 (14.3%)	1/14 (7.1%)
Boys 15 ≤ 18 years	5/11 (45.5%)	7/15 (46.7%)	12/26 (46.2%)	2/7 (28.6%)	2/14 (14.3%)	4/21 (19.0%)
All boys ≥ 7 ≤ 18 years	12/34 (35.3%)	10/20 (50.0%)	22/54 (40.7%)	2/14 (14.3%)	3/22 (13.6%)	5/36 (13.9%)
Girls ≥ 7<15 years	0/6 (0.0%)	2/8 (25.0%)	2/14 (14.3%)	0/0 (0.0%)	2/7 (28.6%)	2/7 (28.6%)
Girls 15 ≤ 18 years	1/5 (20.0%)	3/6 (50.0%)	4/11 (36.4%)	1/5 (20.0%)	0/1 (0.0%)	1/6 (16.7%)
All girls ≥ 7 ≤ 18 years	1/11 (9.1%)	5/14 (35.7%)	6/25 (24.0%)	1/5 (20.0%)	2/9 (22.2%)	3/13 (23.1%)
All patients ≥ 7 ≤ 18 years	13/45 (28.9%)	15/34 (44.1%)	28/79 (35.4%)	3/19 (15.8%)	5/30 (16.7%)	8/49 (16.3%)

Table 2: Prevalence of hyperuricemia (HU)[a] in children with IgAN and CKD 1 /2 (i.e. eGFR ≥ 60 ml/min/1.73m²)
[a]HU defined as SUA >5.88 mg/dl(>350 μ Mol/L) in all girls and boys ≥ 7<15 years of age; >7.06 mg/dl (>420 μ Mol/L) in boys 15 ≤ 18 years of age.

Association between BP and SUA levels

We restricted our evaluation of the relationship between BP and SUA to 69 patients who were not on an ACEi for the reasons describe previously in Methods. In these patients, the correlation between systolic BP and SUA was r=-.346 (p=0.010), between systolic BP and HU, r=.278 (p=0.040). The correlation between diastolic BP and SUA was r=.072 (p=0.600), between diastolic BP and HU, r=.154 (p=0.262).

Relationship between UP/C and SUA levels

Positive correlations were observed in the combined populations between UP/C and SUA, r=.188, p=0.036; and between UP/C and HU, r=.201, p=0.024.

Impact of medications on SUA levels

The SUA was 5.77 ± 1.64 mg/dl in the 56 patients who were receiving an ACEi versus 5.19 ± 1.47 in the other 69 patients, r=.186, p=.037, n=125. However, there was no correlation between patients with HU and those on an ACEi, r=0.058, p=0.518. HU was seen in 4/7 patients on fish oil; 0/6 patients on corticosteroids; 0/5 patients on thiazides, and 3/5 on angiotensin receptor blockers.

Discussion

The observations made in this study demonstrate clearly that both HU and obesity/overweight are more prevalent in USA/CAN patients

than similarly aged CZE/GER patients with IgAN, and that HU and obesity/overweight are associated with one another. The HU findings are not surprising since epidemiologic studies have documented that the prevalence of HU in the US population has increased in recent years. Zhu et al. [16] found that the prevalence of HU in adults increased by approximately 15% from 1988/1994 to 2007/2008 [14]. Many studies have shown that HU is a risk factor for progressive disease in adult IgAN patients (8-10), including those with well-preserved renal function. For example, Syrjänen et al. [8] and Ohno et al. [9] both found HU in 23% of IgAN patients with well-preserved GFRs.

Although studies of the impact of HU in children with CKD have been limited (2), many studies have shown that higher SUA levels in children are associated with hypertension [3,5,6]. Feig et al. [17] reported that reducing SUA levels in such patients had a significant beneficial effect on blood pressure (BP). In addition, Soletsky and Feig [18] reported that reducing the SUA levels using allopurinol in a group of children with SUA ≥ 5 mg/dl and pre-hypertension, reduced the systolic and diastolic BP significantly and Assadi [19] found that the combination of allopurinol and enalapril had a greater effect of BP than enalapril alone. This may be important in patients with IgAN since hypertension is known to be an important risk factor and treatment with enalapril or one of the other angiotensin-converting enzyme inhibitors has become standard therapy.

The importance of obesity and overweight in adult patients with IgAN was first highlighted by Bonnet et al. in 2001 [12]. Bonnet et al. found that being overweight at the time of diagnosis of IgAN correlated significantly with more severe renal biopsy lesions and increased levels of proteinuria and favored the subsequent development of both hypertension and deterioration of renal function. This issue was "re-visited" by the same group 12 years later in a larger number of patients (333 versus 162 in the original report), at which time the prevalence of obesity (10.3% versus 9.3%) and overweight (30.8% versus 32.1%) were essentially unchanged [13]. At the latest follow-up, there was a greater prevalence of CKD Stage 3 or more of the overweight/obese group (43.3% versus 21.0%, $p<0.0001$) and more of them progressed to dialysis or death.

The role of obesity in determining the severity of IgA nephropathy was studied in Japanese patients by Tanaka et al using quantitative analysis of renal biopsy features in 2009 [20]. They found that obese patients had significantly larger glomeruli ($p<0.0001$), thicker glomerular basement membranes ($p<0.001$), and more marked proteinuria than the non-obese group ($p<0.05$).

Kovács et al. addressed the prevalence of obesity, as well as other components of the metabolic syndrome, in 223 Hungarian patients with IgAN [21]. Sixty-eight (31%) of the patients were obese (BMI ≥ 30 kg/m^2). Patients with obesity had a greater risk of progressing to CKD Stage 3. It is noteworthy that HU was also found to be an independent risk factor for progression, but this was not mentioned in the other papers that examined the role of obesity. The harmful impact of the combination of HU and obesity deserves additional study in the future.

Our observations regarding the high prevalence of HU and obesity/overweight in children and adolescents with IgAN in the USA/CAN raise a number of questions with respect to causation, risk and treatment options. We did not collect diet histories in our patients but a higher consumption of certain foods containing fructose is a factor that has been proposed for the increasing prevalence of hypertension, HU, cardiac disease, and obesity in the USA population in general; it may also be playing a role in the USA/CAN pediatric population with IgAN [22]. Although, it is not possible at the present time to determine the optimal approach to the management of HU and obesity in children with IgAN, appropriate dietary recommendations should certainly be adopted. Hopefully, the issue will be addressed in future clinical trials. In the meantime, it will be up to physicians caring for the patients with IgAN+HU and/or obesity to discuss the pros and cons of current options with the parents and child and determine the therapy on an individual basis.

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