Original Research Article

A FURTHER STEP IN THE RELATIONSHIP BETWEEN URIC ACID AND VASCULAR RISK: A TUBULAR HANDLING OF URIC ACID IN HYPERTENSION STUDY.

ABSTRACT

Background

Uric acid poses a major risk in instances of both cardiovascular as well as kidney disease. It is not just an indication of progressive renal failure, it also provokes it, causing its development. We analysed uric acid kidney metabolism in a group of hypertensive patients, by comparing its results with those of a healthy group of people. We also studied it in cases of chronic kidney disease, the use of diuretics, as well as in cases of obesity.

Methods

We conducted a descriptive, cross-sectional and retrospective study of 95 hypertensive patients, whereby we studied the parameters of renal excretion of uric acid. We compared the results of hypertensive patients with pre-existing data of healthy people. We studied the impact of chronic kidney disease, the use of diuretics and the consequences of obesity in the renal metabolism of uric acid.

Results

The clearance (5,56 ml/min) and fractional excretion of uric acid (6,65%) are lower in hypertensive people than in the healthy population (UACl: 8-12 ml/min and UAEF: 8-10 %). The clearance also decreases significantly in hypertensive patients with chronic kidney disease compared to hypertensive patients with normal renal function (3.38 vs. 6.16 ml / min) and in patients treated with diuretics (6.1 vs. 6.4 ml/min). Obesity also contributes to a reduced renal excretion of uric acid.

Conclusions:

Renal excretion of uric acid was found to be reduced in cases of hypertension with normal renal function without diuretic therapy, in chronic kidney disease and where

treatment with diuretics was given. Given these findings, we need to ask ourselves if this could be a contributing factor to the pathogenic basis of many forms of essential hypertension, or whether it is the translation of the prejudicial impact of hypertension in the kidney.

KEY WORDS: Diuretics, Hypertension, Obesity, Uric acid

INTRODUCTION

Asymptomatic hyperuricemia is defined as the increase of uric acid (UA) to levels above 0,39 mmol/L in men and 0,33 mmol/L in women (due to the estrogen uricosuric effect) [1], which increases the risk of arthritis and nephrolithiasis.

Although the actual prevalence of hyperuricemina in our environment is unknown, we know it has increased in recent decades due to factors such as increased life expectancy, diets rich in fructose and higher rates of hypertension (HT), obesity and metabolic syndrome [1,2].

UA levels are a significant factor in the risk of cardiovascular and renal disease, especially in patients with hypertension, diabetes mellitus (DM) or heart failure. Hyperuricemia is a major cause of hypertension in humans, including the development of proteinuria – also occurring in laboratory animals – which may support the hypothesis that it induces renal damage, or its progression. Recent evidence suggests that UA is not only a possible indication of renal damage, but that it also carries with it the risk of progressive renal deterioration. [3].

Uric acid induces, in the vessels, a reduction in nitric oxide (NO) and the onset of reactive oxygen species, vascular inflammation, smooth muscle cell proliferation and the inhibition of endothelial growth factors. In the kidneys, apart from reducing NO, it increases renin values [4] and is associated with interstitial inflammation and microvascular damage, that leads to the development of interstitial fibrosis and afferent arteriolopathy, which induces vasoreactive HT [4,5].

The urate-anion exchanger (URAT1), responsible for the UA tubular reabsorption and regulation of its blood levels is expressed on the endothelial surface and in the smooth muscle cells of the afferent glomerular arteriole and makes possible a direct intracellular action of uric acid [6]**.**

The kidney is responsible for the elimination of 75% of UA. There are certain factors, which, by themselves or by their renal effects, may alter its excretion, such as renal failure (CRF), diuretics, hypertension or hyperinsulinemia [7]. The latter produces a 20 to 30 per cent reduction in the clearance of net and fractional UA, an effect observed notably in patients with insulin resistance, HT and obesity [8].

Thus, UA is an important risk factor in the loss of renal function independently of HT [7,9].

The objectives of our study:

- To assess the baseline of renal handling of UA in hypertensive patients, both with and without hyperuricemia, in the hypertension and kidney consultation of the Nephrology Department of our hospital.
- To examine whether the different parameters of tubular handling of UA are altered in situations of CRF (CrCl <60 ml/min).
- To study, in patients with normal renal function, the behaviour of tubular handling of UA parameters in cases of obesity and diuretics.

MATERIAL AND METHODS

This is a descriptive, cross-sectional and retrospective study of hypertensive patients seen in the Hypertension and Kidney department of our hospital in 2013, whose data was obtained from the medical records review.

The study protocol was approved by the local Ethics Committee and followed the tenets of the Declaration of Helsinki. Written consent was obtained from all patients.

Demographic and epidemiological characteristics, the existence of target organ damage, drug treatment received and conventional analytical parameters (using ‘fasting’ blood and 24-hour urine samples) were studied.

The LDL-cholesterol was calculated using the Friedewald formula. The presence of creatinine, uric acid, and phosphates in urine was established using a centrifuge

analyzer. Magnesium was determined by atomic absorption spectrophotometry and the sodium and potassium were obtained directly by flame photometry.

The study was conducted in 4 phases in order to avoid possible contradicting factors. Thus, in the first step the different parameters that influence UA renal metabolism in our hypertensive patients - as reflected in the records - were compared with those of healthy people. In the second step we examined whether the presence of CRF would bring to light differences in the UA metabolism in our patient group. In the third and fourth phases we wanted to find out if taking diuretics, or obesity, would have an effect on any of these parameters on a group of hypertensive patients with normal renal function.

A comparison of the two groups was made using non-parametric tests, since the variables studied did not have a normal distribution. The Mann-Whitney test for independent samples was used. The significance level was set at $p < 0.05$. The statistical power of the 4 phases study was calculated post hoc with the G* Power v. 3.1.6 program for MAC OS 10.6.8

(http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/).

The SPSS v.20.0 package for MAC OS 10.6.8 was used for the statistical treatment of the data. Cuantitative variables are expressed as median and interquartile range while quantitative variables are expressed as frequencies.

RESULTS

The first phase of the study was to compare the different parameters of UA renal metabolism in our hypertensive patients (n=95) with those without HT. The statistical power of this first phase is 60%.

Clearance and fractional excretion of UA values are lower than those of the healthy population (UACl: 8 to 12 ml/min and UAFE: 8-10%). Patients on diuretics have statistically significant higher glucose, creatinine and UA levels ($p < 0.05$), but no statistically significant differences were observed in UA elimination. The rest of the results are shown in table 1.

In the second stage of our inquiry we aimed to establish if the parameters of excretion of UA are influenced by CRF stage III (CrCl 30 to 60 ml/min), so we divided our groups into two categories: hypertensive CRF (n=22) and hypertensive patients with normal renal function (n=73).

The HTA-CRF group was slightly older (74 as opposed to 51 years), increased duration of hypertension (19 vs. 8 years), a higher percentage of diabetics (54.5% vs. 14%) and increased vascular impact of vascular disease at other levels. In this group there was a higher percentage of patients treated with allopurinol (47.6% vs. 19%) and diuretics (91% vs. 52%), particularly loop diuretics (77.3% vs. 17.3%). These patients also had significantly higher serum levels of glucose (7,88 vs. 5,72 mmol/L) and UA (0,36 vs. 0,3 mmol/L). The UACl was almost half that in the group of hypertensive patients with normal renal function (3.38 vs. 6.16 ml/min), which is a statistically significant result. However, the AUFE remained at similar values due to the correction of the renal elimination of UA with the degree of renal function. The rest of the results can be seen in table 2.

The statistical power of this study is 65,3%.

The third phase of the study was to determine if diuretic treatment affects the renal excretion of UA in hypertensive patients. We selected patients from the group hypertensive group with normal renal function (n=73) and divided them into two categories; those taking diuretics in their antihypertensive therapy (n=38) and those without the drug (n=35).

Both groups share similar characteristics in age, gender, weight, toxic habits, DM and dyslipidemia.

The group treated with diuretics had a longer history of HT (11 vs. 5 years), greater cardiovascular impact (stroke: 5.45% vs. 2.9%; left ventricular hypertrophy: 34.2% vs. 14.3%) higher percentage of kidney stones (36.8% vs. 14,5%); obesity (73.7% vs. 25.7%) and patients treated with allopurinol (23.5% vs. 13.8%).

The statistical readings of the third part of the global study is 68.0%. The results are shown in table 2.

In the last phase of our work, we wanted to test if obesity affects the renal handling of UA in our population of hypertensive patients. Thus, we selected our hypertensive patients with normal renal function (n=73) and divided them into two groups based on the coexistence of obesity (BMI> 30 kg/m^2); the obese hypertensive group, consisting of 37 patients and the hypertensive - but not obese - group consisting of 36 patients.

Both groups shared similar age, sex and degree of control of blood pressure. The obese group presented a longer HT history (11 years vs. 6), a higher percentage of alcohol consumption (25% vs. 2.8%), DM (18.9% vs. 8.3%), gout (8.1% vs. 2.8%), kidney stones (32.4% vs. 19.4%) and greater vascular disease.

The statistical power of the last study is 68.1%. The remaining results of this phase of the study can be seen in table 2.

DISCUSSION

UA is the end product of the catabolism of purines (adenine and guanine) in humans. Their low plasma protein binding allows freely glomerular filtering, almost 100% [1], so that proximal tubule is responsible for its disposal through a complex reabsorption, secretion and post-secretory reabsorption mechanism, whose carriers we know from recent years [6].

We know the relationship between uric acid and HT [8.9], kidney damage, obesity and diuretics use [5]. However, it is not clear if the CRF [9] is the cause of the impairment in the renal excretion of UA observed in these cases or simply another feature that occurs simultaneously.

There is evidence that supports the idea that serum UA levels influence blood pressure by activating the aldosterone-renin-angiotensin II system [9] and increases peripheral vascular resistances, causing contraction of the afferent arteriole - resulting in the loss of renal autoregulation with intraglomerular HT and renal hypoperfusion, which can lead to HT, tubulointerstitial inflammation and renal fibrosis [10,11]. UAC, therefore, may be an earlier indicator of impaired kidney perfusion than CrCl.

The results of our study indicates a lower renal elimination of UA in our hypertensive patients than that reported in studies of healthy groups. This lower clearance also came to light when we analysed patients with diuretic therapy or obesity. These results would

indicate that the pathogenic relationship between vascular disease and UA may be dependant on the processing of uric acid in the kidney - and not only for its serum level [12]. However, these results should be understood as partially ‘biased’, as the group itself is made up of hypertensive patients referred to the HTA-Nephrology department by their primary care general practitioners.

CRF significantly reduces renal clearance of UA [4], justifying hyperuricemia that accompany different stages of renal impairment. However, we note that the fractional excretion of UA (UAFE) parameter is a simple calculation, which may be useful in both epidemiological studies and therapeutic intervention in patients at cardiovascular risk who often have renal damage in context with target organ involvement [2].

The group of patients treated with diuretics has significantly higher levels of both glucose and UA; both known side effects of diuretic therapy. This group also revealed a lower UA renal clearance, although the observed differences were not statistically significant. The volume contraction induced by diuretics helps to reduce renal elimination, which was determined "per se" to act on these different transporters of the proximal convoluted tubule [6]. Both thiazide diuretics and the loop diuretics inhibit the NPT4 transporter from the apical membrane of the proximal tubule, which is responsible for the secretion of the UA [13,14]. The characterization of the different UA tubular transporters and understanding of the molecular mechanisms of its tubular metabolism may lead to the creation of new diuretics with uricosuric effects [13].

Obese patients tend to have a higher incidence of hyperuricemia and kidney stones, certainly in relation to the increased intake, but also by reducing the elimination of UA because of hyperinsulinism [15], which often accompanies obesity. In our study obese patients showed higher levels of UA and, although its elimination was significantly higher, by correcting it with the degree of renal function, the differences disappeared. There is a proven relationship between hyperuricemia, obesity and metabolic syndrome, secondary to widespread diets rich in fructose [16], which is the only carbohydrate known to increase the production and release of UA [9].

Our work, however, has several limitations, inasmuch as these studies are univariate (consequently, this does not rule out the possibility of additional influencing factors) and, owing to a lack of financial resources in the initial phase, the means of finding and representing a suitable research group was problematic. This necessitated drawing our

comparisons with data from existing records, meaning our studies are retrospective with low statistical authority (mainly due to a smaller cross section).

Notwithstanding, the results of our study show that renal excretion of uric acid is reduced in patients with HT and normal renal function for those not on diuretics, as well as in patients with chronic kidney disease and in diuretic therapy. Thus we must ask ourselves whether this reduction in renal clearance of UA could be the pathogenic basis for many forms of essential HT or whether, by contrast, it could be the result of the harmful impact of HT in the kidney.

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Table 1: Results of demographic variables, vascular risk factors and conventional analytical paramethers

VARIABLE	RESULT
Age	55 (44 -73)
Male/female	52 (54.7%)/42 (45.3% postmenopausal)
HTA evolution	10 (4 -20)
Smokers/non smokers/ex-smokers	20.4%/69.9%/9.7%
Alcoholism	12.8%
Obesity (BMI)	47.7% [BMI 30.32 (26.69 to 34.23)]

DM	22.1%
Hypercholesterolemia	49.5%
Hypertriglyceridemia	18.9%
Gout attack	7.4%
Stroke	3.2%
Left ventricular hypertrophy	29.5%
CRF (CrCl <60 ml/min)	23.2%
Kidney stone	26.3%
Antihypertensive treatment	92.6%
Diuretics	61.1%
Calcium antagonists	46.8%
ACE inhibitors	18.1%
AIIR antagonists	57.4%
Beta-blockers	33.7%
Alpha-blockers	9.8%
Other vasodilators	2.2%
Glucose	5,99 (5,38-7,16)
Urea	3,62 (2,83-5,48)
UA	0,5 (0,35-0,6)
Creatinine	80 (70-120)
Calcium	2,4 (2,3-2,48)
Phosphorus	1,1 (0,97-1,23)
Magnesium	0,9 (0,7-0,9)
Total cholesterol/HDL/LDL	4,9 (4,4-5,6)/1,2 (1,1-1,5)/2,9 (2,4-3,6)
Triglycerides	1,3 (0,9-2)
Sodium	139 (138-141)
Potassium	4.4 (4-4.6)
CRP	0,02 (0.01-0.03)
Homocysteine	0,74 (0.54-0.97)
HbA1c	5.7 (5.4-6.2)
CrCl	83.34 (59-127)
UA elimination	0.48 (0.36-0.64)
UACl	5.56 (3.74-7.67)

Table 2: Comparison of UA metabolism parameters depending on renal function, use of diuretics and obesity

VARIABLE	CrCl GROUP> 60 ml/min (n = 73)	CRF GROUP (n = 22)	p
Glucose (mmol/L)	5,72 (5,38-6,33)	7,88 (5,77-8,88)	p <0.05
UA (mmol/L)	0,3 (0,24-0,36)	0,36 (0,24-0,47)	p <0.05

CrCl (ml/min)	102 (78-134.4)	46.4 (41-54.7)	NSS
Microalbuminuria (mg/g)	9.7 (6.5-27)	47.25 (17.36-264.5)	NSS
Protein/Creatinine (mg(mmol)	0.08 (0.06-0.15)	0.29 (0.14-0.73)	NSS
UACl (ml/min)	6.16 (4.8-8.3)	3.38 (2.4-4.8)	NSS
UAFE (%)	6.4 (4.9-8.1)	7 (5.9-8.7)	NSS
UA elimination (g/day)	0.52 (0.37-0.68)	0.37 (0.2-0.45)	NSS
NaFE (%)	0.82 (0.55-1.26)	1.57 (1.1-2.2)	NSS
UAFE/NaFE	7.7 (4.8-11.8)	3.69 (3-7.4)	NSS
VARIABLE	**NON DIURETIC GROUP (n=35)**	**DIURETIC GROUP (n = 38)**	**p**
Glucose (mmol/L)	5,55 (5,27-5,55)	6,05 (5,58-7,07)	p <0.05
UA (mmol/L)	0,27 (0,22-0,34)	0,31 (0,28-0,36)	p <0.05
CrCl (ml/min)	106.8 (81.6-137.4)	96.7 (74.5-133.6)	NSS
UACl (ml/min)	6.45 (5.15-8.54)	6.1 (4.4-8.12)	NSS
UAFE (%)	6.73 (5.15-8.23)	6.14 (4.55-8.1)	NSS
UA elimination (g/day)	0.56 (0.4-0.7)	0.49 (0.4-0.7)	NSS
NaFE (%)	0.8 (0.44-1.15)	0.93 (0.67-1.3)	NSS
UAFE/NaFE	8.5 (5.9-14.4)	6.7 (4-11.3)	NSS
VARIABLE	**NON OBESITY GROUP (n = 36)**	**OBESITY GROUP (n = 37)**	**p**
UA (mmol/L)	0,27 (0,22-0,33)	0,33 (0,28-0,38)	p <0.05
CrCl (ml/min)	88.1 (68.6-122.4)	118.3 (83-137.7)	NSS
Microalbuminuria (mg/g)	8 (5.6-26.8)	9.96 (7.4-31.8)	NSS
UACl (ml/min)	6.09 (4.42-7.21)	6.84 (5.25-10.9)	NSS
UAFE (%)	6.67 (4.95-8.17)	6.1 (4.5-7.9)	NSS
UA elimination (g/day)	0.46 (0.3-0.6)	0.62 (0.48-0.76)	p <0.05
NaFE (%)	0.87 (0.5-1.3)	0.82 (0.56-1.26)	NSS
UAFE/NaFE	7.86 (5.8-10.7)	7.4 (4.5-12.8)	NSS

NSS: not statistically significant