Original Research Article

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

ABSTRACT

Background

Uric acid is a major cardiovascular risk factor and a risk for kidney disease. It is not only a marker of progression of renal injury, but it also provoques it and makes it progress. We analyze its kidney metabolism in hypertensive patients, to find differences with the healthy population, and whether it is altered in situations such of hypertension with chronic renal failure, use of diuretics and obesity.

Methods

We performed a descriptive, cross-sectional and retrospective study of 95 hypertensive patients, in which we study the parameters of renal excretion of uric acid. We compared the results of our hypertensive patients with the literature data of healthy people, and we study the effect of chronic kidney disease, use of diuretics and 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 reduced renal excretion of uric acid.

Conclusions:

In hypertension with normal renal function without diuretic therapy, in chronic kidney disease and in treatment with diuretics, renal excretion of uric acid is reduced. So, we must ask ourselves whether this fact could be the pathogenic basis for 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 seric 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], figures that increase the risk of arthritis and nephrolithiasis.

Although its true prevalence in our environment is unknown, we can say that it has increased in recent decades, due to factors such as increased life expectancy, diets rich in fructose and higher prevalence of hypertension (HT), obesity and metabolic syndrome [1,2].

UA level is an important cardiovascular and renal disease (RD) risk factor, especially in patients with hypertension, diabetes mellitus (DM) or heart failure. It is known that hyperuricemia is a risk factor for hypertension in humans and even in experimental animal level and also for the development of proteinuria, which promotes the hypothesis that it induces renal damage or its progression. Recent evidence suggests that the UA is not only a marker of progression of renal injury but also it is a risk marker that causes the progression of renal injury [3].

Uric acid induces at the vessels level, a reduction in nitric oxide (NO) and the onset of reactive oxygen species, vascular inflammation, smooth muscle cell proliferation and inhibition of endothelial growth factors, and at renal level, apart from reducing NO, increases renin values [4] and is associated with interstitial inflammation and microvascular alterations that lead to the development of interstitial fibrosis and afferent arteriolopathy that induces vasoreactive hypertension that is salt sensitive [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 the UA (the rest is excreted through the digestive tract). There are certain factors, which, by themselves or by their

renal effects, may alter the excretion of it, such as renal failure (CRF), taking diuretics, hypertension or hyperinsulinemia [7]. The latter produces a 20-30% reduction in the clearance of net and fractional UA, effect seen significantly in patients with insulin resistance, hypertension and obesity [8].

Thus, UA is an important risk factor for loss of renal function independently of hypertension [7,9].

OBJECTIVES

The objectives of our study are:

- To assess baseline of renal handling of UA in hypertensive patients attending to the hypertension and kidney consultation of the Nephrology Department in our hospital, with and without hyperuricemia.
- 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 situations of obesity and taking diuretics.

MATERIAL AND METHODS

This is a descriptive, cross-sectional and retrospective study of hypertensive patients seen in the hypertension and kidney consultation 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 informed consent was obtained from the patients.

Demographic and epidemiological characteristics were studied, and the existence of target organ damage and drug treatment received. In addition, fasting blood samples and 24-hour urine were obtained.

The analytical parameters studied are summarized in the table 1:

The LDL-cholesterol was calculated using the Friedewald formula. The determination of creatinine, uric acid, and phosphates in urine was performed in 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, to avoid interference of possible confounder factors. Thus, in a first step the different parameters that influence the UA renal metabolism of our hypertensive patients, as reflected in the literature were compared with healthy people. In the second step we examined whether the presence of CRF determines differences in the UA metabolism in our patient population. The third and fourth phases consisted in studying, in our group of hypertensive patients with normal renal function, if taking diuretics or obesity would create differences in any of these parameters.

Descriptive statistics were performed to characterize the groups and the variables were expressed as median and interquartile range if quantitative and frequencies for qualitative variables.

Comparison of groups was performed using non-parametric tests, since the variables studied did not have a normal distribution. The Mann-Whitney test for independent samples was used. The level of significance 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 package SPSS v.20.0 was used for MAC OS 10.6.8 for the statistical treatment of the data.

RESULTS

The first phase of the study was to compare the different parameters of UA renal metabolism of our hypertensive patients (n=95) with the information reported in the literature regarding people without hypertension. Results are shown in Tables 2 and 3. The statistical power of this first phase is 60%.

Clearance and fractional excretion of UA values are lower than the reference in 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 estatistically significant differences were observed in UA elimination.

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

The HTA-CRF group has a higher age (74 vs 51 years), increased duration of hypertension (19 vs. 8 years), higher percentage of diabetics (54.5% vs 14%) and increased vascular impact of vascular disease at other levels. In this group there is 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 have serum levels of glucose (7,88 vs 5,72 mmol/L) and UA (0,36 vs. 0,3 mmol/L) significantly higher. The UACl is almost half than 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 remains at similar values due to the correction of the renal elimination of UA with the degree of renal function.

The other results of the comparison of the groups are shown in Table 4.

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 our population of hypertensive patients who had normal renal function (n=73) and divided them into two groups for comparisons, those taking diuretics in their antihypertensive therapy (n=38) and those without the drug (n=35).

Both groups have similar characteristics of age, sex, weight, toxic habits, DM and dyslipidemia.

The group of patients treated with diuretics has a longer history of hypertension (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 power of the third part of the global study is 68,0%.

Table 5 shows the results of the analytical data relating to UA metabolism.

In the last phase of our work, we wondered whether 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 consists of 37 patients and the hypertensive but not obese group consists of 36 patients.

Both groups have similar age, sex and degree of control of blood pressure. The obese group presents a longer HTA 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%.

Table 6 shows the analytical results and the parameters related to renal UA metabolism.

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 situations such as hypertension [8.9], kidney damage, obesity and diuretics use [5], however it is not clear if the CRF [9] is the cause of the alterations in the renal excretion of UA observed in these cases or simply another feature that takes place at the same time.

There is evidence that supports that serum UA levels influence blood pressure by activating the aldosterone-renin-angiotensin II system [9] and increase peripheral vascular resistances, which cause contraction of the afferent arteriole, resulting in loss of the ability of renal autoregulation with intraglomerular hypertension and renal hypoperfusion, which can lead to hypertension, tubulointerstitial inflammation and renal fibrosis [10].

Several studies have also shown that in populations with good renal function and hypertension (including pregnancy), the UA level, and in particular its tubular handling can assess in advance the impact or damage the blood pressure itself could be causing, and its study as potential early indicator of acute kidney injury is targeted [11]. UAC therefore may be an earlier indicator of impaired kidney perfusion than CrCl.

The results of our study, in an unselected population referred for HTA to an HTA-nephrology consultation, show renal elimination of UA lower than that reported in studies of healthy population. This lower clearance is shown not only in the whole group, but also when we analyzed patients without diuretic therapy or obesity. These results make us wonder if maybe the pathogenic relationship between vascular disease and UA could not be conditional to the handling of uric acid in the kidney and not only for its serum level [12]. However, we should keep in mind that this is a biased population of hypertensive patients since they are patients referred for HTA-nephrology consultation 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 calculation of the fractional excretion of UA (UAFE) parameter is a simple calculation, which could be useful in both epidemiological studies and therapeutic intervention in patients with cardiovascular risk who often have renal injury as part of the context of target organ involvement [2].

We note that the group of patients treated with diuretics has significantly higher values of both glucose and UA, both known side effects to the 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 of it, 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 could 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 and also by reducing the elimination of UA because of hyperinsulinism [15], that often come with 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 disappear. There is a demonstrated relationship between hyperuricemia, obesity and metabolic syndrome secondary to widespread diets rich in fructose [16], which is the only carbohydrate known to increase the generation and release of UA [9].

Our work has several limitations: our studies are univariate (which does not avoid the interference of confusion factors), there is not a control group in the first phase (due to the lack of financial means for the characterization of a suitable control group), which forced us to make our comparison with data from the literature, and our studies are retrospective with low statistical power (mainly due to a small sample size).

CONCLUSIONS

The high relationship between known vascular risk factors such as hypertension, hyperuricemia, obesity and CRF make difficult to determine a pathogenic role of the UA in clinical and epidemiological studies. Hyperuricemia is relevant to cardio-vascular-renal disease. Our patients did not have hyperuricemia, as were those on treatment with allopurinol to maintain a serum uric acid in range, but we observed a reduced UAFE.

The results of our study show that in situations such as CKD and diuretic therapy, renal excretion of uric acid is reduced but also in patients with hypertension and normal renal function who are not on diuretics, renal elimination is also reduced in relation to the data published in the healthy population. Thus we must ask whether this reduction in renal clearance of UA could be the pathogenic basis for many forms of essential hypertension or whether, by contrast, is the translation of the harmful impact of hypertension in the kidney.

Despite the limitations previously exposed, we want to draw attention to the study of tubular handling of uric acid. The study of the fractional excretion of uric acid in the context of HTA from early stages and follow along with BP control and hipotensive medication could provide information on renal perfusion.

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Table 1: Analytical parameters studied

PARAMETER		
Glucose (mmol/L)	Urea (mmol/L)	Creatinine (umol/L)
Sodium (mmol/L)	Potassium (mmol/L)	Calcium (mmol/L)
Phosphorus (mmol/L)	Magnesium (mmol/L)	Total Cholesterol (mmol/L)
HDL (mmol/L)	LDL (mmol/L)	Triglycerides (mmol/L)
HbA1c (%)	C-reactive protein (mmol/L)	Homocysteine (mmol/L)
Uric Acid (mmol/L)	CrCl (ml/min)	UACl (ml/min)
Microalbuminuria (mg/g)	UAEF (%)	NaEF (%)
UAEF/NaFE	Protein Index/Creatinine	UA Daily Disposal (g/day)

Table 2: Demographic variables and vascular risk results

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%

Table 3: Median and interquartile range of conventional analytical determinations

VARIABLE	RESULT
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)
UAEF	6.65 (5.04-8.17)

NaFE	0.99 (0.62-1.42)
UAFE/NaFE	6.73 (4.26-11.08)

Table 4: UA metabolism parameters depending on renal function

VARIABLE	CrCl GROUP> 60 ml/min (n = 73)	CRF GROUP (n = 22)
Glucose (p <0.05)	5,72 (5,38-6,33)	7,88 (5,77-8,88)
UA (p <0.05)	0,3 (0,24-0,36)	0,36 (0,24-0,47)
CrCl	102 (78-134.4)	46.4 (41-54.7)
Microalbuminuria	9.7 (6.5-27)	47.25 (17.36-264.5)
Protein/Creatinine	0.08 (0.06-0.15)	0.29 (0.14-0.73)
UACl	6.16 (4.8-8.3)	3.38 (2.4-4.8)
UAFE	6.4 (4.9-8.1)	7 (5.9-8.7)
UA elimination	0.52 (0.37-0.68)	0.37 (0.2-0.45)
NaFE	0.82 (0.55-1.26)	1.57 (1.1-2.2)
UAFE/NaFE	7.7 (4.8-11.8)	3.69 (3-7.4)

Table 5: Analytical results based on taking diuretics

VARIABLE	NON DIURETIC GROUP (n=35)	DIURETIC GROUP (n = 38)
Glucose (p <0.05)	5,55 (5,27-5,55)	6,05 (5,58-7,07)
UA (p <0.05)	0,27 (0,22-0,34)	0,31 (0,28-0,36)
CrCl	106.8 (81.6-137.4)	96.7 (74.5-133.6)
UACl	6.45 (5.15-8.54)	6.1 (4.4-8.12)
UAFE	6.73 (5.15-8.23)	6.14 (4.55-8.1)
UA elimination	0.56 (0.4-0.7)	0.49 (0.4-0.7)
NaFE	0.8 (0.44-1.15)	0.93 (0.67-1.3)
UAFE/NaFE	8.5 (5.9-14.4)	6.7 (4-11.3)

Table 6: Analytical results based on the coexistence of obesity

VARIABLE	NON OBESITY GROUP (n = 36)	OBESITY GROUP (n = 37)
UA (p <0.05)	0,27 (0,22-0,33)	0,33 (0,28-0,38)
CrCl	88.1 (68.6-122.4)	118.3 (83-137.7)
Microalbuminuria	8 (5.6-26.8)	9.96 (7.4-31.8)
UACl	6.09 (4.42-7.21)	6.84 (5.25-10.9)
UAFE	6.67 (4.95-8.17)	6.1 (4.5-7.9)

UA elimination (p <0.05)	0.46 (0.3-0.6)	0.62 (0.48-0.76)
NaFE	0.87 (0.5-1.3)	0.82 (0.56-1.26)
UAFE/NaFE	7.86 (5.8-10.7)	7.4 (4.5-12.8)

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