Original Research Article

A FURTHER STEP 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 of uric acid (5,56 ml/min) and its fractional excretion (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 reduce renal excretion of uric acid.

Conclusions:

Renal excretion of uric acid is reduced in the case of hypertension with normal renal function without diuretic therapy, in chronic kidney disease and in treatment with diuretics. 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 accretion 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]. This elevation increases the risk of arthritis and nephrolithiasis.

Although its true prevalence in our environment is unknown, it has rised in recent decades, due to factors such as increased life expectancy, rich in fructose diets 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. Hyperuricemia is a risk factor for hypertension experimental animals and humans and also for the development of proteinuria, which promotes the hypothesis that it induces renal damage or its progression if previously present. Recent evidence suggests that the UA is not only a marker of progression of renal injury but it is also an independent risk factor for progression of renal injury [3].

Uric acid induces a reduction in endothelial nitric oxide (NO) production and the onset of reactive oxygen species, vascular inflammation, smooth muscle cell proliferation and inhibition of endothelial growth factors. In kidneys also increases renin values [4]. This is associated with interstitial inflammation and micro vascular injuries leading to the development of interstitial fibrosis and afferent arteriolopathy, both are the cause of salt sensitive vasoreactive hypertension [4,5].

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

The kidney is responsible for the elimination of 75% of the 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 20-30% 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].

The objectives of our study are:

- To assess baseline of renal handling parameters of UA in hypertensive patients (with and without hyperuricemia) 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 diuretics.

MATERIAL AND METHODS

This is a descriptive, cross-sectional and retrospective study of hypertensive patients seen in the Hypertension and Kidney Office in 2013 of our hospital, 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, the existence of target organ damage, drug treatment received and conventional analytical parameters (using fasting blood samples and 24-hour urine) were studied.

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 (table 1) 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 obesity or taking diuretics 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 carried out 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. 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 statistically significant differences were observed in UA elimination. The rest of the results are shown in table 1.

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 prevalence of diabetics patients (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 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 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%. The results of the comparison of these two groups are shown in table 2.

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%. The rest of the 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 hypertension [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 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 increases peripheral vascular resistances, which causes contraction of the afferent arteriole (resulting in loss of the ability of renal auto regulation 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 (in particular its tubular handling), can predict the impact or damage caused by high blood pressure itself, and its study as potential early indicator of kidney injury is targeted (recommended?)[11]. UAC therefore may be an earlier indicator of impaired kidney perfusion than CrCl.

The results of our study show a lower renal elimination of UA in our hypertensive patients than that reported in studies of healthy population. This lower clearance is also shown when we analyze patients with diuretic therapy or obesity. These results make think that maybe the pathogenic relationship between vascular disease and UA could be dependant to the handling of uric acid in the kidney and not only for its serum level [12]. However, we should think that this is a biased population of hypertensive patients since they are patients referred for HTA-nephrology office 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 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].

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 convey 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 comes 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).

The results of our study show that renal excretion of uric acid is reduced in patients with hypertension and normal renal function who are not on diuretics, as well as in patients with chronic kidney disease and in diuretic therapy. 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.

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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