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A Further Step in the Relationship between Uric Acid and Vascular Risk: Tubular Handling of Uric Acid in Hypertension Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors CR and CF designed, wrote the paper and made all the statistics. Authors RM, BA, AF and CC collected all the data and author JM supervised the whole work. All authors read and approved the final manuscript.

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ABSTRACT

Background: Uric acid poses a major risk to cardiovascular function which, in turn, increases the chances of kidney disease. This is not only an indication of renal damage, but also precipitates its development. We analyzed the kidney metabolism in hypertensive patients in order to establish any disparities compared to those of healthy individuals, and to ascertain if there were any changes in cases such as hypertension with chronic renal failure, including the use of diuretics in cases of obesity.
Methods: We performed a descriptive, cross-sectional and retrospective study of 95 hypertensive patients to determine the parameters of renal excretion of uric acid. We compared the results of the hypertensive patients with the existing data of healthy individuals; examining the effects of chronic kidney disease - the administration of diuretics including cases of 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 healthy individuals (UACl: 8-12 ml/min and UAEF: 8-10%). This

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clearance decreases significantly in hypertensive patients with chronic kidney disease compared to hypertensive patients with normal renal function (3.38 vs. 6.16 ml / min) including patients treated with diuretics (6.1 vs. 6.4 ml/min). Obesity also contributes to the reduction of renal excretion of uric acid.

Conclusion: Renal excretion of uric acid is reduced in cases of hypertension with normal renal function and no diuretic therapy, in cases of chronic kidney disease and in treatment with diuretics. So, the question here is whether this could be the pathogenic basis for many forms of essential hypertension, or whether it is caused by the negative impact of hypertension in the kidney.

Keywords: Diuretics; hypertension; obesity; uric acid.

1. INTRODUCTION

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

Although the exact figures are unknown, it has seen an increase in recent decades, owing to factors such as longevity, a higher prevalence of hypertension (HT), obesity, metabolic syndrome [1,2] and diets rich in fructose.

UA levels play a major part in cardiovascular and renal disease (RD), especially in patients with hypertension, diabetes mellitus (DM) or heart disease. Hyperuricemia has proven to be a cause of hypertension in both laboratory animals and humans, and also in the development of proteinuria, which suggests that it may lead to renal damage and even contribute to its development [3].

Uric acid brings about a reduction in endothelial nitric oxide (NO) production and the onset of reactive oxygen species, vascular inflammation, smooth muscle cell proliferation and the obstruction of endothelial growth factors. In also increases the renin level in kidneys [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 sodium chloride 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 facilitates the direct intracellular activity of uric acid [6] and plays a role in tubular reabsorbtion and regulation of UA blood levels.

The kidney is responsible for the expulsion of seventy five percent of Uric Acid. There are certain factors, however, which may alter its excretion, such as renal failure (CRF), diuretics, hypertension or hyperinsulinemia [7]. The latter causes a 20 to 30 percent reduction in the clearance of net and fractional UA. This can be observed in patients with insulin resistance, hypertension and obesity [8].

Thus, UA plays a significant role in the loss of renal function, independent of hypertension [7,9].

The three main objectives of our study were:

- To assess the baseline parameters in the renal handling of UA in hypertensive patients (with and without hyperuricemia) who attend the “hypertension and kidney consultation” at the hospital’s Nephrology Department.
- To examine whether the different parameters of tubular treatment of UA alter in situations of CRF (CrCl <60 ml/min).
- To evaluate the effects of tubular treatment within UA parameters, on patients with obesity and diuretics, but with normal renal function.

2. MATERIALS AND METHODS

This is a detailed, cross-sectional and backdated study of hypertensive patients seen in the hospital’s Hypertension and Kidney department in 2013. The data was obtained from the medical records review.

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

We analyzed the demographic and epidemiological characteristics, including the effects of target organ damage, drug treatment

received and conventional analytical parameters (using fasting blood - and 24-hour urine samples).

LDL-cholesterol levels were calculated using the Friedewald formula. The levels of creatinine, uric acid, and phosphates in urine were determined by using a centrifuge analyzer. Levels of magnesium were established by atomic absorption spectrophotometry and the sodium and potassium were obtained directly through flame photometry.

The study was conducted in 4 phases in order to avoid possible influences from other, unrelated, sources. Thus, in step one we compared the figures (Table 1) that influence the UA renal metabolism in our hypertensive patients with those reviewed using the data of healthy individuals. In the second step we examined whether the presence of CRF effects changes in the UA metabolism of our patients. In the third and fourth phases we set out to establish whether obesity or taking diuretics would effect changes in our group of hypertensive patients with normal renal function.

Data was collected from both groups and the results categorised into qualitative variables, which were expressed as median and interquartile.

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 indication level was set at $p < 0.05$. The validity of the four phase 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.

3. 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 figures of those without hypertension. The statistical legitimacy of this first phase is 60%.

Clearance and fractional excretion levels of UA are lower than those recorded in healthy individuals (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 significant differences were observed in UA elimination. The remaining results are shown in Table 1.

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)

In the second stage of our study we wanted to find out whether the amount of excretion of UA is influenced by CRF stage III (CrCl 30 to 60 ml/min). We divided our test cases into two groups: hypertensive CRF (n=22) and hypertensive patients with normal renal function (n=73).

The HTA-CRF group had a higher average age (74 vs 51 years), a longer history of hypertension (19 vs. 8 years), higher amount of diabeties (54.5% vs. 14%) as well as other issues relating to vascular disease. In this group there were 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 significantly higher serum levels of glucose (7,88 vs. 5,72 mmol/L) and UA (0,36 vs. 0,3 mmol/L). The significance finding here is that the UACl was almost half that in the group of hypertensive patients with normal renal function (3.38 vs. 6.16 ml/min). However, the AUFE remains similar owing 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.

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

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 accuracy 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 tested the effects of obesity in the renal handling of UA in our hypertensive patients. We took our hypertensive patients with normal renal function (n=73) and divided them into two groups based on the instances of obesity (BMI> 30 kg/m^2). The group with obesity numbered 37 patients and those with a healthy weight 36.

The two groups were of similar age, sex and degree of blood pressure control. The obese group presented a longer history of HTA (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 accuracy of the last study is 68,1%. The rest of the results of this phase of the study can be seen in Table 2.

4. 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 are known to us from recent years [6].

We know the connection between uric acid and hypertension [8.9], kidney damage, obesity and diuretics use [5]. What is not clear, however, is whether the CRF [9] is the cause of the impairment in the renal excretion of UA observed in these cases or simply another feature that occours independently.

There is evidence to suggest 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 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 suggest a pathogenic relationship between vascular disease and UA that may be dependant on the handling of uric acid in the kidney and not only for its serum level [12]. However, these specific figures may be due to the fact that they were obtained from patients referred for HTA-nephrology office by their 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) is a simple calculation, which could be useful in both epidemiological studies and therapeutic intervention in patients at risk of cardiovascular disease and who often have renal damage associated with target organ involvement [2].

Patients treated with diuretics have significantly higher levels of both glucose and UA, both known side effects of diuretic therapy. This group also showed a lower UA renal clearance, although the differences recorded were not statistically significant. The volume contraction induced by diuretics helps to reduce renal elimination of it, which was determine, as such, 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 distinction of the

different UA tubular transporters and the understanding of the molecular mechanisms and its tubular metabolism may lead to the creation of new diuretics with uricosuric effects [13].

Those with obesity tend to have higher incidences of hyperuricemia and kidney stones, certainly in relation to the increased intake, but also by reducing the elimination of UA through hyperinsulinism [15] which often accompanies obesity. The results showed obese patients with higher levels of UA and, although its elimination was significantly higher, by adjusting it with the degree of renal function, the differences disappear. There is an established relationship between hyperuricemia, obesity and metabolic syndrome, secondary to diets rich in fructose [16], which is the only carbohydrate known to increase the production, and release, of UA [9].

Our work has several limitations: our studies are univariate; so we cannot rule out the possibility of additional influences. There is no research group in the first phase owing to the lack of financial resources in finding a suitable group to represent. For this reason we found it necessary to draw our comparisons from pre-existing records; thus our studies are backdated and their statistical authority should be viewed as such.

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, it could be the result of the harmful impact of hypertension in the kidney.

5. CONCLUSION

Study of the renal excretion of the uric acid should be extended to all hipertensive patients, in order to better understand the way in which hypertension affects the kidney.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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