MEDWIN PUBLISHERS
Committed to create value for Researchers

Haematology International Journal
ISSN: 2578-501X

The Role of Uric Acid in Carbohydrate Metabolism among Hypertensive Individuals

Papavasileiou MV[1], Patsianis S[1], Moustakas G[1], Vrakas CS[2], Kalogeropoulos P[3], Karamanou A[1]* and Pittaras A[4]

[1]Department of Cardiology, Sismanogleion General Hospital, Greece

[2]Department of Cardiology, Tzaneion General Hospital, Greece

[3]Department of Cardiology, GONK General Hospital, Greece

[4]Mediton Cardiology Center, Greece

Research Article

Volume 2 Issue 1

Received Date: January 22, 2018

Published Date: February 09, 2018

DOI: 10.23880/hij-16000115

***Corresponding author:** Karamanou G Alexandra, Department of Cardiology, Sismanogleion General Hospital, 16 Edessis Street, Athens, 17343, Greece, Tel: 00306946639524; E-mail: alexandrakar7@gmail.com

Abstract

The association between fasting blood glucose and insulin and serum uric acid levels in general population, as well as the positive association between serum uric acid levels and development of type 2 diabetes mellitus have been reported.

Objective: Correlation of serum uric acid (SUA) levels with various parameters indicative of carbohydrate metabolism among treated and newly diagnosed, untreated hypertensive individuals.

Research Design and Methods: We studied 2803 hypertensive patients treated or newly diagnosed untreated. The levels of SUA and other parameters of carbohydrate metabolism, such as fasting glucose (gl0), fasting insulin levels (IN0), glycated hemoglobin (HbA1c), fasting insulin resistance index (HOMA0), loading insulin resistance index (HOMA120), fasting c-peptide (c-pept0) and loading c-peptide (c-pept120) were calculated. The study population was divided into two groups: group A (N=543): SUA levels above normal range and group B (N=2260): SUA levels within normal range.

Results: In the overall study population SUA levels showed a statistically significant positive correlation with gl0 ($p<0.001$), in0 ($p<0.001$), HbA1C ($p=0.002$) and HOMA0 ($p<0.001$), gl120 ($p=0.003$), in120 ($p=0.007$), HOMA120 ($p=0.002$) and c-pept0 ($p<0.001$). In the glucose loading subgroups SUA levels showed a statistically significant positive correlation with gl120 ($r=0.142$, $p=0.003$), in120 ($r=0.119$, $p=0.007$), HOMA120 ($r=0.184$, $p=0.002$) and c-pept0 ($r=0.292$, $r<0.001$).

Conclusion: The levels of SUA in hypertensive individuals are both associated with and dependent on different parameters of carbohydrate metabolism and insulin resistance, either suggesting a potential role of uric acid in the pathogenesis of metabolic syndrome and deranged glucose metabolism, or verifying that it constitutes an aspect of the underlying pathologic condition.

Keywords: Carbohydrate metabolism; Hyperuricemia; Hypertension; Diabetes mellitus; Insulin; Metabolic syndrome

Abbreviations: SUA: Serum Uric Acid; RAS: Renin-Angiotensin System; OGTT: Oral Glucose Tolerance Test; IFG: Impaired Fasting Glucose; NGT: Normal Glucose Tolerance

Introduction

Serum uric acid (SUA) is the end product of purine metabolism in humans. It plays a key-role in maintaining the BP, the kidney blood perfusion and the Na+ homeostasis, through the activation of the renin-angiotensin system (RAS), while it also functions as an antioxidant agent [1,2]. The lack of liver uricase leads to elevated SUA levels, in the range of 3.0-5.5 mg/dL. SUA can reach even higher values, often >7.5-8.0 mg/dL in high risk groups, including males and postmenopausal females, in the obesity insulin-resistance syndrome, in blacks and in patients with renal disease, indicating that it correlates with high cardiovascular and metabolic risk [3].

Although several studies on humans and/or animal models, which rendered hyperuricemic, demonstrated a positive correlation among SUA levels, arterial HTN and impaired glucose metabolism (prediabetes, progression to diabetes, Mets), other studies demonstrated a declining trend of the SUA levels with increasing blood glucose levels, as well as conflicting data about the UA levels especially in type 2 diabetes mellitus, where they seem to be associated with risk factors and complications [4-6].

Thus, the present study aims to define the correlation between SUA and different parameters of carbohydrate metabolism in a special population, namely hypertensive individuals, in an attempt to clarify the existence of UA either as a “bystander” with predictive value or as a culprit in glucose metabolism among hypertensive individuals, the modification of which is of clinical significance.

Materials and Methods

Patient Population

Among the 2803 consecutively studied hypertensive white patients, (based on the current definition of HTN), 1522 were female and 1281 were male, either under anti-hypertensive treatment or not (newly diagnosed), either under diabetes treatment or not, of average age 57.4 ± 13.4 years, without any known cardiovascular disease. The patients were self- referred to our outpatient cardiology-hypertensive clinic for BP evaluation.

An informed consent was given by all participants and the study was approved by the Local Research Ethics Committee. Patients were excluded from the study, if they suffered from secondary hypertension and any other clinically significant concurrent medical condition such as thyroidal, psychiatric, neuromuscular, kidney (estimated glomerular filtration rate <60 ml/min), respiratory, hepatic or gastrointestinal illness or systemic disease. None of the participants had any history or clinical/laboratory evidence of recent infection, inflammation or underwent any medical treatment (including anti-inflammatory treatment and hormone replacement therapy) the last month before the entry into the study. Patients under treatment for hyperuricemia were also excluded from the study.

For the distinction between normourecemic and hyperurecemic patients, the cut-off values of 7.0 mg/dl for men and 6.0 mg/dl for women were used.

Measuring Study Variables

The anthropometric variables were measured according to the written protocol. WC was measured on a horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest, using a tape measure. In the first visit resting sitting BP was measured twice with at least 5 minute intervals, using an automatic sphygmomanometer. If the difference between the first and second measurement was more than 10 mmHg, then repeated measurements were performed. The average of the last two measurements was used for screening. New BP measurements were made in our outpatient clinic according to the recent guidelines, at three separate visits with a mean elapsing time of 1 week. In each visit, participants were encouraged to relax for almost 10 minutes and subsequently in a quiet room with a stable temperature and luminosity, an experienced cardiologist after having explained the procedure to the participants, performed three different BP measurements at 5-minute intervals by using an automatic blood pressure recorder. Korotkoff phase 1 and 5 were used to determine SBP and DBP, respectively in each visit, the second and third BP measurements were averaged and the final office BP, consisted of the mean of the three visits. Furthermore, on the first visit a bilateral measurement was performed to define the arm subjected to the relatively

higher haemodynamic load and accordingly was used for all the following measurements.

Venal blood samples were collected after at least an 8 hour fast. Enzymatic methods were applied to measure SUA levels, fasting plasma glucose (gl0), fasting insulin (in0), HbA1c and fasting insulin resistance index (HOMA0: Homeostatic Model Assessment of Insulin Resistance) was calculated. Plasma urea and creatinine were also measured and e-GFR by using Cockcroft Gault formula was calculated.

Furthermore, in 322 of the total study population, untreated for diabetes, an oral glucose tolerance test (OGTT) using 75 grams of glucose was carried out and the glucose loading serum glucose and insulin levels (gl120), (in120), in 120 min after glucose loading, were measured and glucose loading insulin resistance index (HOMA120) was calculated. In 143 of the above mentioned patients a fasting c-peptide0 (c-pept0) and loading c-peptide120 (c-pept120) was also measured.

The total study population was divided into two groups according SUA levels: hyperurecemic with SUA levels above normal range (men≥7mg/dl, women ≥6mg/dl) and normourecemic patients with SUA levels within normal range. Accordingly, 543 of the total number of patients were defined as hyperurecemic, while 2260 were normourecemic.

Statistical Analysis

All the descriptive continuous variables are represented as means ± standard deviation and categorical variables are described as frequencies. Pearson's or Spearman rank correlation coefficient, where appropriate, was calculated to assess associations between clinical and laboratory variables. Significant differences between the groups were determined using the student's t-test or chi-square test where appropriate. Regression analysis was used to determine the independent predictors of SUA. All reported p-values are based on two-sided tests and p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc, Chicago, IL).

Results

Clinical and laboratory characteristics of the overall patient population as well as differences between hyperurecemic and patients with normal uric acid levels are shown in Table 1. It is evident from Table 1 that all the components that are associated with MetS, as well as, all the parameters which are associated with carbohydrate metabolism and kidney function differ statistically significantly, between normourecemic and hyperurecemic patients, despite the fact that BP is better controlled and maintained at nearly normal values in the hyperurecemic patient group. Moreover, it seems that gl0, as well as other biochemical parameters, which relate to glucose tolerance, carbohydrate metabolism and insulin secretion and functionality, such as gl120, IN0, c-pept0, HOMA0 and HOMA120, exhibit a positive correlation with SUA levels, among hypertensive patients, either treated or untreated (Table 2). In the overall population, after adjusted for sex and age, all biochemical parameters concerning glucose metabolism and insulin levels were positively and statistically significantly correlated to SUA levels (with the exception of c-pept120) and also independent predictors of SUA levels.

	Overall (n=2803)	Normourecemic (n=2260)	Hyperurecemic (n=543)	P value
Age (years)	57.4±13.4	57.0±13.1	61.3±13.8	<0.001
Female sex (%)	54.3	54.5	53.8	NS
BMI (kg/m^2)	28.2±4.5	27.9±4.2	29.7±4.9	<0.001
Waist (cm)	96.1±12.9	95.3±12.8	99.6±11.3	<0.001
SBPo (mmHg)	148.9±20.3	149.2±20.3	146.1±21.5	0.002
DBPo (mmHg)	92.2±13	92.6±12.8	88.7±13.8	<0.001
HRo (beats/minute)	75.5±11.1	75.4±10.9	74.6±11.3	0.126
Treated (%)	50.5	48.8	69.2	<0.001
Uric Acid (mg/dl)	5.2±1.6	4.6±1.1	7.5±1.1	<0.001
gl0 (mg/dl)	103.9±28	102.9±28.5	108.5±27.6	<0.001
gl120 (mg/dl)	117.3±47.5	112.97±44.4	138.4±57.4	<0.001
In0 (mU/l)	12.6±12.4	12.0±11.7	14.9±15.3	0.01
In120 (mU/l)	58.5±55.6	53.7±48.0	85.7±87	<0.001
c-peptide0 (ng/ml)	2.6±1.7	2.5±1.4	3.2±2	<0.001
c-peptide120 (ng/ml)	8.9±3.9	8.7±3.8	9.99±4.7	0.126
HbA1c (%)	5.8±1.6	5.8±1.1	5.96±0.9	0.025

HOMA0 (U/mol)	3.3±3.8	3.2±3.6	4.1±4.9	0.009
HOMA120 (U/mol)	20.6±25.9	18.1±21.7	35.1±41.5	<0.001
Urea (mg/dl)	40.5±16.7	39.2±13.7	45.7±18.9	<0.001
Creatinine (mg/dl)	0.93±0.24	0.9±0.2	1.03±0.3	<0.001
e-GFR (ml/min)	92.9±32	94.33±31.32	87±34.42	<0.001

SBPo: Systolic Blood Pressure at office, DBPo: Diastolic Blood Pressure at office, HRo: Heart Rate at office, gl0: Fasting plasma glucose, gl120: Plasma glucose 120 minutes after oral glucose tolerance test, In0: Fasting plasma insulin, In120: Plasma insulin 120 minutes after oral glucose tolerance test, c-peptide0: Fasting plasma c-peptide, c-peptide120: plasma c-peptide 120 minutes after oral glucose tolerance test, HbA1c: Glycated hemoglobin, HOMA0: Homeostatic Model Assessment of Insulin Resistance, HOMA120: Homeostatic Model Assessment of Insulin Resistance 120 minutes after oral glucose tolerance test, e-GFR: estimated- Glumerular Filtration Rate (Cockcroft Gault Formula).

Table 1: Clinical and laboratory characteristics of study population.

	r	p-value
gl0	0.09	<0.001
Gl120	0.142	0.003
In0	0.119	0.001
In120	0.156	0.007
c-pept0	0.292	<0.001
c-pept120	0.036	0.676
HbA1c	0.091	0.002
HOMA0	0.114	0.001
HOMA120	0.184	0.002

gl0: Fasting plasma glucose, gl120: Plasma glucose 120 minutes after oral glucose tolerance test, In0: Fasting plasma insulin, In120: Plasma insulin 120 minutes after oral glucose tolerance test, c-peptide0: Fasting plasma c-peptide, c-peptide120: plasma c-peptide 120 minutes after oral glucose tolerance test, HbA1c: Glycated hemoglobin, HOMA0: Homeostatic Model Assessment of Insulin Resistance, HOMA120: Homeostatic Model Assessment of Insulin Resistance 120 minutes after oral glucose tolerance test.

Table 2: Correlation between serum uric acid levels and biochemical parameters relative to carbohydrate metabolism in the overall study population (including glucose loading subgroups).

Among treated and untreated hypertensive patients, slightly different correlations between glucose metabolism parameters and SUA seem to emerge. More specifically, in the untreated group of hypertensive patients SUA was not significantly correlated to fasting insulin and glucose levels and to HOMA0 index which, however, was the case for the rest of the measured parameters (Table 3).

	b coefficient*	95% Confidence Interval	p value	b coefficient**	95% Confidence Interval	p value
gl0	0.001	-0.006	NS	-0.001	-0.006	NS
gl120	0.006	0.002-0.010	0.004	0.003	0.012-0.007	0.016
In0	0.006	-0.023	NS	0	-0.023	NS
In120	0.007	0.003-0.011	<0.001	0.006	0.002-0.010	0.006
c-pept0	0.193	0.006-0.381	0.044	0.196	-0.4	0.05
c-pept120	0.117	0.016-0.217	0.024	0.117	0.016-0.219	0.025

* All variables are adjusted for sex and age.

** adjusted for sex, age, BMI and SBPo.

gl0: Fasting plasma glucose, gl120: Plasma glucose 120 minutes after oral glucose tolerance test, In0: Fasting plasma insulin, In120: Plasma insulin 120 minutes after oral glucose tolerance test, c-peptide0: Fasting plasma c-peptide, c-peptide120: plasma c-peptide 120 minutes after oral glucose tolerance test, HOMA0: Homeostatic Model Assessment of Insulin Resistance, HOMA120: Homeostatic Model Assessment of Insulin Resistance 120 minutes after oral glucose tolerance test, HbA1c: Glycated hemoglobin.

Table 3: Regression analysis with SUA levels as the dependent variable in the untreated hypertensive patients (including glucose loading sub groups).

On the contrary, among the group of treated hypertensive patients, which according to Table 1 and, generally exhibited higher values of SUA, the loading parameters (gl120, In120, c-pept120) were not statistically significantly correlated to SUA, moreover introducing BMI as a confounder eliminated the significance of the other factors (Table 4). While, in hyperuricemic hypertensive patients no correlation was found between SUA and carbohydrate metabolism parameters (Table 5), in normourecemic hypertensive patients, SUA levels were significantly and positively correlated with fasting levels of glucose, insulin and c-peptide. Moreover, fasting inuslin and c-peptide levels emerged as independent predictors of SUA levels even after adjusting for age, sex and BMI (Table 6).

	b coefficient*	95% Confidence Interval	p value	B coefficient**	95% Confidence Interval	p value
gl0	0.003	0.000-0.005	0.034	0	-0.005	NS
gl120	0.003	-0.009	NS	0.002	-0.008	NS
In0	0.018	0.008-0.028	<0.001	0.013	0.003-0.022	0.013
In120	0.003	-0.007	NS	0.002	-0.007	NS
c-pept0	0.291	0.189-0.394	<0.001	0.251	0.149-0.353	<0.001
c-pept120	-0.018	-0.114	NS	-0.031	-0.148	NS
HOMA0	0.043	0.014-0.072	0.004	0.025	0.014-0.072	NS
HOMA120	0.007	-0.015	NS	0.005	-0.014	NS
HbA1c	0.02	0.010-0.030	<0.001	-0.002	-0.224	NS

* All variables are adjusted for sex and age.
** All variables are corrected for sex, age and BMI.
gl0: Fasting plasma glucose, gl120: Plasma glucose 120 minutes after oral glucose tolerance test, In0: Fasting plasma insulin, In120: Plasma insulin 120 minutes after oral glucose tolerance test, c-peptide0: Fasting plasma c-peptide, c-peptide120: plasma c-peptide 120 minutes after oral glucose tolerance test, HOMA0: Homeostatic Model Assessment of Insulin Resistance, HOMA120: Homeostatic Model Assessment of Insulin Resistance 120 minutes after oral glucose tolerance test, HbA1c: Glycated hemoglobin.
Table 4: Regression analysis with SUA levels as the dependent variable in the treated hypertensive patients (including glucose loading sub groups).

	B coefficient*	95% Confidence Interval	p value	B coefficient**	95% Confidence Interval	p value
gl0	0,003	0,000-0,007	0.07	0,003	0,000-0,007	0.055
gl120	-0.001	-0.008	NS	-0.001	-0.008	NS
In0	0.007	-0.02	NS	0.004	-0.02	NS
In120	-0.002	-0.007	NS	-0.001	-0.006	NS
c-pept0	0.055	-0.155	NS	0.023	-0.172	NS
c-pept120	-0.056	-0.177	NS	-0.022	-0.133	NS
HOMA0	0.024	-0.062	NS	0.012	-0.061	NS
HOMA120	-0.0034	-0.014	NS	-0.002	-0.013	NS
HbA1c	0.073	-0.26	NS	0.089	-0.258	NS

* All variables are adjusted for sex and age.
**All variables are adjusted for sex, age and BMI
gl0: Fasting plasma glucose, gl120: Plasma glucose 120 minutes after oral glucose tolerance test, In0: Fasting plasma insulin, In120: Plasma insulin 120 minutes after oral glucose tolerance test, c-peptide0: Fasting plasma c-peptide, c-peptide120: plasma c-peptide 120 minutes after oral glucose tolerance test, HOMA0: Homeostatic Model Assessment of Insulin Resistance, HOMA120: Homeostatic Model Assessment of Insulin Resistance 120 minutes after oral glucose tolerance test, HbA1c: Glycated hemoglobin.
Table 5: Regression analysis with serum uric acid levels as the dependent variable in the hyperurecemic hypertensive patients (including glucose loading sub groups).

	B coefficient*	95% Confidence Interval	p value	B coefficient*	95% Confidence Interval	p value
gl0	0.047	0.000-0.004	0.028	-0.001	-0.003	NS
gl120	0.001	-0.006	NS	0	-0.005	NS
In0	0.076	0.000-0.014	0.048	0.004	-0.012	0.048
In120	0.002	-0.006	NS	0.002	0.000-0.004	NS
c-pept0	0.157	0.036-0.2	0.005	0.088	0.011-0.166	0.025
c-pept120	-0.009	-0.104	NS	0.006	-0.099	NS
HOMA0	0.059	-0.046	NS	0.009	-0.04	NS
HOMA120	0.097	-0.012	NS	0.004	-0.011	NS
HbA1c	0.062	-0.13	NS	0.039	-0.123	NS

* All variables are corrected for sex and age.
**All variables are adjusted for sex, age and BMI
gl0: Fasting plasma glucose, gl120: Plasma glucose 120 minutes after oral glucose tolerance test, In0: Fasting plasma insulin, In120: Plasma insulin 120 minutes after oral glucose tolerance test, c-peptide0: Fasting plasma c-peptide, c-peptide120: plasma c-peptide 120 minutes after oral glucose tolerance test, HOMA0: Homeostatic Model Assessment of Insulin Resistance, HOMA120: Homeostatic Model Assessment of Insulin Resistance 120 minutes after oral glucose tolerance test, HbA1c: Glycated hemoglobin.
Table 6: Regression analysis with serum uric acid levels as the dependent variable in the normourecemic hypertensive patients (including glucose loading sub groups).

Discussion

In the present study we evaluated the relationship between the SUA levels, with various parameters indicative of carbohydrate metabolism in a large cohort of 2803 hypertensive, treated (n=1480) or newly diagnosed, untreated (n=1323) individuals, hyperuricemic (n=543) or not (n=2260). We used the most recent acceptable cut-off levels for normal or abnormal SUA levels for the subgroups of the study population, we used the 2hPG, (2-hour postload plasma glucose, insulin, c-peptide measurements during the 75gr glucose tolerance test (OGTT) and the Homeostatic Model Assessment of Insulin Resistance to calculate HOMA0 and HOMA120.

We found in the overall study hypertensive population, (including glucose loading subgroups) a significantly positive correlation between SUA levels with gl0, in0, HbA1C and HOMA0 and with gl120, in120, HOMA120 and c-pept0, (in glucose loading subgroup). The regression analysis with SUA as independent variable (in the above mentioned groups), revealed that gl0, in0, HbA1c, HOMA0, gl120, in120, HOMA120 and c-pept0, are all independent predictors of SUA levels. In newly diagnosed untreated hypertensive patients (including glucose loading subgroups) we found a statistically significant positive correlation of SUA levels only with in120, c-pept120 and HOMA120 while in the regression analysis with SUA as independent variable was revealed that gl120, in120, HOMA120, c-pept120 as well as c-pept0 and HbA1c were independent predictors of SUA levels. In treated hypertensive patients we found a statistically significant positive correlation between SUA and gl0, gl120, in0, c-pept0 and HOMA0. In the regression analysis of this study group with SUA levels to be an independent variable, gl0, in0, c-pept0, HOMA0 as well as HbA1c were independent predictors of SUA levels. In normourecemic hypertensive patients treated or untreated a statistically significant correlation was found between SUA levels and gl0, in0, c-pept0. In hyperurecemic hypertensives patients we found statistically significant higher levels of gl0, gl120, in0, in120, c-pept0, HOMA0, HOMA120, HbA1c, while there were older than normourecemic and also they had greater values of BMI and WC. Finally a significantly higher proportion of hyperurecemic patients were under anti-hypertensive treatment relative to normourecemic patients.

In our study, SUA levels were significantly higher in treated versus untreated hypertensives, partly because of the HCTZ, included in the antihypertensive treatment, while e-GFR was significantly statistical higher in newly diagnosed untreated hypertensive patients, vs treated patients. Similarly, significantly higher e-GFR levels were noticed among normourecemics patients relatively to hyperourecemics. As far as the S/DBPo levels are concerned in our study population, they were statistically significant lower, respectively in hyperurecemic group hypertensive patient's vs normourecemics, but statistically significant more hyperurecemic patients were under treatment.

Many studies during many decades, suggest the relationship between SUA levels and components of carbohydrate metabolism in different studies population. In a past study in normal volunteers

Fachchini, et al. [7], found that the magnitude of insulin resistance was significantly related with the SUA concentration, as the urinary UA clearance was decreased in proportion of the increases of insulin resistance [7].

In a relatively recent meta-analysis of Kodama S, et al. [1] of 11 cohort studies of 42834 participants, seemed a positive association of SUA levels with the development of type 2 diabetes, during a follow-up period of 2-13.5 years, regardless the different characteristics in different studies, in which the pooled RR of a 1mg/dl increase in SUA was 1.17, (indicating that the risk of developing diabetes type 2, increases 17% for each increase for 1mg/dl of SUA) with these results to be consistently significant between different characteristics of participants, (country of origin, men, women, amount of alcohol consumption, metabolic profile) showing a strong and independent correlation between SUA and carbohydrate metabolism in the general population. Similarly in a previous study of 4536 subjects free from diabetes at baseline the SUA levels were a strong and independent risk factor for diabetes type 2 in a period of follow-up of 10.1 years [8].

Contrary the Third National Health and Nutrition Examination Survey revealed a bell-shaped relation between SUA levels and HbA1c levels. The SUA levels increased with increasing serum HbA1c levels up to the category of 6-6.9% and thereafter decreased with further increasing HbA1c levels, in 14664 participants of the general population, showing that individuals, particularly women, with moderately elevated HbA1c (pre-diabetes) had higher levels of SUA being probably in a higher risk for hyperuricemia and gout [9].

Similarly in a prospective study of Liu Y, et al. [10] also in general population adults, non diabetics in North China, who examined the correlation between SUA levels and the risks of impaired fasting glucose (IFG), they found that there was a higher risk of developing IFG in association with low or high SUA concentrations in men, independently of other known risk factors [10].

This U-shape in the correlation between SUA levels and incidence of IFG in men could perhaps relate to the bi-directional effect of SUA on oxidative stress (anti-oxidant and pro-oxidant properties). On the contrary no significant correlation was observed for women, a possible reason for this differentiation being attributed to alterations of sex hormones (as estrogens have a uricosuric effect).

As far as hypertensive patients are concerned, there is some data about the important role of SUA levels in the carbohydrate metabolism. In a study in 500 uncomplicated hypertensive non diabetic patients Perticone, et al. [11] showed that both hyperuricemia and endothelium dysfunction increased the risk to develop new diabetes [11].

Furthermore, in hypertensive patients, with left ventricular hypertrophy as LIFE study has showed, SUA levels were independently associated (after adjustment for treatment with losartan vs atenolol, baseline serum glucose, urinary albumin/creatinine ratio and e-GFR) with new onset diabetes during a follow –up period of 4.9 years, suggesting a strong correlation of SUA levels with the serum glucose levels in these high risk hypertensive patients [12].

But there is limited available information regarding the relationship of SUA levels with every component of carbohydrate metabolism and the progression from the fasting glycemia, (impaired or not), (it is known that approximately 50% of patients with primary hypertension have insulin resistance,) to impaired glucose tolerance and to overt DM, in hypertensive treated or newly diagnosed untreated patients, hypertensives without DM, hypertensives pre-diabetics or hypetensives diabetics, treated or not, even in a normal range of SUA levels, a point of interest, of the possible very early metabolic disturbance, possibly in the base of fructose and glucose metabolism, the development of fatty liver, elevated triglycerides, ATP depletion, inflammation and uric acid generation, the presence of endothelial dysfunction and pro-atherogenic status of hypertensive patients, as hyperuricemia is linked not only with hypertension but also with dyslipidemia, insulin resistance, that is a main characteristic in the subjects with type 2 diabetes, and also precedes the development of type 2 diabetes, aging, menopause and sedentary lifestyle, conditions that strongly correlate with oxidative stress, accelerated breakdown of the nitric oxide, causing as subsequence endothelial dysfunction by a multiplicative rather than an additive way.

In a study of Perticone F, et al. [13] in 1200 middle-aged uncomplicated untreated hypertensive subjects, was investigated the possible relationship between UA levels and 1- h postload plasma glucose [13]. The conclusions were of great clinical significance, as it was proven that SUA levels between normal range, is associated with 1-h postload plasma glucose, thus confirming the strong role of UA in the development of insulin resistance and also its value is further enhanced by the observation that 1-h postload glucose in normal glucose tolerance (NGT) subjects is associated with subclinical organ damage, that represents an intermediate stage in the continuum of vascular

disease, as well as a determinant of the overall cardiovascular risk.

Similarly in our study we found a significant correlation between SUA and 2-h postload plasma glucose (gl120) as well as in 120 and HOMA120, in the subgroup of the glucose loading of the overall study hypertensive population, as well as the gl120, in 120 and HOMA120, to be an independent predictor of SUA levels, for these hypertensive patients.

These results were also partially found (except gl120) in newly diagnosed untreated subgroup population, of our study, in which and the cpept120 correlated significantly with SUA levels, but not in treated patients , in which the correlation of SUA was significant and dependent of gl0 , in0, cpept0 and Homa0, possibly showing a more severe , established and clear, glucose metabolic disturbance in treated than in newly diagnosed untreated patients, or a possible role of confounders in the glucose metabolism as antihypertensive treatment without be needed of loading test glucose.

As for the relationship of SUA levels to insulin resistance in hypertensive patients, the significant correlation and the predictive value of SUA levels with components of Mets, which is the clinical manifestation of insulin resistance, is known according to the findings in one of our previous studies in hypertensive treated or newly diagnosed untreated patients [14].

Once more, in our present study HOMA0 and HOMA120 were significantly correlated with SUA in the overall and subgroup study hypertensive population with predictive value and in treated but not HOMA0 in untreated patients.

This data is not surprising from a pathophysiological point of view, since as it has already been mentioned herein the association between uric acid and insulin resistance that for many years precedes the clinical appearance of diabetes may be explained according to the pro-oxidant and pro-inflammatory effects of UA that interfere with glucose uptake, impairing of blood flow to skeletal muscles and peripheral tissues (by reducing the endothelial NO bioavailability and increasing free radical production, factors that collectively contribute to increased oxidative stress), deteriorating tissue resistance to insulin, thus causing a more intense insulin production by the β-pancreatic cells, which gradually will result in their depletion. Moreover, there are studies verifying the causal of uric acid in direct pancreatic β-cell death through activation of NF-κB signaling pathways, speeding up insulin secretion and progression to diabetes [15].

A similar study, concluded that elevated SUA in individuals with pre-diabetes, defined as IFG and HA1c, was significantly associated with higher 2-hour postload glucose and risk of developing type 2 diabetes, independent of recognized risk factors, such as FPG and HbA1c, and that lowering SUA was related to decreased incidence of diabetes. These two studies point out the crucial role of SUA in the deterioration of glucose tolerance, and suggest that it could be useful to use the uric acid evaluation so as to identify hypertensive people or individuals with IFG and/or HA1c who are at risk for insulin resistance and diabetes [16].

C-peptide, is part of proinsulin protein (precursor) and was considered to be a reliable marker of residual beta-cell function. It has been suggested that insulin precursor has different biological properties than insulin, that must be more important in predicting cardiovascular disease. Measuring c-peptide can help to determine how much of their own natural insulin a person is producing, as c-peptide is secreted in equimolar amounts to insulin. C-peptide levels are measured instead of insulin levels because c-peptide can assess a person's own insulin secretion even if they receive insulin injections, and because the liver metabolizes a large and variable amount of insulin secreted into the portal vein but does not metabolise c-peptide, meaning blood c-peptide may be a better measure of portal insulin secretion than insulin itself.

Insulin resistance, a common situation in hypertensive patients, is characterized by hyperinsulinemia, reflected in elevated fasting and glucose loading insulin and c-peptide concentrations [17].

C-peptide has been found to be in higher levels in hypertensives than in normotensives, with the BMI and waist to hip ratio to play an important role to these results [18].

In the glucose loading subgroup hypertensive population of our study, we found a significantly correlation and predictive value of SUA and c-pept0 in treated as well as in untreated patients and in the normourecemic hypertensive patients (as well as in0), meaning the important role of SUA in insulin secretion in hypertensive patients, but not in hyperurecemic patients, whose number, in our study, was much less than normourecemics.

As concern as the long term glucose status expressed by plasma HbA1c, that is known that correlates significantly with the SUA levels in newly diagnosed diabetics [19], we found, in our study, that HbA1c was significantly correlated with SUA levels in the overall

hypertensive study population, while it had a predictive value for SUA levels in overall, treated or newly diagnosed untreated hypertensive patients.

The results were most pronounced in treated hypertensive patients than in newly diagnosed untreated hypertensives possibly indicating, the more severe metabolic derangement as concern as "insulin resistance syndrome", that these patients suffer.

There are some limitations in our study as the small number of hyperurecemic treated or untreated hypertensive patients in glucose loading groups that may explains the absence of any significant correlation between SUA levels and parameters that express the carbohydrate metabolism.

The levels of serum fasting glucose in some patients in our study, are influenced from diabetic medications (as diabetics under treatment or not, or non diabetics, were included) and this may be a reason for the abcence of significance in correlation with SUA levels in untreated hypertensive patients. All variables were measured once. Menopause status in women is not available and is known that there is an interaction between sex hormone and SUA levels. SUA levels are higher in postmenopausal women because estrogen is uricosuric. In the treated group diuretic's treatment is included and the SUA levels may be influenced and are not the real ones, other medication as b-blockers and RAAS blockers interfere with insulin sensitivity and could have an impact on the results of our study. It is not clear if the administration of HCTZ influences the correlation of the above mentioned variables, except of the known effect in the level of SUA and this may be a confounder in the analysis, that needs further investigation.

The gold standard for assessment of insulin sensitivity is the hyperinsulinemic-euglycemic clamp method and not the HOME we have used. Few patients of glucose loading subgroup for the measurement of fasting and after glucose loading c-peptide. Finally in the group of hyperuricemic patients both treated and untreated hypertensive patients are included and it is not clear if the reduction of BP itself alters the glucose metabolism status.

Clinical Implications

Our study implicated that SUA levels may be part of the glucose metabolism, in every step of the progression from the fasting glycemia, (impaired or not), to impaired glucose tolerance and to overt DM in hypertensives and could be incorporated into the routine assessment of hypertensive patients treated or not, in order to identify patients with high cardiovascular risk and risk for gout, to treat theme entirely for their total cardiovascular risk.

The view that uric acid is simply a marker of metabolic disorders and cardiovascular disease, will likely have to be modified. However, it cannot yet be stated that elevated uric acid levels cause, rather than sustain or even deteriorate insulin resistance and glucose tolerance. It seems that there is a vicious circle between insulin sensitivity, uric acid production and endothelial function that interconnects them and finally leads to cardiovascular (coronary artery, hypertension) and metabolic disease (diabetes, metabolic syndrome). Future studies are needed to determine the causality of these findings.

Conclusion

The levels of SUA in hypertensive individuals are both associated with and dependent on different parameters of carbohydrate metabolism and insulin resistance, either suggesting a potential role of uric acid in the pathogenesis of metabolic syndrome and deranged glucose metabolism, or verifying that it constitutes an aspect of the underlying pathologic condition. Its evaluation could serve for the identification of individuals at risk of developing diabetes, whereas the lowering of its serum levels may be a novel treatment target for the prevention of diabetes.

References

1. Kodama S, Saito K, Yachi Y, Mihoko A, Ayumi S, et al. (2009) Association between serum uric acid and development of type 2 diabetes. Diabetes Care 32(9): 1737-1742.

2. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, et al. (2002) Uric acid, hominoid evolution and the pathogenesis of salt-sensitivity. Hypertension 40(3): 355-360.

3. Richette P, Perez-Ruiz F (2013) Serum uric acid and metabolic risk. Curr Med Res Opin 29: 9-15.

4. Feig DI, Kang DH, Johnson RJ et al. (2008) Uric acid and cardiovascular risk. N Engl J Med 359(17): 1811-1821.

5. Shabana S, Sireesha M, Satyanaranya U (2012) Uric acid in relation to type 2 diabetes Mellitus Associated with Hypertension. J Clin Diagn Res 6(7): 1140-1143.

6. Menè P, Punzo G (2008) Uric acid: bystander or culprit in hypertension and progressive renal disease. J Hypertens 26(11): 2085-2092.

7. Facchini F, Chen YD, Hollenbeck CB, Reaven GM (1991) Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 266(21): 3008-3011.

8. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC (2008) High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes. Diabetes Care 31(2): 361-362.

9. Choi HK, Ford ES (2008) Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels-the Third National Health and Nutrition Examination Survey. Rheumatology (Oxford) 47(5): 713-717.

10. Liu Y, Jin C, Xing A, Liu X, Shuohua C, et al. (2013) Serum Uric acid levels and the risk of impaired Fasting glucose: A prospective study in adults of North China. PLoS One 8(12): e84712.

11. Perticone F, Maio R, Tassone JE, Perticone M, Pascale A (2013) Interaction between uric acid and endothelial dysfunction predicts new onset of diabetes in hypertensive patients. Int J Cardiol 167(1): 232-236.

12. Høieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, et al. (2004) The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 65(3): 1041-1049.

13. Perticone F, Sciacqua A, Tassone EJ, Miceli S, Maio R, et al. (2012) One-hour post-load plasma glucose and IGF-1 in hypertensive patients. Eur J Clin Invest 42(12): 1325-1331.

14. Papavasileiou MV, Karamanou AG, Kalogeropoulos P, Moustakas G, Patsianis S, et al. (2015) Uric acid blood levels and relationship with the components of metabolic syndrome in hypertensive patients. J Hum Hypertens 30(7): 414-417.

15. Jia L, Xing J, Ding Y, Shen Y, Shi X, et al. (2013) Hyperuricemia causes pancreatic b-cell death and dysfunction through NF-κB signaling pathway. PLoS One 8(10): e78284.

16. Fan HQ, Tang W, Wang ZX, Su-Juan W, Yue-Hua Q, et al. (2013) Association of serum uric acid with 2-hour postload glucose in Chinese with impaired fasting plasma glucose and/or HbA1c. PLoS One 8(7): e67759.

17. Bonora E, Coscelli C, Butturini U (1985) Relationship between insulin resistance, insulin secretion and insulin metabolism in simple obesity. Int J Obes 9(5): 307-312.

18. Toft I, Bonaa KH, Jenssen T (1998) Insulin resistance in hypertension is associated with body fat rather than blood pressure. Hypertension 32(1): 115-122.

19. Gill A, Kukreja S, Malhotra N, et al. (2013) Correlation of the serum Insulin and the Serum Uric acid Levels with the glycated haemoglobin Levels in the patients of type 2 Diabetes mellitus. J Clin Diagn Res 7(7): 1295-1297.