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Long-term increase in serum uric acid and its predictors over a 25 year follow-up: Results of the PAMELA study

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Abstract *Background and aims:* Hyperuricemia (HU) has been shown to be associated with an adverse impact on cardiovascular and metabolic risk. Scanty data are available in the general population on the longitudinal changes in serum uric acid (SUA), the occurrence of HU and their potential predictors. We examined during a 25-year follow-up the SUA changes and the factors associated with HU development in the Pressioni Arteriose Monitorate E loro Associazioni (PAMELA) study.

Methods and results: We analyzed data collected in 561 subjects of the PAMELA study evaluated during an average follow-up time amounting to 25.4 ± 1.0 years (mean ± SD). HU was defined by the Uric Acid Right for Heart Health (URRAh) cutoff (5.1 for females and 5.6 mg/dl for males). Mean SUA values during follow-up increased from 4.7 ± 1.1 to 5.0 ± 1.2 mg/dl ($P<0.001$), the average SUA elevation amounting to of 0.3 ± 1.1 mg/dl 26.7 % of the subjects displayed HU at the follow-up. This was associated at the multivariable analysis with female gender, office, home and 24-h blood pressure, diuretic treatment, serum triglycerides and baseline SUA, as well as the increase in waist circumference and the reduction in renal function.

Conclusion: The present study provides longitudinal evidence that in the general population during a 25 year follow-up there is a progressive increase in SUA and HU development. Baseline SUA represents the most important factor associated with these modifications. Gender, renal dysfunction, triglycerides, obesity, diuretic treatment and blood pressure represent other variables capable to predict future occurrence of HU.

1. Introduction

Cross-sectional studies have shown that serum uric acid [SUA] levels are significantly related to a number of nominal, anthropometric, hemodynamic, renal and metabolic variables, such as gender, age, body mass index, blood pressure, estimated glomerular filtration rate, plasma glucose, plasma cholesterol and triglycerides levels [1–8]. Information on the relationships between SUA and the above mentioned variables provided by longitudinal

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investigations appears to be much more scanty, however, and the only two available studies were performed in selected patients populations or with a follow-up of limited temporal duration [9,10].

The Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) epidemiological study was carried out on a sample of a general urban population of Northern Italy, enrolled in the early 1990s and followed up for many years [4,11]. Both at the baseline evaluation and at the assessment carried out 25 years later, each subject underwent a general medical examination, including collection of clinical history, presence of cardiovascular diseases and risk factors, any drug treatment modification, physical examination with measurement of anthropometric variables, "in-office" and "out-of-office" blood pressure [BP] and heart rate [HR], 24-h BP and HR variability as well as biochemical variables, including estimated glomerular filtration rate, blood glucose, serum lipids and SUA.

The present study, based on the analysis of the data collected in the frame of the PAMELA study, was planned to identify the variables predicting the long-term increase in SUA and the appearance of hyperuricemia [HU], defined accordingly to the recently identified SUA cutoff values [6]. The unique feature of the study was represented by the evaluation of the data collected over a 25 year observational period, which represents the longest follow-up never performed before for this analysis.

2. Methods

2.1. Population

The methodology of the PAMELA study has been described in detail elsewhere [4,11]. Briefly, 3200 residents in Monza (a town located in the north-east outskirts of Milan, Italy), aged from 25 to 74 years, were randomly selected to be representative of the general population, stratified for gender and age decades, according to the criteria of the World Health Organization Monitoring Diseases project performed in the same geographic area. The initial evaluation was carried out between 1990 and 1993 with a participation rate amounting to 64 %. The demographic and clinical characteristics of participants and non-participants, as assessed by phone interviews, were similar. Five hundreds and sixty one subjects, contacted again between 2017 and 2018, accepted to be re-examined after a mean time ($\pm$ standard deviation) interval from the first examination amounting to 25.4 $\pm$ 1.0 years, following the same protocol used for the first evaluation. In both occasions medical visits were carried out in the outpatient section of the Saint Gerardo Hospital of Monza, during the morning of a working day, following an overnight fast and abstinence from alcohol and smoking since the previous day.

2.2. Data collection

After obtaining an informed consent, a full medical history was collected in each subject. Data collected included weight, height, body mass index [BMI], waist circumference [WC], office, home, 24-h ambulatory BP and heart rate [HR] values, the overall 24-h BP and HR variability profile being taken as the corresponding standard deviation around the average. Blood examinations included SUA, blood glucose, total serum cholesterol, high density lipoprotein (HDL) serum cholesterol, serum triglycerides and serum creatinine. Glomerular Filtration Rate was estimated by the Chronic Kidney Disease EPI demiology (CKD-EPI) equation [12]. Low density lipoprotein [LDL] serum cholesterol was estimated according to the Friedewald equation. HU was diagnosed using the cutoff values recently identified by the URRAH study, i.e. 5.1 mg/dl for females and 5.6 mg/dl for males [6]. Office BP was measured three times with the subject in the sitting position, using a mercury sphygmomanometer and taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. Office HR was assessed by the palpatory method at the level of the radial artery. To assess 24-h ambulatory BP subjects were fitted with a monitoring device (Spacelabs 90207, Issaquah, WA, USA) set to obtain automated oscillometric BP and heart rate (HR) readings every 20 min over the 24 h [4,11]. Subjects were asked to pursue their normal activities during the monitoring period, holding the arm still at time of the BP readings, going to bed not later than 11.00 pm and arising not before 7.00 am. Subjects were also asked to self-measure BP and HR at home, with a validated semi-automatic oscillometric device (model HP 5331, Philips, USA), with a cuff size appropriate to each individual's arm circumference, at 7.00 pm and 7.00 am, using the arm contralateral to the one used for ambulatory BP measurements [4,11]. After editing for artifacts all ambulatory BP recordings were analyzed to obtain 24-h, systolic BP, diastolic BP, and HR values. As mentioned above 24-h BP and HR variability were also obtained. The study protocol complied with the Declaration of Helsinki and it was approved by the Ethics Committee of the Institutions involved.

2.3. Data analysis

Data related to subjects' characteristics were analysed by descriptive statistics. Normality of continuous variables was tested by qq-plot and Kolmogorov-Smirnov test. Non-normal variables were log transformed. Continuous variables were reported as means $\pm$ standard deviation. For discrete variables, percentages were reported. Paired t-test and McNemar test were used to compare baseline with follow-up characteristics. Groups were compared using t-test, Chi-square test or Fisher's Exact.

New onset HU calculation was made on subjects displaying normal SUA values at baseline and becoming or not hyperuricaemic at follow-up. The correlation of different factors with the occurrence of HU at the second evaluation was first performed by univariable logistic regression model. Factors considered included sex, age, BMI, WC, office, home and 24-h ambulatory systolic BP, diastolic BP, HR, antihypertensive treatment, use of diuretic agents, blood glucose, total serum, LDL and HDL

cholesterol, serum triglycerides, estimated glomerular filtration rate, baseline SUA, and change (difference between value measured at baseline and at the second evaluation 25 years later) of all the afore mentioned variables. Factors found to be significantly associated with the occurrence of HU at univariable analysis were then included as independent variables in the multivariable logistic model (with stepwise selection), aimed at identifying factors independently associated with the occurrence of HU. Then, after exclusion of subjects in whom SUA decreased at the second evaluation, the association of the same factors with the change of SUA between baseline assessment and the second survey was examined via univariable linear regression models. Factors found to be significantly associated with increased SUA at univariable analysis were then used as independent variables of the multivariable analysis, aimed at identifying factors independently associated with increased SUA values (stepwise selection). All analyses were carried out using a SAS 9.4 software (SAS Institute, Cary, NC, USA) and a $P < 0.05$ was considered statistically significant.

3. Results

Table 1 illustrates the prevalence of genders, age, smoking habit, alcohol intake, BP, HR, anthropometric and metabolic variables in the 561 subjects included in the study, assessed at baseline and at the second evaluation performed about 25 years later.

3.1. Baseline values

Mean age at baseline was 41.8 ± 9.8 years and male prevalence amounted to 49.7 %. 6.3 % of subjects were treated for hypertension, of which 2.0 % was under diuretic treatment at baseline evaluation. Mean systolic/diastolic BP amounted to 122.2 ± 14.8/80.8 ± 9.7 mmHg respectively, while the corresponding 24-h and home BP values to 116.2 ± 9.1/73.2 ± 6.7 and 116.0 ± 14.8/73.4 ± 9.6 mmHg, respectively. Mean serum creatinine, fasting blood glucose and triglycerides, BMI and WC were all within the normal range, while serum cholesterol was slightly greater the normal values. In the study population as a whole, mean baseline SUA levels were also within the normal range (4.7 ± 1.2 mg/dl), HU being detectable in $^1/_4$ of the study population.

3.2. Follow-up

During the follow-up all the variables underwent significant variations, the majority of them showing an increase. This was the case for office, home and 24-h ambulatory BP, while the corresponding HR values did not display any significant change, with the exception of 24-h HR which showed a significant reduction. The percentage of subjects under antihypertensive drug treatment in general and specifically diuretic medications significantly raised to 49.0 % and to 17.5 %, respectively. Serum creatinine values significantly increased, and the corresponding estimated glomerular filtration rate significantly reduced. Blood glucose, serum triglycerides, BMI and WC also significantly increased, the exception being total serum cholesterol and LDL cholesterol, both variables showing a reduction. SUA significantly increased, reaching at follow-up the value of 5.0 ± 1.3 mg/dl, the total amount of HU also significantly increasing to 37.2 %.

Table 1 Baseline and follow-up data of the 561 subjects evaluated at baseline and at second examination 25 years later.

Variable	Baseline	Follow-up	*P-value*
Male, %	49.7	–	–
Age, years	41.8 ± 9.8	66.0 ± 9.8	–
Smoking, %	23.53	11.05	<0.0001
Alcohol, %	43.67	53.3	<0.0001
Office SBP, mmHg	122.2 ± 14.8	136.9 ± 18.1	<0.0001
Office DBP, mmHg	80.8 ± 9.7	83.4 ± 9.0	<0.0001
Office HR, b/min	70.5 ± 9.5	70.8 ± 10.3	0.6119
Home SBP, mmHg	116.0 ± 14.8	128.0 ± 16.2	<0.0001
Home DBP, mmHg	73.4 ± 9.6	77.6 ± 8.9	<0.0001
Home HR, b/min	72.4 ± 9.6	72.6 ± 10.7	0.7616
24h SBP, mmHg	116.2 ± 9.1	133.6 ± 14.1	<0.0001
24h DBP, mmHg	73.2 ± 6.7	77.8 ± 7.7	<0.0001
24h HR, b/min	76.23 ± 8.3	72.17 ± 7.7	<0.0001
24h SD SBP,mmHg	12.8 ± 3.07	22.01 ± 5.8	<0.0001
24h SD DBP, mmHg	11.5 ± 2.4	17.3 ± 5.4	<0.0001
24h SD HR, mmHg	13.1 ± 3.5	12.5 ± 3.6	<0.0001
Antihypertensive treatment, %	6.3	49.0	<0.0001
Diuretics, %	2.0	17.5	<0.0001
BMI, Kg/m^2	24.4 ± 3.6	26.4 ± 4.4	<0.0001
WC, cm	82.0 ± 91.2	91.2 ± 13.8	<0.0001
Glucose, mg/dl	86.6 ± 11.9	95.7 ± 22.5	<0.0001
Total Cholesterol, mg/dl	214.6 ± 40.8	201.1 ± 36.2	<0.0001
HDL-Cholesterol, mg/dl	56.7 ± 15.2	59.1 ± 17.1	<0.0001
LDL-Cholesterol, mg/dl	138.1 ± 38.0	120.5 ± 32.1	<0.0001
Triglycerides, mg/dl	98.5 ± 56.7	108.4 ± 58.8	<0.0001
Creatinine, mg/dl	0.85 ± 0.1	0.93 ± 0.2	<0.0001
eGFR, ml/min	93.2 ± 13.8	79.0 ± 16.7	<0.0001
SUA, mg/dl	4.7 ± 1.2	5.0 ± 1.3	<0.0001
Hyperuricemia (SUA≥5.1/5.6 mg/dl), %	26.7	37.2	<0.0005

Data are shown as means ± SD or as percent (%) values. SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR=Heart Rate; SD=Standard deviation; BMI = Body Mass Index; WC = Waist Circumference; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; eGFR = Estimated Glomerular Filtration Rate; SUA = Serum Uric Acid.

3.3. Long-term increase in SUA

After exclusion of subjects in which SUA showed a reduction between baseline and follow-up (n = 204), an analysis was performed on the relationships between the different above mentioned variables and the increase of SUA detected at the second evaluation (ΔSUA). In Supplemental Table 1 the univariable correlations are shown. The variables significantly associated with ΔSUA were age, BMI, BP values, WC, antihypertensive treatment and diuretic drug use, triglycerides, glucose, as well as changes from baseline to the second evaluation of several metabolic variables. Gender was not found to be

significantly associated with ΔSUA. When factors with a significant univariable relationship with ΔSUA were included in a multiple regression model, the ones resulting to be independent predictors of the SUA increase over time included age, diuretics use at follow-up, home diastolic BP, as well as variations during the 25 year follow-up of BMI, triglycerides and estimated glomerular filtration rate (Fig. 1, upper panel).

3.4. New onset HU

Subjects already displaying at baseline evaluation a HU state (n = 150, 26.7 %) were excluded from the present analysis. Table 2 shows baseline data collected in the study population, when classified according to the development of HU. Out of 411 subjects with normal SUA at initial assessment, 107 (26.0 %) developed HU at follow-up. When compared to individuals not displaying at follow-up HU, subjects with new onset HU were older and more frequently males. They showed greater BMI and WC values, higher office, home and 24-h BP values but similar 24-h BP variability. Subjects developing HU were characterized by greater baseline SUA, greater blood glucose, serum triglycerides and lower serum HDL cholesterol, the other lipid variables being not significantly different as compared to individuals not developing HU. Subjects developing HU also displayed a larger use of antihypertensive drugs in general and specifically of diuretic medications.

Table 3 shows the univariable correlations of several variables with the development of HU, a significant number of which being found statistically significant, namely male gender, age, BMI and WC, office, home and 24-h SBP, DBP, HR, antihypertensive treatment at follow-up, use of diuretic agents, blood glucose, serum HDL-cholesterol, serum triglycerides, serum LDL-cholesterol, and baseline SUA. In virtually all cases the relationship of the changes of these variables between baseline and follow-up evaluation achieved statistical significance.

Factors displaying a significant association with the development of HU at univariable analysis were included in a multiple regression model. As shown in Fig. 1, lower panel, the independent predictors of new-onset HU resulted female gender, office systolic BP, diuretic treatment, serum triglycerides, baseline SUA, as well as the increase in WC and the reduction in estimated glomerular filtration rate during follow-up.

4. Discussion

Three are the novel findings provided by the present study. The first finding refers to the data on the incidence of new HU recorded in the general population of the PAMELA study in the 25 year follow-up, which represents the longest period of observation never followed before for a SUA longitudinal data analysis. The results show that a consistent fraction of the general population (1/4 of the recruited individuals) may develop hyperuricemia during

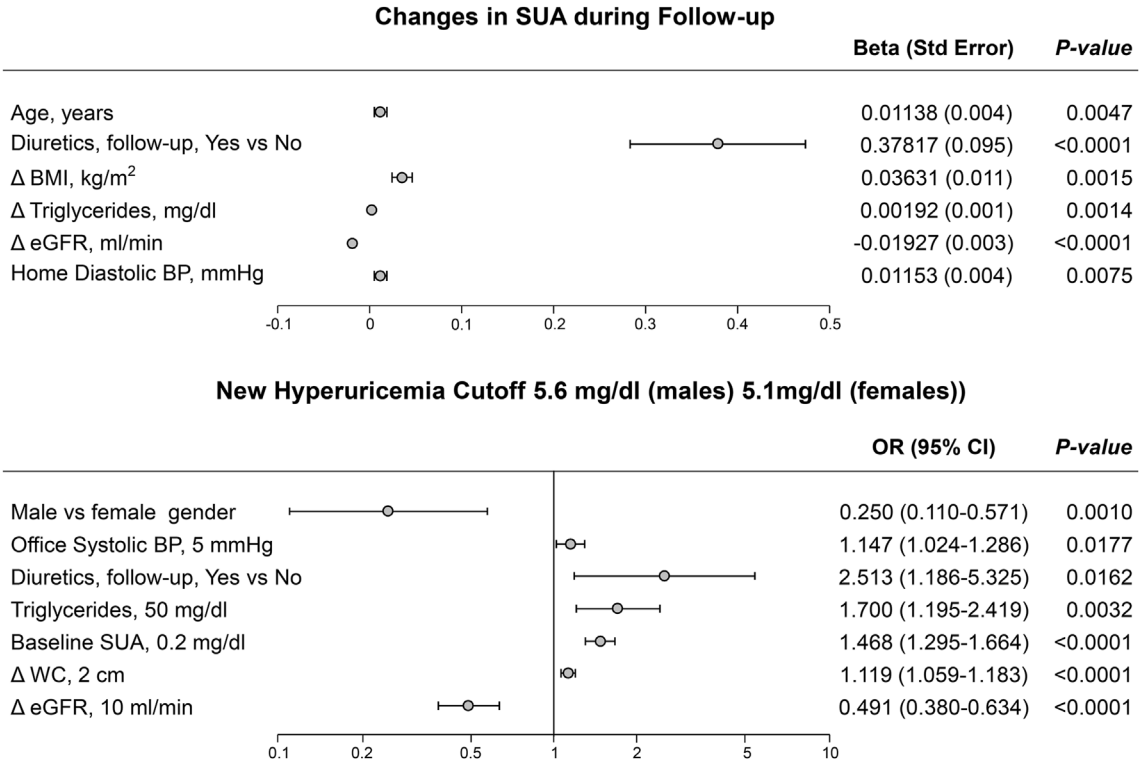

Figure 1 Multiple regression model (linear or logistic) for association with changes in serum uric acid (SUA, upper panel) or development of new hyperuricemia (lower panel). Δ BMI: changes in body mass index during follow-up, ΔeGFR: changes in estimated glomerular filtration rate during follow-up, ΔWC: changes in waist circumference during follow-up, BP: blood pressure, OR: odds ratio.

Table 2 Baseline data of 411 subjects with normal SUA at baseline, separately for those not developing vs those developing hyperuricemia at follow-up.

Variable	SUA Cutoff 5.6 mg/dl (Males) or 5.1 mg/dl (Females)		*P-value*
	No new Hyperuricemia	New Hyperuricemia	
N	304	107	
Male, %	33.6	51.4	0.0011
Age, years	40.4 ± 9.1	43.1 ± 10.9	0.0161
Smoking, %	23.36	26.17	0.5584
Alcohol, %	36.84	48.6	0.0327
Office SBP, mmHg	118.4 ± 13.0	126.2 ± 16.0	<0.0001
Office DBP, mmHg	78.6 ± 9.0	82.3 ± 10.1	0.0004
Office HR, b/min	71.0 ± 8.6	69.3 ± 9.4	0.0785
Home SBP, mmHg	112.3 ± 14.1	119.3 ± 13.9	<0.0001
Home DBP, mmHg	71.2 ± 9.38	75.9 ± 9.14	<0.0001
Home HR, b/min	73.6 ± 8.8	72.4 ± 9.9	0.2649
24h SBP, mmHg	113.9 ± 8.4	118.9 ± 8.9	<0.0001
24h DBP, mmHg	71.8 ± 6.3	74.7 ± 6.7	<0.0001
24h HR, b/min	77.2 ± 7.2	76.2 ± 8.9	0.3096
24h SD SBP,mmHg	12.6 ± 2.8	13.3 ± 3.5	0.0670
24h SD DBP, mmHg	11.4 ± 2.3	11.8 ± 2.8	0.1399
24h SD HR, mmHg	13.5 ± 3.5	12.6 ± 3.5	0.0199
Antihypertensive treatment, %	3.0	5.7	0.2311
Diuretics,%	0.3	4.7	0.0053
BMI, Kg/m^2	23.6 ± 3.5	24.5 ± 3.0	0.0188
WC, cm	79.0 ± 12.0	82.1 ± 10.8	0.0191
Glucose, mg/dl	84.8 ± 10.2	88.1 ± 15.3	0.0263
Total Cholesterol, mg/dl	208.2 ± 39.1	216.8 ± 43.7	0.0787
HDL-Cholesterol, mg/dl	59.5 ± 15.6	55.4 ± 14.2	0.0132
LDL-Cholesterol, mg/dl	132.2 ± 36.1	140.4 ± 38.3	0.0568
Triglycerides, mg/dL	82.2 ± 43.8	105.2 ± 54.6	<0.0001
eGFR, mL/min	95.2 ± 13.6	93.0 ± 13.3	0.1514
Uric Acid, mg/dl	4.0 ± 0.8	4.6 ± 0.5	<0.0001

Data are shown as means ± SD or as percent (%) values. SUA = Serum Uric Acid; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR=Heart Rate; SD=Standard deviation; BMI = Body Mass Index; WC = Waist Circumference; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; eGFR = estimated Glomerular Filtration Rate.

the quarter century follow-up. This information extends to the mediterranean population data collected in studies observing a much shorter follow-up and performed in extra-European populations or in selected patient groups [9,10].

The second new finding concerns the predictors of the SUA increase and of the occurrence of HU observed during the follow-up and thus concerns the factors which may be responsible for SUA elevation during years. In our study we found that SUA increase over time and occurrence of new onset HU are independently associated with a number of variables, such as advanced age, female sex, elevated systolic BP values during 24-h BP ambulatory monitoring, increase in BMI and in serum triglycerides values and reduction estimated glomerular filtration rate. For both SUA increase and new onset HU the most relevant predictor is diuretics use and, for HU only, elevated baseline SUA values. Taken together the results of the present study provide long-term evidence on the relevance of diuretic treatment as predictor of HU development [13], which, according to recent data, has clearcut prognostic relevance, being associated with an increase risk of fatal and non-fatal cardiovascular events [4,5,11,13–19].

The third new finding of the present study concerns the evaluation of the longitudinal relationships between HU and "out-of-office" BP, previous studies limiting this information to "in-office" BP [8–10]. The results show that home diastolic BP represents an independent predictor of the time-related SUA increase, while office systolic BP remains the most relevant hemodynamic variable directly and independently related to new onset HU. No predictive value was found, on the other hand, for other BP variables examined in the present study for the first time for their relationships with SUA, namely systolic and diastolic 24-h BP variability. This evaluation has relevant clinical implications, considering that 24-h BP variability has an impact on cardiovascular prognosis greater for magnitude than absolute 24-h BP load [20].

Several other results of our study deserve to be briefly mentioned. In our survey neither office nor home or 24-h ambulatory HR values were significantly related to the long-term increase in SUA values and the new onset HU. Since HR is regarded as a sympathetic marker [21], our findings at first glance appear not to confirm the relevance of sympathetic neural mechanisms as driver of SUA modifications [22–24]. It should be emphasized, however, that the sympathetic-SUA relationships may become manifest only when cardiac sympathetic drive is activated with the corresponding detection of HR greater than 80 beats/minute cutoff value [25]. This was not the case in our study population whose "in-office" and "out of office" HR values are around 70 beats/minute.

An element of novelty of our findings concerns the relation of the time-related SUA increase and the new onset HU with the overweight/obesity condition and the hypertriglyceridemic profile. The findings of the present study provide longitudinal evidence on the close relationships between SUA and triglycerides mostly described in cross-sectional studies only [4,7,9,10,26–29]. A number of factors may be responsible for this metabolic interaction. For example oxidative stress determined by biochemical reactions catalyzed by the xanthine oxidase may favour mitochondrial dysfunction and citrate release, thereby increasing the *de-novo* lipogenesis and triglycerides synthesis [29,30]. Furthermore, SUA may inhibit lipoprotein lipase activity in endothelial cells triggering an increase in circulating triglycerides [31]. Finally, in our study population female gender was associated with elevated SUA levels, similarly to what found in males. This finding can be explained taking into account that the women at the follow-up evaluation were all in the postmenopausal status, a condition well known to be characterized by the absence of the favorable lowering effects of estrogens on SUA levels [1].

Table 3 Univariable logistic regression model for hyperuricemia development.

Variable	SUA Cutoff 5.6 mg/dl (Males) 5.1 mg/dl (Females)			
	OR	CI 95 %		*P-value*
Male, vs Female	2.10	1.34	3.28	0.0012
Age, 1 year	1.03	1.01	1.05	0.0168
BMI, 1 kg/m^2	1.08	1.01	1.15	0.0201
WC, 2 cm	1.05	1.01	1.08	0.0228
Smoke, Yes vs No	1.16	0.70	1.93	0.5586
Alcohol, Yes vs No	1.62	1.04	2.53	0.0334
Office SBP, 5 mmHg	1.21	1.12	1.31	<0.0001
Office DBP, 5 mmHg	1.24	1.10	1.39	0.0005
Office HR, 5 b/min	0.89	0.79	1.01	0.0795
Home SBP, 5 mmHg	1.18	1.09	1.28	<0.0001
Home DBP, 5 mmHg	1.30	1.14	1.47	<0.0001
Home HR, 5 b/min	0.93	0.82	1.06	0.2645
24h SBP, 5 mmHg	1.39	1.22	1.59	<0.0001
24h DBP, 5 mmHg	1.40	1.18	1.66	0.0001
24h HR, 5 b/min	0.92	0.80	1.06	0.2602
24h SD SBP, 1 mmHg	1.08	1.00	1.16	0.0415
24h SD DBP, 1 mmHg	1.08	0.99	1.18	0.1041
24h SD HR, 1 mmHg	0.93	0.87	0.99	0.0208
Antihypertensive treatment, baseline, Yes vs No	1.96	0.68	5.65	0.2119
Antihypertensive treatment, follow-up, Yes vs No	2.31	1.47	3.62	0.0003
Diuretics, baseline, Yes vs No	14.85	1.72	128.51	0.0143
Diuretics, follow-up, Yes vs No	4.28	2.47	7.41	<0.0001
Glucose, 5 mg/dL	1.11	1.02	1.22	0.0199
Total Cholesterol, 5 mg/dL	1.03	1.00	1.05	0.0591
HDL-Cholesterol, 5 mg/dL	0.91	0.84	0.98	0.0176
LDL-Cholesterol, 5 mg/dL	1.03	1.00	1.06	0.0482
Triglycerides, 50 mg/dL	1.58	1.26	1.98	<0.0001
eGFR, 10 mL/min	0.88	0.75	1.05	0.1518
Uric Acid, 0.20 mg/dL	1.31	1.21	1.41	<0.0001
Δ BMI, 1 kg/m^2	1.12	1.04	1.20	0.0022
Δ WC, 2 cm	1.10	1.06	1.15	<0.0001
Δ Office SBP, 1 mmHg	0.98	0.97	1.00	0.0193
Δ Office DBP, 1 mmHg	0.98	0.96	1.00	0.039
Δ 24h SBP, 1 mmHg	0.98	0.97	1.00	0.0481
Δ 24h DBP, 1 mmHg	0.97	0.94	0.99	0.0142
Δ Glucose, 1 mg/dL	1.01	0.99	1.02	0.4244
Δ Total Cholesterol, 1 mg/dL	1.00	0.99	1.00	0.2092
Δ HDL-Cholesterol, 1 mg/dL	0.98	0.96	1.00	0.025
Δ LDL-Cholesterol, 1 mg/dL	1.00	0.99	1.00	0.3902
Δ Triglycerides, 50 mg/dL	1.04	0.85	1.26	0.7126
Δ eGFR, 10 mL/min	0.56	0.47	0.68	<0.0001

OR. Odds ratio,; CI: confidence Interval; SUA = Serum Uric Acid; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR=Heart Rate; SD=Standard deviation; BMI = Body Mass Index; WC = Waist Circumference; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; eGFR = estimated Glomerular Filtration Rate.

4.1. Strenghts and limitations

Our study has elements of strenght and limitations. The main strenght is the unique feature of the study which provides novel longitudinal data on the behaviour of SUA during half century in the general population, also examining the predictors of the SUA changes over time. Limitations include: 1) the relatively small sample size of the population evaluated at follow-up, 2) the lack of information about dietary habits which could have affected SUA, and 3) the impossibility to distinguish the different conditions of reduced excretion and overproduction of SUA (due to the lack of data on urinary uric acid) and thus selectively discriminate the different impact of these two causes of hyperuricemia. A further limitation is that no information was available on the use of allopurinol or febuxostat in the PAMELA study leading to a possible underestimation of our results (i.e. some subjects could have lower SUA levels due to SUA lowering drug treatments). However, subjects who already displayed HU at baseline or subjects showing a reduction in SUA during the follow-up were excluded from the analysis.

5. Conclusion

In conclusion, the present study provides evidence that in the PAMELA population a consistent fraction of subjects experiences during the 25-year follow-up a significant increase in SUA levels, developing a HU state. Diuretic use as well as baseline SUA levels represent the main predictors of the time-related SUA modifications. Other important factors participating at the above mentioned modifications are represented by gender, renal dysfunction, hypertriglyceridemic profile, as well as anthropometric and BP alterations during follow-up.

Authors contribution

AM, RD, MB, RF, FQT contributed to formal analysis, investigation and methodology, AM and RD wrote the first draft. GM and GG critically reviewed the paper and were responsible for the final draft.

Declaration of competing interest

The authors have no conflicts of interests to declare.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.10.009.

References

[1] Cigolini M, Targher G, Tonoli M, Manara F, Muggeo M, De Sandre G. Hyperuricaemia: relationships to body fat distribution, and other components of the insulin resistance syndrome on 38-yer old healthy men and women. Int J Obes Relat Metab Disord 1995;19:92–6.
[2] Xiong Y, Wangsheng F, Wang S, Zhou W, Huang X, Bao H, et al. Positive association between body fat percentage and hyperuricemia in patients with hypertension: the China H-type hypertension registry study. Nutr Met Cardiovasc Dis 2012:3076–84.
[3] Kim T, Lee SS, Yoo JH, Kim SR, Yoo SJ, Song HC, et al. The relationship between the regional abdominal adipose tissue

distribution and the serum uric acid levels in people with type 2 diabetes mellitus. Diabetol Metab Syndrome 2012;4:3.
[4] Bombelli M, Quarti-Trevano F, Tadic M, Facchetti R, Cuspidi C, Mancia G, et al. Uric acid and risk of new-onset metabolic syndrome, impaired fasting glucose and diabetes mellitus in a general Italian population: data from the Pressioni Arteriose Monitorate E Loro Associazioni study. J Hypertens 2018;36:1492–8.
[5] Ni Q, Lu X, Chen C, Du H, Zhang P. Risk factors for the development of hyperuricemia. A STROBE-compliant cross sectional and longitudinal study. Medicine 2019;98:42.
[6] Virdis A, Masi S, Casiglia E, Tikhonoff V, Cicero AF, Ungar A, et al. Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years. Hypertension 2020;75:302–8.
[7] Wang X, Zhong S, Guo X. The associations between fasting glucose, lipids and uric acid levels strengthen with the decile of uric acid increase and differ by sex. Nutr Metabol Cardiovasc Dis 2022;32:2786–93.
[8] Li S, Feng L, Sun X, Ding J, Zhou W. Association between serum uric acid and measures of adiposity in Chinese adults: a cross-sectional study. BMJ Open 2023;13:e072317.
[9] Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. Eur J Epidemiol 2007;22:439–45.
[10] Choe JY, Park SH, Kim JY, Shin IH, Kim SK. Change in serum uric acid between baseline and 1-year follow-up and its associated factors in male subjects. Clin Rheumatol 2008;27:483–9.
[11] Bombelli M, Facchetti R, Fodri D, Brambilla G, Sega R, Grassi G, et al. Impact of body mass and waist circumference on the cardiovascular risk and all-cause death in a general population: data fron the PAMELA study. Nutr Met Cardiovasc Dis 201;23;650-656.
[12] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[13] Maloberti A, Bombelli M, Facchetti R, Barbagallo CM, Bernardino B, Rosei EA, et al. Relationships between diuretic-related hyperuricemia and cardiovascular events: data from the URic acid Right for heArt Health study. J Hypertens 2021;39:333–40.
[14] Bos MJ, Koudstaal PJ, Hofman A, Witterman JCM, Breteler MMB. Uric acid is a risk factor for myocardial infarction and stroke. Stroke 2006;37:1502–7.
[15] Zhu P, Liu Y, Han L, Xu G, Ran JM. Serum uric acid is associated with incident chronic kidney disease in middle-aged populations: a meta-analysis of 15 cohort studies. PLoS One 2014;9:e100801.
[16] Storhaug HM, Toft I, Norvik JV, Jenssen T, Eriksen BO, Melsom T, et al. Uric acid is associated with microalbuminuria and decreased glomerular filtration rate in the general population during 7 and 13 years of follow-up: the Tromsø Study. BMC Nephrol 2015;16:210.
[17] Muiesan ML, Salvetti M, Virdis A, Masi S, Casiglia E, Tikhonoff V, et al. Serum uric acid predicts heart failure in a large Italian cohort: search for a cut-off value. The URic acid Right for heArt Health (URRAh) study. J Hypertens 2021;39:62–9.
[18] Lai X, Gao B, Zhou G, Zhu Q, Zhu Y, Lai H. The Association between baseline, changes in uric acid and renal failure in the elderly Chinese individuals: a Prospective Study with a 3-Year Follow-Up. Internet J Endocrinol 2022:4136373.
[19] Muiesan ML, Agabiti-Rosei C, Paini A, Casiglia E, Cirillo M, Grassi G, et al. Serum uric acid and left ventricular mass independently predict cardiovascular mortality:the URic acid Right for heArt Health (URRAh) project. Eur J Intern Med 2023;114:58–65.
[20] Mancia G, Grassi G. Mechanisms and clinical implications of blood pressure variability. J Cardiovasc Pharmacol 2000;35(Suppl 4):S15–9.
[21] Grassi G, Vailati S, Bertinieri G, Seravalle G, Stella ML, Del'Oro R, et al. Heart rate as marker of sympathetic activity. J Hypertens 1998;16:1635–9.
[22] Grassi G, Ram VS. Evidence for a critical role of the sympathetic nervous system in hypertension. J Am Soc Hypertens 2016;10:457–66.
[23] Lambert EA, Hachem M, Hemmes R, Straznicky NE, Eikelis N, Sari CI, et al. Serum uric acid and the relationship with subclinical organ damage in adults. J Hypertens 2017;35:745–52.
[24] Palatini P, Parati G, Virdis A, Reboldi G, Masi S, Mengozzi A, et al. High heart rate amplifies the risk of cardiovascular mortality associated with elevated uric acid. Eur J Prev Cardiol 2021;29:1501–9.
[25] Grassi G, Quarti-Trevano F, Seravalle G, Dell'Oro R, Facchetti R, Mancia G. Association between the European Society of Cardiology/European Society of Hypertension heart rate thresholds for cardiovascular risk and neuroadrenergic markers. Hypertension 2020;76:577–82.
[26] Lurbe E, Torro MI, Alvarez-Pitti J, Redon J, Borghi C, Redon P. Uric acid is linked to cardiometabolic risk factors in overweight and obese youths. J Hypertens 2018;36:1840–6.
[27] Maloberti A, Vanoli J, Finotto A, Bombelli M, Facchetti R, Redon P, et al. Uric acid relationships with lipid profile and adiposity indices: impact of different hyperuricemic thresholds. J Clin Hypertens 2023;25:78–85.
[28] Palatini P, Virdis A, Masi S, Mengozzi A, Casiglia E, Tikhonoff V, et al. Hyperuricemia increase the risk of cardiovascular mortality associated with very high HDL-cholesterol level. Nutr Metabol Cardiovasc Dis 2023;33:323–30.
[29] Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA. Uric acid and oxidative stress. Curr Pharmaceut Des 2005;11:4145–51.
[30] Otani N, Toyoda S, Sakuma M, Hayashi K, Ouchi M, Fujita T, et al. Effects of uric acid on vascular endothelial function from bedside to bench. Hypertens Res 2018;41:923–31.
[31] Radi R, Rubbo H, Bush K, Freeman BA. Xanthine oxidase binding to glycosaminoglycans: kinetics and superoxide dismutase interactions of immobilized xanthine oxidase-heparin complexes. Arch Biochem Biophys 1997;339:125–35.