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ORIGINAL

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Serum uric acid shows a J-shaped trend with coronary mortality in non-insulin-dependent diabetic elderly people. The CArdiovascular STudy in the ELderly (CASTEL)

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Abstract The relationship between serum uric acid (SUA) and risk of coronary heart disease (CHD) mortality remains controversial, particularly in diabetic subjects. The aim of the present study is to evaluate whether SUA independently predicts CHD mortality in non-insulin-dependent elderly people from the general population and to investigate the interactions between SUA and other risk factors. Five hundred and eighty-one subjects aged ≥65 years with non-insulin-dependent diabetes mellitus were prospectively studied in the frame of the CArdiovascular STudy in the ELderly (CASTEL). Historical and clinical data, blood tests and 12-year fatal events were recorded. SUA as a continuous item was divided into tertiles and, for each tertile, adjusted relative risk (RR) with 95% confidence intervals (CI) was derived from multivariate Cox analysis. CHD mortality was predicted by SUA in a J-shaped manner. Mortality rate was 7.9% (RR 1.28, CI 1.05–1.72), 6.0% (reference tertile) and 12.1% (RR 1.76, CI 1.18–2.27) in the increasing tertiles of SUA, respectively, without any difference between genders. In diabetic elderly subjects, SUA independently predicts the risk of CHD mortality in a J-shaped manner.

Key words Elderly • J-shaped • Mortality • Relative risk • Uric acid • Coronary

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Introduction

Ever since Gertler et al. [1] reported an association between increased serum uric acid (SUA) levels and incidence of myocardial infarction in men in 1951, many epidemiological studies have investigated the predictive role of SUA on overall and coronary mortality [2–11]. However, few studies were population-based [3, 8, 12] and people aged <65 years were mainly enrolled. Despite the strength of the association between SUA and coronary mortality, the prognostic role of SUA remains uncertain; in fact a significant [2–5] as well as a non-significant [6–11] relationship between SUA mortality has been observed. The current opinion is that the above-mentioned conflicting results are in part attributable to differences in pre-existing coronary heart disease (CHD) and to inappropriate or absent adjustment for confounders such as diuretic treatment [9], obesity [12], hypertension [13] and diabetes [14]. Moreover, in diabetic subjects, the role of SUA as a predictor of CHD mortality it is still under debate [15, 16].

The aim of the present study was to investigate the predictive role of SUA on CHD mortality among a cohort of elderly subjects having non-insulin-dependent diabetes mellitus at baseline.

Materials and methods

The CArdiovascular STudy in the ELderly (CASTEL) is a prospective population-based study performed during 1983–1985, aimed at identifying the cardiovascular risk factors and, more generally, the predictors of mortality in the elderly. CASTEL enrolled 3282 subjects (1281 men and 2001 women) aged 65 years or over, representing 73% of elderly subjects from the Northern Italian towns of Castelfranco and Chioggia. The study was approved by the local Ethics Committee and all the procedures were in accordance with the Helsinki declaration and with institutional guidelines. Each subject gave informed consent to the study.

Data collection

The protocol of the study has been previously published elsewhere [17] and included gathering of demographic information, medical and social questionnaires, fasting blood tests, anthropometrics, spirometry, electrocardiogram and blood pressure measurement.

Procedures for taking and preparing blood specimens and laboratory analysis were standardised. Fasting SUA was measured in 3257 subjects and determined in the laboratory of the Department of Clinical and Experimental Medicine of the University of Padova by the enzymatic method. Subjects with fasting blood glucose repeatedly ≥7.0 mmol/l or under treatment with oral antidiabetic drugs were considered to be diabetic [18].

During the initial survey, heart rate and blood pressure were measured 8 times in a 3-month period (3 times at 15-min intervals at the first meeting with the patient, 3 times at 15-min intervals 1 month later and twice with a 15-min interval one further month later); in order to avoid any effects of white coat/alert reaction, only the average of the last two measurements were considered for data analysis. Arterial hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current treatment with antihypertensive medications. As 22% of men and 26% of women received antihypertensive medication, antihypertensive therapy (including diuretics: 7.2% of subjects took diuretics, 6.8% in men and 7.7% in women) was tested as a dichotomic independent covariate in the multivariate Cox analysis of risk (see below).

According to the World Health Organization, subjects with BMI ≥30 kg/m^2 were labelled as obese. Subjects were classified into never and current (≥1 cigarette daily) smokers. Total daily consumption of alcohol was calculated by questionnaire; intake of wine, beer and spirits was reported separately. Most of the alcohol consumed was wine and one drink corresponded to 10–12 g ethanol. Diagnosis of proteinuria required a urine level of 200 mg/dl or over. Creatinine clearance (CrCl, in ml/min) was calculated from serum creatinine (SCr, in mg/dl) using the formula of Cockcroft and Gault [19, 20]:

$$CrCl=[(140-age_{years})\times Weight_{kg})]/(SCr_{mg/dl}\times 72) \text{ in men}$$
$$CrCl=0.85\times[(140-age_{years})\times Weight_{kg})]/(SCr_{mg/dl}\times 72) \text{ in women.}$$

Electrocardiogram was analysed on the basis of the Minnesota code by an expert who did not know the aim of the study. CHD at baseline was defined as a history of myocardial infarction confirmed by hospital files and/or angina pectoris confirmed by hospital or physician's files and/or electrocardiographic signs of ischaemia (Minnesota Code 4-1, 4-3, 5-1 or 5-3, if codes 6-4, 7-1 and 7-2 were absent) and/or positive myocardial scintigraphy. Left ventricular hypertrophy (LVH) required the Minnesota code 3-1 or 3-3.

Mortality data

All-cause 12-year mortality was assessed yearly through the Register Office, hospital discharge records and death certificates. Causes of death were collected from hospital files, from retirement home files and by questioning general practitioners. All records were coded according to ICD-9-CM by a trained research worker. The codes for CHD mortality were 410–414. No cause of death was missed.

Statistical analysis

Continuous variables were expressed as mean±SD. Analysis of covariance was used to compare groups, and Pearson's χ^2 test to compare the prevalence of categorical variables. Statistics were computed using BMDP software (BMDP Version 8.0, 2000, Los Angeles, CA, USA); a p value of <0.05 was considered statistically significant.

The effect of prognostic factors on survival was evaluated by Cox models, after selecting the covariables (age, gender, historical CHD, duration of diabetes, obesity, systolic blood pressure, antihypertensive treatment, cigarette smoking, alcohol consumption, serum total cholesterol (TC), low-density-lipoprotein serum cholesterol (LDL-C), high-density-lipoprotein serum cholesterol (HDL-C), serum triglycerides (TG), LVH, CrCl and proteinuria) because of their potential relation with either SUA or mortality.

As mortality rate did not increase linearly with SUA (see below), the analysis was performed separately by two approaches: continuous and categorical.

1. Multivariate stepwise proportional hazard Cox regression was used to identify the variables having a prognostic role in CHD mortality.
2. Relative risk (RR) with 95% confidence intervals ($_{95\%}$CI) adjusted for the above-mentioned confounders was calculated – for CHD mortality – for 1st and 3rd *vs*. 2nd tertile of SUA.

Results

The general characteristics of the study population are summarised in Table 1, also showing gender stratification.

In the three tertiles of SUA, the SUA levels were 0.21±0.05, 0.31±0.02, 0.35±0.01 and 0.42±0.05 mmol/l, respectively (all tertiles $p<0.0001$ *vs*. each other). The risk

Table 1 General characteristics of the type 2 diabetic subjects

	Entire population (n=581)	Men (n=202)	Women (n=389)	p-value between genders
SUA (mmol/l)	0.32±0.1	0.33±0.1	0.31±0.1	NS
Age (years)	74.3±5.3	73.0±4.7	75.1±5.7	<0.0001
Creatinine clearance (ml/min)	70.5±28.0	69.9±20.6	68.4±23.8	NS
Total cholesterol (mmol/l)	5.6±1.2	5.4±1.1	5.7±1.3	<0.001
LDL-cholesterol (mmol/l)	3.4±1.0	3.3±0.9	3.4±1.1	NS
HDL-cholesterol (mmol/l)	1.5±0.4	1.3±0.2	1.4±0.3	<0.05
Triglycerides (mmol/l)	1.9±1.3	1.8±1.1	2.0±1.1	<0.05
Alcohol consumption (g/day)	11.3±5.2	16.4±7.6	7.2±4.9	<0.001
History of diabetes (years)	20.3±8.6	21.1±9.3	19.8±7.9	NS
Historical CHD (%)	12.3	11.4	12.9	NS
Arterial hypertension (%)	60.1	59.4	60.4	NS
Obesity (%)	30.1	29.1	30.6	NS
Proteinuria (%)	20.1	19.8	21.7	NS
Smoking habits (%)	11.0	19.0	4.5	<0.001

SUA, serum uric acid; *LDL* and *HDL*, low and high density lipoprotein; *CHD*, coronary heart disease

Table 2 The risk pattern of the type 2 diabetic subjects according to tertiles of SUA, adjusted for age, obesity, creatinine clearance (CrCl) and antihypertensive therapy

	Tertiles of SUA (mmol/l)		
	1st (≤0.29)	2nd (0.30–0.36)	3rd (≥0.37)
Men/women	61/133‡	71/122	70/124*‡
Age (years)	72.6±4.9‡	74.2±5.1	75.1±5.1*‡
Glucose (mmol/l)	9.1±3.1‡	8.6±3.0	8.4±2.2*‡
Duration of diabetes (years)	18.4±7.1‡	19.0±7.4	22.1±8.0*‡
Systolic BP (mmHg)	162.1±24.4‡	164.9±25.4	165.8±25.8*‡
Diastolic BP (mmHg)	87.7±10.9‡	89.4±11.3	89.8±11.9*‡
Pulse pressure (mmHg)	74.1±18.2‡	76.0±19.4	76.3±20.1*‡
Antihypertensive treatment (%)	21.1‡	23.8	21.6*‡
Arterial hypertension (%)	56.4‡	57.1	64.9*‡
Total cholesterol (mmol/l)	5.4±1.2‡	5.5±1.1	5.5±1.1*‡
Triglycerides (mmol/l)	2.1±1.2†	1.8±1.1	1.9±1.3*‡
HDL cholesterol (mmol/l)	1.4±0.5‡	1.5±0.4	1.6±0.6*‡
LDL cholesterol (mmol/l)	3.4±1.1‡	3.5±1.3	3.4±1.6*‡
CrCl (ml/min)	78.1±23.8‡	74.1±22.8	59.4±22.2*‡
Alcohol intake (g/day)	11.2±9.4‡	11.8±9.6	12.0±8.1*‡
Historical CHD (%)	8.7‡	10.8	17.5*†
Obesity (%)	31.1†	29.1	28.9*‡
Smokers (%)	31.3‡	34.4	33.2*‡
LVH (%)	26.4‡	29.5	38.6*†
Proteinuria (%)	18.2‡	19.3	21.4*‡

ANOVA with post-hoc tests, or χ^2 test: *p<0.0001 *vs*. 1st; †p<0.004 *vs*. 2nd; ‡p<0.04 *vs*. 3rd
BP, blood pressure; *LVH*, left ventricular hypertrophy; *SUA*, serum uric acid; *LDL* and *HDL*, low and high density lipoprotein; *CHD*, coronary heart disease

pattern of subjects in the three tertiles of SUA is shown in Table 2. Subjects in the 3rd tertile were older and had, compared to the other tertiles, significantly higher duration of diabetes, systolic BP and low HDL-C levels and a higher prevalence CHD, arterial hypertension, proteinuria and LVH. Subjects in the 1st tertile had higher serum blood glucose, TG and CrCl levels, and a higher prevalence of obesity as well.

Univariate prediction of mortality

At the 12th year of follow-up, 369 subjects were dead and 212 were still alive (mortality rate 63.5%); 51 of them were due to CHD (mortality rate 8.7%), more precisely 22 in men and 29 in women (insignificant difference between gender). In the entire population, CHD mortality rate was significantly distributed (p=0.001) with SUA in a J-shaped manner (7.9% in the 1st, 5.9% in the intermediate and 12.1% in the last tertile of SUA). Cumulative survival in relationship with SUA tertiles is shown in Figure 1. No between-gender difference was found in CHD mortality by SUA tertiles (6.5%, 9.8% and 7.1% in men; 8.7%, 7.0% and 10.4% in women).

Multivariate prediction of mortality

In the entire population, CHD mortality was significantly predicted by age, historical CHD, TG and SUA, and inversely by CrCl and HDL-C. Inclusion of antihypertensive treatment as a covariate did not influence the model (Table 3).

The curve of the adjusted RR of CHD mortality was J-shaped with SUA. Rate was 1.28 (CI 1.05–1.72) in the first and 1.76 (CI 1.18–2.27) in the last compared to the intermediate reference tertile of SUA (Fig. 2).

Discussion

In the belief of the majority of physicians, SUA simply means *gout* and reminds of the classic caricature of the middle-aged obese alcohol-drinking hypertensive [21]. We often forget that SUA, even when below the gout-related levels, can be an independent predictor of death

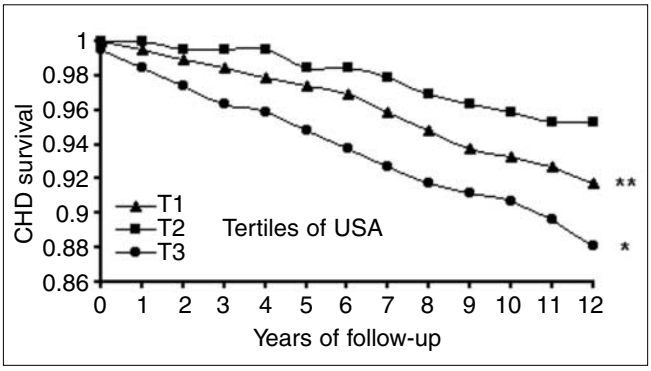

Fig. 1 Coronary (CHD) cumulative survival in the three tertiles (T1, T2, T3) of SUA. *p<0.001 *vs*. 2nd tertile, **p<0.05 *vs*. 2nd tertile

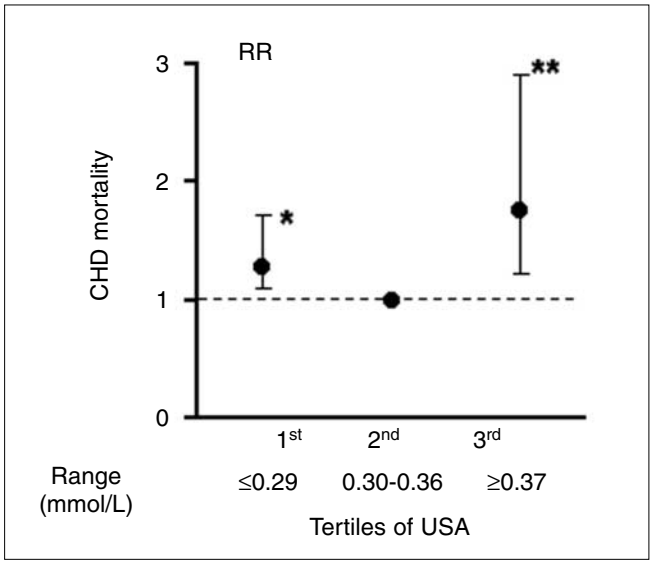

Fig. 2 Adjusted relative risk (RR) of coronary (CHD) mortality by tertiles of SUA. **p<0.001 *vs*. 2nd tertile; *p<0.05 *vs*. 2nd tertile

Table 3 Multivariate Cox analysis for coronary mortality. *SUA*, serum uric acid; *LDL* and *HDL*, low and high density lipoprotein; *CHD*, coronary heart disease

Items	Improvement χ^2	p value	Coefficient±SE	RR
Age (years)	26.4	<0.0001	0.10±0.01	1.23
Historical CHD (yes, no)	16.2	<0.0001	0.08±0.03	1.25
Creatinine clearance (ml/min)	11.4	<0.0001	-0.11±0.04	0.91
Triglycerides (mmol/l)	8.6	<0.01	0.01±0.05	1.16
HDL cholesterol (mmol/l)	4.9	<0.02	-0.01±0.01	0.97
Uric acid (mmol/l)	4.1	<0.01	0.14±0.03	1.21
Antihypertensive treatment (yes, no)	5.7	–	–	–
Total cholesterol (mmol/l)	9.8	–	–	–
LDL cholesterol (mmol/l)	4.3	–	–	–
LVH (yes, no)	4.4	–	–	–
Alcohol consumption (g/day)	5.3	–	–	–
Cigarette smoking (yes, no)	7.3	–	–	–
Obesity (yes, no)	4.5	–	–	–
Proteinuria (yes, no)	4.1	–	–	–

[1–3]. Overwhelming evidence suggests that SUA is linked to many components of the metabolic syndrome [22], namely obesity, hypertension, low HDL-cholesterol, hypertriglyceridaemia and impaired glucose tolerance. Nevertheless, in subjects with diabetes or impaired glucose tolerance the role of SUA as predictor of CHD mortality is still under debate [15].

In disagreement with the recent meta-analysis by Wheeler et al. [23], in our study SUA was shown to be able to maintain its predictive role also after extensive adjustment for the above-mentioned confounders of the metabolic syndrome, and it is therefore conceivable that it contributes to independently increase CHD risk in diabetic subjects.

Although the present study was not aimed at investigating the mechanisms by which SUA increases CHD mortality, it is the common opinion that the atherosclerotic plaque contains more SUA than control arteries [24], and that SUA via purine metabolism may promote thrombus formation, particularly in diabetic subjects [25, 26]. Moreover, it is conceivable that SUA contributes independently to increase coronary risk by favouring vascular injury and platelet adhesiveness [27].

Interestingly, in our diabetic population the relationship between SUA and CHD mortality was clearly J-shaped, probably reflecting the unfavourable risk pattern of subjects in the 1st and 3rd tertile of SUA. Actually, the components of metabolic syndrome were differently distributed in the three tertiles: obesity, high TG and low HDL-C were mainly represented in the lowest, arterial hypertension in the higher.

As regards the relationship between SUA and hypertension, in a recent survey on older Chinese subjects increased SUA levels were found in one third of subjects with untreated essential hypertension [15], a finding that could partially explain its lethal potential. Nevertheless, in keeping with the NHANES study [2], in our experience the relationship between SUA and CHD mortality persisted after adjustment for hypertension.

Moreover, subjects in the 1st tertile of SUA had higher serum glucose levels (apparently worse control of diabetes), while those in 3rd tertile had higher prevalence of LVH, proteinuria and historical CHD.

The relationship between increased SUA levels and LVH is not a completely new observation and the recent findings from the LIFE study in hypertensive subjects with LVH [28] even suggest the possibility that a treatment-induced decrease of SUA may attenuate the risk of CHD mortality.

The high prevalence of proteinuria, as well as the decrease of CrCl observed in the 3rd tertile of SUA, suggest that glomerular filtration [29] rate is probably the main factor influencing SUA levels in our diabetic population. Diabetes could in fact contribute both to reduce SUA (1st tertile) by enhancement of oxidative stress [25, 26] and/or hyper-filtration [30], and to increase SUA (3rd tertile) promoting renal function impairment (decreased CrCl and proteinuria). As regards this latter aspect, renal impairment may also amplify both the severity of the diabetes and the prevalence of the other above-mentioned risk factors, thus promoting CHD risk. In our experience the higher prevalence of historical CHD found in subjects both with high SUA and low CrCl values confirmed, in part, this evidence [8, 10].

Furthermore, in the Cox analysis, SUA predicted CHD mortality independent of historical CHD, ClCr, arterial hypertension and proteinuria, suggesting that it could be a marker of increase glomerular permeability in subjects with type 2 diabetes mellitus [30]; on the contrary, hyper-filtration is probably the main mechanism responsible for decreased SUA levels in our diabetic subjects. It is common opinion among the diabetologists that hyper-filtration is the earliest sign of initial renal impairment during the natural history of diabetic disease [16], while diabetic nephropathy occurs in a later phase; actually, in our experience subjects with lower levels of SUA were both younger (hyper-filtration) and had a lower duration of diabetes than those with higher SUA levels (overt nephropathy).

However the relationship between SUA and mortality found in the present is not a completely new finding because Hsu et al. observed a J-shaped association between SUA and all-cause mortality in haemodialysis patients [29]. Finally, in disagreement with other evidence [31], no between-gender difference was found in CHD mortality by SUA tertiles.

A possible limitation of our study was lack of information about glycated haemoglobin (HbA1c); unfortunately, at the time of the initial screening of the CASTEL, the measurement of HbA1c was not available. Another limitation is that the amount of individual contribution of SUA in CHD risk is not exactly quantified. In our experience, adding SUA modifies the multivariate prognostic model in a significant manner, with χ^2=4.1 and p<0.01, producing a significant RR of 1.21. Modifying the model is universally considered a good way to demonstrate the prognostic role of a covariable. A more potent way should be to limit the analysis to subgroups having different SUA and comparable levels of other covariables. We applied this method in the past, with other items, but we decided not to replicate this method because the study is population-based and any stratifications would alter the population, because in matched subgroups the Cox analysis cannot be used, and because each subgroup would be smaller than the entire population, possibly leading to type 2 error.

In conclusion, in elderly diabetic subjects from the general population SUA independently predicted CHD mortality in a J-shaped manner. In practical terms, for a diabetic aged ≥65 years, the risk of dying of CHD was 1.76 and 1.28 when in the 3rd (≥0.37 mmol/l) and in the

1st (≤0.29 mmol/l) rather than in the 2nd tertile of SUA. Determination of SUA should be considered a factor influencing prognosis of elderly diabetics and added to the classic risk factors mentioned in the guidelines on CHD prevention [32].

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