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On the non-linear association between serum uric acid levels and all-cause mortality rate in patients with type 2 diabetes mellitus

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ABSTRACT

Background and aims: High levels of serum uric acid (SUA) are associated with increased mortality risk in the general population. Contrasting results are available in people with diabetes. The aim of our study was to investigate the association and its functional form between SUA and all cause-mortality in patients with type 2 diabetes mellitus (T2DM).

Methods: We studied three cohorts of patients with T2DM: Gargano Mortality Study, Foggia Mortality Study, Pisa Mortality Study. All-cause mortality rate was the end point of this study.

Results: The most reliable relationship between SUA levels and all-cause mortality rate was quadratic, with such model being well approximated by SUA tertiles. Both tertiles 1 and 3 were at higher risk of mortality as compared to tertile 2: Hazard Ratio (HR) [95% Confidence Interval (CI)] = 1.34 (1.07–1.68) and 1.61 (1.29–1.99), respectively. In the pseudo-sample, created from the real pooled sample, the best relationship between SUA and all-cause mortality rate was quadratic. In a tree-based Recursive Partitioning and Regression Tree analysis two subgroups at increased risk of mortality were identified, namely those with SUA levels ≥7.28 mg/dl and with SUA levels <4.16 mg/dl as compared to patients with intermediate SUA levels (i.e. 4.16–7.28), thus providing further evidence on the J-shaped relationship between SUA levels and mortality rate.

Conclusions: SUA was not linearly associated with all-cause mortality rate in patients with T2DM. For clinical and public health purposes such association is J-shaped.

1. Introduction

Diabetes mellitus is nowadays one of the most challenging global health problems, affecting an estimated 415 million people worldwide [1]. Patients with diabetes, especially type 2 diabetes mellitus, (T2DM) are indeed at increased mortality risk [2] due predominantly to vascular complications, including cardiovascular, renal and cerebrovascular disease [3,4]. The pathogenic background of such increased mortality rate has been so far only partially described, thus calling for a better knowledge of modifiable risk factors for tackling this devastating clinical outcome. Among these, metabolic syndrome (MS), a cluster of several cardiovascular (CV)

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risk factors such as hyperglycemia, dyslipidemia, arterial hypertension and visceral adiposity, is an established predictor of mortality, also in patients with T2DM [5]. Several epidemiological studies have suggested that increased serum uric acid (SUA) levels may belong to the MS [6–8]. As a matter of fact, the Atherosclerosis Risk in Communities study reported that SUA levels are associated with carotid intima-media thickness (an early marker of atherosclerosis), thus assuming an atherogenic role of SUA [14]. Along the same line, high SUA levels are associated with increased mortality risk, mainly of cardiovascular origin, in the general population [9–13].

Contrasting results about the relationship between mortality risk and SUA are available in people with diabetes [15–22]. Furthermore, whether the relationship in patients with T2DM, if any, applies across all serum uric acid levels (linear relationship) it is still uncertain [15].

Aimed at adding our own contribution to the understanding of this subject, we analyze d three samples of patients with T2DM from Italy and investigated the association between SUA and all cause-mortality as well as the functional form of this association.

2. Materials and methods

We studied prospectively three cohorts of patients with T2DM (according to ADA 2003 criteria), recruited at the diabetes clinic of three research-based hospitals from Central-Southern Italy, whose clinical features have been already described [23,24].

2.1. Gargano Mortality Study (GMS)

One-thousand-twenty-eight Whites from Italy, with T2DM, were consecutively recruited at Scientific Institute "Casa Sollievo della Sofferenza" in San Giovanni Rotondo (Apulia, Southern Italy) for a study aimed at unraveling predictors of incident all-cause mortality.

A poor life expectancy due to cancer of any type was the only exclusion criterion.

Up to date, this cohort has been followed-up for a mean of 10.3 ± 3.7 years (median: 11.75, range: 0.08–14.08) with the last information on vital status being obtained on November 30th, 2014. After excluding patients (i) whose information on vital status at follow-up was not available (n = 9) and (ii) whose information on SUA levels was not available (n = 35), 984 patients (95.7% of the initial cohort) constituted the eligible sample for the present investigation.

2.2. Foggia Mortality Study (FMS)

One-thousand-one-hundred-two Whites from Italy with T2DM were consecutively recruited at Endocrine Unit of University of Foggia (Apulia, Southern Italy) from January 2nd, 2002 to April 30th 2010, for a study aimed at unraveling predictors of incident all-cause mortality. A poor life expectancy due to cancer of any type was the only exclusion criterion.

To address the main objective of the study a subgroup of 558 patients, whose information on SUA levels was available, was evaluated. This cohort has been followed-up for a mean of 7.0 ± 2.8 years (median: 7.50, range: 0.04–12.92) with the last information on vital status being obtained on March 31st, 2015.

2.3. Pisa Mortality Study (PMS)

Nine hundred seventy-two Whites from Italy with T2DM were consecutively recruited at Endocrine Unit of University of Pisa from January 1st, 2002 to February 14th, 2008, for a study aimed at unraveling predictors of incident all-cause mortality. Also in this case, a poor life expectancy due to cancer of any type was the only exclusion criterion.

Up to date, this cohort has been followed-up for a mean of 10.8 ± 1.9 years (median: 11.25, range: 0.25–12.67) with the last information on vital status being obtained on February 28th, 2015.

After excluding patients (i) whose information on SUA levels was not available (n = 2), 970 patients (99.7% of the initial cohort) constituted the eligible sample for the present analysis.

2.4. Data collection

As previously described [24], smoking habit, age at diagnosis and duration of diabetes, ongoing therapies for hypertension, hyperglycaemia, and dyslipidemia were recorded at baseline.

All subjects enrolled in the study underwent physical examination, including measurements of height, weight, body mass index and blood pressure. SUA, standardized serum creatinine, total serum cholesterol, high density lipoprotein cholesterol, serum triglycerides were measured by enzymatic methods. Glycated hemoglobin was assessed by HPLC while low density lipoprotein cholesterol was then calculated by the Friedewald formula. Urinary albumin and creatinine concentrations were determined the same morning of the clinical examination from an early-morning first void sterile urine sample. The urinary Albumin to Creatinine Ratio was then calculated. Glomerular filtration rate was estimated by Epidemiology Chronic Kidney Disease equation [25]. The study protocol was approved by local institutional review boards and was conducted according to the Helsinki Declaration. Informed consent was obtained from each participant.

2.5. Study endpoint

All-cause mortality was the only pre-specified end point of this study. At follow-up, the vital status of study patients was ascertained by two authors for each study. For GMS and PMS the last follow-up was carried out by queries to the Italian Health Card (http://sistemats1.sanita.finanze.it/wps/portal/portalets/cittadinots/ts) while for the FMS the vital status was ascertained by Edotto System that is an Health Information System of the Apulia Region (https://edotto.aslfg.rsr.rupar.puglia.it/nsisr/).

2.6. Statistical analysis

Patients' baseline characteristics were reported as mean ± standard deviation (SD) or median (first-third quartiles) and frequency (percentage) for continuous and categorical variables, respectively. Age and sex-adjusted mortality rates were estimated using Poisson models and were reported as number of deaths per 100 person-years. The overall survival was defined as the time between enrollment and death; for subjects who did not experience the end point, survival time was censored at the time of the last available follow-up visit. Time-to-death analyses were performed using univariable and multivariable Cox proportional hazards regression models and risks were reported as hazard ratios (HR) along with their 95% confidence intervals (CI).

To properly assess the most reliable relationship between SUA levels and all-cause mortality rate, SUA level was included into Cox models as: 1) a linear term only, 2) a quadratic term only, 3) both linear and quadratic terms. Goodness of fit of each Cox model was evaluated by Akaike Information Criterion (AIC). The model including the quadratic term only achieved the best fit (i.e. minimum AIC), even though the representation of SUA tertiles was also provided, for ease of clinical interpretation.

Observed crude mortality rates over SUA levels deciles, along