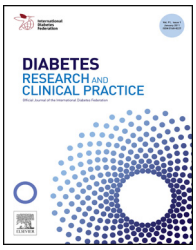
Contents available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Serum uric acid levels and incidence of impaired fasting glucose and type 2 diabetes mellitus: A meta-analysis of cohort studies

Zhaotong Jia [a,*], *Xiaoqian Zhang* [b], *Shan Kang* [c], *Yili Wu* [c]

[a] *Department of Endocrinology, The Affiliated Hospital of Medical College, Qingdao University, Qingdao 266003, China*
[b] *09 Grade 10 Class of Medical College, Qingdao University, Qingdao 266021, China*
[c] *Department of Epidemiology and Health Statistics, Qingdao University Medical College, Qingdao 266021, China*

ARTICLE INFO

Article history:
Received 9 November 2012
Received in revised form
3 March 2013
Accepted 21 March 2013
Published on line 19 April 2013

Keywords:
Serum uric acid
Type 2 diabetes mellitus
Meta-analysis
Dose–response analysis

ABSTRACT

Aims: A meta-analysis of cohort studies was conducted to assess the association between serum uric acid (SUA) levels and incidence of impaired fasting glucose (IFG) and type 2 diabetes mellitus (T2DM).

Methods: A comprehensive search was conducted to identify eligible studies. The fixed or random effect pooled measure was selected based on between-study heterogeneity. Dose–response relationship was assessed by restricted cubic spline model and multivariate random-effect meta-regression.

Results: Twelve studies with fifteen results were included involving 6340 cases and 62,834 participants. The pooled multivariate-adjusted relative risk (RR) (95%CI) of IFG and T2DM for the highest vs. lowest level of SUA was 1.54 (1.41–1.68), $I^2 = 42.2\%$. The association was consistent and significant across subgroup analysis. A nonlinear relationship was found of SUA levels with incidence of IFG and T2DM ($P < 0.01$), and the multivariate-adjusted RRs (95%CI) of IFG and T2DM were 1.02 (0.95–1.10), 1.04 (0.94–1.15), 1.10 (0.99–1.22), 1.25 (1.16–1.35), 1.43 (1.31–1.55), 1.50 (1.38–1.63) and 1.49 (1.34–1.67) for 2.5, 3.5, 4.5, 5.5, 6.5, 7.5 and 8.5 mg/dl of SUA. The RR (95%CI) of T2DM for the highest vs. lowest level of SUA was 1.67 (1.51–1.86), and a nonlinear relationship was also found between SUA levels and incidence of T2DM.

Conclusions: SUA levels are positively associated with incidence of IFG and T2DM, and the association might be nonlinear.

1. Introduction

Today 366 million individuals suffer from diabetes worldwide, and the number is predicted to reach over 552 million by 2030, making it one of the most serious diseases of humankind [1,2]. Identifying the risk factors for developing type 2 diabetes mellitus (T2DM) is key for its early screening and prevention. Serum uric acid (SUA) is the metabolic end product of purine metabolism in humans, and is degraded by urate oxidase to allantoin that is freely eliminated in urine. SUA, an antioxidant in the extracellular environment, can induce oxidative stress in a variety of cells including vascular smooth muscle cells and adipocytes [3,4]. SUA is an independent risk factor for the development of coronary heart disease [5], all major forms of death from cardiovascular disease [5], insulin resistance

* *Corresponding author*. Tel.: +86 532 82911740; fax: +86 532 82991712.
E-mail address: jiazt1963@163.com (Z. Jia).
0168-8227/$ – see front matter
http://dx.doi.org/10.1016/j.diabres.2013.03.026

and metabolic syndrome [6] and might be a marker of risk of future incident T2DM [7]. Pre-diabetes includes impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), and IFG is one component of the metabolic syndrome [8]. Identifying pre-diabetes is useful for early screening and prevention of T2DM.

Recently, hyperuricemia has been proposed as novel risk factors for diabetes [7], and a number of cohort studies have assessed the association of SUA levels with incidence of IFG and T2DM with conflicting results reported. Therefore, we assessed the relative risks (RRs) and relationship of SUA for IFG and T2DM. Categories of SUA levels differed between studies which might complicate the interpretation of the pooled results across study populations with different categories. This can be overcome by performing a dose–response meta-analysis with restricted cubic spline functions [9] from which a summary risk estimate can be derived for a standardized increase and specific SUA levels. Thus we conducted a dose–response meta-analysis to quantitatively assess the association of SUA levels with incidence of IFG and T2DM.

2. Methods

2.1. Search strategy

We performed a literature search to February 2013 using the databases of Pubmed, Web of Knowledge, China Biology Medical literature database (CBM), Database of Chinese Scientific and Technical Periodicals (VIP), China National Knowledge Infrastructure (CNKI), and Google scholar, restricting the publications in English or Chinese. Medical Subject Headings (MeSH) were used as the search terms without restriction to MeSH Major Topic, and the search strategy was as follows: "*uric acid*" *and* "*diabetes mellitus*" *and* "*cohort studies*". In addition, we searched the reference lists of all identified relevant publications and relevant reviews.

2.2. Inclusion criteria

Two investigators independently reviewed all identified studies, and studies were included if they met the following criteria: (1) cohort study design; (2) the exposure of interest was SUA levels; (3) the outcome of interest was IFG and/or T2DM; (4) RRs estimates with 95% confidence intervals (CIs) were reported; (5) for dose–response, the cases, and participants or person-years for each category of SUA levels must be also provided (or data to calculate these). If the data were published more than once, we included the study with the largest participants.

2.3. Data extraction

The following data were extracted from each study by two investigators: the first author's last name, publication year, country where the study was performed, follow-up duration (years), measure of IFG and/or T2DM, mean age (years), SUA levels (mg/dl) at baseline, male sex percentage, number of participants and cases, RR (95%CI) for the highest vs. lowest categories of SUA level. Variables adjusted for in the original analysis. We extracted the RR (95%CI) that reflected the greatest degree of control for potential confounders. If available, we also extracted the crude RR (95%CI), age/sex-adjusted RR (95%CI), and the separate RR (95%CI) for men and women, respectively. In dose–response analysis, the RRs (95%CI), cases, and participants or person-years for each category of SUA levels were extracted. The median or mean SUA levels for each category were assigned to each corresponding RR for every study. If the upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category [10].

2.4. Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI to assess the association of SUA levels with incidence of IFG and T2DM. The DerSimonian and Laird random effect model (REM) and the fixed effect model (FEM) were selected based on the homogeneity test among studies that was evaluated with I^2 [11]. I^2 is the proportion of total heterogeneity attributable to between-study variation as opposed to random error or chance, and does not depend on the number of the studies [12]. Based on the tentative categorization of I^2 values quantifying heterogeneity (0%, 25%, 50%, and 75% represents no, low, moderate, and high heterogeneity, respectively) [12], we adopted REM under the presence of high heterogeneity ($I^2 > 50\%$) otherwise, the FEM was used as the pooling method. Meta-regression with restricted maximum likelihood estimation [13] was performed to assess the potentially important covariates of publication year, country (categorized as Asia, Europe and USA), follow-up duration (years), diagnosis of IFG and T2DM (measure, report or both of them), mean age (years), SUA levels (mg/dl) at baseline, male sex percentage, number of participants that might exert impact on between-study heterogeneity. Influence analysis was conducted to describe how robust the pooled estimator is to removal of individual studies, and an individual study is suspected of excessive influence when the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis [14]. Publication bias was detected using Egger's linear regression test [15]. Subgroup analysis was conducted by several key study characteristics. The sensitive analysis was carried out using $I^2 > 50\%$ as the criteria to identify the studies exerting substantial impact on and reduce between-study heterogeneity [16].

In the dose–response analysis for SUA levels with incidence of IFG and T2DM, we performed a 2-stage random-effects dose–response meta-analysis taking into account the between-study heterogeneity proposed by Orsini et al. [17] to compute the trend from the correlated log RR estimates across categories of SUA levels. Briefly, a restricted cubic spline model, with 4 knots at the 5th, 35th, 65th, and 95th percentiles [18] of the SUA levels, was estimated using generalized least square regression taking into account the correlation within each set of published RRs [19]. Then we combined the study-specific estimates using the restricted maximum likelihood method in a multivariate random-effects meta-analysis [20]. A P value for nonlinearity and overall significance was calculated using the method