Endocrinol Diabetes Nutr. 2018;65(6):335–341

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Impact of uric acid levels on the risk of long-term cardiovascular mortality in patients with type 2 diabetes mellitus☆

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Received 22 November 2017; accepted 15 January 2018
Available online 17 July 2018

KEYWORDS
Uric acid;
Type 2 diabetes mellitus;
Mortality

Abstract
Background: Hyperuricemia is associated to cardiovascular disease. However, the contribution of uric acid (UA) to cardiovascular mortality in diabetic patients is controversial.
Objective: To assess the impact of UA levels on the risk of cardiovascular mortality risk in a cohort of patients with type 2 diabetes mellitus (T2DM).
Patients and methods: A prospective cohort study on outpatients with T2DM. The clinical endpoint was cardiovascular death. Anthropometric, demographic, clinical, and biochemical variables were collected, including UA levels, urinary albumin excretion and estimated glomerular filtration rate. The independent contribution of UA levels to cardiovascular mortality was assessed using multivariate Cox regression models, progressively adjusted for potential confounders.
Results: A total of 452 patients with a mean age of 65.9 (SD 9.5) years were enrolled. Mean UA level was 4.2 mg/dl. Quartiles of UA levels were Q1 < 3.3; Q2: 3.3–4.2; Q3: 4.3–5.1; Q4 > 5.1 mg/dl. UA levels significantly correlated with estimated glomerular filtration rate (Rho = −0.227; $p < 0.001$). During a median follow-up time of 13 years, cardiovascular mortality

☆ Please cite this article as: Ilundain-González AI, Gimeno-Orna JA, Sáenz-Abad D, Pons-Dolset J, Cebollada-del Hoyo J, Lahoza-Pérez MC. Influencia de los niveles de ácido úrico sobre el riesgo de mortalidad cardiovascular a largo plazo en pacientes con diabetes de tipo 2. Endocrinol Diabetes Nutr. 2018;65:335–341.

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https://doi.org/10.1016/j.endien.2018.01.005

rates were higher in Q4 of the UA distribution (Q1: 10.7; Q2: 11.7; Q3: 10.7; Q4: 21.6 per 1000 patient-years; $p = 0.027$). UA was a predictor of cardiovascular mortality in the univariate analysis (HR1mg/dl = 1.30; $p = 0.002$), but not in a multivariate analysis adjusted for urinary albumin excretion and eGFR (HR1 mg/dl = 1.20; $p = 0.12$).
Discussion and conclusions: High UA levels are associated to cardiovascular mortality in patients with T2DM. However, the role of UA may be mediated by impaired kidney function in patients with hyperuricemia.

PALABRAS CLAVE
Ácido úrico;
Diabetes tipo 2;
Mortalidad

Influencia de los niveles de ácido úrico sobre el riesgo de mortalidad cardiovascular a largo plazo en pacientes con diabetes de tipo 2

Resumen
Antecedentes: La hiperuricemia se asocia a enfermedad cardiovascular. Sin embargo, la contribución del ácido úrico (AU) sobre la mortalidad cardiovascular (MCV) en pacientes diabéticos es controvertida.
Objetivo: Evaluar la contribución del AU al riesgo de MCV en pacientes con diabetes de tipo 2 (DM2).
Pacientes y métodos: Se incluyó a pacientes con DM2 atendidos en consultas externas hospitalarias. Se recogieron variables demográficas, clínicas y bioquímicas, incluidos niveles de AU, excreción de albúmina urinaria y tasa de filtración glomerular (TFG). La contribución independiente del AU a la MCV se evaluó con modelos de regresión de Cox con ajuste progresivo para potenciales factores de confusión.
Resultados: Se incluyó a 452 pacientes con edad media de 65,9 años (DE 9,5). La media de AU fue de 4,2mg/dl y los cuartiles (Q) de AU fueron: Q1<3,3; Q2: 3,3–4,2; Q3: 4,3-5,1; Q4>5,1mg/dl. La correlación entre AU y TFG fue significativa (Rho = −0,227; p<0,001). Durante una mediana de 13 años de seguimiento las tasas de MCV fueron más elevadas en el Q4 de la distribución de AU (Q1: 10,7; Q2: 11,7; Q3: 10,7 y Q4: 21,6 por cada 1.000 pacientes/año; p=0,027). El AU fue un factor predictor de MCV en análisis univariante (HR_1mg/dl=1,30; p=0,002), pero no en multivariante ajustado para la excreción de albúmina urinaria y TFG (HR_1mg/dl=1,20; p= 0,12).
Discusión y conclusiones: Los niveles de AU se asocian a incremento de MCV en pacientes con DM2. No obstante, la asociación puede no ser causal, sino mediada por la afectación de la función renal en los pacientes con hiperuricemia.

Introduction

The presence of type 2 diabetes mellitus (DM2) increases cardiovascular risk and is considered a coronary risk equivalent.[1] However, not all patients with DM2 have the same probability of experiencing vascular events,[2] which makes it necessary to search for biomarkers that may help discriminate individual risk.

There is a firmly established causal relationship between hyperuricemia (HU) and the occurrence of gout and nephrolithiasis. The clinical guides therefore recommend the administration of drugs with the aim of securing uric acid (UA) levels <5 mg/dl in patients with recurrent gout attacks or with gout associated with complications (tophi, chronic kidney disease [CKD], urolithiasis).[3,4]

A number of epidemiological studies have moreover found a relationship between UA and other diseases such as metabolic syndrome or insulin resistance syndrome (MS), DM2, cardiovascular disease and CKD. However, the causal role of UA in these disorders has not been conclusively demonstrated.[5] In patients with DM2, the contribution of UA to the cardiovascular mortality (CVM) risk is subject to controversy, with some studies reporting an independent association,[6] while others do not.[7,8] The differences among the studies can be explained by the patient profiles involved and by the different adjustment variables entered in the regression models. Specifically, the main confounders may be the finding of MS and the presence of CKD, both being associated with HU and CVM.[9,10]

Of special importance is the presence of CKD, which increases UA by lowering its renal excretion, and also increases CVM risk as a result of both increased urinary albumin excretion (UAE) and a decreased glomerular filtration rate (GFR).[11] Urinary albumin excretion and the GFR provide additive and independent information concerning patient vascular risk.[12]

The objectives of our study, based on the long-term follow-up of a cohort of patients with DM2, were as follows: