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Relation of elevated serum uric acid levels to first-degree heart block and other cardiac conduction defects in hospitalized patients with type 2 diabetes

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ABSTRACT

Aims: Several studies have reported that moderately elevated serum uric acid levels are associated with an increased risk of tachyarrhythmias (mainly atrial fibrillation) in patients with and without type 2 diabetes mellitus (T2DM). It is currently unknown whether an association also exists between elevated serum uric acid levels and cardiac conduction defects in patients with T2DM.
Methods: We retrospectively analyzed a hospital-based sample of 967 patients with T2DM discharged from our Division of Endocrinology over the years 2007–2014. Standard electrocardiograms were performed on all patients and were interpreted by expert cardiologists.
Results: Overall, 267 (27.6%) patients had some type of conduction defects on electrocardiograms (defined as at least one block among first-degree atrio-ventricular block, second-degree block, third-degree block, left bundle branch block, right bundle branch block, left anterior hemi-block or left posterior hemi-block). Patients in the 3rd serum uric acid tertile had a higher prevalence of any cardiac conduction defects than those belonging to 2nd or 1st tertile, respectively (35.8% vs. 25.0% vs. 22.6%; $p < 0.0001$). Elevated serum uric acid levels were associated with a nearly twofold increased risk of cardiac conduction defects after adjustment for age, sex, hemoglobin A1c, diabetes duration, metabolic syndrome, chronic kidney disease, chronic obstructive pulmonary disease, ischemic heart disease, valvular heart disease and medication use (adjusted-odds ratio 1.84, 95% confidence intervals 1.2–2.9; $p = 0.009$).
Conclusions: Moderately elevated serum uric acid levels are associated with an increased prevalence of any cardiac conduction defects in hospitalized patients with T2DM, independent of multiple risk factors and potential confounding variables.

1. Introduction

Bradycardia may occur when the conduction of impulse across the atrio-ventricular (AV) node is altered with the eventuality of concomitant symptoms (e.g., fatigue or syncope) and even death, particularly when ventricular rates are entirely inefficient.[1,2]

Transient AV conduction defects are relatively frequent in healthy young individuals and are caused by high vagal tone in most cases.[1,2] Conversely, acquired and persistent AV conduction defects are infrequent in healthy individuals, but becomes more frequent in the setting of older age, myocardial ischemia, type 2 diabetes mellitus (T2DM) or infiltrative diseases.[1,2] Although it is known that high-degree AV blocks (i.e., second-degree AV block and third-degree AV block) strongly increase risk of future cardiovascular events in affected patients, accumulating evidence now suggests that even PR interval prolongation, first-degree AV block or bundle branch blocks are independently associated with a poor cardiac prognosis.[3–8] In a meta-analysis of 14 observational studies involving >400,000 individuals, Kwok et al. reported a strong association between PR interval prolongation or first-degree AV block and increased risks of atrial fibrillation, heart failure and death.[9]

For several decades, moderately elevated levels of serum uric acid have been considered as a simple biochemical abnormality with little or no clinical significance. However, in the last years, it has become

Abbreviations: AV, atrio-ventricular; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiograms; HbA1c, hemoglobin A1c; IHD, ischemic heart disease; LAH, left anterior hemi-block; LBBB, left bundle branch block; LPH, left posterior hemi-block; RBBB, right bundle branch block; SUA, serum uric acid; T2DM, type 2 diabetes mellitus; VHD, valvular heart disease.

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increasingly clear that moderately elevated serum acid uric levels are independently associated with increased cardiovascular morbidity and mortality in the general adult population, in patients with T2DM and in other high-risk patient groups.[10,11] Convincing evidence has also emerged of a strong association between elevated serum uric acid levels and increased risk of atrial fibrillation in patients with and without T2DM.[12–19]

To our knowledge, it is currently unknown whether an association also exists between moderately elevated serum uric acid levels and risk of cardiac conduction defects in patients with T2DM, a group of individuals in whom these two pathologic conditions are somewhat recurrent. We believe that this topic merits further in-depth investigation as it may further explain the increased risk of cardiovascular mortality and morbidity observed in patients with chronic hyperuricemia.

Thus, the main aim of this hypothesis-generating study was to ascertain whether elevated serum acid uric levels are associated with an increased prevalence of cardiac conduction defects on standard electrocardiograms in a large hospital-based sample of patients with T2DM.

2. Methods

2.1. Patients

We conducted a retrospective, cross-sectional study identifying all white patients with known T2DM, who were discharged from our Division of Endocrinology during 2007–2014. If a patient had multiple discharges from the hospital during this period, the first discharge with complete data was taken into consideration for statistical analysis. Most of these patients were admitted to the hospital for chronic decompensated diabetes, diabetic foot ulcers or infections.

A total of 1252 hospitalized patients with T2DM were initially identified in our database. We subsequently excluded 285 patients (22.8% of total) with pacemakers or implantable cardioverter defibrillators, pre-existing atrial fibrillation or flutter, severe valvular heart disease (VHD) (including those with prosthetic heart valves), end-stage renal disease, acute electrolyte abnormalities, decompensated cirrhosis, thyroid dysfunction as well as those with missing serum uric acid data and those treated with amiodarone, propafenone, digitalis, non-dihydropyridine calcium-channel blockers (CCB) or other anti-arrhythmic agents, except beta-blockers. As a result of this selection, 967 (77.2%) patients were included in the final analysis.

The local ethics committee approved the study protocol. The ethics committee exempted our research from the informed consent requirement because we only accessed retrospectively a de-identified database for the purpose of data analysis.

2.2. Clinical and laboratory data

Data on age, sex, anthropometric variables (weight, height and body mass index [BMI]) and blood pressure were recorded during medical visits. Patients were considered to have arterial hypertension if their blood pressure was ≥140/90 mm Hg or if they were taking any anti-hypertensive agents (*including* beta-blockers or diuretics). Detailed information on comorbid conditions and current use of medications was collected in all patients by interviews during medical visits.

Venous blood samples were performed in the morning after an overnight fast. Complete blood count, serum uric acid, creatinine, electrolytes and other biochemical blood measurements were determined using standard laboratory procedures. Hemoglobin A1c (HbA1c) was measured by a high-performance liquid chromatography analyzer on Tosoh G7 automated analyzer (Tosoh Bioscience Inc., San Francisco, CA; USA). Albuminuria was measured by an immuno-nephelometric method on a morning spot urine sample and expressed as the albumin/creatinine ratio on Beckman-Coulter IMMAGE (Beckman-Coulter Instruments, Fullerton, CA; USA); macroalbuminuria was defined as an urinary albumin/creatinine ratio > 300 mg/g creatinine. The presence of chronic kidney disease (CKD) was defined as presence of $eGFR_{MDRD}$ < 60 ml/min/1.73 m^2 (estimated by using the Modification of Diet in Renal Diseases [MDRD] study equation) or macroalbuminuria9.[20] Metabolic syndrome was diagnosed by a modified Adult Treatment Panel (ATP)-III definition,[21,22] as waist circumference was not available for all patients. In accordance with this modified ATP-III definition, a T2DM patient was classified as having the metabolic syndrome if he/she had at least two of the following four risk abnormalities: (i) BMI > 28 kg/m^2 in men or >27 kg/m^2 in women; (ii) triglycerides ≥ 150 mg/dl; (iii) HDL-cholesterol < 40 mg/dl in men and <50 mg/dl in women or receiving any lipid-lowering drugs; and (iv) blood pressure ≥ 130/85 mm Hg or receiving any anti-hypertensive drugs.[21,22]

Ischemic heart disease (IHD) was defined as a documented history of myocardial infarction, angina, coronary revascularization procedures or typical electrocardiographic abnormalities according to the Minnesota code.[23] Pre-existing history of mild-to-moderate VHD was confirmed by reviewing medical records of the hospital, including diagnostic symptoms patterns and echocardiograms (when available). As previously reported, those with severe VHD or prosthetic valves were excluded from the study. The pre-existing history of peripheral artery disease was based on medical history and examination (e.g., intermittent claudication, rest pain or lower-extremity revascularizations) and was confirmed by reviewing medical records of the hospital of patients, including radiologic imaging results. The pre-existing history of chronic obstructive pulmonary disease (COPD) was confirmed by reviewing medical records of the hospital, including diagnostic symptoms patterns, and results of lung function tests. In most patients, the presence of microvascular diabetic complications such as lower-extremity sensory polyneuropathy (by biothesiometer or 5.07/10-g monofilament) and diabetic retinopathy (by fundoscopy) were also recorded.

2.3. Resting electrocardiograms

A standard 12-lead electrocardiogram (ECG) was performed in all patients during the first 1–2 days of the hospital stay (and then repeated when necessary). A 24-hour ECG Holter monitoring was not regularly carried out. The diagnosis of cardiac conduction defects was made on the basis of ECGs and confirmed by expert cardiologists, who were blinded to patient's clinical data. In particular, the first-degree AV block was defined as a PR interval duration of 200 ms or more with no variation.[23] The diagnosis of second-degree AV block was made in accordance with the progressive prolongation of PR interval, culminating in a non-conducted P wave.[23] Afterwards second-degree AV block was classified in Mobitz type I or Mobitz type II. A third-degree AV block was identified, when P waves were not followed by QRS complexes.[23] Analogously, the presence of complete right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior hemi-block (LAH or left anterior fascicular block) or left posterior hemi-block (LPH or left posterior fascicular block) were diagnosed in accordance with standard ECG criteria.[23] In this study, a conventional echocardiography was not available for all patients.

2.4. Statistical analysis

Data are reported as means ± SD, medians and inter-quartile ranges (IQR) or percentages. Differences in main clinical and biochemical characteristics of patients grouped according to tertiles of serum uric acid levels (i.e., 1st tertile: ≤4.2 mg/dl, 2nd tertile: 4.3–5.7 mg/dl, and 3rd tertile: ≥5.8 mg/dl) were assessed using the one-way analysis of variance for normally distributed variables and the Kruskal-Wallis test for non-normally distributed variables (i.e., diabetes duration, serum triglycerides and liver enzymes). The chi-squared test was used to test for between-group differences among the categorical variables. Logistic regression analysis was used to examine the association between serum uric acid tertiles and risk of