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Original article

Uric Acid and Gamma-glutamyl Transferase Activity Are Associated With Left Ventricular Remodeling Indices in Patients With Chronic Heart Failure

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ABSTRACT

Introduction and objectives: Uric acid and gamma-glutamyl transferase are prognostic indicators in chronic heart failure. Nevertheless, the mechanism underlying the association between uric acid, gamma-glutamyl transferase, and chronic heart failure progression and prognosis remains largely unknown.

Methods: The association of uric acid and gamma-glutamyl transferase with flow-mediated dilation and echocardiographic indices of cardiac remodeling was addressed in 120 patients with chronic ischemic heart failure. To determine the independent contribution of uric acid and gamma-glutamyl transferase to the flow-mediated dilation and echocardiographic indices of remodeling, a series of multiple linear regression models, based on traditional and nontraditional risk factors impacting upon these parameters, were constructed.

Results: Uric acid, but not gamma-glutamyl transferase, was an independent predictor of flow-mediated dilation. Uric acid was associated with all the echocardiographic indices of left ventricular dysfunction tested in 3 multiple-regression models. Uric acid correlated with left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular end-systolic volume, and left ventricular end-diastolic volume (r = 0.337; r = 0.340; r = 0.321; r = 0.294; P = .001, respectively). Gamma-glutamyl transferase was an independent predictor of left ventricular end-systolic volume and left ventricular end-diastolic volume, after adjustment for all variables. Gamma-glutamyl transferase correlated with left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular end-systolic volume, and left ventricular end-diastolic volume (r = 0.238, P = .009; r = 0.219, P = .016; r = 0.359, $P < .001$; r = 0.369, P = .001, respectively).

Conclusions: Serum uric acid and gamma-glutamyl transferase levels are associated with left ventricular remodeling in patients with chronic ischemic heart failure.

El ácido úrico y la actividad de gammaglutamil transferasa se asocian a los índices de remodelado ventricular izquierdo en pacientes con insuficiencia cardiaca crónica

Palabras clave:
Gammaglutamil transferasa
Ácido úrico
Insuficiencia cardiaca crónica
Remodelado
Dilatación mediada por flujo
Estrés oxidativo

RESUMEN

Introducción y objetivos: El ácido úrico y la gammaglutamil transferasa son indicadores pronósticos en la insuficiencia cardiaca crónica. No obstante, el mecanismo subyacente a la asociación observada entre ácido úrico, gammaglutamil transferasa y progresión y pronóstico de la insuficiencia cardiaca crónica sigue siendo en gran parte desconocido.

Métodos: Se estudió la asociación del ácido úrico y la gammaglutamil transferasa con la dilatación mediada por flujo y con los índices ecocardiográficos del remodelado cardiaco en 120 pacientes con insuficiencia cardiaca isquémica crónica. Para determinar la contribución independiente del ácido úrico y la gammaglutamil transferasa en la dilatación mediada por flujo y en los índices ecocardiográficos del remodelado, se construyó una serie de modelos de regresión lineal múltiple, basados en los factores de riesgo tradicionales y no tradicionales que influyen en estos parámetros.

Resultados: El ácido úrico es un factor independiente predictivo de dilatación mediada por flujo, pero no la gammaglutamil transferasa. El ácido úrico se asocia a todos los índices ecocardiográficos de disfunción

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ventricular izquierda evaluados en tres modelos de regresión múltiple; también muestra correlación con los diámetros telesistólico (r = 0,337) y telediastólico (r = 0,340) y los volúmenes telesistólico (r = 0,321) y telediastólicos (r = 0,294) del ventrículo izquierdo (p = 0,001). La gammaglutamil transferasa es un factor independiente predictivo de los volúmenes telesistólico y telediastólico del ventrículo izquierdo tras introducir un ajuste por todas las variables. El gammaglutamil transferasa muestra correlación con los diámetros telesistólico (r = 0,238; p = 0,009) y telediastólico (r = 0,219; p = 0,016) y los volúmenes telesistólico (r = 0,359; p < 0,001) y telediastólico (r = 0,369; p = 0,001) del ventrículo izquierdo.
Conclusiones: El ácido úrico y la actividad de gammaglutamil transferasa se asocian a los índices de remodelado ventricular izquierdo en pacientes con insuficiencia cardiaca isquémica crónica.

Abbreviations

CHF: chronic heart failure
FMD: flow-mediated vasodilation
GGT: gamma-glutamyl transferase
NYHA: New York Heart Association
UA: uric acid

INTRODUCTION

Chronic heart failure (CHF) is a highly prevalent syndrome all over the industrialized world and is associated with significant morbidity and mortality. Several types of biomarkers reflecting neurohumoral activation, systemic inflammation, oxidative stress, metabolism and renal dysfunction, as well as anemia, have been shown to be associated with disease severity and progression.[1] In addition to brain natriuretic peptide, its derivatives and C-reactive protein, particular attention in CHF prognosis has been paid to 2 inexpensive and easily accessible, highly sensitive laboratory tests, namely, uric acid (UA) and gamma-glutamyl transferase (GGT) determination in plasma. Although elevated plasma levels of UA and GGT are significantly associated with disease severity, their prognostic significance is still controversial in CHF.[2,3] Recent work by Poelzl et al[4] have indicated a mutual relationship between these biomarkers, since GGT levels were also associated with higher levels of UA and C-reactive protein.[4] Nevertheless, the mechanism underlying the association between UA, GGT and CHF progression and prognosis remains largely unknown.

Both GGT and the enzyme xanthine oxidase, one of the putative sources of elevated UA in CHF, are involved in free radical production, followed by enhanced oxidation of biological macromolecules. Free radicals and oxidative stress byproducts are implicated in the key pathophysiological events in the course of CHF progression–endothelial dysfunction and remodeling. Thus, free radicals produced by xanthine oxidase and in GGT-mediated reactions may contribute to sequestration of nitric oxide and the resulting endothelial dysfunction in CHF. Endothelial function, as determined by the dilation of the brachial artery following transient occlusion (flow-mediated vasodilation [FMD]), is inversely correlated with serum UA levels in persons participantswith asymptomatic hyperuricemia associated with essential hypertension,[5] as well as in patients with chronic kidney disease.[6] Conversely, reduction of UA with a xanthine oxidase inhibitor improves endothelial function in persons participantswith asymptomatic hyperuricemia, as well as in patients with CHF.[7,8] Although endothelial dysfunction has been documented in peripheral and coronary arteries in CHF patients,[9] the relationship between UA and endothelial function has been investigated in only 1 study, while data on the association between GGT activity and endothelial dysfunction are lacking. In addition, a growing body of evidence suggests an important role of increased oxidative stress in adverse left ventricular remodeling after myocardial infarction.[10,11] Our previous study and the others[12,13] have shown that the level of the oxidative stress byproduct, malondialdehyde, correlates with the degree of ventricular remodeling in CHF secondary to myocardial infarction and represents an independent predictor of death in these patients. Moreover, recent evidence shows that hyperuricemia contributes to the pathogenesis of myocardial remodeling in experimental heart failure,[14–16] Nevertheless, there are no data on the role of UA or GGT in cardiac dysfunction in the clinical settings. We hypothesized that elevated UA and upregulated GGT activity correlate with endothelial dysfunction and ventricular remodeling. Additionally, we hypothesized that potential association of these 2 laboratory markers with endothelial or ventricular dysfunction may be mediated by oxidative stress.

In this translational study, we addressed the association of plasma GGT activity and UA level with FMD and echocardiographic indices of cardiac dysfunction in 120 patients with ischemic CHF and investigated whether these effects are mediated by enhanced oxidative stress.

METHODS

Study Group

This study enrolled 120 consecutively recruited CHF patients with angiographically confirmed cardiovascular disease at the *Bezanijska Kosa Medical Center* between 2008 and 2009. The diagnoses of CHF were based on patient history, physical examination, electrocardiography, chest radiology, echocardiography, and coronary angiography. The major inclusion criteria were left ventricular ejection fraction < 45% and steady state of CHF for a 4-week period with conventional pharmacological treatment including diuretics, β-blockers, and angiotensin-converting enzyme inhibitors. Antioxidants and allopurinol were excluded in the previous 2 months. Acute events such as infection, arrhythmia or discontinuation of therapy, which could precipitate manifestations of acute heart failure, were not present in these patients. Regarding decompensation as an exclusion criterion, all New York Heart Association (NYHA) classes III and IV patients were on diuretics and dietary sodium restriction. Patients with severe comorbidity, renal failure, liver disease, and severe disturbances in lung function, as well as those