ORIGINAL ARTICLE

Hypertensive patients exhibit an altered metabolism. A specific metabolite signature in urine is able to predict albuminuria progression

LAURA GONZALEZ-CALERO, MARTA MARTIN-LORENZO, PAULA J. MARTÍNEZ, MONTSERRAT BALDAN-MARTIN, GEMA RUIZ-HURTADO, JULIAN SEGURA, FERNANDO DE LA CUESTA, MARIA G. BARDERAS, LUIS M. RUILOPE, FERNANDO VIVANCO, and GLORIA ALVAREZ-LLAMAS

MADRID AND TOLEDO, SPAIN

Hypertension (HTN) is increasing in prevalence, and albuminuria is a strong indicator of cardiovascular risk and renal damage progression. Despite blood pressure control with chronic treatment, a relevant subgroup of patients develop albuminuria. However, the biological factors responsible for albuminuria development and progression are underexplored. We aimed to identify key metabolic targets and biological pathways involved in the negative progression of cardiovascular and renal damage in hypertensives undergoing chronic treatment. A series of 1533 patients were followed for 5 years to investigate the evolution of albuminuria. Patients were classified as: (1) patients with persistent normoalbuminuria; (2) patients developing de novo albuminuria; and (3) patients with maintained albuminuria. At the end of follow-up, urine from 30 nonhypertensive subjects (control group) and a representative cohort of 118 patients was collected for metabolomic analysis. Metabolic patterns of interest were identified in a first discovery phase by nuclear magnetic resonance and further confirmed by liquid chromatography-mass spectrometry. Metabolites corresponding to HTN or albuminuria were measured in a prospective study carried out in 35 individuals still in normoalbuminuria, to evaluate their potential as predictors of albuminuria development. Nine metabolites were significantly altered, linking β-alanine metabolism, arginine and proline metabolism, and tricarboxylic acid cycle. The prospective study revealed a panel composed of guanidinoacetate, glutamate, and pantothenate, which was able to predict development of albuminuria. These metabolic signatures open new possibilities in hypertensive therapy and cardiovascular risk control, providing prompt and more efficient intervention, particularly in patients with worse cardiovascular prognosis. (Translational Research 2016;■:1–13)

From the Departamento de Inmunologia, IIS-Fundacion Jimenez Diaz, UAM, Madrid, Spain; Laboratorio de Fisiopatologia Vascular, Hospital Nacional de Paraplejicos SESCAM, Toledo, Spain; Unidad de Hipertension, Instituto de Investigacion i+12, Hospital Universitario 12 de Octubre, Madrid, Spain; Instituto Pluridisciplinar, Universidad Complutense de Madrid, Spain; Departamento de Bioquimica y Biologia Molecular I, Universidad Complutense de Madrid, Spain.

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Reprint requests: Gloria Alvarez-Llamas, Laboratorio de Inmunoalergia y Proteomica, Departamento de Inmunologia, IIS-Fundacion Jimenez Diaz, Avda. Reyes Catolicos 2, 28040 Madrid, Spain; e-mail: galvarez@fjd.es or Luis M. Ruilope, Unidad de Hipertension, Instituto de Investigacion i+12, Hospital Universitario 12 de Octubre, Avenida de Córdoba s/n, 28041, Madrid, Spain; e-mail: ruilope@ad-hocbox.com.

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Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ACR = albumin to creatinine ratio; ARB = angiotensin receptor blockers; AUC = area under the curve; BMI = body mass index; BP = blood pressure; dnA = de novo albuminuria; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein cholesterol; HMDB = human metabolome database; HTN = hypertension; LC-MS/MS = liquid chromatography-mass spectrometry in tandem; LDL = low-density lipoprotein cholesterol; MHA = maintained albuminuria; N = normoalbuminuria; NMR = nuclear magnetic resonance; RAS = renin-angiotensin system; ROC = receiver operating characteristic; sCr = serum creatinine; SRM = selected reaction monitoring; TSP = sodium trimethylsilyl propionate

AT A GLANCE COMMENTARY

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Background

Hypertension is one of the main risk factors for cardiovascular disease. A relevant group of hypertensives develops albuminuria despite of being under chronic treatment, and albuminuria is a strong indicator of cardiovascular and renal damage progression. Currently, there are no clinical markers that are able to predict albuminuria development and increased cardiovascular risk. We identified metabolic alterations in urine in response to hypertension and albuminuria. Specifically, a metabolic signature composed by 3 metabolites was revealed to predict future albuminuria development in hypertensives with normal levels.

Translational Significance

These metabolic signatures open a new way to face hypertensive therapy and cardiovascular risk control, addressed toward a prompt and more efficient intervention particularly in patients with worse cardiovascular prognosis.

INTRODUCTION

Hypertension (HTN) is a multifactorial disease of increasing prevalence and a major risk factor for cardiovascular mortality, even in the presence of apparently adequate treatment.[1] Albuminuria has been clearly demonstrated to be a marker of cardiovascular damage.[2,3] Chronic suppression of the renin–angiotensin system (RAS) has been shown to facilitate blood pressure (BP) control, prevent the development of new-onset albuminuria, and diminish the amount of urinary albumin in patients with persistent high or very high albuminuria.[3] However, high albuminuria has been observed in a relevant subgroup of patients undergoing chronic RAS suppression, either as maintained (MHA) or as de novo–developed albuminuria (dnA).[3] These patients are likely at the highest risk of progression of cardiovascular and renal disease. The discovery of predictors of progression or development of albuminuria during chronic RAS suppression would provide a helpful tool to detect where pharmacological therapy must be intensified and also where new drugs should be tested.

We recently published a study reporting the existence of specific plasma and urinary-protein alterations able to predict albuminuria development in chronically RAS-suppressed patients.[4,5] In this project, we have hypothesized that, during chronic suppression of RAS, HTN is reflected in urinary metabolome and that this reflection may be influenced by the presence and progression of albuminuria. The metabolome is made up of the low-molecular-weight end-products of metabolism, representing the ultimate response of the body to a certain condition (eg disease). Metabolomic studies thus nicely complement genetic and protein studies. Urine is a rich resource with which to investigate molecular alterations associated with renal physiology and kidney diseases. The metabolome was previously investigated in cardiovascular[6-8] and kidney diseases[9,10] by our group and others. However, very few studies have been carried out in the context of HTN, and publications dealing with human samples are particularly scarce and focused on kidney-disease progression in diabetic individuals.[11-13]

We present an in-depth metabolic study aimed at identifying novel metabolite targets and biological pathways involved in the negative progression of hypertensives under chronic RAS suppression. First, variable metabolic response to HTN and albuminuria was investigated. Second, the capacity of metabolites identified as predicting development albuminuria was evaluated in a prospective study carried out in normoalbuminuric individuals.

MATERIAL AND METHODS

Patient classification and selection. Patient selection was based on a previous study showing the development of de novo albuminuria in patients during chronic RAS suppression.[14] Briefly, the study tracked the evolution of 1533 patients from the Hospital 12 de Octubre Hypertension Unit who had been under chronic RAS suppression for at least 5 years (2 before arrival to the

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