Can J Diabetes 39 (2015) 239–246

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Uric Acid as a Biomarker and a Therapeutic Target in Diabetes

Yuliya Lytvyn HBSc [a,b], Bruce A. Perkins MD, MPH [c], David Z.I. Cherney MD, PhD [b,*]

[a] Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada
[b] Department of Medicine, Division of Nephrology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada
[c] Department of Medicine, Division of Endocrinology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 3 July 2014
Received in revised form
21 August 2014
Accepted 10 October 2014

Keywords:
cardiovascular dysfunction
diabetes mellitus
diabetic nephropathy
kidney disease
uric acid

ABSTRACT

Diabetic nephropathy is a long-standing microvascular complication of diabetes mellitus and is the leading cause of end stage renal disease in developed countries. Current therapeutic strategies used to prevent or delay diabetic nephropathy exert limited clinical protective effects and can have serious adverse effects. Thus, identification of new pharmacologic agents that protect against the initiation and progression of complications of diabetes is of the utmost importance. Uric acid (UA) recently emerged as an inflammatory factor that increases oxidative stress and promotes activation of the renin angiotensin aldosterone system. As a consequence, higher UA levels are associated with various stages of the onset and progression of diabetic nephropathy, including metabolic, cardiovascular and kidney function abnormalities. If UA-lowering drugs, such as the xanthine oxidase inhibitors, block the mechanisms responsible for micro- and macrovascular injury in diabetes, these agents could represent a critical step toward preventing the progression of diabetes. This review focuses on the evidence that supports serum UA levels as a biomarker of renal and cardiovascular risk and as a potential additional therapeutic target in diabetes.

Mots clés :
dysfonctionnement cardiovasculaire
diabète sucré
néphropathie diabétique
maladie rénale
acide urique

RÉSUMÉ

La néphropathie diabétique est une complication microvasculaire à long terme du diabète sucré, qui constitue la principale cause de l'insuffisance rénale terminale dans les pays développés. Les stratégies thérapeutiques qui sont actuellement utilisées pour prévenir ou retarder la néphropathie diabétique ont des effets protecteurs cliniques limités et peuvent avoir des effets indésirables sérieux. Par conséquent, l'identification de nouveaux agents pharmacologiques qui protègent contre l'apparition et la progression des complications du diabète revêt la plus haute importance. L'acide urique (AU) est récemment apparu comme un facteur inflammatoire qui augmente le stress oxydatif et promeut l'activation du système rénine-angiotensine-aldostérone. En conséquence, des concentrations plus élevées d'AU sont associées aux différentes étapes de l'apparition et de la progression de la néphropathie diabétique, dont les anomalies des fonctionnements métabolique, cardiovasculaire et rénal. Bien que les médicaments abaissant l'AU, tels les inhibiteurs de la xanthine oxydase, bloquent les mécanismes responsables des lésions microvasculaires et macrovasculaires, ces agents pourraient représenter une étape cruciale en vue de prévenir la progression du diabète. La présente revue souligne les données scientifiques qui soutiennent que les concentrations sériques d'AU sont un biomarqueur du risque rénal et cardiovasculaire, et un objectif thérapeutique additionnel potentiel du diabète.

Introduction

Diabetic nephropathy (DN) is the most common microvascular complication of diabetes, and it causes more than 40% of end stage renal disease cases requiring dialysis worldwide. Dialysis patients with diabetes have a high risk for coronary disease, stroke and peripheral arterial disease (1). Moreover, even mild chronic kidney disease (CKD) is associated with the development of cardiovascular complications (1).

Despite what is known about the risk associated with DN, the responsible mechanisms are complex and remain incompletely understood. Chronic hyperglycemia increases the risk for DN through the activation of hemodynamic and metabolic pathways, including cytokines, chemokines, growth factors, intracellular signaling cascades and neurohormonal mechanisms, such as the renin angiotensin aldosterone system (RAAS). These changes result

* Address for correspondence: David Z.I. Cherney, MD CM, PhD, FRCP(C), Toronto General Hospital, 585 University Avenue, 8N-845, Toronto, Ontario M5G 2N2, Canada.
E-mail address: david.cherney@uhn.ca

1499-2671/$ – see front matter © 2015 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2014.10.013

in increased intraglomerular pressure, oxidative stress, inflammation and endothelial dysfunction, ultimately leading to the structural kidney abnormalities characteristic of diabetes (1). Many of these abnormalities are clinically silent for many years. As a consequence, DN progresses slowly, and by the time DN presents clinically as albuminuria and loss of renal function, significant renal parenchymal damage has already occurred. It is, therefore, important to identify novel biomarkers of DN risk to target high-risk patients with earlier therapies prior to the onset of albuminuria or renal function decline.

The current gold-standard therapeutic strategies to decrease the risk for DN progression are intensive glycemic control and RAAS inhibition. The first recognition of the intensive glycemic control benefit stemmed from the Diabetes Control Complications Trial (DCCT) where intensive glycemic control over a period of 6.5 years resulted in a 39% reduction in the frequency of microalbuminuria and a 54% reduction in the frequency of macroalbuminuria compared to the frequencies found in patients with type 1 diabetes who had been treated by conventional glycemic therapy (2). The long-lasting benefits of intensive glycemic control were also shown in patients with type 2 diabetes (3). Unfortunately, the use of glycemic control is limited by side effects, such as hypoglycemia and weight gain. Despite the 2 decades that have elapsed since the DCCT, optimal glycemic control remains difficult to achieve, and a substantial proportion of patients with diabetes fail to reach the glycated hemoglobin (A1C) target levels and progress to develop renal and cardiovascular complications (1,4). RAAS inhibition emerged as an additional protective treatment but, unfortunately, angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs) and direct renin inhibitors (DRIs) lead to incomplete suppression of the RAAS, resulting in persistent efferent renal arteriolar vasoconstriction, high intraglomerular pressure and renal hyperfiltration (5,6). From a clinical perspective, RAAS inhibitors have also failed to eliminate renal and cardiovascular complications (1,7). Moreover, dual RAAS blockade is associated with serious side effects, such as renal dysfunction and hyperkalemia (1,7). Finally, RAAS blockade has failed as a primary prevention therapy in type 1 diabetes (7). Normoalbuminuric, normotensive patients with type 1 diabetes, therefore, do not benefit clinically from the early institution of RAAS blockade therapies. The identification of new, safe pharmacologic agents that protect against the initiation and progression of diabetic complications is, therefore, of the utmost importance.

More recently, it has been demonstrated that uric acid (UA) exerts deleterious effects on blood pressure and renal function, even when baseline UA levels are within the normal range (8). UA activates the RAAS, increases oxidative stress and promotes inflammation (8). As a consequence, higher UA levels are associated with metabolic abnormalities (insulin resistance, hyperglycemia); cardiovascular disease (hypertension, endothelial dysfunction, arterial stiffness, cardiac diastolic dysfunction) and kidney dysfunction (1,5,7). Experimental work has suggested that pharmacologic lowering of UA also blocks the RAAS, suppresses inflammation and promotes renal and cardiovascular protection (9). Thus, there is evidence that UA is involved in the mechanisms of various stages of DN onset and progression. If UA-lowering drugs, such as the xanthine oxidase (XO) inhibitors allopurinol and febuxostat, attenuate some of the mechanisms responsible for micro- and macrovascular injury in patients with diabetes, then these agents could represent a critical step toward preventing the progression of diabetes. Serum UA levels could, therefore, serve as an earlier biomarker and an effective therapeutic target to supplement the current hemoglobin A1C, cholesterol and blood pressure targets.

Uric acid homeostasis

In humans, UA is a breakdown product of purine nucleotides (Fig. 1). The exogenous pool of UA varies with dietary intake, including purine-rich products, fructose and glucose. Of interest is the suggested association between high fructose consumption and high UA levels. Upon ingestion, fructose is absorbed into cells and is phosphorylated by fructokinase, leading to depletion of adenosine triphosphate (ATP) and subsequently increased production of adenosine monophosphate, which results in increased UA levels (10). Human trial data linking high fructose intake to increased serum UA levels has, however, been mixed, with some data attributing the association to the hypercaloric state rather than to fructose directly (10). Given that the increased worldwide intake of fructose in the form of high-fructose corn syrup parallels the rise in metabolic syndrome and hyperuricemia, additional studies are needed to confirm this association. The endogenous pool of UA is regulated mainly by xanthine oxidoreductase-mediated hepatic production, intestinal secretion and renal excretion (5). Because UA is excreted primarily by the kidney, studying the role of UA in kidney disease is difficult because the

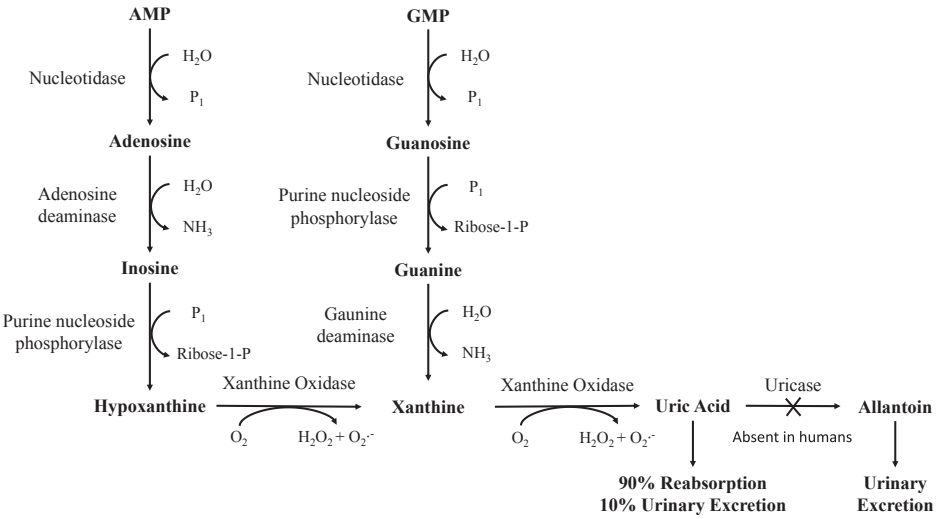

Figure 1. Summary of purine metabolism in humans.