Journal of Advanced Research 8 (2017) 537–548

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

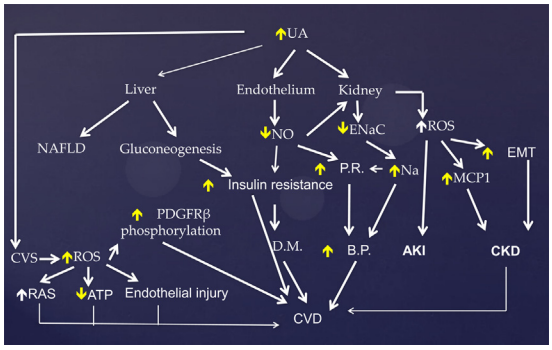
Review

Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review

Usama A.A. Sharaf El Din [a,*], Mona M. Salem [b], Dina O. Abdulazim [c]

[a] Nephrology Unit, Internal Medicine Department, School of Medicine, Cairo University, Egypt
[b] Endocrinology Unit, Internal Medicine Department, School of Medicine, Cairo University, Egypt
[c] Rheumatology and Rehabilitation Department, School of Medicine, Cairo University, Egypt

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 11 September 2016
Revised 26 November 2016
Accepted 27 November 2016
Available online 3 December 2016

Keywords:
Uric acid
Insulin resistance
Non-alcoholic fatty liver disease
Acute kidney injury
Chronic kidney disease
Cardiovascular disease

ABSTRACT

The association between uric acid (UA) on one side and systemic hypertension (Htn), dyslipidemia, glucose intolerance, overweight, fatty liver, renal disease and cardiovascular disease (CVD) on the other side is well recognized. However, the causal relationship between UA and these different clinical problems is still debatable. The recent years have witnessed hundreds of experimental and clinical trials that favored the opinion that UA is a probable player in the pathogenesis of these disease entities. These studies disclosed the strong association between hyperuricemia and metabolic syndrome (MS), obesity, Htn, type 2 diabetes mellitus (DM), non-alcoholic fatty liver disease, hypertriglyceridemia, acute kidney injury, chronic kidney disease (CKD), coronary heart disease (CHD), heart failure and increased mortality among cardiac and CKD patients. The association between UA and nephrolithiasis or preeclampsia is a non-debatable association. Recent experimental trials have disclosed different changes in enzyme activities induced by UA. Nitric oxide (NO) synthase, adenosine monophosphate kinase (AMPK), adenosine monophosphate dehydrogenase (AMPD), and nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase are affected by UA. These changes in enzymatic activities can lead to the observed biochemical and pathological changes associated with UA. The recent experimental, clinical, interventional, and epidemiologic trials favor the concept of a causative role of UA in the pathogenesis of MS, renal, and CVDs.

Peer review under responsibility of Cairo University.
* Corresponding author. Fax: +20 222753890.
E-mail address: usamaaas@gmail.com (U.A.A. Sharaf El Din).

http://dx.doi.org/10.1016/j.jare.2016.11.004
2090-1232/

Introduction

UA is a weak acid (M.W. = 168) produced in the liver, muscles, and intestines [1]. Purines are the precursors of UA. Xanthine oxidoreductase (XO) is the enzyme responsible for UA production. Exogenous sources that can increase serum UA include fatty meat, organ meat, and seafood [2]. Fructose is another source of exogenous UA. Fructose is present in fruits and added sugar. Fructokinase enzyme catalyzes the phosphorylation of fructose by consuming adenosine triphosphate (ATP). Adenosine monophosphate (AMP) thus generated finally converts to UA [3]. UA was incriminated in the pathogenesis of gout and kidney stones. However, for more than 140 years ago, high serum UA (SUA) was proposed in association with other diseases including Htn [4], CKD and DM [5]. The association between hyperuricemia and CHD was first reported in 1951 [6]. SUA bears a highly significant positive correlation with insulin resistance (IR) and insulin response to oral glucose load. Hyperuricemia encountered in case of increased IR is the sequence of decreased renal urate clearance [7]. Accumulating data point toward a possible etiologic role of increased UA in the pathogenesis of MS, CVD and renal disease [8]. Experimental and clinical trials have demonstrated the reversal or amelioration of different diseases associated with hyperuricemia after administration of hypouricemic agents. These agents are either inhibitors of the XO enzyme or stimulants of renal UA excretion. This later group supports that the therapeutic effect is a consequence of UA lowering rather than inhibition of release of free oxygen radicals on inhibition of XO enzyme. In this review, we are going to discuss the possible impact of hyperuricemia on metabolic, renal, and CVDs.

Uric acid and metabolic syndrome

MS is a group of clinical and laboratory abnormalities. Out of the five established manifestations, three or more are needed to diagnose MS. These manifestations are (1) waist circumference $\geqslant$ 90 and 80 cm in men and women respectively; (2) serum triglyceride $\geqslant$ 150 mg/dL; (3) high-density lipoprotein cholesterol (HDLc) < 40 and 50 mg/dL in men and women respectively; (4) blood pressure (BP) $\geqslant$ 130/85 mmHg; and (5) fasting blood sugar $\geqslant$ 100 mg/dL [9]. The different manifestations of MS are considered as consequences of excess fat deposition in the adipose tissue [10]. Excess intake of sugars beside purine rich foods can lead to increased incidence of hyperuricemia, obesity and DM [11]. In adults with normal body mass index, MS is 10 times higher in those having SUA $\geqslant$ 10 mg/dL compared to those with SUA < 6 mg/dL [12]. The hazard ratio of incident MS shows a steady increase when normal adults were allocated into four quartiles according to SUA. These results were still observed after considering the body composition [13]. When children (10–15 years at baseline) were followed for 10 years, high SUA was a significant predictor of incident MS in male subjects [14]. On the other hand, when elderly hyperuricemic subjects above sixty-five years were followed for more than 4 years, only female subjects showed increased incidence of MS [15]. Another prospective study assessed 1511 men and women 55–80 years old, who were not affected initially by any of the components of MS. Follow-up has demonstrated a significantly higher incidence of many components of MS, namely, hypertriglyceridemia, low HDL, and Htn in subjects with highest sex-adjusted quartile of UA [16]. A meta-analysis of eleven studies of more than fifty-four thousand participants showed that elevated SUA is associated with increased risk of MS and non-alcoholic fatty liver disease (NAFLD) [17]. By inhibiting endothelial NO synthase, decreased NO might underlie insulin resistance [18]. Hyperuricemia is significantly associated with insulin resistance in normal subjects and to lesser extent in type 1 diabetic subjects [19]. Lowering SUA by a uricosuric agent [20] or allopurinol [21] is associated with improved insulin sensitivity in human subjects (Fig. 1).

Glucose intolerance and diabetes mellitus

The link of UA to hyperglycemia was first described in the nineteenth century [22]. Elevated SUA predicted DM and insulin resistance in a fifteen-year follow-up study. Baseline SUA in this cohort of 5012 young adults was not associated with a change in serum insulin, indicating that hyperuricemia is an independent risk factor for insulin resistance and type 2 DM [23]. High normal SUA was also associated with future development of type 2 DM among lean healthy and normoglycemic women [24]. Increased hepatic glucose production is a distinguished feature of insulin resistance and type 2 DM. Intracellular UA stimulates AMPD and inhibits AMPK enzyme activity (Fig. 2). Intracellular AMPK inhibits hepatic gluconeogenesis. AMPD stimulates hepatic gluconeogenesis [25]. Decreased endothelial NO synthase (eNOS) activity in hyperuricemic patients causes increased insulin resistance [18,19]. Treatment of asymptomatic hyperuricemic personnel with allopurinol for 3 months results in significant decrease in insulin resistance and inflammation parameters [21].

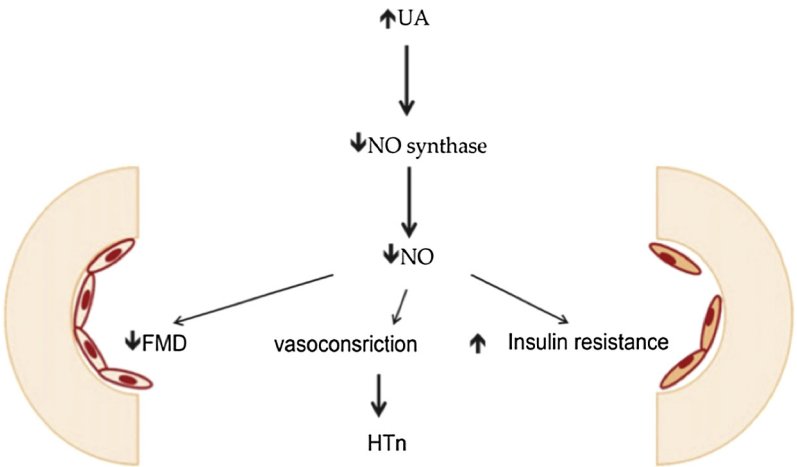


Fig. 1. Effect of intra-cellular uric acid on nitric oxide synthesis within vascular endothelium UA = uric acid; NO = nitric oxide; FMD = flow mediated dilation; Htn = systemic hypertension.