Clinical Biochemistry 50 (2017) 1289–1297

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Review

Effect of allopurinol and uric acid normalization on serum lipids hyperuricemic subjects: A systematic review with meta-analysis

Verônica Moreira Ferreira de Castro[a], Angelita Cristine de Melo[b,d], Vinícius Silva Belo[c], Valéria Ernestânia Chaves[a,*]

[a] Laboratory of Physiology, Federal University of São João del-Rei, Divinópolis, Minas Gerais, Brazil
[b] Research Group on Epidemiology and Public Health, Federal University of São João del-Rei, Divinópolis, Minas Gerais, Brazil
[c] Laboratory of Parasitology, Federal University of São João del-Rei, Divinópolis, Minas Gerais, Brazil
[d] Research Group on Clinical Pharmacy, Federal University of São João del-Rei, Divinópolis, Minas Gerais, Brazil

ARTICLE INFO

Keywords:
Hyperuricemia
Dyslipidemia
Serum cholesterol
Serum triacylglycerol

ABSTRACT

Although uric acid is not part of any definition of metabolic syndrome, a number of studies have shown strong associations between the concentration of uric acid and metabolic syndrome or its components. The purpose of this systematic review with meta-analysis was to evaluate, using prospective interventional studies, the effects of allopurinol therapy and uric acid normalization on serum concentrations of triacylglycerol, total-cholesterol, LDL-cholesterol and HDL-cholesterol in hyperuricemic subjects. A systematic search of the PubMed and Scopus databases was performed following the guidelines described in the PRISMA statement. Seven studies were included in the meta-analysis, including six randomized controlled trials and one controlled before-and-after study. Despite differences in the follow-up periods (4, 12 and 24 weeks) and allopurinol dose (100–300 mg/day), all the studies showed decreases in the mean serum uric acid level (95% confidence interval: − 2.61 to − 1.55 (4 weeks), − 2.94 to − 1.09 (12 weeks) and − 2.59 to − 1.22 (24 weeks); $p < 0.05$). However, no effect was observed based on differences in mean serum triacylglycerol and total- and LDL-cholesterol concentrations, independent of the follow-up period. Allopurinol therapy during weeks 4 and 12 induced a decrease in the mean HDL-cholesterol level (95% confidence interval: − 7.22 to − 0.47 (4 weeks) and − 7.18 to − 0.32 (12 weeks); $p < 0.05$). This review suggests that allopurinol and uric acid normalization does not improve serum lipid levels, although larger and longer trials of higher quality are needed to confirm this.

1. Introduction

Uric acid is the end product of purine metabolism in humans [1], as the uricase gene became nonfunctional through evolution [2]. Uric acid can be derived from exogenous sources, such as diets of high protein, and from endogenous sources, such as the catabolism of genetic material [1]. Xanthine oxidase catalyzes the last two steps of uric acid synthesis: the conversion of hypoxanthine into xanthine and uric acid [1,3]. Clinically, overproduction or sub-excretion of uric acid results in hyperuricemia [3], which has been established as the primary etiologic factor for gout [4]. Hyperuricemia is caused by genetic and environmental factors such as alcohol, drug-use and fructose consumption [3,5,6]. Gout is characterized by the crystallization of uric acid within the joints, inducing inflammatory arthritis [5], and its major treatment is pharmacological.

Allopurinol, an analog of hypoxanthine, is hydrolyzed by xanthine oxidase to produce oxypurinol, which binds strongly to the reduced molybdenum ion, Mo(IV), enzyme and thereby inhibits the synthesis of uric acid [4,7]. Febuxostat [2-(3-cyano-4-isobutoxy-phenyl)-4-methyl-1,3-thiazole-5 carboxylic acid] is structurally distinct from allopurinol and is able to inhibit both the oxidized Mo (VI) and reduced Mo (IV) forms of xanthine oxidase, thus resulting in a more effective blockade of uric acid and reactive oxygen species production [4,7,8]. The enzyme xanthine oxidoreductase is widely distributed in various organs including the liver, adipose tissue, heart, lung, and brain, as well as the plasma [9–11]. It exists in one of two forms, xanthine dehydrogenase or xanthine oxidase [9–11].

There are reports that the loss of uricase activity is related to protection from oxidative damage and the prolonged life span, due to the antioxidant properties of uric acid [12,13]. On the other hand, several

Abbreviations: ALT, alanine transferase; GGT, γ-glutamil transferase; HDL, high density lipoprotein; HOMA-IR, homeostatic model of assessment-insulin resistance; LDL, low density lipoprotein; MeSH, Medical Subject Headings; OLETF, Otsuka Long Evans Tokushima Fatty; PRISMA, preferred reporting items for systematic review and meta-analysis

* Corresponding author at: Avenida Sebastião Gonçalves Coelho, 400, Chanadour, 35.501-296 Divinópolis, Minas Gerais, Brazil.
E-mail addresses: valeria.chaves@gmail.com, valeriachaves@ufsj.edu.br (V.E. Chaves).

http://dx.doi.org/10.1016/j.clinbiochem.2017.07.013
Received 6 May 2017; Received in revised form 21 July 2017; Accepted 24 July 2017
Available online 25 July 2017

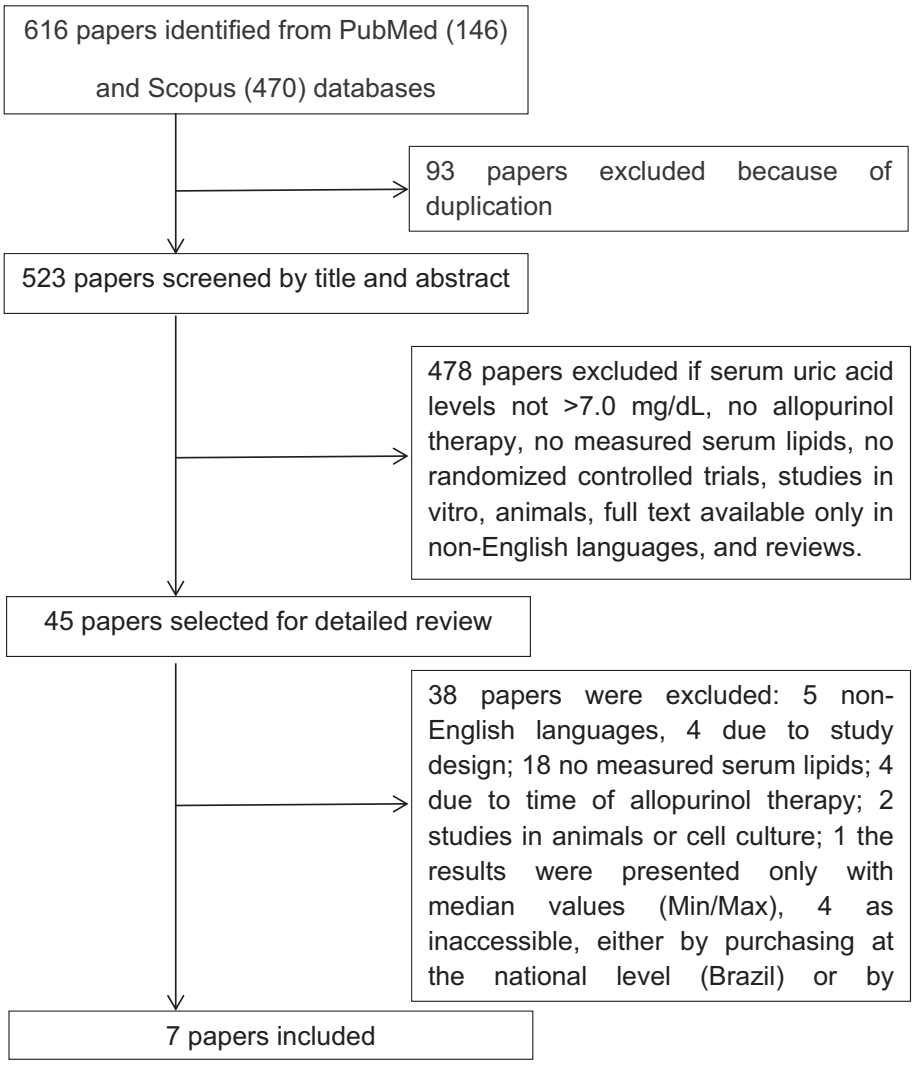

Fig. 1. Flow diagram of the study selection.

studies have shown a strong association between increases in serum uric acid level and metabolic syndrome or its components [14–28]. However, hyperuricemia is not considered in the cluster of signals of metabolic syndrome.

A study of 3518 employed subjects without clinical cardiovascular disease demonstrated that hyperuricemia, independently of metabolic syndrome, is associated with hepatic steatosis, increased ratio of triacylglycerol and high density lipoprotein (HDL), and high-sensitivity C-reactive protein [24]. In 541 type 2 diabetic patients, serum uric acid was found to be specifically associated with nonalcoholic fatty liver disease in men, but not in women, independent of insulin resistance and other metabolic factors [27]. In obese children, serum concentrations of uric acid were shown to be associated with carotid atherosclerosis, independent of classical risk factors, insulin resistance and components of the metabolic syndrome [23]. In addition, uric acid levels were significantly associated with systolic blood pressure, triacylglycerol, HDL-cholesterol, alanine transferase (ALT), γ-glutamil transferase (GGT), creatinine, insulin, and homeostatic model of assessment-insulin resistance (HOMA-IR), after adjustment for age, gender, and pubertal stage [23]. In US children and adolescents, serum concentrations of uric acid were significantly associated with abdominal obesity, hypertriglyceridemia, and hyperglycemia, even after adjustment for age, sex, race or ethnicity, concentrations of C-reactive protein, and other components of metabolic syndrome [22]. A meta-analysis of prospective cohort studies provides strong evidence that a high level of serum uric acid is independent of other established risk factors, especially metabolic syndrome components, for developing type 2 diabetes in middle-aged and older people [26]. In rodents, lowering of uric acid with either allopurinol or febuxostat prevents or reverses features of metabolic syndrome, such as hyperinsulinemia, hypertension, hypertriglyceridemia and/or weight gain, induced by a high-fructose diet [18,29,30].

Recently, we summarized the current knowledge of the effects of uric acid on the regulation of glucose and lipid metabolism [3]. In the present study, a systematic review with meta-analysis, using prospective interventional studies, was performed to evaluate the effects of uric acid normalization by allopurinol therapy on the serum levels of triacylglycerol, total-, HDL- and low density lipoprotein (LDL)-cholesterol, in hyperuricemic subjects. Despite the strong association between