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Review Article

Hyper-homocysteinemia Inducing Hyperuricemia: What are the Mechanisms?

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Hyperuricemia is related to metabolic syndrome, and is defined as an over-production or under-excretion of uric acid (UA), with increased UA serum concentration. Among other causes, Hyper-homocysteinemia (H-Hcy) can be responsible for hyperuricemia. The mechanisms underlying the association between these two conditions are unclear, but increased UA serum levels can be a consequence of renovascular atherosclerosis, with reduced UA excretion. An alternative hypothesis is the over-production of UA from adenosine (originating from S-adenosyl-homocysteine). Genetic polymorphism (C677T) of methyl-enetetrahydrofolate reductase (MTHFR) may contribute. A possible mechanism is purines biosyinthesis originating from this gene variant. However, the results obtained from several studies and meta-analyses of the relationship between H-Hcy and hyperuricemia are ambivalent, and broader research is needed. **(J Rheum Dis 2017;24:127-130)**

Key Words. Uricemia, Uric acid, Homocysteine, MTHFR C677T polymorphism

INTRODUCTION

Hyperuricemia is related with metabolic syndrome, and defined such as a plasma uric acid (UA) level greater than 6.8 mg/dL at physiological temperature and neutral pH [1,2]. The metabolite is produced by the breakdown of purines giving from some structures (old or damaged cells) present in the body. Purines also derive from the metabolism of definite rich-purines foods, such as asparagus and red meets. Once produced, UA is not further metabolized but eliminated by kidneys and through bowels. Physiologically, UA serum increases with advancing age and is higher in men than in women, possibly by estrogens' presence [3,4]. From clinical point of view, hyperuricemia may be asymptomatic or symptomatic. Asymptomatic hyperuricemia is a term applied to settings in which the serum urate concentration is elevated but neither symptoms or uric renal disease have occurred. On the contrary, symptoms of hyperuricemia are acute inflammatory arthritis, tenosynovitis, bursitis, chronic arthropathy and accumulation of urate crystals (such as tophaceous deposits) in some articulations. In few cases, renal complications can also occur (UA nephropathy). The prevalence of asymptomatic hyperuricemia in the general population is estimated of 2% to 13%, and is augmented in recent decades [5]. The increase in serum UA levels may be linked to the rising prevalence of overweight and obesity, as well as, the increased consumption of sugar-sweetened beverages, foods rich in purine or alcohol [6,7]. Accumulating evidences show that increased UA level represents a risk factor for metabolic syndrome and cardiovascular diseases [8,9]. The causes of hyperuricemia are the result of UA underexcretion or overproduction. Sometimes, a combination of both may be responsible for increased serum UA concentration. But, also increased homocysteine (Hcy) serum levels were found to be positively correlated with high UA levels in several studies [10-12].

HOMOCYSTEINE

Hcy is an intermediate product of the methionine me-

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tabolism, produced via demethylation of dietary methionine. This undergoes adenosylation, forming S-adenosyl-methionine (SAM). The compound is the principal methyl-donor for all methylation reactions. SAM demethylation leads to the formation of S-adenosyl-homocysteine (SAH), through the surrender of methyl-groups to some substrates. Finally, hydrolysis of SAH leads to the formation of Hcy and adenosine. The increased UA production in hyper-homocysteine (H-Hcy)-patients probably depends on an excess of adenosine production originating from SAH [13]. Precisely, adenosine is degraded to form UA as its end product, as illustrated in Figure 1.

Another cause of hyperuricemia in patients with increased Hcy levels could be due to the renovascular atherosclerosis causing an impairment of UA renal clearance, with consequent elevated levels of UA serum concentration [13-16]. It is known that H-Hcy favors atherosclerosis by several mechanisms, such as the reduction of methylation index inducing endothelial dysfunction and smooth muscle cell proliferation. Other mechanisms are: oxidative stress, nuclear factor kb activation, inflammation, and inhibition of endothelial nitric oxide synthase or increased platelets' aggregation [17-19]. Recently, it was also affirmed that both hyperuricemia and H-Hcy could become mutually stronger [20]. In the past decade a number of genetic studies have been performed on attempt to specifically demonstrate that the genetic variants responsible for high Hcy concentration can increase also serum UA levels.

Among all variants, methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism was considered as a major risk factor, because this gene variant is the most common mutation leading to accumulation of Hcy and shows only 65% of normal enzyme activity, with consequent higher Hcy levels [21-25]. MTHFR is a main regulator enzyme able to catalyzes the reduction of 5,10-methylene-tetra-hydrofolate to 5-methyl-tetra-hydrofolate, which acts as the carbon donor in the remethylation of homocysteine to methionine. Although the mechanisms of the relationship between MTHFR C677T polymorphism and serum UA is still unknown, it can be hypothesized that this MTHFR gene mutation could favor de novo synthesis of purines via 10-formyl-tetrahydrofolate, resulting in increased production of UA [26]. Concordantly, 10-formyl-tetrahydrofolate acts as a donor of formyl groups for the biosynthesis of purines, that induce an increase of UA concentration [27]. But, a disagreement still exists about the relationship between the MTHFR C667T polymorphism and increased UA levels In fact, several authors described that MTHFR C677T polymorphism may be a risk factor for hyperuricemia [22-30]. In addition, recently two meta-analyses further confirmed this association [27-31]. On the contrary, two large studies conducted on Japanese and Chinese populations reported no association between MTHFR C677T polymorphism and hyperuricemia [32,33]. Probably, these controversies suffer of some limitations, such as high hetereogenicity in age among the patients. In agreement, previous studies revealed the relationship is present in middle-aged men and absent in young and elderly women [32,33]. In addition, it must be remembered the lack of detailed informations between the genes and environmental factors, such as diet and lifestyle of the patients enrolled. Finally, the different ethnicity may be also considered. In this connection, some twin studies as well as epidemiological data about ethnic groups have suggested that genetic factors could modify serum UA levels [34-36]. On the other hand, the greater part of populations examined only belongs to the eastern world. Concordantly, MTHFR genotype frequencies differed among the populations having different ethnic background [37].

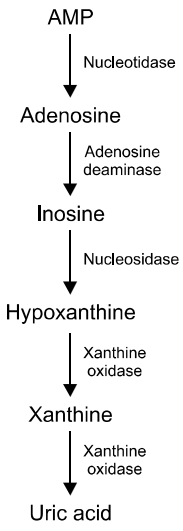

Figure 1. Synthesis of uric acid from adenosine monophosphate (AMP).

CONCLUSION

Therefore, further well-designed studies performed in larger sample sizes are requested, to better evaluate if truly exists a relationship between MTHFR C677T polymorphism and hyperuricemia and what are the mecha-

nisms existing between them.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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