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EDITORIAL

Homocysteine and chronic kidney disease: an ongoing narrative

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Chronic kidney disease (CKD) patients are a growing population worldwide, affected by a high cardiovascular risk. The cause of this increase is certainly multifactorial; one of the possible culprits that have been invoked may lie in the marked derangement in the complex sulfur metabolism peculiar to these patients, leading to altered levels of several compounds in this pathway (Fig. 1). Homocysteine is probably the most studied among these; however, despite the huge amount of evidence that homocysteine, and/or one of its precursors/metabolites, is toxic [1, 2], the negative interventional trials brought the scientific community to consider it as the epitome of something that does not come through [3]. It is possibile that the negative results of the trials in CKD patients, conducted by the way in countries where folate fortification is mandatory, can be ascribed to the presence in the intervention of cianocobalamin [4]. Vitamin B_{12} is necessary for correct homocysteine remethylation, but cianocobalamin in CKD can accumulate and be detrimental. Another reason could be related to the possible adverse effects of high-dose folic acid, for example due to the presence of circulating UnMetabolized Folic Acid [UMFA, 5]. Slowly, however, new evidence is arising. In the China Stroke Prevention Primary Prevention Trial (CSPPT), it has been shown that low-dose folic acid (0.8 mg/day) is able to reduce the incidence of primary stroke in hypertensive patients [6]. In addition, a pre-specified CSPPT substudy demonstrates that low-dose folic acid is effective in slowing down the progression of CKD. Patients with moderate CKD (eGFR between 30–60 ml/min) benefit the most. The common methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism influences homocysteine levels and the renal outcome response [7]. Thus, if data are confirmed also in other populations, low-dose folic acid could constitute another tool to contrast CKD progression in our still scarce therapeutic armamentarium.

The cross-sectional study by Cohen et al. [8] conveys a wealth of information in a very large cohort of subjects (n = 17,010) on the homocysteine issue [8]. Patients were referred for screening by their employers, and were 67% men. Israel is a country, like China, where no folic acid fortification is implemented. The association between homocysteine concentrations and CKD was looked upon and is confirmed at all levels of renal disease, while also adjusting for confounders which can affect CKD, such as age, smoking status, body mass index, hypertension and diabetes mellitus. The association is present in both men and women. Subjects with homocysteine > 15 μM were more likely to have an eGFR < 60 ml/min, and to have proteinuria. At a GFR < 60 ml/min, homocysteine was progressively higher in stages 3a, 3b, and 4 of CKD, with quite a large discrepancy between stage 3a and 3b, particularly in women. This could be of interest, given the fact that stage 3b is the one were cardiovascular disease hits the most, and it is therefore most likely to benefit from low-dose folic acid.

This is the first study carried out in such an elevated number of patients, outside China, in a country with no folate fortification policy. While it does not prove cause and effect relationships (homocysteine and CKD, homocysteine and CKD progression, homocysteine and atherosclerosis, etc.), Spence et al. have shown for example that homocysteine accounts for a significant part of the effect of renal impairment on atherosclerosis [9]. This paper by Cohen et al. therefore paves the way for future studies on this topic.

A detailed scheme of the metabolic interconnections of homocysteine with sulfur amino acids, folate cycle, B vitamins, and one carbon (C1) metabolism is provided in Fig. 1. Methionine is converted into *S*-adenosylmetionine (SAM; AdoMet), the universal methyl donor for several tens of SAM-dependent methyltransferases (MTs) in humans. Methyl acceptors include small molecules (guanidino

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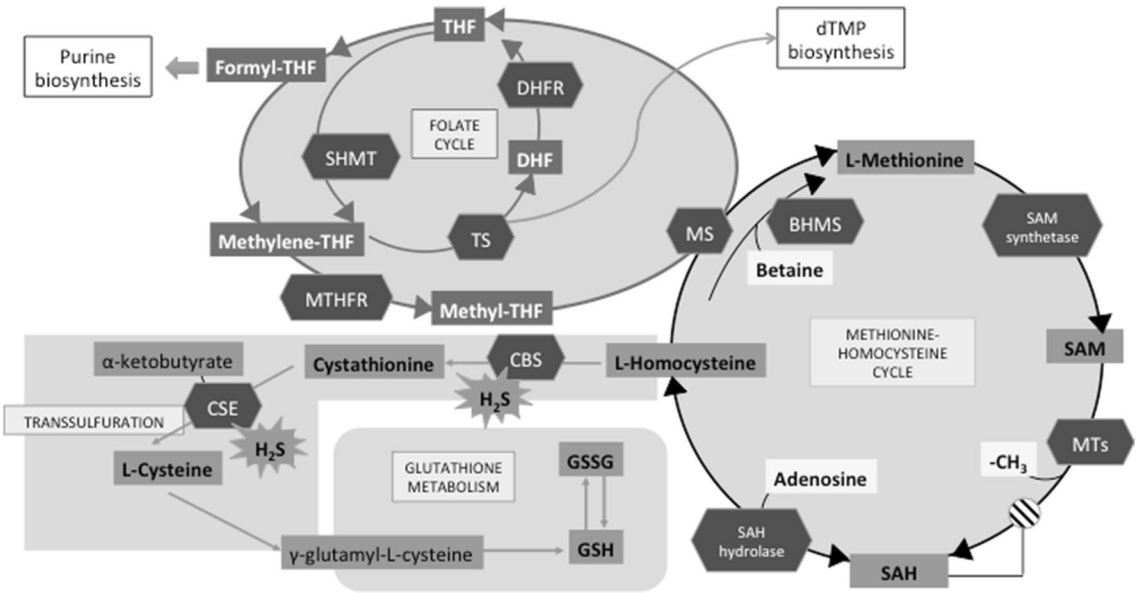

Fig. 1 Metabolic interconnections of homocysteine with sulfur amino acids, folate cycle, B vitamins, and one carbon (C1) metabolism

acetate, phospholipids, amino acids and their derivatives, etc.) and macromolecules. The demethylated product of SAM-dependent MTs is *S*-adenosylhomocysteine (SAH; AdoHcy), a thioether which is also a powerful competitive product inhibitor of all SAM-dependent MTs. SAH hydrolysis is catalyzed by SAH hydrolase (EC 3.3.1.1). Although thermodynamics favors SAH biosynthesis over hydrolysis, the prompt removal of hydrolysis products (homocysteine and adenosine) prevents SAH intracellular accumulation and the relevant MTs inhibition. Homocysteine concentration crucially depends on the rate of its formation (transmethylations), as well as on the rate of homocysteine removal. Homocysteine is mostly carried out in circulation covalently bound to serum albumin, thus preventing its excretion as such. Decreased metabolic clearance, possibly due to the effect of another uremic toxin [1], rather than increased production, supports the mechanism of onset of hyperhomocysteinemia in CKD. On a quantitative basis, small molecule methylation is more prominent than macromolecule methylation (DNA, RNA, proteins) in determining homocysteine production.

Homocysteine can be remethylated to methionine. Two enzymes are capable of catalyzing this reaction: the first (methionine synthase, MS; EC 2.1.1.13), the product of *MTR* gene, is vitamin B_{12}-dependent and utilizes methyl tetrahydrofolate (methyl-THF) as the methyl donor. The other one (BHMT; EC 2.1.1.5) uses betaine as the methyl donor. Methyl-THF is generated from methylene-THF in a previous reaction catalyzed by methylene-THF reductase (MTHFR; E.C.1.5.1.20). The homocysteine remethylation lays at a crucial intersection between the methionine-homocysteine and the folate cycle. Vitamin B_{12}, in the form of methylcobalamin linked to the MS apoenzyme, is required for this reaction, as well as SAM itself. The active B_{12} coenzyme is regenerated by the action of methionine synthase reductase (MTR; EC 1.16.1.8) the product of *MTRR* gene, a $NADP^+$-dependent oxidoreductase; MTR is a flavoprotein containing FAD and FMN. The substrate of the enzyme is the inactive form of MS. Defects in these enzymes lead to hereditary hyperhomocysteinemia. Folate coenzymes are involved in the biosynthesis of both purine (formyl-THF) and dTMP biosynthesis, as crucial building blocks in DNA biosynthesis. TS (Thymidylate synthase; EC 2.1.1.45) oxidizes tetrahydrofolate (THF) to dihydrofolate (DHF). The latter must be reduced by the action of DHF-reductase (DHFR; EC 1.5.1.3), a NADPH-dependent oxidoreductase, which is the in vivo molecular target of the antifolic methotrexate (not shown).

Alternatively, homocysteine can be transsulfurated to cysteine, in a two-step, pyridoxal phosphate (PLP)-dependent pathway; this pathway depends on a key supply of B_6, the PLP precursor. The transsulfuration rate-limiting reaction is catalyzed by cystathionine-β-synthase (CBS; EC 4.2.1.22), which catalyzes the condensation of serine with homocysteine, thus yielding cystathionine, a non-protein amino acid intermediate. Cystathionine is, in turn, hydrolyzed to α-ketobutyrate and cysteine by cystathionine-γ-lyase (cystathionase; CSE; EC 4.4.1.1). Cysteine is important for its role as a substrate for glutathione (GSH) biosynthesis. Both CBS or CSE are also bi-functional enzymes, in that they can

independently use cysteine to synthesize hydrogen sulfide (H_2S; evidenced by a star), the third gaseous vasodilator, after nitric oxide and carbon monoxide, thus yielding lanthionine as a side product. Lanthionine is regarded as a novel uremic toxin [10]. Dashed circle indicates inhibition. All enzymes are indicated in hexagonal boxes.

Compliance with ethical standards

Conflict of interest Author AFP has received research funding from Gnosis spa, and EUTox. DI holds a 3rd mission collaboration with Gnosis, spa through a contract stipulated with the Department of Precision Medicine, University "Luigi Vanvitelli".

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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