

Circulating Homocysteine Is An Inflammation Marker And A Risk Factor of Life-Threatening Inflammatory Diseases

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Deficiency in vitamin B₆, B₁₂ or folate is the major cause of hyperhomocysteinemia. Since inflammation promotes cell proliferation at the expense of excess amount of vitamins, therefore, hyperhomocysteinemia may indicate the presence of inflammation. Moreover, inflammation enhances the synthesis of nitric oxide, which again produces hyperhomocysteinemia through binding with vitamin B₁₂. Consequently, varying degrees of hyperhomocysteinemia are detectable in all inflammatory diseases. Hyperhomocysteinemia is also considered as a risk factor for inflammatory diseases including life-threatening cardiovascular disease, stroke, renal failure and cancer. It should be noted that hyperhomocysteinemia not only is produced from inflammation, but the oxidative stress generated from hyperhomocysteinemia will again promote inflammation. As a result, elevated homocysteine and inflammation markers are frequently being detected at the same time but are not correlated with each other. On the other hand, because of their different inflammatory pathways, measuring simultaneously the homocysteine and inflammation markers will improve the overall sensitivity of detection.

Key words: *Hyperhomocysteinemia, inflammation marker, risk factor, inflammatory diseases, vitamin deficiency*

As Marker of Inflammation

Listed below are reports from literature supporting the fact that elevation of circulating homocysteine is associated with inflammation and may be considered as a marker of inflammation:

Vitamine deficiency

In most cases, hyperhomocysteinemia is the result of the vitamin deficiency in B₆, B₁₂ or folate, or a combination of them [1]. Because these vitamins are essential cofactors of key enzymes related to the metabolism of homocysteine (Diagram 1), deficiencies of these vitamins would impair the activity of these enzymes and lead to the accumulation

of homocysteine and the appearance of hyperhomocysteinemia. For example, decreased blood levels of folate, vitamin B₆, or vitamin B₁₂ often accompany the onset of hyperhomocysteinemia in patients with inflammatory disease such as rheumatoid arthritis. Because borderline deficiencies of these vitamins are relatively common in elderly, this also explains why mild hyperhomocysteinemia is frequently found in people with old age [2].

It is well known that vitamin deficiency can be derived from cell proliferation. Since inflammation promotes cell proliferation at the expense of excess vitamins leading to hyperhomocysteinemia, therefore, homocysteine can be used as a marker of inflammation to indicate the presence of inflammation. It should be noted that the nuclear transcription factors (NF- κ B) not only is responsible for regulating the transcription of genes involved in inflammatory responses [3] but also with the regulation of cell proliferation [4].

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Effect of increased nitric oxide (NO) production by inflammation

Nitric oxide, through binding of vitamin B₁₂, will raise the level of circulating homocysteine by inhibiting the enzymatic activity of methionine synthase in the remethylation reaction (Diagram 1). Since inflammation increases the synthesis of nitric oxide [5], therefore, it further support the fact that circulating homocysteine is a marker related to inflammation.

Reduction by anti-inflammatory medications

Association of hyperhomocysteinemia with inflammation is also supported by the fact that the level of circulating homocysteine can be effectively reduced by the administration of anti-inflammatory medications. Several anti-inflammatory compounds such as resveratrol, aspirin, salicylic acid and atorvastatin have all been shown to down-regulate the release of homocysteine from stimulated human peripheral blood mononuclear cells [6,7].

Hyperhomocysteinemia in Inflammatory Diseases

Because of the association of inflammation with the elevation of circulating homocysteine, it is not surprising that varying degrees of hyperhomocysteinemia are detectable in all inflammatory diseases. In fact, detection of hyperhomocysteinemia has been reported not only in patients with well-known inflammatory diseases such as rheumatoid arthritis [8], inflammatory bowel disease [9], but also in psoriasis [10], a chronic inflammatory skin disease. Hyperhomocysteinemia has also been reported in patients with cardiovascular disease [11], with type 2 diabetes [11], with chronic kidney disease [12] and cancer [13,14]. All these clinical disorders were only being recognized as inflammatory diseases in recently years.

Since multiple risk factors are present today that will elicit inflammation [15], mild hyperhomocysteinemia is expected to be frequently detected even among asymptomatic healthy individuals who either smoke or are just exposed to air pollutants [16]. For the same reason that individuals who are obese, a major risk factor of chronic inflammation, are also expected to show mild hyperhomocysteinemia [17]. Because chronic inflammation is often associated with old age, it is not surprising to find mild hyperhomocysteinemia among elderly [18]. It should be noted that mild hyperhomocysteinemia has been detected in individuals who take common drugs, such as lipid-lowering drugs (like fibrates and niacin) or oral hypoglycemic drugs (like metformin), insulin, drugs used in rheumatoid arthritis, and anticonvulsants [19]. It appears that circulating homocysteine is a sensitive

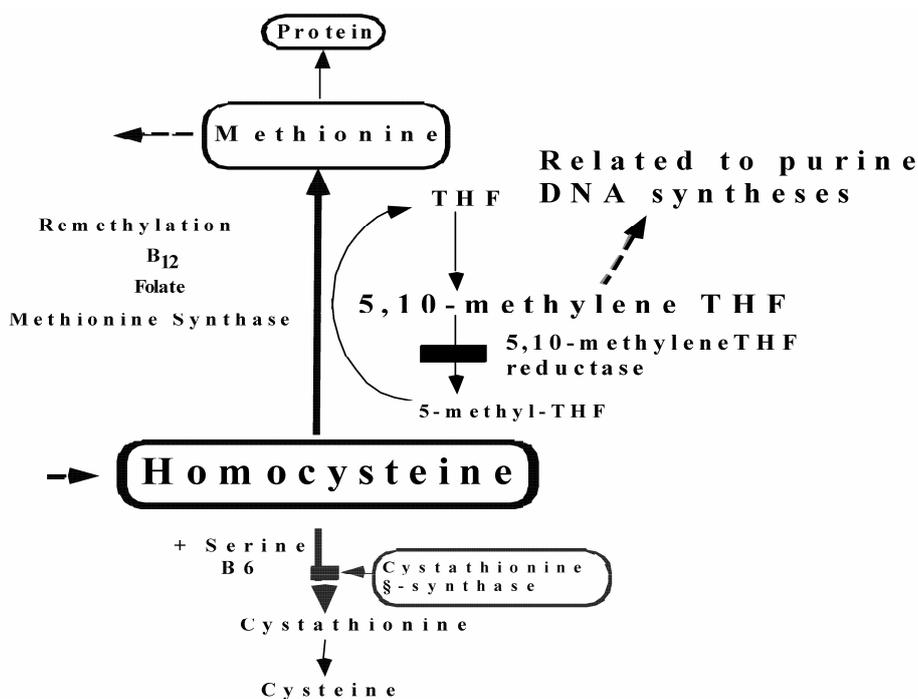


Diagram 1

marker reflecting the presence of inflammation.

Association with Markers of Acute and Chronic Inflammation

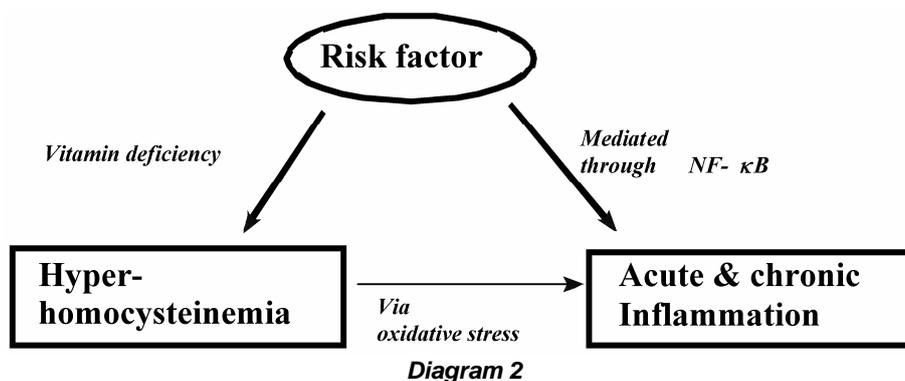
There have been many reports in the recent literature finding the presence of acute and chronic inflammation and hyperhomocysteinemia were in the same individuals [20]. However, it has also been noted in a number of reports that these markers of inflammation were not correlated with the circulating levels of homocysteine [21]. It is most likely, as shown in the Diagram 2, that it is because various inflammatory risk factors not only will initiate the sequential inflammatory pathway including acute and chronic inflammation but will also produce hyperhomocysteinemia through vitamin deficiency, a different pathway. However, it has also been reported that the oxidative stress derived from hyperhomocysteinemia will again induce acute and chronic inflammation via the regulation of NF- κ B transcription factor [22,23]. As pointed out by Mansoor et al. and by Li et al. that expression of adhesion molecules, the early phase of chronic inflammation, can be induced by hyperhomocysteinemia. Because there are two different inflammatory pathways, one for the production of hyperhomocysteinemia and one for the generation of elevated markers of acute and chronic inflammation (Diagram 2), therefore, the elevated circulating homocysteine and elevated markers of acute and chronic inflammation do not always correlate with each other even though they have been detected at the same time. It is also believed that the appearance of the number and level of all these inflammation markers will depend on how long does the inflammatory factor present. It should also be noted, as we have discovered in our early liposuction study [24], that short-lived acute inflammation would cause the elevation of acute phase proteins such as C-reactive proteins (CRP) but not circulating homocysteine.

The Diagram 2 also explains why investigators [25] failed to reduce the level of inflammation markers when they had successfully lowered the level of circulating homocysteine with the administration of vitamins. As it is depicted in the Diagram 2 that as long as the risk factor (s) is not removed, the risk factor would continue to generate acute and chronic inflammation regardless whether there is vitamin deficiency or not.

As A Risk Factor

Hyperhomocysteinemia has long been considered as a risk factor for the development of coronary, cerebral and peripheral vascular disease and deep-vein thrombosis [26]. Hyperhomocysteinemia has been known to exert its detrimental effects through induction of the acute and chronic inflammation pathway such as endothelial dysfunction, leukocyte adhesion, oxidative stress and the reduction of nitric oxide bioavailability, all components [27]. However it should be noted these detrimental effects are caused by the oxidative process produced during the oxidation of homocysteine (RSH) released from the cell into the blood circulation not by the circulating homocysteine (RS-SR') it self. We know that homocysteine produced inside cells contains active sulfhydryl (-SH) group. When the homocysteine (RSH) released from the cell into the blood circulation, it is oxidized forming disulfide bond (-S-S-) with another homocysteine (RSH) or protein (PSH), at the same time superoxide free radical is released. This then leads to oxidative and nitrosative stress and initiates inflammation via NF- κ B regulation. Therefore, the product of oxidized homocysteine (RSH) (so called circulating homocysteine (RS-SR') found in hyperhomocysteinemia) is not a risk factor. RS-SR' does not lead to any damage.

As a risk factor, the risk of hyperhomocysteinemia is not limited to heart disease. The risk can be extended further to include other inflammatory diseases such as



cardiovascular disease, Alzheimer's dementia, inflammatory bowel disease and even pregnancy complications, neural tube defects [28] and osteoporotic fracture [29]. Because inflammation is now recognized to play a critical role in the pathogenesis and progression of all these life-threatening diseases it is not surprising that hyperhomocysteinemia is detectable in diseases including stroke, renal failure and cancer.

As depicted in Diagram 1, the risk of hyperhomocysteinemia with cancer is not only related to the gene mutation, which may be derived from the progression of the acute and chronic inflammation but may also from the folic acid deficiency accompanied the elevated homocysteine. Deficiency of folate will cause the intracellular incorporation of uracil, instead of thymidine, to DNA and lead to double-stranded DNA breaks [30, 31]

The risk of hyperhomocysteinemia may also be associated with the formation of homocysteine thiolactone by certain aminoacyl-tRNA synthetases during editing or proofreading reactions [32]. As reported by Jakubowski et al. that homocysteine thiolactone will acylate proteins, which may also contribute to some of the detrimental effects of hyperhomocysteinemia [33].

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血液中的同半胱胺酸是發炎指標 也是造成足以威脅生命之發炎疾病的危險因子

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缺乏維生素B₆、B₁₂或葉酸是造成高同半胱胺酸血症的主要原因。由於發炎反應會促進細胞增生，在增生過程中會消耗掉大量的維生素。因此，高同半胱胺酸血症可代表著體內有發炎的情形。此外，發炎反應也會增加一氧化氮的生成，一氧化氮會與維生素B₁₂結合，更促進了高同半胱胺酸血症的產生。目前已知，在幾乎所有的發炎疾病中都可偵測到不同程度的高同半胱胺酸血症。而高同半胱胺酸血症也可視為心血管疾病、中風、腎衰竭及癌症等嚴重發炎疾病的危險因子。值得注意的是，高同半胱胺酸血症不只是發炎反應的產物，它所造成的氧化壓力會反回去促進發炎反應的產生。所以經常可以在血液中同時偵測出同半胱胺酸與發炎標誌的升高，但是升高的量彼此之間沒有相關性。換句話說，因為同半胱胺酸與發炎標誌是經由不同的發炎途徑產生，同時檢驗二種標誌將有助於發炎反應的偵測敏感度。

關鍵詞：高同半胱胺酸血症、發炎標誌、危險因子、發炎疾病、維生素缺乏

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