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Association between Homocysteine, Systemic Lupus Erythematosus and Microalbuminuria

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Abstract:

At present, the relationship between serum homocysteine and microalbuminuria (MAU) in systemic lupus erythematosus (SLE) patients is still unclear. Therefore, the aim of our review article is to analyze the association between serum homocysteine and MAU in SLE patients.

Keywords: homocysteine, systemic lupus erythematosus and microalbuminuria.

Introduction:

Homocysteine is a sulfur-containing amino acid derived from the demethylation of an essential amino acid, methionine. It is an intermediate amino acid in the biosynthetic pathway able to carry out Met conversion into cysteine-C **(1).**

This molecule originates from catabolism of proteins or varied dietary sources, and its metabolism occurs by two main pathways: remethylation and transsulphuration **(2).**

The normal homocysteine concentration is 5 -13 μmol/L. Several factors are known to increase homocysteine level including older age, male gender, higher body weight, cigarette smoking, alcohol abuse, lower folic acid and vitamin B dietary intake, chronic renal disease, as well as certain medications such as diuretics and fibrate **(3).**

Hyperhomocysteinemia is a medical condition with abnormally high homocysteine level in the blood, classified into three categories according to the fasting homocysteine elevation extent: mild (14-24 μmol/L); moderate (25-100 μmol/L); severe (>100 μmol/L) **(4).**

Hyperhomocysteinemia is a trigger for many diseases, such as atherosclerosis, congestive heart failure, age-related macular degeneration, Alzheimer's disease and hearing loss. There are many studies showing a positive relationship between homocysteine level and various symptoms. High level of homocysteine can be the sole reason or an aggravating factor in numerous diseases for which causal links are not fully understood **(5).**

It was reported that serum homocysteine level is high in patients with ESRD **(6).**

Plasma homocysteine may also play a pivotal role in the development of hypertension-induced kidney damage, as plasma homocysteine levels are frequently increased in patients with renal failure, in addition to traditional risk factors as hypertension (HTN), diabetes mellitus (DM) and hyperlipidaemia **(7, 8).**

I. Homocysteine and systemic lupus erythematosus

Medical conditions characterized by systemic inflammation like SLE have been strongly associated with atherosclerosis. Evidence show that inflammation process is crucial for the development of accelerated atherosclerosis

in SLE. Therefore, it is plausible to assume that SLE inflammation It integrates four inflammatory biomarkers such as homocysteine, high-density lipoprotein (HDL), TNF-like weak inducer of apoptosis, and leptin and two risk factors (age and diabetes) **(9).**

Several studies have demonstrated the relationship between HHCys and SLE.

Timlin et al. (10) performed a retrospective review of patients who had both biopsy-proven lupus nephritis (class II-VI) and measured homocysteine levels and reported that of the 15 patients with lupus nephritis, 10 (33.33%) had elevated homocysteine levels. These patients with elevated serum levels of homocysteine have also primary atherogenic and prothrombotic properties.

Moreover, **Sam et al. (11)** performed a meta-analysis 36 articles including 2919 SLE patients and 3120 healthy controls. Results demonstrated higher HCY levels in patients with SLE than healthy controls, suggesting a possible role of HCY in the disease and that homocysteine is closely related to the mechanisms of SLE. The study also reveals a significant correlation between homocysteine levels and the various indexes of disease activity.

An earlier Russian study, **Reshetniak et al. (12)** studied a total of 125 participants and reported HHCys (> 15 mcg/l) was diagnosed in 82 of 125 (66%) patients; elevated levels of HHCys were related to development of thromboses.

In addition, a study conducted in Kuwait, **Refai et al. (13)** found that HHCys was detected in (61.8%) SLE patients. Those patients with elevated homocysteine concentration had a threefold increase in odds ratio of thrombotic events after adjusting for other risk factors.

II. Homocysteine and microalbuminuria

While numerous studies also showed that enhanced plasma homocysteine level is associated with increasing urinary albumin excretion in diabetic patients. There is also evidence supporting that homocysteine abundance is closely related to renal status in the elderly. These results all suggest that homocysteine is a marker of impaired renal function in diabetic patients. However, it remains unclear whether homocysteine accumulation is playing a causative role that precedes early renal injury, or is only a secondary effect caused by impaired renal function in diabetic patients **(14).**

On the other hand, microalbuminuria is considered to be a marker of endothelial dysfunction and is a predictor of CVD and mortality. Likewise, plasma homocysteine is a marker known to be associated with endothelial dysfunction and shown to predict CVD and mortality in epidemiological studies **(15).**

It has been suggested that microalbuminuria could only be observed after severe renal dysfunctions, such as impaired glomerular filtration barrier, have already occurred so that it is not a good early marker. Moreover, a large number of diabetic patients could still develop nephropathy even if their urinary albumin levels are normal, which challenges the sensitivity of albuminuria as a specific marker for nephropathy **(16).**

For instance, **Kuang et al (17)** studied 450 Chinese hypertensive subjects and multiple logistic regression modelling revealed that patients with a higher homocysteine level (> 15 μmol/L) were more likely to have microalbuminuria.

Likewise, a metanalysis by **Mao et al. (18)** found that diabetic patients with macroalbuminuria demonstrated a significantly higher level of plasma homocysteine than diabetics without albuminuria and diabetic nephropathy with microalbuminuria.

Moreover, **Cho et al. (19)** performed a case-control study in South Korea that included 887 patients with type 2 diabetes who did not have microalbuminuria at baseline. The results showed that 76 of them developed microalbuminuria during follow-up and that baseline plasma homocysteine concentrations and mean HbA1C levels

during follow-up were significantly higher in patients who developed microalbuminuria than in those who remained normoalbuminuric.

An earlier study by **Chico et al (20)** in Spain that included 165 diabetic patients also showed albumin excretion rate was proven to be the parameter with the strongest independent association with homocysteine. Patients with both types of diabetes and nephropathy had higher plasma homocysteine concentrations than those without nephropathy. This elevation plasma homocysteine was related to increases in the severity of the nephropathy.

III. Mechanism of hyperhomocysteinemia

The relationship between diabetes and HHCys is relatively complex. It is generally believed that secondary pathological changes caused by diabetes, such as renal dysfunction, often lead to elevated plasma homocysteine level, and the impact of diabetes itself on homocysteine needs further study. The possible mechanism is that glucose metabolism disorder and homocysteine metabolism worsen each other, resulting in the increase of homocysteine level **(21).**

The pathophysiological pathway linking homocysteine level and risk of (micro)albuminuria is unknown. Some evidence as we mentioned earlier suggests that HHCys enhances oxidative stress, which could induce endothelial and mesangial cell dysfunction **(22).**

Intact renal endothelial and mesangial cell function is important for regulating intraglomerular pressure and glomerular charge and size selectivity. Dysfunction of these cells may increase intraglomerular pressure and/or decrease glomerular charge and size selectivity and thus cause microalbuminuria. Alternatively, HHCys and (micro)albuminuria could be associated through a common pathophysiological pathway; e.g., inadequate vitamin B6, B12, and/or folate status could be the common antecedent leading to HHCys on the one hand and to the development of (micro)albuminuria on the other. However, there is no evidence that inadequate B-vitamin status can directly cause (micro)albuminuria. HHCys could also be indirectly related to (micro)albuminuria; ie, HHCys may influence another factor, such as blood pressure, which directly causes the development of (micro)albuminuria **(23).**

Homocysteine can cause endothelial cells (ECs) damage through various intracellular mechanisms. Such as induction of inflammation and cell death, interference with nitric oxide (NO) production, reactive oxygen species (ROS) accumulation and oxidative stress, cellular hypomethylation. There is a complex interaction between these mechanisms, which leads to a series of reactions in the local and circulation of AS lesions. In addition, abnormal lipoprotein metabolism major as an extracellular mechanism also causes ECs damage. Protein homocysteinylation can cause endothelial damage through both intracellular and extracellular mechanisms. A brief illustration of these mechanisms is shown in (Figure 1) and described in detail below **(21).**

The mechanism of homocysteine disturbance of NO synthesis is relatively complex, asymmetric dimethylarginine (ADMA) plays an important role in it, which is an endogenous inhibitor of NOS. Specifically, homocysteine post-translationally inhibits dimethylarginine dimethylaminohydrolase (DDAH) activity, the enzyme that degrades ADMA **(24).**

Therefore, homocysteine can cause ADMA to accumulate and inhibit NO synthesis. homocysteine can also inhibit NOS and reduce NO synthesis in ECs by activating protein kinase C (PKC). Reduced NO synthesis causes endothelial injury by aggravating oxidative stress and inflammation **(25).**

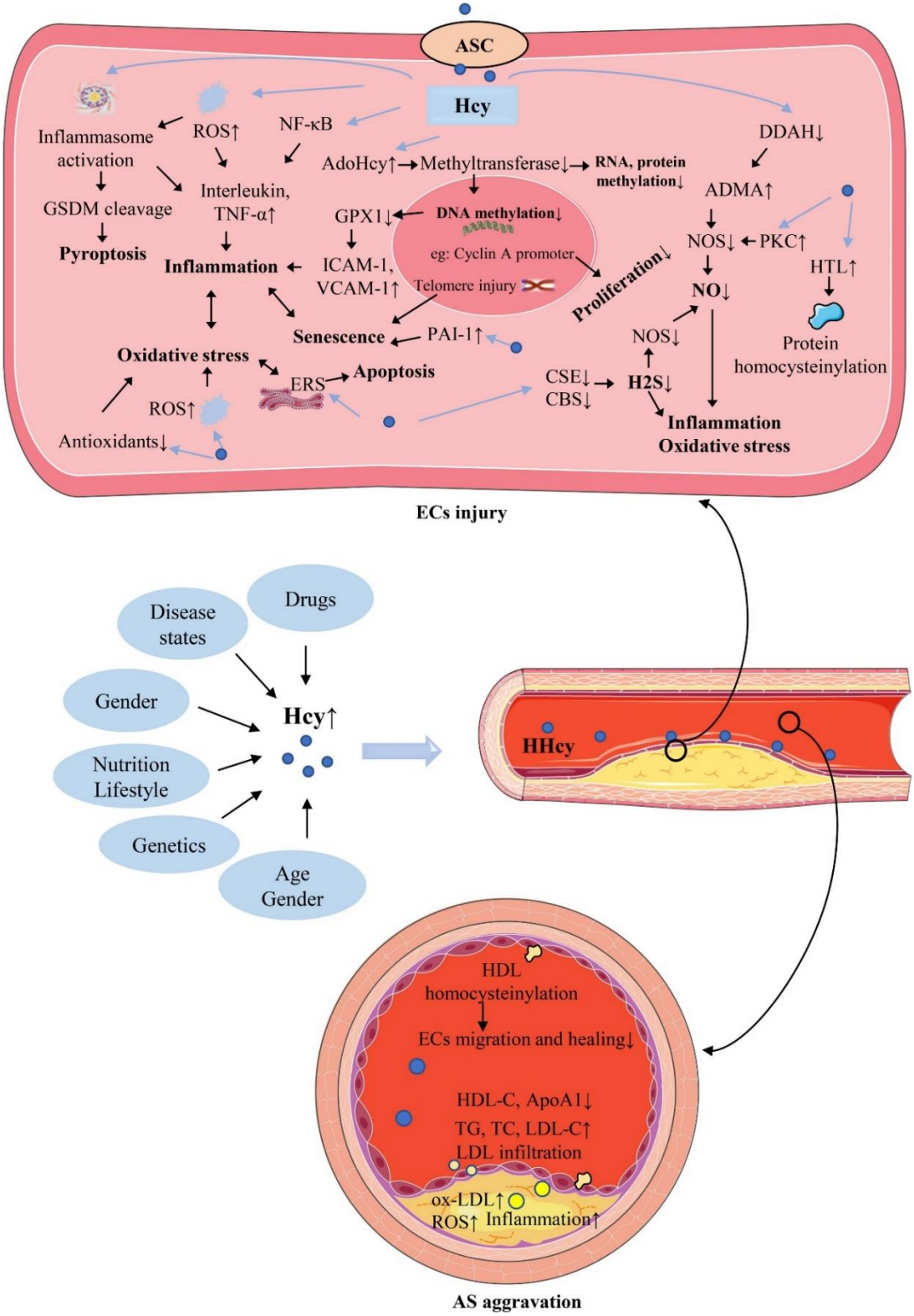

Figure (1): The causes of hyperhomocysteinemia and the mechanism of homocysteine–mediated endothelial cells injury and its consequences for atherosclerosis. ADMA: Asymmetric dimethylarginine, ApoA: Apolipoprotein A, AS:

Atherosclerosis, CBS: Cystathionine β-synthase, CSE: Cystathionine-gamma-lyase, DDAH: Dimethylarginine dimethylaminohydrolase, ECs: Endothelial cells, HDL-C: High-density lipoprotein, Hcy: Homocysteine, ICAM-1: Intercellular adhesion molecule-1, PKC: Protein kinase C, ROS: Reactive oxygen species, NF-κB: Nuclear factor kappa-B, PAI: Plasminogen activator inhibitor, TC: Total cholesterol, TG: Triglycerides, TNF-α: Tumor necrosis factor-α, VCAM-1: Vascular cell adhesion molecule-1 **(21).**

Other possible mechanisms by which homocysteine causes vascular injury include endothelial injury, DNA dysfunction, proliferation of smooth muscle cells, reduced activity of glutathione peroxidase and promoting inflammation **(26).**

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