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Homocysteine: From an Emerging Biomarker to a Functional Indicator of Endothelial Dysfunction

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Abstract

Homocysteine has emerged over recent decades as a significant biomarker associated with cardiovascular and cardiometabolic risk. Elevated plasma homocysteine levels have been linked to endothelial dysfunction, oxidative stress, inflammation, and prothrombotic states, all of which play a central role in the development and progression of atherosclerotic disease. This article provides an updated overview of the biological mechanisms through which homocysteine contributes to vascular damage, with particular attention to its impact on endothelial homeostasis.

The paper reviews current evidence on homocysteine metabolism, genetic and nutritional determinants of hyperhomocysteinemia, and its clinical relevance as a functional indicator rather than a mere biochemical marker. Special emphasis is placed on the interaction between homocysteine and B-group vitamins, oxidative pathways, and nitric oxide bioavailability, highlighting the multifactorial nature of endothelial impairment.

In addition, the role of targeted nutritional strategies and cardiovascular nutraceuticals in the management of elevated homocysteine levels is discussed, with reference to their potential contribution to primary and secondary prevention of cardiovascular disease.

Rather than presenting new experimental data, this article aims to integrate existing clinical and pathophysiological knowledge to support a more comprehensive interpretation of homocysteine in cardiovascular risk assessment.

Overall, homocysteine is proposed as a clinically relevant functional indicator of endothelial dysfunction, offering useful insights for personalized prevention strategies in cardiometabolic medicine.

Keywords: Homocysteine, endothelial dysfunction, cardiovascular risk, oxidative stress, cardiometabolic prevention, nutraceuticals

1. INTRODUCTION

Homocysteine has long been a subject of interest in cardiovascular research, initially regarded as a simple biomarker associated with atherothrombotic risk (Refsum et al., 1998). More recent evidence has broadened its clinical significance, demonstrating that hyperhomocysteinemia represents a factor actively involved in processes of endothelial dysfunction, oxidative stress, and disruption of thrombotic balance (Lentz, 2005).

Within the context of modern cardiovascular prevention, homocysteine emerges as a transversal indicator capable of integrating metabolic, nutritional, and genetic information, particularly in patients with residual cardiovascular risk not explained by traditional risk factors (Nygård et al., 1997).

2. BIOCHEMISTRY OF HOMOCYSTEINE AND METHYLATION METABOLISM

Homocysteine is a sulfur-containing amino acid produced endogenously during methionine metabolism (Refsum et al., 1998). It occupies a central position between two fundamental pathways: remethylation to methionine and transsulfuration to cysteine. Proper functioning of these pathways depends on the availability of folates, vitamin B12, and vitamin B6, as well as on the efficiency of the enzymes involved (Refsum et al., 1998).

Even mild alterations in this balance can lead to an accumulation of plasma homocysteine, reflecting an impairment of cellular methylation capacity and antioxidant defenses, particularly glutathione synthesis (Lentz, 2005).

3. MECHANISMS OF VASCULAR DAMAGE

Hyperhomocysteinemia exerts a direct effect on the vascular wall through multiple pathogenetic mechanisms, including:

- reduction of nitric oxide bioavailability, resulting in loss of endothelium-dependent vasodilation;
- increased production of reactive oxygen species, leading to lipid and protein oxidation;
- induction of a pro-inflammatory state through up-regulation of endothelial adhesion molecules;
- activation of the coagulation cascade and inhibition of fibrinolytic mechanisms.

These processes contribute to the progression of atherosclerosis and promote the formation of unstable plaques, increasing the likelihood of acute ischemic events (Lentz, 2005).

4. HOMOCYSTEINE AND CARDIOVASCULAR DISEASE

Numerous epidemiological studies have shown that an increase of 5 μmol/L in homocysteine levels is associated with a 20–30% increase in the relative risk of cardiovascular events (Homocysteine Studies Collaboration, 2002). This association is particularly evident in early ischemic heart disease, cerebrovascular disease, and peripheral arterial disease (Wald et al., 2002).

The effect of homocysteine is not isolated but synergistic with other risk factors such as dyslipidemia, hypertension, diabetes, and smoking, contributing significantly to the so-called residual cardiovascular risk (Clarke et al., 2010).

5. CLINICAL EVIDENCE AND LIMITATIONS OF INTERVENTION TRIALS

Large randomized trials investigating vitamin supplementation (NORVIT, HOPE-2, VISP) have demonstrated effective reductions in plasma homocysteine levels; however, they failed to show a clear reduction in major cardiovascular endpoints in the general population (Bønaa et al., 2006; Lonn et al., 2006).

These findings do not negate the clinical relevance of homocysteine but suggest that it functions more as a marker of metabolic dysfunction than as an isolated therapeutic target. Timing of intervention, the form of folates used, and appropriate patient selection appear to be crucial determinants of clinical efficacy.

6. APPLICATIONS IN CARDIOVASCULAR CLINICAL PRACTICE

Measurement of homocysteine is particularly useful in patients with early cardiovascular events, progression of atherosclerosis despite optimal lipid profiles, or unexplained thrombotic events (Refsum et al., 1998). In these contexts, homocysteine helps identify subclinical metabolic alterations and guide personalized nutritional and nutraceutical interventions.

Interpretation should always be integrated with assessment of folates, vitamin B12, vitamin B6, and, in selected cases, genetic profiling—particularly MTHFR polymorphisms (Nygård et al., 1997).

7. AI AS ACADEMIC SUPPORT: OPPORTUNITIES AND AMBIVALENCE

Despite these challenges, AI also offers significant opportunities for higher education. For lecturers and researchers, AI can automate repetitive tasks, support data analysis, and facilitate personalized learning environments (Zawacki-Richter et al., 2019). When used responsibly, AI can reduce cognitive overload and allow academic staff to focus on mentoring, dialogue, and conceptual development.

However, this supportive role must be carefully regulated. Without clear institutional guidelines, AI risks becoming a substitute for intellectual engagement rather than a tool that enhances it.

8. CONCLUSIONS

Homocysteine currently represents a functional biomarker of endothelial dysfunction and vascular vulnerability. More than a simple risk factor, it reflects a systemic imbalance between methylation metabolism, oxidative stress, and inflammation (Lentz, 2005).

Integrating homocysteine measurement into advanced cardiovascular assessment pathways allows for more refined risk stratification and supports a preventive and personalized medicine approach focused on pathophysiology rather than on the control of traditional parameters alone.

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