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CARDIOMETABOLIC INJURY INSIGHTS: A COMBINED BIOMARKER PERSPECTIVE USING HOMOCYSTEINE AND HS-TROPONINS

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Abstract. Cardiometabolic diseases represent a major global health challenge characterized by a complex interplay between metabolic dysfunction, vascular injury, chronic inflammation, oxidative stress, and progressive myocardial damage. In recent years, circulating biomarkers have become increasingly important for the early detection of subclinical cardiovascular injury and for improved risk stratification in cardiometabolic disorders. Among these biomarkers, homocysteine and high-sensitivity cardiac troponins (hs-cTn) have emerged as complementary indicators of vascular dysfunction and subclinical myocardial injury, respectively. Hyperhomocysteinemia contributes to endothelial dysfunction, oxidative stress, inflammation, thrombogenesis, and accelerated atherosclerosis, whereas hs-troponins provide highly sensitive detection of ongoing cardiomyocyte injury and myocardial stress. Experimental and clinical evidence increasingly supports the concept that combined assessment of homocysteine and hs-troponins may provide superior prognostic and diagnostic information compared with either biomarker alone. Mechanistic studies have demonstrated that homocysteine-mediated oxidative stress, mitochondrial dysfunction, protein homocysteinylation, and endothelial injury contribute to myocardial remodeling and cardiomyocyte damage associated with hs-troponin release. This review summarizes the historical foundations, molecular mechanisms, experimental evidence, and translational implications of combined homocysteine and hs-troponin assessment in cardiometabolic diseases. Particular emphasis is placed on pioneering discoveries by McCully and Jakubowski, as well as recent contributions from Djuric and coworkers investigating integrated biomarker approaches in experimental cardiometabolic models.
Keywords: biomarkers; cardiometabolic disease; high-sensitivity troponins; homocysteine; subclinical myocardial injury

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Introduction

Cardiometabolic diseases encompass a broad spectrum of interrelated disorders including obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disease (CVD). These conditions are among the leading causes of morbidity and mortality worldwide and are characterized by chronic low-grade inflammation, endothelial dysfunction, oxidative stress, and progressive myocardial injury [1]. Over the past decades, increasing attention has been directed toward identifying biomarkers capable of detecting early (or subclinical) cardiovascular injury before the development of clinically overt disease. Traditional biomarkers such as lipid profiles, glucose parameters, and inflammatory markers remain clinically valuable; however, they often fail to identify subclinical myocardial damage and early vascular dysfunction. Consequently, novel biomarkers capable of reflecting multiple pathophysiological pathways have become increasingly important in cardiovascular medicine. Homocysteine and high-sensitivity cardiac troponins (hs-cTnI and hs-cTnT) are among the most extensively investigated biomarkers in this context. Homocysteine reflects metabolic and endothelial disturbances associated with oxidative stress and vascular injury, whereas hs-troponins represent highly sensitive indicators of ongoing cardiomyocyte damage [2]. Emerging evidence suggests that combined evaluation of these biomarkers may provide a more comprehensive assessment of cardiometabolic injury by integrating information regarding both vascular pathology and myocardial injury.

This narrative review summarizes current evidence regarding the role of homocysteine and hs-troponins in cardiometabolic disease, emphasizing historical discoveries, molecular mechanisms, experimental studies, translational perspectives, and clinical implications of integrated biomarker approaches.

Historical Foundations of Homocysteine-Mediated Cardiovascular Injury

Homocysteine itself was first isolated and identified in 1933 by Vincent du Vigneaud, an American biochemist who later received the Nobel Prize in Chemistry. The association between homocysteine and cardiovascular disease was firstly recognized through the pioneering work of Kilmer S. McCully, who described premature vascular lesions in children with inherited homocystinuria. In his landmark publication, McCully demonstrated that severe hyperhomocysteinemia was associated with diffuse arteriosclerotic lesions, endothelial injury, and thrombosis, leading to the formulation of the "homocysteine theory of arteriosclerosis" [3]. McCully subsequently proposed that homocysteine promotes vascular injury through oxidative stress, endothelial dysfunction, lipid peroxidation, and smooth muscle proliferation [4]. These concepts fundamentally changed the understanding of cardiovascular pathology by introducing metabolic (protein) toxicity as a major contributor to atherogenesis. A major mechanistic advance was later provided by Hieronim Jakubowski, whose studies identified homocysteine thiolactone as a highly reactive toxic metabolite capable of modifying proteins through N-homocysteinylation [5, 6]. Jakubowski demonstrated that protein homocysteinylation induces structural protein damage changing their functions (like fibrinogen), endothelial

dysfunction, inflammation, oxidative stress, and autoimmunity, thereby contributing to cardiovascular injury [7]. Importantly, homocysteine thiolactone has been shown to exert direct cardiotoxic effects through mitochondrial dysfunction, reactive oxygen species generation, apoptotic signaling, and impaired nitric oxide bioavailability. These mechanisms provide important molecular links between hyperhomocysteinemia and myocardial injury associated with elevated hs-troponin concentrations.

Homocysteine and Cardiometabolic Injury

Homocysteine is a semi-essential sulfur-containing amino acid formed during methionine metabolism. Homocysteine has an important physiological role in metabolism; it stores the sulfur molecule and transfers the methyl group. Under physiological conditions, homocysteine undergoes remethylation to methionine or transsulfuration to cysteine through vitamin B6-, vitamin B12-, and folate-dependent enzymatic pathways [8]. Elevated plasma homocysteine concentrations may result from genetic polymorphisms, nutritional deficiencies, aging, chronic kidney disease, diabetes mellitus, and adverse lifestyle factors. Hyperhomocysteinemia is now recognized as an important contributor to endothelial dysfunction and cardiovascular pathology. Several mechanisms have been implicated in homocysteine-mediated vascular injury. Homocysteine increases reactive oxygen species generation, reduces nitric oxide bioavailability, impairs endothelial-dependent vasodilation, and promotes lipid peroxidation [9]. In addition, homocysteine activates inflammatory signaling pathways including nuclear factor kappa B (NF-κB), resulting in increased expression of cytokines, adhesion molecules, and pro-inflammatory mediators [10]. Experimental evidence further demonstrates that homocysteine contributes to mitochondrial dysfunction, cardiomyocyte apoptosis, extracellular matrix remodeling, and myocardial fibrosis. These alterations play important roles in the development of arterial stiffness, coronary artery disease, heart failure, and cerebrovascular disease [11]. Moreover, homocysteine thiolactone-mediated protein homocysteinylation contributes to impaired lipoprotein metabolism, thrombogenesis, inflammatory activation, and vascular injury, thereby linking metabolic dysfunction with cardiovascular pathology. Interestingly, neurovascular complications were evaluated in patients with inflammatory bowel disease, both of venous and arterial type. Pathogenic mechanisms of these vascular complications are complex, low serum folate levels, of vitamin B6 and B12 being associated with elevation of homocysteine levels, high activation of platelets and microvascular endothelial dysfunction [12]. However increased level of homocysteine is toxic, and its thiolactone metabolites are very toxic. Homocysteine and its thiolactone metabolites interact with other molecules in the body including proteins (ie. fibrinogen), lipid molecules (ie. LDL, HDL/PON-1) etc. Although it is known that micronutrients deficit in vitamins B6, folate and B12 lead to hyperhomocysteinemia especially following high methionine intake, administration of folic acid and/or vitamin B6 have shown mild favorable cardioprotective (or paradoxical) effects in used experimental cardiometabolic models in rats. Although homocysteine levels correlate with severity of coronary artery disease it is not quite clear if it is a biomarker of subclinical myocardial injury. From translational point of view homocysteine can be considered as an indirect epigenetic biomarker because in animal

hyperhomocysteinemia altered epigenetic marks were registered: oxidative stress, decreased SAM/SAH ratio ("changed dynamic balance"), decreased (or changed) DNA methylation, RNA- and histone modifications. In certain clinical cohorts, there is a need to perform advanced detection of the methylation process with the determination of homocysteine and the related B vitamins.

High-Sensitivity Troponins as Biomarkers of Subclinical Myocardial Injury

Cardiac troponins are regulatory proteins involved in calcium-mediated interactions between actin and myosin within cardiomyocytes. Troponin I and troponin T are highly specific indicators of myocardial injury. The introduction of high-sensitivity assays has revolutionized cardiovascular diagnostics by enabling detection of extremely low circulating troponin concentrations [13]. Although hs-troponins are primarily used for diagnosing acute myocardial infarction, numerous studies have demonstrated detectable elevations in chronic cardiometabolic conditions including obesity, hypertension, diabetes mellitus, metabolic syndrome, chronic kidney disease, and heart failure [14]. The mechanisms responsible for chronic low-grade hs-troponin elevation include subclinical ischemia, oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, increased myocardial wall stress, and microvascular injury. Importantly, hs-troponins may identify ongoing cardiomyocyte damage even in asymptomatic individuals and are strongly associated with increased long-term cardiovascular risk and mortality. Consequently, hs-troponins have emerged as highly sensitive biomarkers for detecting subclinical myocardial injury in cardiometabolic disorders.

Synergistic Relationship Between Homocysteine and hs-Troponins

Increasing evidence suggests that homocysteine and hs-troponins reflect interconnected pathophysiological pathways in cardiometabolic disease. Homocysteine-mediated oxidative stress, endothelial dysfunction, inflammation, and vascular injury may contribute to myocardial ischemia and cardiomyocyte damage, ultimately leading to increased hs-troponin release.

Experimental studies demonstrate that hyperhomocysteinemia induces myocardial fibrosis, ventricular remodeling, mitochondrial dysfunction, and apoptotic signaling pathways involving oxidative injury and caspase activation [15]. These mechanisms may explain chronic low-grade myocardial injury detectable by hs-troponin assays. It has been proposed that simultaneous evaluation of homocysteine and hs-troponins may improve cardiovascular risk prediction by combining information regarding endothelial dysfunction and myocardial injury [16]. Experimental studies from the same research group demonstrated that homocysteine-related compounds impair coronary flow, alter cardiac contractility, and increase oxidative stress markers in isolated rat hearts [17]. Additional investigations showed that homocysteine thiolactone modulates NMDA receptor activity and contributes to oxidative myocardial injury and changed cardiac excitability, further supporting mechanistic links between hyperhomocysteinemia and cardiomyocyte dysfunction [18]. From personal research on rat heart, aorta and brain Djuric et al. confirmed certain effects following DL-homocysteine or DL-homocysteine

thiolactone application: decreased heart rate, increased vasoconstriction, pro-arrhythmogenesis, increased NMDA stimulation, inhibition of Na^+ K^+, ATP-ase enzyme activity, inhibition of acetilcholinesterase activity, increase activities of matrix metalloproteinases, decrease of myocardial oxygen consumption, increase ROS/RNS production, disturbed RSS/RCS production, increased content of collagen (remodelling), pro-inflammation, and pro-thrombogenesis [19, 20].

Clinical studies additionally demonstrate positive correlations between elevated homocysteine and hs-troponin concentrations in patients with acute coronary syndromes, diabetes mellitus, heart failure, and chronic kidney disease. Combined elevation of these biomarkers is frequently associated with worse cardiovascular outcomes and increased mortality risk. Associations between homocysteine metabolism, subclinical myocardial injury, and cardiovascular mortality were also evaluated in subjects without CVD. Plasma tHcy, not folate or vitamin B12, is significantly associated with elevated hs-cTnT, hs-cTnI, and NT-proBNP in adults without CVD. Subclinical myocardial injury may substantially mediate Hcy-related cardiovascular mortality risk [21].

Experimental and Translational Perspectives

Experimental cardiometabolic models have substantially improved understanding of the relationship between hyperhomocysteinemia and myocardial injury. Animal studies demonstrate that elevated homocysteine concentrations induce endothelial dysfunction, oxidative stress, ventricular hypertrophy, myocardial fibrosis, and impaired cardiac metabolism. In rat model of experimental hyperhomocysteinemia, aerobic exercise modulated cardiac matrix metalloproteinase activity, oxidative stress markers, and metabolic enzyme activity, indicating the importance of lifestyle interventions in attenuating cardiometabolic damage [22]. The same research group also investigated folic acid supplementation in monocrotaline-induced heart failure models, demonstrating improvements in oxidative stress parameters, cardiometabolic biomarkers, and myocardial histopathology. These findings support the hypothesis that homocysteine-lowering strategies may exert cardioprotective effects beyond simple reduction of circulating homocysteine concentrations [23]. Furthermore, experimental research on homocysteine-related cardiovascular pathology in diabetic rat model, particularly through studies investigating homocysteine, oxidative stress, myocardial damage, endothelial dysfunction, and the protective role of B vitamins such as pyridoxine and folic acid were also done [24]. Further investigations in isoprenaline-induced myocardial injury models demonstrated that modulation of translocator proteins and nitric oxide synthase pathways influences inflammatory and oxidative biomarkers associated with myocardial damage [25]. Collectively, these experimental and translational findings support the concept that integrated biomarker approaches combining homocysteine and hs-troponins may improve early detection and monitoring of cardiometabolic injury.

The Importance of Environmental and Nutritional Factors in the Pathogenesis of Cardiovascular Diseases: Homocysteine in Focus

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide (especially in Central and Eastern Europe), and modern research approaches increasingly point to the complex interaction of genetic, epigenetic, environmental and nutritional factors in their pathogenesis. Traditional risk factors, such as hypertension, dyslipidemia, and smoking, are now viewed in the broader context of environmental and dietary influences. Environmental factors, including air pollution, exposure to heavy metals and organic compounds, noise, electromagnetic radiation, and climate change, contribute to the development of endothelial dysfunction, oxidative stress, and systemic inflammation. Endothelial dysfunction represents an early and reversible disturbance of cardiovascular homeostasis and is a key pathogenetic mechanism in the development of cardiovascular and metabolic diseases. It is characterized by altered bioavailability of nitric oxide (NO) and other gasotransmitters (H_2S, CO), reduced vasodilation, prooxidative, proinflammatory and prothrombotic phenotype of the endothelium. Among the most significant causes of these processes are oxidative stress and the semi-essential amino acid homocysteine. Elevated concentration of homocysteine (hyperhomocysteinemia) can occur for nutritional, genetic and iatrogenic reasons, as well as in chronic diseases and metabolic disorders [26]. It is associated with increased production of reactive oxygen species (ROS) and other reactive species (RNS, RHS, RCS), decreased activity of endothelial NO-synthase (eNOS), oxidation of lipids and proteins, and activation of inflammatory mechanisms. Oxidative stress further disrupts the balance between vasodilator and vasoconstrictor factors, promotes inflammation of the vascular wall, proliferation of smooth muscle cells and remodeling of blood vessels, which contributes to the development of hypertension, atherosclerosis, insulin resistance, diabetes, and leads to myocardial infarction, stroke, heart failure and peripheral circulation diseases. Nutritional factors have a dual role — as protective and as risky. Inadequate intake of micronutrients (e.g. folic acid, vitamins B6 and B12) is associated with homocysteine metabolism disorders, the development of hyperhomocysteinemia, oxidative stress, inflammation, endothelial dysfunction and atherosclerosis, while a diet rich in saturated fats, trans-fats and refined sugars contributes to the development of metabolic syndrome with similar consequences. In contrast, the Mediterranean diet, rich in fruits, vegetables, whole grains and omega-3 fatty acids, as well as moderate physical activity, show protective effects. Modern concepts also point to the role of intestinal microbiota, epigenetic modifications and the interaction between nutritional and environmental factors, which opens up space for personalized prevention and therapy of cardiovascular diseases. Integrating this knowledge into daily practice is a key step towards more effective control of cardiovascular risk.

Clinical Implications and Future Directions

The growing prevalence of cardiometabolic disorders highlights the need for sensitive biomarkers capable of detecting early cardiovascular injury and improving risk stratification. Combined assessment of homocysteine and hs-troponins may provide complementary information regarding vascular dysfunction and myocardial damage, thereby enabling more comprehensive cardiovascular evaluation. However, several

challenges remain. Homocysteine concentrations are influenced by nutritional status, renal function, genetic polymorphisms, and age, whereas hs-troponins levels may vary according to assay sensitivity and comorbid conditions. Standardization of biomarker thresholds and establishment of clinically relevant cut-off values remain important objectives for future research. Future studies should focus on prospective multicenter validation of integrated biomarker strategies, longitudinal monitoring of cardiometabolic patients, and incorporation of biomarker profiles into precision medicine approaches. Integration with imaging modalities, genomic profiling, metabolomics, and artificial intelligence-based risk prediction models may further improve cardiovascular prevention and individualized therapeutic strategies.

Conclusions

Homocysteine and high-sensitivity troponins represent complementary biomarkers reflecting interconnected mechanisms of cardiometabolic injury. Homocysteine primarily reflects endothelial dysfunction, oxidative stress, inflammation, and vascular pathology, whereas hs-troponins provide highly sensitive detection of ongoing cardiomyocyte injury. Historical discoveries by McCully and Jakubowski established the conceptual and molecular foundations of homocysteine-mediated cardiovascular injury, while contemporary investigations by others further emphasized the translational relevance of integrated biomarker approaches in cardiometabolic disease. Increasing experimental and clinical evidence supports the concept that combined evaluation of homocysteine and hs-troponins may improve early detection of subclinical cardiovascular injury, enhance risk stratification, and facilitate individualized preventive and therapeutic strategies. Continued multidisciplinary research is essential to further clarify the mechanistic interactions and clinical utility of these biomarkers in modern cardiovascular medicine.

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Competing interests

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