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Homocysteine as a Risk Biomarker for Chronic Cardiovascular and Neurodegenerative Diseases

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Abstract

Homocysteine is an amino acid metabolite that has been increasingly recognized as a significant biomarker for the risk of various chronic diseases, including cardiovascular diseases (CVDs) and neurodegenerative conditions. Elevated homocysteine levels are associated with endothelial dysfunction, oxidative stress, and inflammation, which are pivotal in the development and progression of these diseases. Although its role in CVDs has been widely studied, the relationship between homocysteine and neurodegenerative diseases remains an area of active research.

Keywords: Homocysteine, Cardiovascular Diseases, Neurodegenerative Diseases, Lipid Profile, Inflammatory Markers

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الهوموسيستين كمؤشر حيوي لخطر الإصابة بأمراض القلب والأوعية الدموية المزمنة والأمراض العصبية التنكسية

اسامة اكرم محسن [1] ، زينب محمد فرحان [2]

المستخلص

الهوموسيستين هو مُستقلب حمض أميني، يُعترف به بشكل متزايد كمؤشر حيوي هام لخطر الإصابة بأمراض مزمنة مُختلفة، بما في ذلك أمراض القلب والأوعية الدموية والحالات العصبية التنكسية. يرتبط ارتفاع مستويات الهوموسيستين بخلل وظيفي في بطانة الأوعية الدموية، والإجهاد التأكسدي، والالتهاب، وهي عوامل محورية في تطور هذه الأمراض وتفاقمها. على الرغم من أن دوره في أمراض القلب والأوعية الدموية قد خضع لدراسة واسعة النطاق، إلا أن العلاقة بين الهوموسيستين والأمراض العصبية التنكسية لا تزال مجالًا للبحث النشط.

الكلمات المفتاحية: الهوموسيستين، أمراض القلب والأوعية الدموية، الأمراض العصبية التنكسية، مستوى الدهون، العلامات الالتهابية

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Introduction

Epidemiological studies have greatly expanded the understanding of homocysteine as a risk factor for CVD over the past fifty years.

it is now considered a risk factor for a wide array of diseases or conditions, spanning from conception to death. It is generally safer to refer to elevated tHcy as a biomarker, as the term ‘risk factor’ often suggests a causal connection. A causal connection necessitates much more robust evidence, usually meeting the Bradford Hill criteria of causation [1].

The most crucial point is that data derived from clinical trials should provide evidence that reducing homocysteine levels will avert a disease. This opinion piece aims to enumerate the diseases for which homocysteine is regarded as a prognostic biomarker and to outline the evidence indicating that reducing homocysteine levels can

prevent certain diseases in some cases. The diseases that will be addressed in relation to the prevention theme include neural tube defects (NTDs), impaired childhood cognition, macular degeneration, stroke, and cognitive impairment or dementia. Since its discovery in 1932, homocysteine has been the subject of much speculation. Its chemical properties were similar to those of cysteine, thus the name homocysteine. This amino acid of interest was obtained by heating the amino acid methionine with sulphuric acid. To underscore the significance of this finding, one must reference the 1955 Nobel Prize in Chemistry awarded to Vincent du Vigneaud "For his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone" [2]. Homocysteine, which contains a sulfhydryl group and is an amino acid, serves as an intermediate in the normal production of the amino acids methionine and cysteine [3]. This amino acid is generated through the demethylation of dietary methionine, which is plentiful in animal protein sources [4]. In plasma, it exists in four different forms: approximately 1% circulates as free thiol, 70–80% is disulphide-bound to plasma proteins (primarily albumin), and 20–30% combines with itself to create the dimer homocysteine or with other thiols [5]. exhibited a marked rise in investigations aimed at comprehending the notoriety of this amino acid of interest more thoroughly as shown in Figure (1).

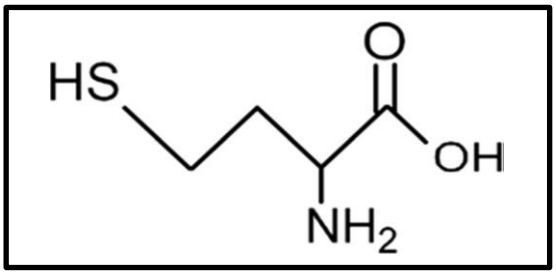

Figure (1) Structure of homocysteine

Homocysteine plays a crucial role in determining the methylation cycle. It gets methylated to methionine, that is subject to S-adenosylation and produces S-adenosylmethionine (SAM). The main methyl donor for all cellular methylation reactions is S-adenosylmethionine [6]. The combination of methionine and ATP results in the creation of SAM (S-Adenosylmethionine). The methyl group on the tertiary sulfur of SAM can be transferred, leading to the methylation of other substances. Since energy is lost during this methylation, the reaction cannot be reversed. SAH (S-adenosylhomocysteine) is produced as a result of the demethylation reaction [7]. as illustrated in figure (2).

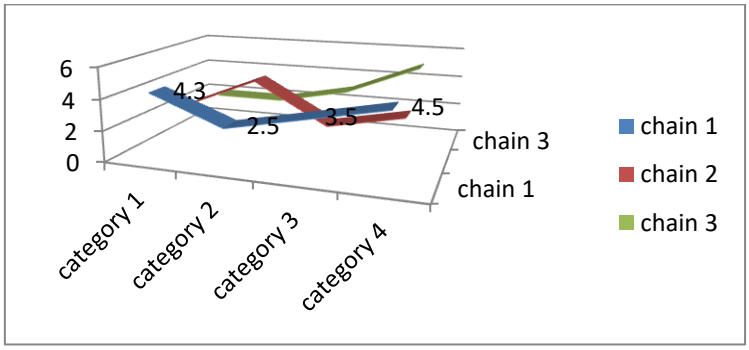

Figure (2): Total concentration of homocysteine in plasma of health humans

Methodology: A total of 100 patients with chronic cardiovascular and neurodegenerative diseases and 50 healthy controls were included. Blood samples were collected from all participants for the measurement of homocysteine levels, lipid profile (LDL/HDL ratio, TC/HDL ratio, non-HDL cholesterol), inflammatory markers (CRP, IL-6, TNF-α, IFN-γ), and neurological biomarkers (BDNF, NSE, S100B, MDA). Statistical analyses, including mean, standard deviation, and p-values, were used to compare the biomarkers between the two groups. Correlation analyses were conducted to explore the relationship between homocysteine and other biomarkers as illustrated in figure (3).

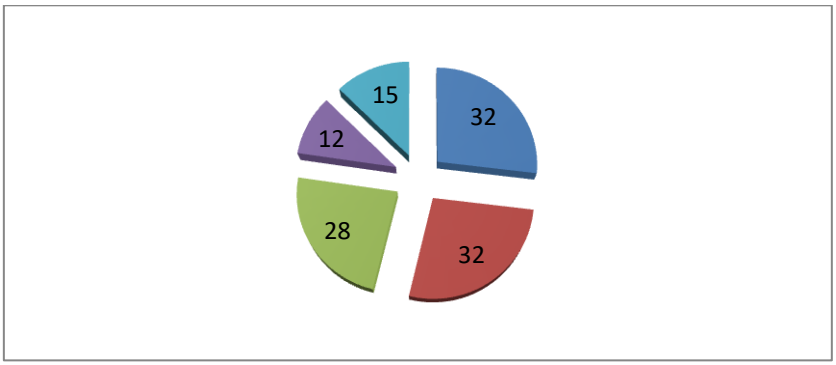

Figure (3) the connection between homocysteine and various other biomarkers

Results and Discussion

Homocysteine as a Risk Biomarker for Chronic Cardiovascular and Neurodegenerative Diseases as shown in table (1).

Table 1: Distribution of the samples according to their socio- demographic characteristics

Parameter	Patients (n = 100)	Control (n = 50)	p-value
Gender (Male/Female)	50 / 50	25 / 25	-
Age (years)	58.2 ± 9.1	56.7 ± 8.4	0.45
BMI (kg/m²)	28.9 ± 4.3	26.5 ± 3.9	0.02*
Smoking (%)	42%	26%	0.03*
Hypertension (%)	60%	34%	0.01*
Diabetes (%)	38%	20%	0.04*

The outcome illustrated in table (1) demonstrates Different mechanisms could explain the increased risk for smokers with high plasma homocysteine levels. Tachycardia, hypertension, and vasoconstriction can be induced by both nicotine and carbon monoxide independently. Moreover, both substances contribute to direct endothelial damage. It is associated with endothelial dysfunction, and research indicates that abnormal flow-mediated vasodilation can occur even with mild hyperhomocysteinemia (8). Smoking can also harm the vascular tree through mechanisms such as platelet activation, lipid peroxidation, increased tissue factor activation, elevated fibrinogen levels, and smooth muscle proliferation. That both of these risk factors can have comparable effects implies that they may interact in a way that causes vascular damage. As suggested by their name,

cardiovascular diseases (CVD) encompass conditions that impact the heart and blood vessels [9]. Cardiovascular disease is estimated to account for one third of global deaths, with its prevalence continuing to rise [10]. CVD is a disease with multiple contributing factors, making it difficult to pinpoint a single cause. The main factor relevant to this study is homocysteine. Coronary artery disease is characterized by the narrowing or blockage of the arteries and vessels that supply oxygen and nutrients to the heart [11]. Researchers have engaged in extended discussions about how much homocysteine should be considered a risk factor for cardiovascular diseases. There are arguments stating that only 50% of cardiovascular disease (CVD) can be linked to "classical" risk factors, indicating that "new" risk factors could greatly improve the predictive capabilities for CVD [12].This has been met with considerable criticism, and other studies show that up to three-quarters, or perhaps even a greater proportion, of coronary heart disease (CHD) events can be attributed to "classical" risk factors.

A risk factor must be strongly causally linked to the target disease in order to function as a screening tool. However, numerous authors question the existence of a connection between homocysteine levels and the risk of cardiovascular disease (coronary, heart, cerebrovascular, and peripheral artery diseases). exists a link between homocysteine and CVD. The Framingham risk score (FRS) is recognized as a vital tool for predicting coronary artery disease in individuals with common risk factors like dyslipidaemia, hypertension, diabetes mellitus (DM), and smoking. However, it appears that individuals with elevated homocysteine plasma levels may underestimate their risk of coronary artery disease [13].

Studies have shown that there is an association between moderate increases in homocysteine levels and the risk of cardiovascular diseases, which encompasses coronary, heart, cerebrovascular, and peripheral artery diseases. As illustrated in figure (4) and Table (2)

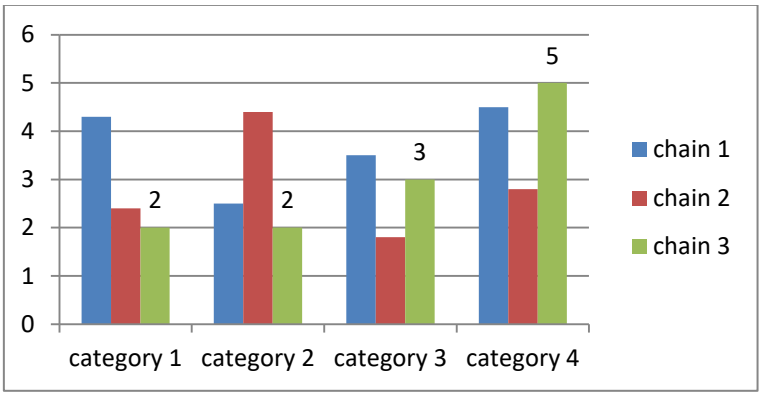

Figure (4): Correlation between plasma homocysteine concentrations in smokers and cardiovascular and other samples study

Table (2): Comparison of Homocysteine and Lipid Profile Between Group

Biomarker	Patients (n = 100)	Control (n = 50)	p-value
Homocysteine (µmol/L)	18.7 ± 4.5	10.2 ± 2.8	<0.001*
LDL/HDL Ratio	4.1 ± 1.0	3.0 ± 0.9	<0.001*
TC/HDL Ratio	5.3 ± 1.2	4.1 ± 0.9	<0.001*
Non-HDL Cholesterol (mg/dL)	171.8 ± 31.5	140.6 ± 28.2	0.01*

The criteria for identifying hyperlipidemia and homocysteine are presented in Table (2) and figure (5). At a P-value of less than **0.001**, there are substantial differences between the levels of homocysteine, high-density lipoprotein (HDL), and triglycerides. We also note considerable disparities between the concentrations of low-density lipoprotein (LDL) and triglycerides, with **P<0.001**. We also note considerable differences in the levels of high-density lipoprotein (HDL) and triglycerides, with a P-value of less than **0.001**. Our research demonstrated that plasma Hcy was significantly linked to conventional atherogenic lipids and, after adjusting for potential confounders, was also independently associated with RC levels beyond the influence of other lipids. This finding indicates that determining the dyslipidemia risk linked to Hcy, including both conventional lipids and residual RC risk, is clinically significant as we enter a new phase of targeting Hcy-lowering therapies to address dyslipidemia and potentially cardiovascular disease [14].

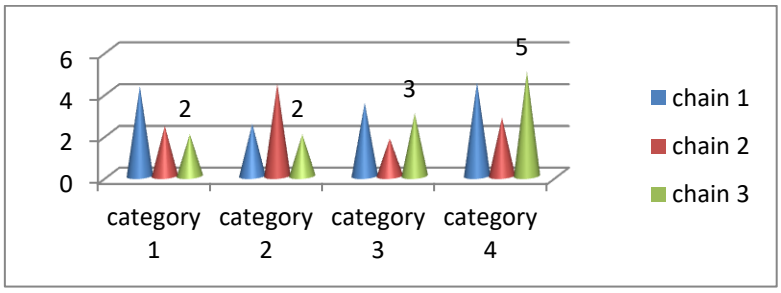

Figure (5): Comparison of Homocysteine and Lipid Profile

The advancement of research into the pathophysiology of Hhcy was contributed to by Hoffmann and Zhou [15]. Most of the harmful effects of Hcy can be attributed to the rise in oxidative stress and inflammatory response, as well as the decrease in nitric oxide bioavailability. These factors are the main mechanisms behind Hcy-related cellular toxicity, whether directly or indirectly. Hcy elevates oxidative stress through the production of free radicals and the suppression of glutathione peroxidase. Endothelial dysfunction can be caused directly by free radicals. Endothelial cells produce NO in reaction to the elevated Hcy level, promoting the creation of S-nitroso-homocysteine, which serves as a protective mechanism against the harmful effects of Hcy. However, when Hcy is present chronically, NO production tends to decline, leading to NO depletion. This depletion can stimulate smooth muscle proliferation, vasoconstriction, and the

adhesion and activation of leukocytes and platelets. Oxidative stress and nitric acid inhibition, along with the direct impact of Hcy on the cell, triggered a series of reactions that resulted in heightened levels of resistin, C-reactive protein (CRP), and cysteinyl leukotrienes—key indicators of inflammation—as well as increases in cholesterol, triglyceride, and LDL levels, and HMG-CoA reductase activity, which could contribute to cardiovascular diseases [16]. Pharmacological data indicated that Hcy stimulates the NMDA receptor. The NMDA receptor is associated with glutamate receptor whose activation causes the ion channel to open (enabling Na+ and Ca2+ to flow into the cell while K+ flows out). When homocysteine activates it, the NMDA receptor raises the influx of Ca2+ ions, resulting in a rapid and sustained phosphorylation of MAP kinase and a transient phosphorylation of c-AMP response element-binding protein (CREB). This process increases oxidative stress and ultimately results in neuronal death [17]. Under typical circumstances, the ongoing activation of CREB serves as a cell pro-survival factor. However, Hcy's temporary activation of CREB led to a prolonged activation of extracellular signal-regulated kinases (ERK). This illustrates that Hcy triggers a negative feedback loop, resulting in ERK's sustained activation and CREB's dephosphorylation, which promotes neuronal death. A further multivariant investigation involving 60% patients with hypertension identified a significant correlation between elevated Hcy levels and the carotid-resistive index, which serves as an estimate of the risk of cerebral infarction. It was determined that Hcy is the most powerful predictor of carotid RI ($p < 0.01$) [18]. Dong *et al.* reported an increase in total Hcy (tHcy) levels due to central retinal vein occlusion in a study involving a Chinesepopulation[19]. In one of their studies, Kwon *et al*. found that the rise in Hcy levels during acute stroke heightened the risk of early neurological deterioration. The findings of these studies indicate that the level of Hcy in the body is still elevated, and this should be regarded as a significant contributor to various vascular diseases [20] .This showed in table (3) and table (4) respectively.

Table 3: Inflammatory and Oxidative Stress Biomarker

Biomarker	Patients (n = 100)	Control (n = 50)	p-value
CRP (mg/L)	**9.8 ± 4.2**	**2.5 ± 1.1**	**<0.001***
IL-6 (pg/mL)	**17.5 ± 5.8**	**4.1 ± 1.3**	**<0.001***
TNF-α (pg/mL)	**12.3 ± 4.6**	**3.9 ± 1.5**	**<0.001***
IFN-γ (pg/mL)	**22.8 ± 6.0**	**9.6 ± 3.8**	**<0.001***

Table 4: Neurological Biomarkers Associated with Homocysteine Levels

Biomarker	Patients (n = 100)	Control (n = 50)	p-value
BDNF (pg/mL)	15.6 ± 3.8	25.2 ± 5.1	<0.001*
NSE (ng/mL)	18.4 ± 5.3	11.9 ± 3.6	<0.001*
S100B (ng/mL)	0.94 ± 0.32	0.62 ± 0.20	0.02*
MDA (nmol/L)	4.7 ± 1.2	2.8 ± 0.8	0.03*

Conclusions

Elevated homocysteine levels are strongly associated with increased cardiovascular and neurodegenerative disease risks. These findings highlight the potential of homocysteine as a biomarker for assessing disease progression and the need for interventions targeting homocysteine metabolism.

Recommendations

This study aims to evaluate the association between homocysteine levels and the risk of chronic cardiovascular and neurodegenerative diseases. Specifically, the study investigates the correlation of homocysteine with lipid profiles, inflammatory markers, and neurological biomarkers in patients diagnosed with cardiovascular and neurodegenerative diseases, compared to healthy controls

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