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Role of Homocysteine in Cardiovascular Disease

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ABSTRACT
Cardiovascular diseases are the most common diseases among the world wide in varying group of population. Elevated concentration of homocysteine (Hcy) in the blood plasma, hyperhomocysteinemia (HHcy), has been implicated in various disorders, including cardiovascular and neurodegenerative diseases. There are many risk associations with premature cardiovascular disease, some of which relate to lifestyle and are potentially modifiable. Hyperhomocysteinemia provide knowledge about which of the homocysteine and folate pathways are linked with disease leading to the high risk for arterial and venous occlusive disease in patients with severe hyperhomocysteinemia irrespective of the location of the defect. The in-depth knowledge on homocysteine is important to treat and reduce high homocysteine levels offering new possibilities for preventing cardiovascular disease.

KEYWORDS: Cardiovasculardiseases, homocysteine (hcy),hyperhomocysteinemia, remethylation, coronary heart disease (chd), vitamin b12 (cobalamin), endothelial dysfunction.

I. INTRODUCTION

Worldwide, cardiovascular conditions, primarily coronary heart disease (CHD), have reached pandemic proportions. More than 75% of these deaths took place in underdeveloped countries. Unlike in affluent countries, where CHD mortality is significantly dropping. Because of population ageing and lifestyle changes, the incidence and prevalence of heart illnesses, which are the leading cause of mortality worldwide, are anticipated to rise. Atherosclerosis risk factors are linked to cardiovascular disease mortality. They are categorised into modifiable (both traditional and new) and nonmodifiable risk factors (e.g., age, gender). Lifestyle (diet, smoking, lack of physical activity) and biochemical and physiological aspects (dyslipidaemia, diabetes, hypertension, obesity, metabolic syndrome, thrombotic factors, homocysteine, inflammatory indicators) are examples of modifiable factors.[1]

Coronary heart disease, cerebrovascular illness, rheumatic heart disease, congenital heart disease, and deep vein thrombosis are the most common cardiovascular diseases, while the most common outpatient cardiac complaints include chest pain, palpitation, dyspepsia, heart burn, DOE, AOE, and giddiness.

Since its discovery in 1932, homocysteine has been the subject of much speculation. Because of its molecular resemblance to cysteine, it was given the name homocysteine. In the normal production of the amino acids methionine and cysteine, homocysteine, a sulfhydryl-containing amino acid, is an intermediate product. Its function is to act as an intermediary in the metabolism of methionine. Homocysteine is found in a crossroads of metabolic pathways.[2]Demethylation of dietary methionine, which is prevalent in animal protein, produces this amino acid.[3] Multiple metabolic processes are required to produce homocysteine from methionine. Homocysteine can be converted to either L-cysteine or L-methionine.[4] Hyperhomocysteinemia (HHcy), or an elevated level of homocysteine (Hcy) in the blood plasma, has been linked to a variety of conditions, including cardiovascular and neurological diseases.[5]Homocysteine levels in a healthy individual range from 5 to 15 micromoles per litre (mmol/L). Homocysteine is almost entirely converted to proteins. The lining of the arteries that convey oxygen-rich blood is damaged when the level exceeds 50 mmol/L. High homocysteine levels usually indicate a vitamin B12 or folate

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shortage. The B vitamins, such as folate and vitamins B6 and B12, are essential for homocysteine metabolism. A lack of either of these B vitamins can cause an increase in total homocysteine (tHcy) levels in the blood, which has been linked to the development of cardiovascular disease.[3] Homocysteine was once thought to be a risk factor for atherosclerosis, which was mostly seen in children with extremely high serum homocysteine levels, as well as premature atherothrombotic disease, and basic studies showed that homocysteine can cause vascular damage by promoting platelet activation, oxidative stress, endothelial dysfunction, hypercoagulability, vascular smooth muscle cell proliferation, and endoplasmic reticulum stress.[6] Health-related habits, such as nutrition, smoking, and leading a sedentary lifestyle, have an impact on plasma homocysteine (Hcy). Plasma [Hcy] is influenced by genetic variables as well.[7] Plasma total homocysteine levels above a certain level have been suggested as a risk factor for cardiovascular morbidity and mortality. H2S levels rise as a result of hyperhomocysteinemia, which disrupts the adenosinergic system and, as a result, promotes CVD. High blood pressure is frequently linked to metabolic disturbances, which result in elevated blood cholesterol levels, which, like glucose in type 2 diabetes, damage blood vessels and lead to atherosclerosis. The renin-angiotensin-aldosterone system, oxidative stress, endothelial dysfunction, and increased endothelin-1 production are the key mechanisms that link the regulation of blood pressure and hypercholesterolemia, their mutual interaction, and their influence on the development of atherosclerosis[8] Because homocysteine can be reduced efficiently, inexpensively, and safely, the public health implications of homocysteine as a cardiovascular risk factor are particularly broad.[9]

B Vitamins—Homocysteine Pathway

B vitamins, such as folate (vitamin B9) and cobalamin (vitamin B12), are water-soluble vitamins that play a role in purine and pyrimidine synthesis, nucleoprotein synthesis, and erythropoiesis maintenance. Folic acid is made up of polyglutamates that are converted to monoglutamates in the intestine and then carried through the mucosal epithelia via a particular carrier. 5-Methyltetrahydrofolate is the circulating form of folic acid (5-MTHF). Vitamin B12 combines with salivary haptocorrin and is quickly liberated from cobalamin by pancreatic proteases in the duodenum after being consumed with nutrients like cobalamin.Cobalamin then attaches to an intrinsic factor released by the stomach's parietal cells, and when this complex reaches the distal ileum, it is endocytosed by enterocytes via cubilin. The plasma transport protein transcobalamin then transports cobalamin into the bloodstream. The glomerulus filters B12, however due to reabsorption in the proximal tubule, urine output is low. Cobalamin is broken down into two active forms in target tissues: adenosyl cobalamin in the mitochondria and methyl cobalamin in the cytoplasm. Methyl cobalamin is a methyl-transfer cofactor that allows homocysteine to be remethylated to methionine by the enzyme methionine synthase. Homocysteine is a thiol-containing amino acid derived from methionine metabolism that is not involved in protein synthesis. Homocysteine levels in the blood are affected by a variety of causes, including genetic changes in methionine processing enzymes or vitamin B12, B6, or folic acid deficiencies. Through a reaction catalysed by methionine synthase reductase, methionine is converted to S-adenosylmethionine (SAM) and ultimately to S-adenosylhomocysteine (SAH) (MTRR). SAM is a cofactor for methyl malonyl-CoA-mutase, one of the most significant methyl group donors, which is generated within mitochondria. This enzyme converts methyl malonyl-CoA to succinyl-CoA, which is an important step in the catabolism of several amino acids and fatty acids. Pyridoxine (vitamin B6) is also required as a cofactor in many processes. The end result of the hydrolysis of SAH to homocysteine and adenosine is homocysteine.This enzyme converts methylmalonyl- CoA to succinyl-CoA, which is an important step in the catabolism of several amino acids and fatty acids. Pyridoxine (vitamin B6) is also required as a cofactor in many processes. The end result of the hydrolysis of SAH to homocysteine and adenosine is homocysteine.[10]

HOMOCYSTEINE METABOLISM

Hcys undergoes two different metabolic processes which follow opposite directions: trasns sulfuration and re-methylation.

A. RE-METHYLATION:

The methionine synthase (MTR) enzyme catalyses homocysteine remethylation to methionine, which connects the folate cycle with homocysteine metabolism. Cobalamin (Cbl) is required as a cofactor for MTR, and the resultant complex, Cbl(I)MTR, binds the methyl group of 5-methyTHF to create methylcbl(III)MTR. Cbl(I) MTR is reconstructed after the methyl group is

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transferred to homocysteine, and it can receive another methyl group from 5-methyltetrahydrofolate (5-methylTHF). Cob(I) alamin can also be oxidised to cob(II)alamin, leaving an inactive Cbl(II)MTR complex behind. By reductive methylation with AdoMet as a methyl donor, methionine synthase reductase (MTRR) reactivates the Cbl(II)MTR complex. While the MTR enzyme is found throughout the body, the betaine homocysteine methyltransferase (BHMT), a homocysteine remethylation mechanism, is found mostly in the liver and kidneys.

B. TRANS-SULPHURATION:

During remethylation and transmethylation events, the homocysteine molecule is maintained, but in the trans sulphuration pathway, homocysteine is irreversibly destroyed to cysteine. The action of two vitamin B6-dependent enzymes, cystathionine synthase (CBS) and cystathionine-lyase, aids transsulphuration (CTH). CBS catalyses the condensation of homocysteine and serine to cystathionine, followed by CTH catalysing cystathionine hydrolysis to cysteine and -ketobutyrate. Human CBS is found in the liver, kidneys, muscle, brain, and ovary, as well as in the neurological and cardiac systems during early embryogenesis. Apart from its involvement in protein synthesis, cysteine glutathione is a powerful antioxidant and an important component in xenobiotic detoxification.[2]

REGULATION OF HOMOCYSTEINE

Homocysteine is either remethylated by methionine synthase or exported out of the cell in most tissues. The liver is the primary organ for degrading excess methionine and maintaining sufficient homocysteine levels, thanks to a unique set of enzymes such as MAT I/III, CBS, CTH, BHMT, and GNMT (glycine N-methyltransferase). MAT I/III, in contrast to MAT II, has a high Km. This leads in an increase in AdoMet in the liver due to elevated methionine levels. High levels of AdoMet suppress MTHFR and stimulate CBS activity, which is one of the key regulating mechanisms. Methionine excess is caused by increased quantities of AdoMet in the transsulphuration route of homocysteine breakdown. During methionine levels are low, such as when fasting, Ado Met does not activate CBS or block MTHFR, leading in homocysteine conservation via remethylation back to methionine.[2]

ROLE OF NUTRIENTS IN HOMOCYSTENEMIA

The absorption of three dietary vitamins, folic acid, vitamin B12 (cobalamin), and vitamin B6, is required for normal homocysteine metabolism (pyridoxal phosphate). Folic acid, also known as pteroylmonoglutamic acid, is a precursor of 5-methyl-THF, which is essential for optimal methionine synthase enzyme activity. Folates transfer 1-carbon moieties to diverse chemical compounds by boosting S-adenosylmethionine (SAM) levels, assisting in the production of essential macromolecules (e.g., purines) required for basic cellular functions including cell development and proliferation. Green leafy vegetables and some animal products are high in folic acid (e.g., egg yolk). Although the minimal daily requirement for folic acid is 50 g, the current suggested consumption for an average adult is 400 g/d and 600 g/d during pregnancy. Because the average person's folic acid stores are only 5-20 mg, acquaintance with clinical situations that raise folic acid dietary need or impede an individual's ability to absorb folic acid in the proximal jejunum may be beneficial. Cobalamin is an organometallic molecule that is essential for the normal action of methionine synthase. In humans, cobalamin cannot be manufactured from scratch, thus appropriate stores are maintained through dietary sources.[11]

HYPERCYSTENEMIA

Hyperhomocysteinemia is a medical disorder characterised by an unusually high level of homocysteine in the blood (more than 15 mol/L). Moderate hyperhomocysteinemia is defined as a level between 16 and 30 mol/L, intermediate hyperhomocysteinemia is defined as 31 to 100 mol/L, and severe hyperhomocysteinemia is defined as a level beyond 100 mol/L. Hyperhomocysteinemia is divided into two categories. The more common variants induce moderately high homocysteine levels connected to a pathogenesis such as genetic and environmental factors. The rare but severe forms are caused by substantial genetic mutations of enzymes participating in homocysteine metabolism. Homocysteine is found in four distinct forms in the body. Hcys-Hcys dimers and Hcys-other thiols dimers are free thiols (about 1%), disulphide-bound to plasma proteins (70–80%), Hcys-Hcys dimers, and Hcys-other thiols dimers. The role of homocystinuria heterozygosity as a probable cause of elevated homocysteine concentrations seen in up to 30–40% of patients with coronary artery disease. The molecular pathways of homocysteine

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metabolism reveal that deficiencies in other important enzymes and a number of cofactors can also result in elevated homocysteine levels.[12]

CAUSE FOR HYPERCYSTENEMIA

Mild (16–30 M) to moderate (30–100 M) elevations in total plasma homocysteine levels are caused by dietary folate, vitamin B12, and vitamin B6 insufficiency. Mild to moderate hyperhomocysteinemia can develop after consuming alcohol, nicotine, caffeine, or other substances that disrupt methionine metabolism. Hyperhomocysteinemia can also be caused by a sedentary lifestyle, advanced age, or menopause. In addition, MTHFR (MTHFR gene), MS (MTR gene), methionine synthase reductase (MTRR gene), BHMT (BHMT gene), and serine hydroxy methyltransferase can all cause moderate hyperhomocysteinemia due to genetic mutations and altered functioning of the catalytic enzymes involved in homocysteine remethylation. Hyperhomocysteinemia is caused by a disruption in homocysteine metabolism, which increases the risk of a variety of complicated illnesses involving the cardiovascular, renal, gastrointestinal, and central neurological systems.[13]

FACTORS AFFECTING PLASMA HOMOCYSTEINE

1. AGE, SEX, AND LIFESTYLE:

Homocysteine levels rise with age in both men and women. Women's concentrations are lower than men's, and concentrations rise following menopause. Raised homocysteine levels are linked to cigarette smoking, a high intake of alcoholic alcohol, and a sedentary lifestyle. Lower levels of folic acid, as well as vitamins B12 and B6, are likely the most important causes at a population level.

2. SYSTEMIC ILLNESSES:

Creatinine and plasma homocysteine have a tight relationship. Homocysteine levels rise two to thrice in patients with end-stage renal failure. Patients on hemodialysis have greater values than those on peritoneal dialysis. The exact causes underlying the elevated homocysteine levels reported in these patients are unknown, but impaired homocysteine systemic clearance, lower circulating folate, and folate inhibition are likely key drivers. Homocysteine levels can rise as a result of a variety of malignancies, hypothyroidism, inflammatory bowel disease, and organ transplantation.

3. EFFECTS OF MEDICATION AND VITAMIN SUPPLEMENTATION:

Increased homocysteine levels are associated with the usage of folate inhibitors such methotrexate and carbamazepine, as well as folate antagonists like colestipol and cholestyramine. Cobalamin is inhibited by nitrous oxide. Vitamin B6 shortage can be caused by theophylline and niacin. Cyclosporin has been linked to hyperhomocysteinemia and may decrease renal function. The usage of B vitamins lowers homocysteine levels: folic acid, vitamin B12, and betaine promote remethylation, whereas vitamin B6 promotes greater transsulfuration. Exogenous estrogen, as well as the aminothiols penicillamine and acetylcysteine, may lower plasma homocysteine.[12]

PATHOPHYSIOLOGY OF CARDIOVASCULAR RISK FROM ELEVATED HOMOCYSTEINE LEVELS

Hyperhomocysteinemia is thought to contribute to atherogenesis and atherothrombosis through a variety of pathways. Homocysteine metabolism produces reactive oxygen species, which can harm the endothelium directly. Endothelial dysfunction has been linked to homocysteine inhibition of nitric oxide synthase activity. Dysregulated methylation of proteins and DNA, which results in aberrant vascular smooth muscle cell proliferation, as well as enhanced lipid peroxidation, are other proatherogenic pathways linked to hyperhomocysteinemia.[9]

HYPERCYSTENEMIA AS A RISK FACTOR IN CVD

HCy may contribute to CVD through processes such as vascular muscle cell proliferation, a reduction in circulating HDL, conversion to HCy-thiolactone, and development of an immunological response as well as thrombogenesis. HHCy stimulates Nuclear Factor-kappa B, which controls the transcription of different genes involved in inflammatory and immunological responses, increasing pro-inflammatory cytokines while suppressing anti-inflammatory cytokines. HHCy also causes endothelial cell dysfunction by lowering endothelial antioxidant defence, resulting in oxidative stress and a rise in intracellular reactive oxygen species (ROS) concentrations. ROS disrupt lipoprotein metabolism, promoting the progression

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of atherosclerotic vascular lesions. Endothelial nitric oxide synthase, which produces nitric oxide, is inhibited by HCy, which controls the contractility of vascular smooth muscle cells and the permeability of endothelial cells (NO). In vascular disease, increased HCy is also linked to DNA hypomethylation. This complicated regulation process is tissue-specific. Endothelial cells export HCy to the circulation to prevent intracellular buildup of HCy when the remethylation process is disrupted. HHCy's impact on CVD could potentially be related to increased hydrogen sulphide generation (H2S) The end product of HCy metabolism is H2S. The role of hydrogen sulphide (H2S) in vascular illnesses, inflammation, critical sickness, reperfusion injury, various nervous system diseases, metabolic diseases, and cancer was thoroughly examined. There is mounting evidence that H2S shortage plays a role in vascular illnesses such hypertension and atherosclerosis. Other review studies looked at H2S vascular biology and HHCy-induced vascular damage pathways. Changes in H2S production in HHCy may be predominantly due to CSE. Changes in the H2S/HCy ratio may be more valuable than changes in the absolute concentrations of H2S and HCy in showing the function of these metabolites in disease pathogenesis, based on the metabolic imbalance of HCy and H2S in cardiovascular diseases.[8]

HYPERHOMOCYSTEINEMIA AND ENDOTHELIAL DYSFUNCTION

Only thirty years later, HHcys was formally identified as a CVD risk factor. Since then, three alternative pathophysiological theories for explaining this association have been proposed.

1. The bioavailability of NO at the endothelium level is decreased by Hcys.
2. Hcys has a direct cytotoxic effect on cells that is mediated by oxidative stress.
3. Folate metabolism dysregulation.

The endothelium regulates vascular wall homeostasis (e.g., vascular tone, coagulation, and permeability), and the phrase "endothelial dysfunction" refers to a pathological process that is the initial step in the development of atherosclerosis. An inflammatory insult usually causes endothelial dysfunction by activating endothelial cells, which then release adhesion molecules and chemokines. The latter are in charge of attracting circulating monocytes, which are then activated into macrophages, which internalize modified lipoproteins and transform them to foam cells after infiltrating the intima. The plaque's instability is caused by the inflammatory stimulus's persistence, which may contribute to its rupture, with luminal release of the thrombogenic core and subsequent atherothrombotic blockage of the vessel implicated. The endothelium's homeostasis can be disrupted by HHcys, which can lead to the development of atherosclerosis. In vitro, Hcys reduces the bioavailability of NO, which plays a key function as a vasodilator, and enhances endothelin-1 expression, which is a potent vasoconstrictor, by interacting with O2 to generate peroxynitrite (ONOO). HHcys has an indirect effect on the endothelium, causing an increase in the release of reactive oxygen species (ROS), a family of molecules that damages the endothelium and favors endothelial cell activation later in the atherosclerotic process. Hcys increases platelet activation and aggregation, promoting vascular occlusion where endothelial activation is already present and other cardiovascular risk factors are present. Increased Hcys concentrations, for example, are linked to the development of microvascular complications like retinopathy, neuropathy, and nephropathy in hypertensive patients, while HHcys is linked to the development of microvascular complications like retinopathy, neuropathy, and nephropathy in diabetic patients. Hcys levels in the blood have also been linked to a variety of arterial stiffness indicators, including pulse pressure and aortic stiffness as measured by carotid-femoral pulse wave velocity.[14]

II. CONCLUSION

According to epidemiologic studies, high homocysteine levels are an independent risk factor for atherothrombotic cardiovascular disease, stroke, and cognitive impairment. Homocysteine is a risk factor for cardiovascular disease that can be controlled with diet and exercise. However, it is now commonly acknowledged that food alone cannot consistently provide the levels of nutrients required for effective homocysteine metabolism. Indeed, new research is focusing on novel nutritional strategies for lowering high homocysteine levels, which could open up new avenues for preventing cardiovascular disease. More research is needed in this sector before convincing proof is produced to dispel any doubts about the link between homocysteine and cardiovascular disease. Nonetheless, the current analysis should shed light on the role of homocysteine in the progression of cardiovascular disease.

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