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Role of Homocysteine as a Risk Factor in Cardiovascular Disease

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Abstract: The primary cause of mortality for people in developed nations is coronary heart disease, or CHD. It is noted that with age the fat deposits in the wall of the coronary arteries as well as the other blood vessels supplying the heart. As a result of this deposition, there is a decrease in the blood supply to the heart causing angina and shortness of breath and may also result in a fatal myocardial infarction. There are several modifiable risk factors for CHD and one of them being the increased level of the amino acid i.e. homocysteine (HCY) which when treated can reduce the risk of CHD. The positive correlation between hyper homocysteinemia and cardio vascular disease (CVD) has established firmly with the data derived from experimental and epidemiological observations. Clinical data authenticate that HCY is an independent risk factor for CVD. The current article is aiming to evaluate potential role of HCY on CVD risk at molecular level, and deep insights into a pathophysiology of CVD and their associations with CVD.

Key Words: Homocysteine, cardiovascular disease, risk factor, hyperhomocysteinemia, vascular health

1. INTRODUCTION

Cardiovascular disease is the term used to describe improper functioning of the heart and blood arteries in the body (CVD) [1]. Stroke, congenital heart abnormalities, hypertension, congestive heart failure, and atherosclerosis the hardening or narrowing of blood vessels including the coronary arteries are among the several forms of cardiovascular disease (CVD) [2]. The twentieth century saw an unparalleled change in the causes of morbidity and mortality, which contributed to the global increase in CVD. This shift, referred to as the epidemiologic transition, affects people of all races, ethnicities, and cultures worldwide and is brought about by urbanization, industrialization, and related lifestyle changes. Almost 30% of deaths globally are caused by CVD, and this percentage is projected to rise. Thirteen percent of all fatalities worldwide in 2010 were caused by CHD, It was also responsible for the majority of disability-adjusted life years (DALYs) and years of life lost (YLLs) globally. Stroke was the second biggest cause of death, accounting for 11.1% of all deaths. Moreover, it ranked as the third most common cause of DALYs and YLLs globally [3].

Consequently, adult heart disease (CHD) is the leading cause of death in developed countries. With aging, fat deposits known as atherosclerotic plaques coat the walls of the coronary arteries and the blood vessels that supply oxygen and nourishment to the heart [4]. As a result, the heart's blood flow is restricted, which can lead to heart attacks, angina (chest symptoms that are typically eased by rest), and dyspnea [4]. Changes in lifestyle can affect many known risk factors for congestive heart failure (CHD), such as physical inactivity, overweight, smoking, and consuming a diet high in fat. A high blood level of the amino acid homocysteine is another potentially modifiable risk factor for coronary heart disease [4].

2. HISTORY OF HOMOCYSTEINE

When American biochemist Vincent DuVigneaud treated methionine with sulfuric acid in 1932, he identified a new amino acid. Homocysteine gets its name because it has an amino acid structure that is identical to cysteine but with one extra carbon atom. More investigation revealed that homocysteine serves as an intermediate in the metabolism of sulfur amino acids and transmethylation activities. Prior to 1962, the biological significance of homocysteine was unknown. It was discovered that children with mental retardation, rapid development, osteoporosis, misplaced ocular lenses, and frequent thrombosis of arteries and veins produced homocysteine in their urine. Cysteine synthase, an enzyme that catalyzes the conversion of homocysteine and serine into cystathionine and is dependent on pyridoxal phosphate, is deficient in most infants with homocystinuria. While homocystine, the homocysteine disulfide dimer, is excreted in the urine, homocysteine and methionine accumulate to high levels in plasma as a result of this enzyme deficit [5].

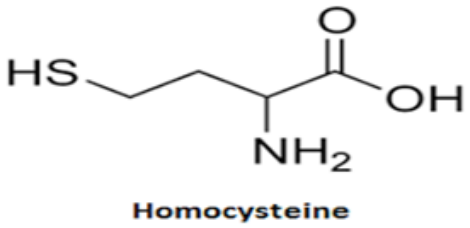

FIGURE 1: Structure of Homocysteine [6]

3. THE HOMOCYSTEINE THEORY OF ARTERIOSCLEROSIS WAS DISCOVERED

An eight-year-old boy's homocystinuria case that was first reported in 1933 was reviewed in 1969, and it was discovered that a major stroke caused by thrombosis and carotid arteriosclerosis was the cause of death. Moreover, the arteries supplying the body's major organs were found to be dotted with arteriosclerotic plaques, suggesting a possible connection between homocysteine and atherogenesis.

It was discovered that a two-month-old infant with a second case of homocystinuria had widespread, advanced arteriosclerotic plaques scattered throughout the arteries. Methionine synthase, a separate enzyme, was deficient in this instance. It was found that homocysteine directly causes arteriosclerotic plaques on the artery's cells and tissues because homocysteine elevation was the only metabolic abnormality shared by these two cases. This is because homocysteine is caused by an enzyme deficiency that results in elevated blood levels of cystathionine and homocysteine and decreased levels of methionine. A few years later, researchers in Chicago demonstrated that homocysteine is an amino acid that causes atherosclerosis by demonstrating similar arteriosclerotic plaques in a child who had the third major kind of homocystinuria, methylenetetrahydrofolate reductase insufficiency [5].

When these homocystinuria cases were first reported, it was proposed that blood homocysteine elevation had a significant role in the etiology of arteriosclerosis in the general population, even in those who did not have these uncommon hereditary abnormalities of homocysteine metabolism. Individuals predisposed to arteriosclerosis by genetics, nutrition, environment, hormones, metabolism, or toxicity experience arterial plaques as a result of homocysteine's damaging effects on the lining cells and tissues of their arteries [5].

4. HOMOCYSTEINE LEVELS IN THE BLOOD AND A HIGHER RISK OF CARDIOVASCULAR DISEASE

Blood homocysteine levels typically range from 5 to 15 umol/L. It can rise to 50-100 times in cases of illness. Age, vitamin B12 or B6 deficiency, tobacco smokers, alcoholics, and hypothyroidism are associated with a moderate increase. A significant rise in congenital enzyme deficits is observed. Hyperhomocysteinemia (HHcy) is the term for an increase in the level of homocysteine in the blood.

4.1. HYPERHOMOCYSTEINEMIA CLASSIFICATION (AS PER SELHUB, 1999)

Extremely High Homocysteinemia: Elevated total homocysteine (tHcy) levels at all times (31>100 mmol/L), which may be brought on by impairments in the B12 metabolism enzymes, MTHFR, or cystathionine beta synthase (CBS).

Sufficient homocysteine level Mild enzyme deficits, such as thermolabile MTHFR, or decreased homocysteine methylation are indicated by slightly higher tHcy levels (15-30 mmol/L) after fasting.

After a Methionine Dose: After a methionine load of 100 mg/kg, there is an abnormal rise in tHcy (>15 mmol/L); this indicates defective homocysteine transsulfuration (heterozygous CBS abnormalities, B6 insufficiency).

Urine contains high levels of homocysteine excretion. There are two types of homocystine (disulfide, -S-S-group) and homoocyteine (with -SH group) in plasma. Normal urine does not contain either of them, but if it does, it will only contain homocystine (disulfide). The risk of coronary heart disease is increased by elevated blood homocysteine levels. There is some data linking elevated blood homocysteine levels to myocardial infarction. An rise in blood homocysteine of 5 umol/L is associated with a 20 mg/dl increase in risk of coronary heart disease. Homocysteine interferes with collagen across linking via interacting with the lysyl residues of collagen. It produces a free radical called homocysteine thiolactone, which thiolates LDL particles. These particles have a propensity to clump, are taken up by macrophages, and heighten the risk of atherogenesis [6].

Methionine is demethylated to produce the amino acid homocysteine (Hcy), which contains sulfhydryl. Normally, cystathionine beta-synthase, an enzyme that is dependent on pyridoxal phosphate, catalyzes the conversion to cystathionine. Additionally, betaine-Hcy methyltransferase and 5-methyltetrahydrofolate-Hcy methyltransferase, two enzymes that depend on vitamin B12, remethylate hcy to methionine. Plasma homocysteine elevations can be brought on by dietary factors such vitamin B12 or B6, folate deficiencies, or both. Genetic diseases like methylene-tetrahydrofolate reductase or cystathionine beta-synthase can also induce elevated levels of homocysteine. Numerous factors, including direct Hcy damage to the endothelium, stimulation of smooth muscle cell proliferation, increased platelet aggregation, enhanced LDL peroxidation, and effects on the coagulation system that lead to capillary damage and cardiovascular disease, may be involved in the pathophysiology of Hcy-induced vascular damage.9. Increased blood homocysteine levels, an amino acid, may also represent a modifiable risk factor for coronary heart disease (CHD). Fortifying grains with folate helps lower blood levels of homocysteine in the population because the enzyme methylene tetrahydrofolate reductase, which is encoded by the MTHFR gene, breaks down and removes homocysteine. Pooled data from prospective observational studies that looked for a connection between homocysteine levels and the development of coronary heart disease (CHD) showed that the reduction in homocysteine levels that can be

achieved by folate supplementation is associated with an 11% lower risk of developing CHD [7].

The molecular basis for the development of arteriosclerotic plaques is linked to the effects of homocysteine on cellular degeneration, damage to artery intima, cellular proliferation, production of connective tissue, deposition of lipoproteins in plaques, and enhanced blood coagulation. Every single one of these crucial atherogenesis pathways depends on homocysteine [8].

Elastic fiber degradation and disintegration is another characteristic of early plaques. The internal elastic membrane of arteries fragments as a result of homocysteine's activation of the elastase enzyme. Furthermore, homocysteine causes overproduction of collagen in cultured smooth muscle cells, which explains the fibrosis observed in both human and experimental plaques. Additionally, vascular smooth muscle cells proliferate in plaques due to homocysteine's activation of cyclins, signaling proteins that facilitate cell division. Because homocysteine releases insulin-like growth factor and promotes the sulfation of animal epiphyseal cartilage, it induces smooth muscle cells to proliferate in forming arteriosclerotic plaques and accelerates skeletal growth in children with homocystinuria [5]. The first human study on homocysteine in vascular disease, done in 1976, found that dietary methionine increases plasma levels of homocysteine and homocysteine cysteine disulfide in individuals with coronary heart disease (CHD). Subsequent studies have demonstrated that individuals with peripheral, cerebral, or coronary arteriosclerosis have elevated blood homocysteine levels. An increase in homocysteine is a stronger risk factor than an increase in cholesterol in patients with early onset arteriosclerosis, with an effect akin to that of smoking [9].

5. MOLECULAR ASPECTS OF HOMOCYSTEINE

There are 2 genes very importantly controls the homocysteine metabolism MTHFR gene (5,10-methylenetetrahydrofolate reductase) situated at 1 p36.3 on chromosome 1 and The 2.2 kilobases long complementary DNA (cDNA) sequence is made up of 11 exons. Two alleles are frequently found with the MTHFR gene. Both the A1298c and C677T alleles.

The primary circulating form of folate, 5-methyltetrahydrofolate, is produced by the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which is important in folate metabolism. The 5-methyl form participates in single-carbon transfers in the production of S-adenosyl-methionine, methylation of proteins, DNA, neurotransmitters, and phospholipids, as well as the remethylation of homocysteine to methionine and nucleotide synthesis. Generally speaking, MTHFR activity helps keep the supply of methionine and folate in the bloodstream and keeps homocysteine from building up [10].

5.1. MTHFR GENE MUTATION

5.1.1. C677T allele

Botto and Yang [9] The MTHFR gene's position 677, which changes a cytosine (C) to a thymine (T), is the point mutation

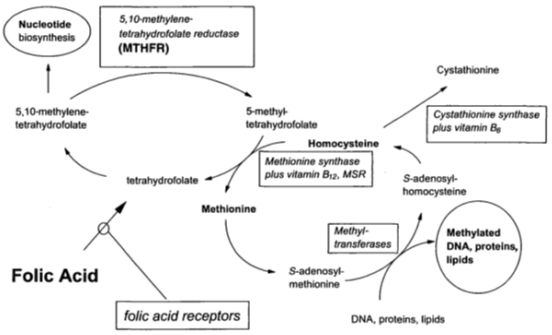

FIGURE 2: 5, 10-Methylenetetrahydrofolate reductase (MTHFR)-related metabolic pathways. Methionine synthase reductase, or MSR [10]

responsible for the C677T allele. This kind of point mutation causes the enzyme to change its amino acid composition from alanine to valine. The C677T allele is "thermolabile", meaning that at 37°C or above, the encoded enzyme's activity decreases. As a result, compared to similarly treated controls, MTHFR activity in C677T homozygotes is 50–60% lower at 37°C and 65% lower at 46°C. Heterozygotes fall into the middle category. When their consumption of folate is inadequate, homozygous individuals for the C677T mutation typically have slightly elevated blood homocysteine levels; when their intake of folate is sufficient, their levels tend to be normal [10].

5.1.2. A1298C

Botto and Yang [9] the enzyme substitutes glutamate for alanine due to the A1298C allele, a point mutation in exon [7]. The C1289A allele is another name for this allele. While still reduced, the encoded enzyme's activity is less than that of the C677T allele. Serum homocysteine levels do not seem to be greater in homozygous A1298C individuals than in controls. Nonetheless, individuals with the A1298CIC677T genotype, who are compound heterozygous for the A1298C and C677Talleles, typically exhibit a biochemical profile that is comparable to that of C677T homozygotes, with elevated serum homocysteine and lower serum folate levels [10].

FTO gene alpha-ketoglutarate-dependent dioxygenase, or FTO, is a protein linked to fat mass and obesity. The enzyme known as FTO, which is encoded by the FTO gene in humans and is found on the Fat Mass and Obesity associated gene region (FTO) at 16q10, is highly linked to an increased body weight and an increased risk of developing type 2 diabetes (T2D) [11].

5.2. GENOTYPE EFFECT ON HOMOCYSTEINE LEVELS

A study conducted on the possible assessment of association of homocysteine with the FTO gene showed that there was a significant increase in the levels of homocysteine by the presence of FTO rs9939609 AA genotype thereby proving that the presence of this FTO gene can alter the levels of homocysteine significantly . Raised homocysteine levels

Source and year	Age, y	Sample Size		Mean Homocysteine, μmol/L			
		Cases	Controls	Cases	Controls	P	
[10]	21-65	99 Cases	39 Controls	0.03 0.7	0.06 0.6 (P)	NS NS	
[12]	<69	241 Cases	202 Controls	5.5	4.3	<.001	
[14]	Mean, 62	99 Cases	259 Controls	13.0	10.5	<.001	
[13]	17-80	80 Cases	22 Controls	0.76	0.40 (P)	<.001	

TABLE 1: Cross sectional studies Reports of Homocysteine and Heart isease [13]

are linked to increased neuroinflammation, hypomethylation caused by decreased Interference with the response of adhesion molecules, B and T lymphocytes, natural killer cells, and S-adelosyl methionine (SAM), an essential methyl donor in a variety of methylation reactions [12]. Future atherosclerosis has been predicted by aortic lipid deposition, which has been linked to hypomethylation. Future atherosclerosis has been predicted by aortic lipid deposition, which has been linked to hypomethylation.

6. COMPARATIVE ANALYSIS OF PREVIOUS STUDIES SHOWING THE RELATIONSHIP BETWEEN HOMOCYSTEINE AND CVD

The diagnosis of CHD in the four cross-sectional investigations on homocysteine and CHD mentioned above was made using angiographic data showing more than 50% blockage of at least one coronary artery. Blood samples were taken at the time that the diagnosis of CHD was made. While there was no difference in mean homocysteine levels between those with and those without CHD in the first number of trials, those with CHD had higher mean homocysteine levels (between 30% and 90% higher) in the second to fourth number of studies, 10-12. People with high homocysteine levels had significantly higher odds of developing coronary heart disease (CHD), according to all four of the cross-sectional studies that characterized elevated homocysteine levels [13].

The aforementioned [15] case control studies on homocysteine and CHD All but three of the fifteen studies that examined mean homocysteine levels (14, 23, 29) discovered that individuals with CHD had considerably higher homocysteine levels (typically 10%-30%), either after a methionine load or after fasting. Fifteen out of sixteen studies that compared proportions with elevated homocysteine levels found that people with elevated homocysteine levels had an increased risk of coronary heart disease (CHD). The increase in risk was statistically significant at the P<05. In most of these investigations, the confidence interval (CI) around the RR estimate excluded the null value of 1.0.

RR stands for relative risk; HR for hazard ratio; OD for odds ratio; Prosp = prospective Review-Meta-Analysis = Rev-Meta cross-sectional = cross-sect Randomized control trial, or RCT Heart failure is referred to as HF, coronary heart disease as CHD, cardiovascular disease as CVD, coronary artery disease as CAD, and cerebrovascular disease as Cerebrovasc. NA stands for not available. W stands for women, and M for men.

In above prospective case control , reviews and meta-analysis, randomized control trials (RCTs) showing that hyperhomocysteinemia is lowering with folic acid ± B vitamins and reduces the complications of CVD and stroke , hence these studies are demonstrating an association of hyperhomocysteinemia with an increased CVD and stroke incidences

7. FUTURE DIRECTIONS

The homocysteine could be potential biomarker for early detection of CVD risk and thereby help in reduction of risk for individual patient and population. The results of recent prospective studies, which suggest that plasma homocysteine has little prognostic power in CVD, highlight the need for a more thorough and quantitative analysis of all the information now available. In conclusion, there is a favorable relationship between high homocysteine levels and cardiovascular disease risk. However further in depth research into the epigenetic aspects of homocysteine causing CVD and the homocysteine as an independent risk factor for CVD needs to be investigated.

CONFLICT OF INTEREST

The authors declare no conflict of interests. All authors read and approved final version of the paper.

AUTHORS CONTRIBUTION

All authors contributed equally in this paper.

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