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HYPERHOMOCYSTEINEMIA: A SILENT HASSLE FOR HUMAN BEINGS, ALLIED COMPLICATIONS AND PRAGMATIC STRATEGIES

Jeetendra Kumar Gupta *, Somdutt Mujwar, Krishna Kumar Varshney and Megha Varshney

Institute of Pharmaceutical Research, GLA University Mathura - 281406, Uttar Pradesh, India.

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Correspondence to Author:
Jeetendra Kumar Gupta

Assistant Professor,
Institute of Pharmaceutical Research,
GLA University Mathura - 281406,
Uttar Pradesh, India.

E-mail: jkgupta81@gmail.com

ABSTRACT: Hyperhomocysteinemia is a metabolic catastrophe characterized by an elevated level of homocysteine above 15 µmol/L in blood. It is an established risk factor for cardiovascular anomalies. The illness has also crucial impact on other organs and tissues of body. Its morbid effects have been seen during many chronic conditions. It is also considered as a metabolic crunch during gestation as well as geriatric conditions. Increased homocysteine has also been seen to play a critical role and key factor in development of many health issues including stroke, cancer, and neurodegenerative diseases. Although, it is an autosomal recessively inherited defect, but can also be developed during intake of vitamin deficient high protein diet. This illness causes many ill effects on our vital organs and becomes a risk factor for several health complications such as venous thrombosis and vascular damage. The existing treatment includes vitamin B_{12}, B_6, and folic acid, but based on the mechanism of this disease methyl donor substance (natural product or synthetic moiety) may also be utilized in order to alleviate the illness.

INTRODUCTION: In the present world life-threatening ailments are growing day-by-day such as cancer, aids, heart disease, pulmonary disease, stroke, *etc*. Besides them, there are certain diseases that may not be life-threatening but at the same time also progressing in order to degrade the quality of life. According to World Health Organization (WHO), quality of life (QoL) is the widespread well-being of individuals and society, indicating gloomy and bright characteristics of life [1, 2]. There are many health-related factors, which affect the quality of life harshly. Factors such as metabolic disorders could be responsible for such upheaval instability.

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Some of the known protein-related metabolic disorders are phenylketonuria, cystinuria, albinism, and hyperhomocysteinemia. Among these, hyperhomocysteinemia has a monstrous role in twisting our fitness and well-being [3]. It is a protein-related metabolic disorder in which an abnormal level of homocysteine rises in blood, *i.e.*, above 15 mcmol/L, which expresses many ill effects on various organs.

Hyperhomocysteinemia is a medical condition and a potential risk factor for many diseases. It arises due to excessive accumulation of homocysteine as well as some genetic factor (autosomal recessively inherited defect) that leads to certain abnormality in the trans-sulfuration pathway or methylation pathway. It is an illness commenced due to aberration in methionine metabolism that further leads to an abnormal accumulation of homocysteine and its metabolites in blood and urine [4]. Homocysteine is a sulfur-containing amino acid that is formed during the accumulation of

methionine in the liver. It is an essential amino acid derived from diet sources such as meats, fish, fruits, nuts, cereal grains, and vegetables. Under normal body conditions, homocysteine is simultaneously and rapidly metabolized in order to prevent an increase in its concentration in blood circulation. Its metabolism is managed by two biochemical pathways: trans-sulfuration and remethylation [5].

Mechanism: Elevated level of homocysteine is a sizable hazardous factor for vital organs like heart, brain, and liver. This disease may exert its pathogenic consequence majorly through metabolic accumulation of S-adenosyl-L-homocysteine, a powerful blocker of catechol-O-methyltransferase induced methylation process. Other mechanism includes oxidative stress induced by reactive oxygen species of the sulfur amino acid [6].

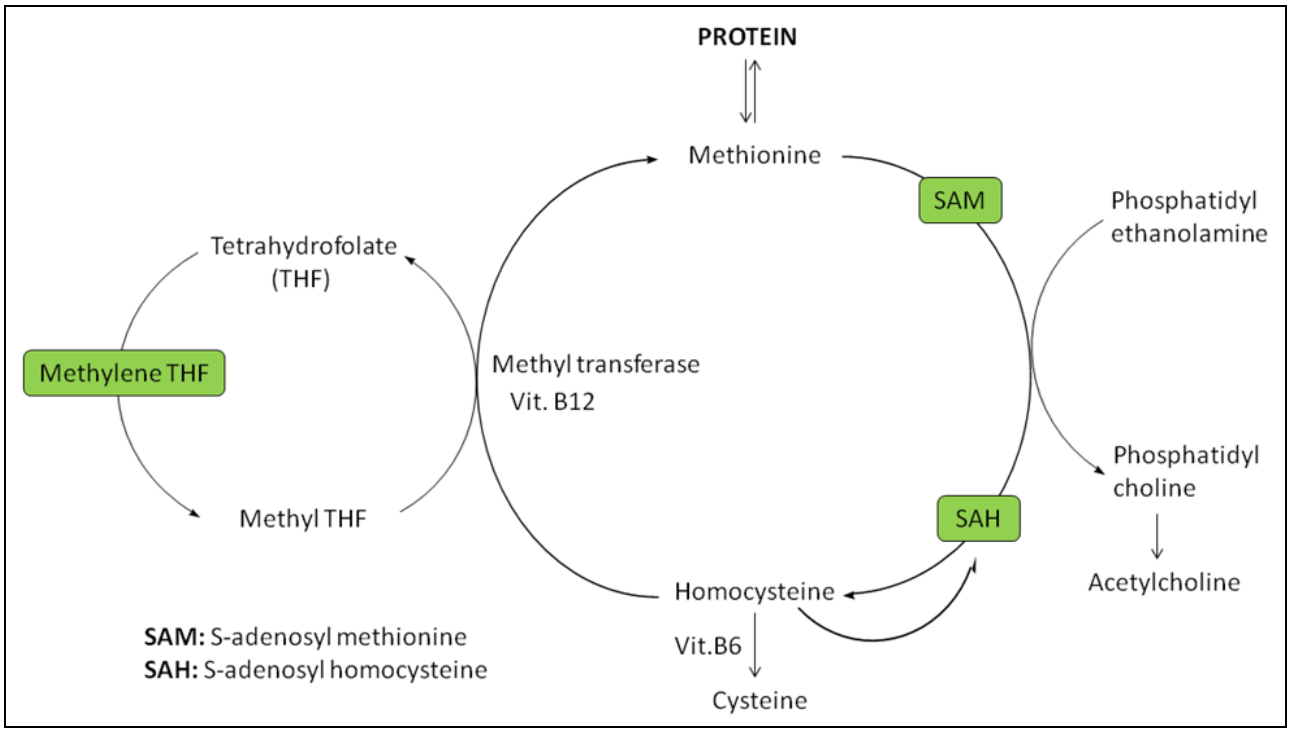

FIG. 1: MECHANISM – BIOSYNTHESIS AND MOBILIZATION OF HOMOCYSTEINE

Factors Affecting Homocysteine Levels in the Blood: Hyperhomocysteinemia is a chronic and sedate occurring disease governed by many factors, such as age and gender, genetic factor, lifestyle, vitamin deficiency, drug factors, alcoholism and Renal malfunctioning [7].

Age and Gender: Although it is reported in many literatures that males have a slightly higher level of homocysteine than females, but it is been studied that gender does not play any significant role in altering the homocysteine levels in the blood. The levels of homocysteine keep increasing with age.

Genetic Factors: Genetic defects lead to a deficiency in enzymes involved in homocysteine metabolism resulting in an excessiveness of homocysteine in blood. The responsible enzyme gets defected due to genetic defect (autosomal recessively inherited defect). This leads to the origin of congenital hyperhomocysteinemia which is marked by fasting plasma homocysteine levels 40 times the upper limit of normal. This homozygous trait is rare, 1 in 200,000 births.

Lifestyle Factors: This illness is also significantly seen in humans living in highly polluted zone and also in cigarette smokers. The number of cigarettes smoked a day is directly proportional to the increase in the concentrations of homocysteine in the blood.

Vitamin Deficiency: When an individual takes a high protein rich diet every day like high mycoprotein, meat, egg, *etc.*, he should also consolidate with certain essential vitamins like vitamin B6, vitamin B12 and folic acid as they are needed for enzymes involved in homocysteine metabolism. Vegetarians generally suffer from hyperhomocysteinemia due to lack of vitamin B_{12}.

Drug Factors: Anticonvulsants such as primidone, phenytoin, valproic acid interfere with folate metabolism and deplete folate level, which leads to an increase in plasma homocysteine. Drugs like 6-azauridine, cyclosporine, theophylline antagonize vitamin B6 and further increase the level of homocysteine in plasma.

Besides these, there are also drugs which have a significant tendency to decrease the plasma concentration of homocysteine such as Folic acid.

Alcohol: Alcohol consumption leads to disturbances in the metabolism of folic acid and cyanocobalamin. It disturbs gastrointestinal tract that leads to a reduction in absorption of vitamins and folic acid that results in an increase in the level of homocysteine. It also inhibits the synthesis of methionine synthase which is required for the metabolism of homocysteine hence elevating the plasma level of homocysteine.

Renal Malfunctioning: Although the needful cause of hyperhomocysteinemia due to renal dysfunction is not established, but it seems to reduce the plasma clearance of homocysteine, which therefore leads to an elevation in plasma concentrations of homocysteine [8].

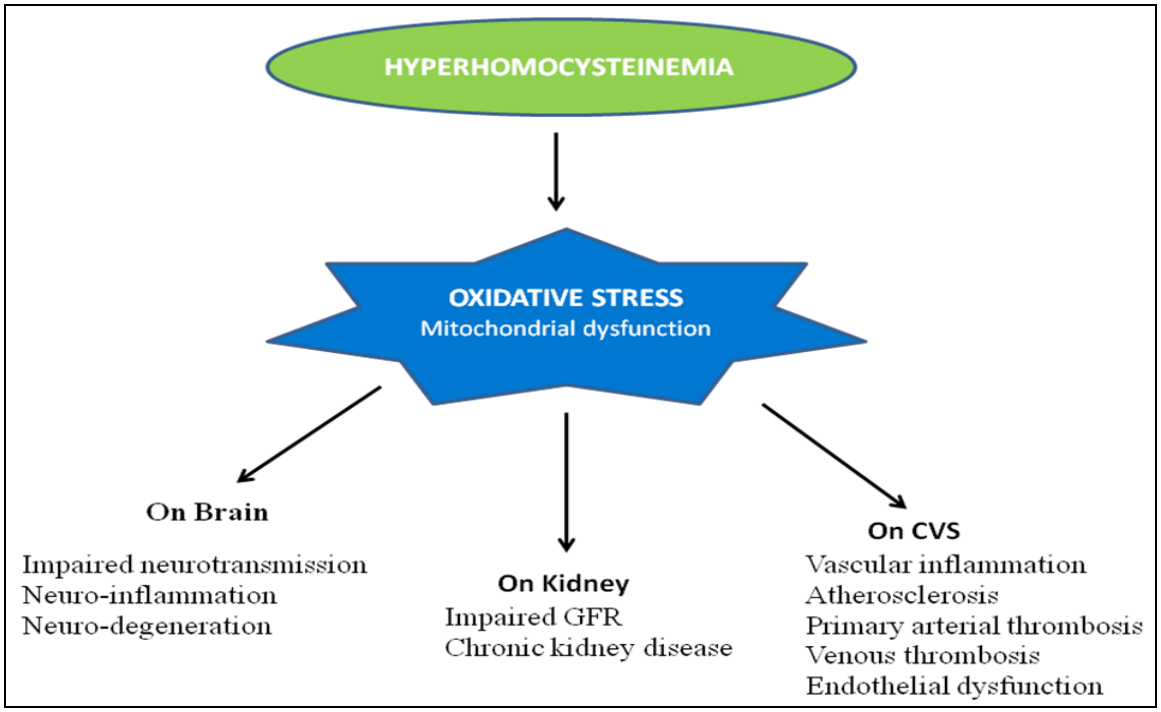

FIG. 2: TOXIC EFFECT OF ELEVATED HOMOCYSTEINE ON VARIOUS ORGANS

Complications: There are many complications which are associated with hyperhomocysteinemia, such as neurological and cardiovascular dysfunctions. Their complications are described below.

Stroke: The second leading cause of death worldwide is the stroke, and also a major cause of adult disability. The clinical study has shown that hyperhomocysteinemia is considered as a preclinical marker of stroke and maybe the cause for stroke-related thrombophilia. A prospective case-control study has revealed that homocysteine levels were found higher in patients with spontaneous cervical artery dissection than in normal subjects while no considerable difference was observed among stroke patients with spontaneous cervical artery dissection and with atherothrombosis without dissection [9].

Mild Cognitive Impairment: Hyper-homocysteinemia is an autonomous risk factor for declining a cognitively healthy person to developing dementia in subjects with Alzheimer's. A Double-blind, randomized controlled study established a positive correlation between hyperhomo-cysteinemia and brain atrophy in patients with mild cognitive disorders. Diversely, abnormal levels of homocysteine lead to the decline in cognitive function, in patients with Alzheimer's disease [10].

Dementia: Hyperhomocysteinemia is a predictive aspect of Alzheimer's, which is the most frequent cause of dementia in the elder population. The mechanism behind the effect of homocysteine on dementia is explained as homocysteine acts as an excitatory neurotransmitter by computing with inhibitory neurotransmitters as gamma-aminobutyric acid (GABA). Additionally, hyperhomo-cysteinemia activates microvascular permeability by constricting the GABA-A/B receptors and increasing the redox stress, in turn, triggering a disintegrin and metalloproteinase, which suppresses tissue inhibitors of metalloproteinase. This action causes depletion of the matrix in the blood-brain barrier and confers to vascular dementia [11].

Parkinson's Disease: Elevated homocysteine exerts multiple pathogenic mechanisms of neurotoxicity. It has been linked to the physiological as well as pathological dysfunctions associated with brain dopamine levels. Recent studies have demonstrated that hyperhomo-cysteinemia is detected in Parkinson's disease patients and may be involved in the pathogenesis of Parkinson's disease neurodegeneration [12].

Multiple Sclerosis: Intriguingly, Hyperhomo-cysteinemia has been detected in patients with multiple sclerosis but no relation to immune activation, oxidative stress, or vitamin deficiency has been established. Since, hyperhomocysteinemia includes methionine availability, which further obstructs with methyl group donor in various biochemical reactions. Hypomethylation of myelin basic protein results in less stable myelin structure that is amenable to degeneration [13].

Cardiac Disorders: Cardiovascular disease is the leading cause of morbidity worldwide. Its risk factors are marked by elevated blood pressure, cholesterol, or glucose level, and smoking. It is considered that a moderately higher level of homocysteine is found to be responsible for cardiovascular diseases. It is also known that genetic mutations lead to hyperhomocysteinemia. In case of less care and when enough attention is not given to the individuals having high homocysteine level this illness leads to various vascular events as myocardial infarction, stroke, and some other thromboembolic complexities.

The genetic factor for hyperhomocysteinemia is a homozygous mutation of MTHFR which leads to premature cardiovascular disease. There is no possible mechanism established explaining the relationship between hyperhomocysteinemia and aortic stiffness. The principal hypothesis behind this is homocysteine has the potential of remodeling the arterial wall which leads to vascular damage. Some studies also state that high homocysteine level enhances reactive oxygen species and cause vascular endothelial cells damage. An increase in homocysteine levels is also a cause for higher risk of venous thrombosis. Although homocysteine does not directly act as a risk factor for cardiovascular diseases such as MI, stroke, and cramping pain in leg during exercise but atherosclerosis is the main pathological event in these diseases, which is one of the main risk factors of hyperhomocysteinemia [14].

Homocysteine induces cardiovascular diseases through various mechanisms, for instance, detrimental effects on vascular endothelium cell, elastic material of arterial walls, and smooth muscles along with resultant alterations in arterial structure and function. Few other concluded mechanisms of the cardiovascular disorder are oxidative stress and increased collagen synthesis [15].

Atherosclerosis: The relation between atherosclerosis and homocysteine was proposed 40 years ago. A prothrombotic state arises in hyperhomocysteinemia due to minor changes in homeostasis. It is seen that homocysteine increases platelet synthesis of thromboxane A2 and enhances the expression of selectin, the platelet adhesion molecule; both conditions cause an increase in platelet adhesiveness and aggregation.

Homocysteine may also produce cytotoxic endothelial cell injury, abnormalities in the blood clotting factors and fibrinolysis, and alteration of cholesterol and lipoprotein metabolism. On examine *in-vivo* and *in-vitro* the effect of homo-cysteine on C-reactive protein and investigation on the associated mechanism on VSMCs explored that homocysteine induced the mRNA expression and the concerned protein in the form of C-reactive protein in vascular smooth muscle cells. The study stated that homocysteine can initiate inflammation in vascular smooth muscle cells by provocating the

production of C-reactive protein-mediated through NMDAr-ROS-ERK1/2/p38-NF-kB signaling pathway. This discovery imparts another evidence for homocysteine playing a role in the pathogenesis of atherosclerosis [16].

Coronary Artery Disease (CAD): According to a paper, the most common and conceivable mechanism for increased risk of coronary artery disease are endothelial dysfunction occurring due to changes in vascular endothelial concurrence and platelet coagulation changes. In various studies, it is already proven that an increase in homocysteine levels leads to a proliferation of vascular smooth muscle cells establishing a positive correlation between increased serum homocysteine with the severity of coronary artery disease [17].

Hypertension: Homocysteine is positively linked with both systolic and diastolic blood pressure. Some studies have revealed that if the concentration of homocysteine increased by 5 m cmol/L the systolic and diastolic blood pressure raises 0.7 mmHg and 0.5 mmHg respectively in men, while in women, the systolic and diastolic blood pressure increases by 1.2 mmHg and 0.7 mmHg respectively. It has been widely accepted that endothelial dysfunction serves as the basis for cardiovascular diseases, including hypertension [18].

Renal Dysfunction: Hyperhomocysteinemia is often linked to chronic renal failure. The level of homocysteine rises with declined renal function and progresses towards End-stage renal failure (ESRF). It was found that 85% of patients with chronic renal failure also suffered from hyperhomocysteinemia, but neither dialysis nor renal transplant could lead to bringing a reduction in the increased level of plasma homocysteine levels. Only 20-40% improvement was found in patients on hemodialysis with parallel folic acid therapy. However, this homocysteine-lowering therapy output could vary as it is influenced by factors such as differences within and between populations in sex, genotype, nutrition, and mandatory fortification. The complications due to hyperhomocysteinemia induced renal dysfunction include unordered addition of methyl group to DNA molecule along with changes in protein repair processes. The human kidney has a significant role in the metabolism of homocysteine. People with renal impairment tend to have a higher level of homocysteine than those who have a sound renal system [19].

Neuro and Respiratory Disorders: High level of homocysteine in the body is neurotoxic. Acute hyperhomocystenemia generates an energy imbalance in the hippocampus and liver of rats by inhibiting cerebral sodium, potassium ATPase activity and increase amygdala cells apoptosis. It also brings a decline to the activities of respiratory enzymes. According to research on scleroderma, it has been seen that the elevated level of homocysteine leads to lung impairment in patients suffering from scleroderma. In individuals with high homocysteine levels and low folate levels, high degree of lung anomalies is reported which could be associated with lung cancer also [20, 21].

Diabetes: Diabetes mellitus is a disease of high concern in today's society. Among which 90% of cases are type 2 diabetes mellitus. It was found that obese patients with type 2 diabetes had a higher level of homocysteine than non-obese diabetic patients. Levels of homocysteine were found higher in Diabetic nephropathy which is a serious complication of type 2 diabetes. It was already established that hyperhomocystenemia is related to albuminuria and impairment in the glomerular filtration rate. It is stated that higher plasma homocysteine levels are indicative of both risk and severity of diabetic nephropathy in type 2 diabetes mellitus. Another complication related to type2 diabetes, *i.e.*, diabetic retinopathy is the leading cause of poor vision and blindness worldwide.

On establishing a link between higher plasma homocysteine levels with diabetic nephropathy and other diseases, researchers took an interest in finding a lead in establishing a link between retinopathy and plasma homocysteine levels. A lot of studies were conducted which concluded to both some consistent and inconsistent results. As in the case of diabetes, the relationship between homocysteine levels and diabetic retinopathy was found to have a positive link, *i.e.*, elevated levels of homocysteine reported a higher risk of proliferative retinopathy. While high pervasiveness of retinopathy was found in patients with type 2 diabetes bearing fasting homocysteine levels to be higher than 15 mumol/L [22].

Osteoporosis: Patients with hyperhomocysteinemia are at higher risk of developing osteoporosis. Osteoporosis is a disease of the bone matrix which needs the synthesis of collagen cross-links and the sulfhydryl group of homocysteine constrains with cross-linking of collagen precursor making people suffering from hyperhomocystenemia at 50% risk of developing osteoporosis by the age of 16. Elevated homocysteine level is a strong risk factor for osteoporotic fracture in elderly people [23].

Risk of Cancer: Various studies are made in the direction of establishing a link between certain cancers and homocysteine levels. In some specimens from cancer patients under treatment, the alteration in levels of homocysteine corresponds with the tumor markers concentration. Various biochemical changes such as folate deficiency, oxidative stress, aberrant DNA methylation, and production of homocysteine thiolactone explain the reason for increased level of homocysteine in cancer patients. Malignant cells are marked by higher growth rates and higher methionine requirements due to the elevation in protein synthesis and transmethylation reactions. Normal cells are able to meet their methionine requirement from synthesized homocysteine. While the methionine dependent malignant cells in organs such as lung, kidney, breast, colon, and bladder are unable to convert homocysteine to methionine that leads to accumulation of homocysteine in the body [24].

Current Status: Currently, the epidemic character of hyperhomocysteinemia has been reported by many researchers [25, 26]. Increased level of homocysteine can cause a number of illnesses and is a well-known risk factor for cardiovascular diseases. It has been found that aged adults are more prone to hyperhomocysteinemia. Its ubiquity increases with age. It has been found that aged adults are more prone to hyperhomocysteinemia if their metabolic mobilization of homocysteine is interrupted or impaired due to certain extrinsic and intrinsic factors. Inherited or age-related metabolic disturbance in the mobilization of homocysteine is the most influential intrinsic factor however external and acquired factors like persistent consumption of folate-deficient diet, lack of vitamin B_{12} and increased level of oxidative stresses have been consistently observed [27, 28]. In an eccentric survey of Indian physicians, it has been found that the prevalence of hyperhomocysteinemia was 92.85% among male physicians and 81.60% among female physicians [29].

This shows a substantial role of sedentary lifestyle in the occurrence of this disease. According to Kumar *et al*., the prevalence of this disease is more in individuals having sedentary lifestyle (46.7%). Hence, it is considered a lifestyle disease. The prevalence of this disease has also been seen in several chronic conditions **Fig. 3** [30].

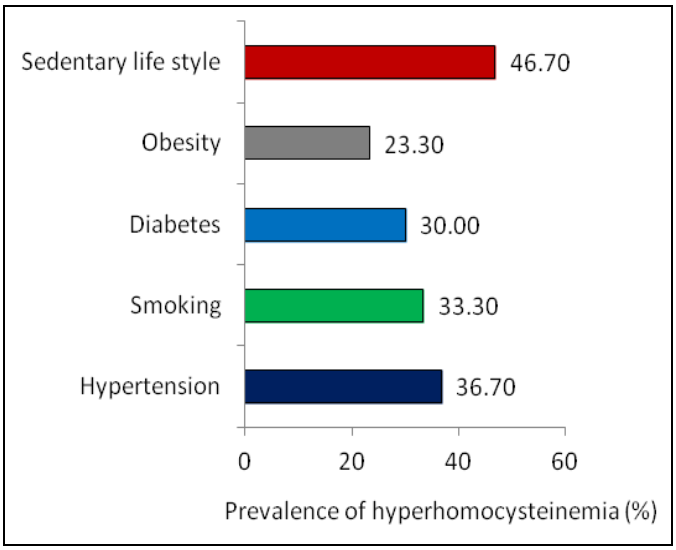

FIG. 3: PREVETANCE OF HYPERHOMOCYSTEINEMIA IN CHRONIC CONDITIONS

Pragmatic Strategies: The most pragmatic strategy for the management of hyperhomocysteinemia resides in dilatory blueprints and lifestyle of the patient. Homocysteine is a sulfur-containing amino acid found in blood and showed toxic effects at elevated levels. The peculiar profile of elevated homocysteine exhibits many biochemical changes and wide range of oxidative stress-induced cellular toxicity **Fig. 1-2**.

Many epidemiological details have demonstrated this disease as unfettered hazards for several organ-systems, including cardiovascular, nervous and renal systems. Based on the biotransformation mechanism of homocysteine, it can be seen that vitamin B_{12} has sufficient capacity to undo the conversion of methionine into homocysteine. Similarly, folic acid and vitamin B_6 have also noteworthy capacity to mobilize excess of homocysteine into their respective metabolites.

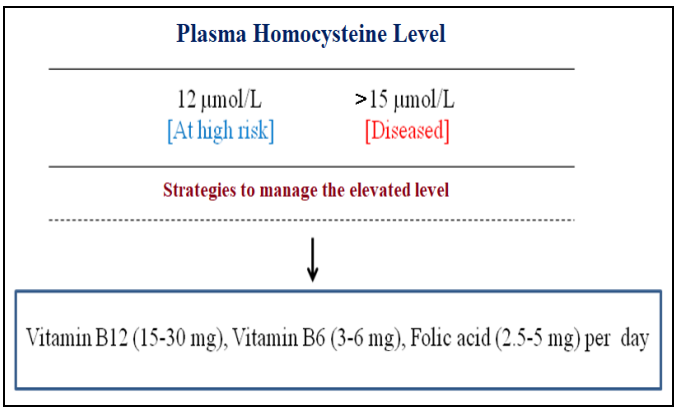

FIG. 4: MANAGEMENT OF HYPERHOMOCYSTEINEMIA THROUGH VITAMIN SUBSTANCES

Hyperhomocysteinemia is not only an autosomal recessively inherited defect but also a metabolic crisis that may be developed during certain conditions as for example, in malnutrition during pregnancy and in case of severe vitamin B_{12}, B_6 and folic acid deficiency in any adult. It is one of the biggest complications of cardiovascular disease. The deficiency of vitamin B_{12}, B_6, and folic acid reduces the enzyme activity and inhibits the breakdown of homocysteine, thus the concentration of homocysteine increases inside the blood and tissues beyond the threshold level [31].

In order to manage the perturbation of homocysteine, the vitamins **Fig. 4**, as well as methyl donor products, can be supplemented in order to activate the functions of methyltransferase and concerned enzyme for successful mobilization of elevated homocysteine.

CONCLUSION: Hyperhomocysteinemia is a metabolic syndrome associated with elevated plasma homocysteine and it is also considered as important jeopardy of morbidity and mortality all over the world. It affects not only humans but animal's physiology also. It has been seen in experimental animals that elevation of homocysteine concentration in their blood is either due to high methionine diet or low B-vitamins or both. Animals or humans suffering from hyperhomocysteinemia are at risk of cardiovascular disorder, renal impairment, and cerebral dysfunction. This illness affects other vital organs also. A sedentary lifestyle and cardiovascular anomalies are closely associated with this illness. Its prevalence is higher in male adults as compared to females. Nowadays, its instances are rapidly increasing in general population.

Several studies reported that plasma homocysteine level increases with age. Other influencing factors are the nutritional and metabolic offset of the patient. As per the existing literature and survey reports, this disease is inordinately visible across all sections of community. There is now an obligation of urgent researches and interventions so that the extreme elevation of serum homocysteine could be mobilized and managed effectively in less time.

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