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The interest in homocysteine has burgeoned during recent years. Homocysteine is now considered a risk factor for several diseases, particularly cardiovascular disease, where elevated levels of the amino acid is associated with increased risk of morbidity and mortality.

The advent of simple assays has changed homocysteine measurement from a research tool into a standard and routine clinical test. The following sections will discuss the biochemical background, as well as the association between elevated levels of homocysteine and disease.

**The History of Homocysteine**

Homocysteine was first described by Butz and du Vigneaud in 1932. It is a sulphur-containing amino acid that is closely related to the essential amino acid methionine and to cysteine.

An association between elevated homocysteine levels and human disease was first suggested in 1962 by Carson and Neil, who found high homocysteine concentrations in the urine of some children with mental retardation. The elevated homocysteine levels in these patients were caused by severe enzyme defects blocking the homocysteine metabolism.

This condition, homocystinuria, was later found to be associated with premature occlusive cardiovascular disease, even in childhood, and about 25% of patients died as a result of cardiovascular events before the age of 30.

In 1969, McCully described the vascular pathology in these patients, including smooth muscle proliferation, progressive arterial stenosis and haemostatic changes.

During the last 15 years it has been thoroughly documented that also moderately elevated homocysteine levels in serum or plasma is a strong and independent risk factor for occlusive arterial disease, and of venous thrombosis, and also predicts vascular and all-cause mortality. As many as 50% of patients with stroke and other atherothrombotic diseases have high homocysteine levels (greater than 15 micromol per litre (µmol/litre)).

In addition, hyperhomocysteinaemia is associated with adverse pregnancy outcome, such as spontaneous early abortion, placental vasculopathy and birth defects. It is not only neural tube defects (NTDs) but also cardiac malformations and cleft lip and/or palate, which are associated with higher homocysteine levels than in controls.

Many studies have also found an association between elevated homocysteine levels and impaired cognitive performance and dementia. Several prospective studies have now shown that folate and/or vitamin B12 status or elevated levels of homocysteine, even within the currently accepted reference range, predisposes for the development of dementia, or increases the rate of disease progress. An association with depression and other neuropsychiatric disorders is also found. There is also much focus on the association between carcinogenesis and impaired homocysteine metabolism.

The recent identification of several fairly common polymorphisms affecting the genes of enzymes participating in the homocysteine metabolism, and resulting in decreased enzyme activity has also lent the research some impetus. Some of these variations are shown to be associated with increased incidence of the mentioned conditions, such as birth defects.

Plasma homocysteine is already proven to be a useful predictor of cardiovascular as well as non-cardiovascular morbidity and mortality. The next step will be to reduce the incidence of these conditions by monitoring homocysteine levels.

There has been an exponential increase in the number of publications on homocysteine during the last decade, and about 7,000 articles are now filed in the MEDLINE database on the subject. Please refer to http://www.homocysteine.net for up-to-date publications on this area.

**Some Biochemistry**

All homocysteine found in human organisms is formed during the metabolism of methionine in the
methionine cycle (see Figure 1). Homocysteine is metabolised through two pathways: re-methylation or trans-sulphuration.

The re-methylation of homocysteine is directly dependent on the enzyme methionine synthase (MS) to which vitamin B_{12} is a co-factor and methyltetrahydrofolate (methylTHF), a substrate. This reaction is indirectly regulated by the activity of methylenetetrahydrofolate reductase (MTHFR), as this enzyme mediates the formation of methylTHF, (see Figure 1). This reaction therefore has a strong, indirect influence on the re-methylation of homocysteine.

In a few tissues, predominantly the liver and kidneys, an alternative pathway for the re-methylation of homocysteine to S-adenosyl methionine (SAMe) exists, but the majority of tissues, including the central nervous system, are entirely dependent on the MS-mediated recycling of homocysteine.

The remaining homocysteine is converted in the trans-sulphuration pathway to cysteine in two reactions requiring vitamin B_{6} as a co-factor. Cysteine is a precursor to glutathione, the major cellular redox buffer. The trans-sulphuration pathway also directs homocysteine to degradation and its ultimate removal as sulphate via urine.

Several common genetic variations of the gene for enzymes involved in the homocysteine metabolism are described in the scientific literature. A thermolabile form of MTHFR due to one such polymorphism (C677T polymorphism) affects between 10% and 20% of most populations in its homozygote form. It results in decreased enzyme activity and causes moderately increased total homocysteine. The impact on total homocysteine is, however, dependent on folate status and total homocysteine can generally be normalised by increased folate intake.

The interplay between the individual genetic background and environmental factors in the pathogenesis of many disorders is currently the subject of intense research. The concept emerges that an individuals’ genetic make-up may substantially affect an individuals’ functional vitamin status.

Thus, disturbances in the homocysteine metabolism, (either caused by deficiency of cofactor(s) or by some genetic enzyme defect) normally results in a cellular accumulation of homocysteine, with subsequent increase in homocysteine levels in the circulation.

Homocysteine exists in several forms. The sum of all homocysteine forms is termed ‘total homocysteine’. During the last decade, several assays for total homocysteine have been developed. The recent introduction

**Figure 1: Homocysteine Metabolism**
of enzyme immunoassays, now allows determination of total homocysteine in most routine laboratories.

**Why Homocysteine is Harmful**

The methyl group of SAMe is required for over 100 known reactions, including methylation of nucleic acids (DNA and ribonucleic acid (RNA)), proteins, phospholipids, myelin, polysaccharides, choline and catecholamines.

It is understandable that reduced methylation capacity may have profound effects on cellular growth, differentiation and function. This may be critical in many situations, not least in the ageing brain, where neurochemical processes related to methylation may be declining; in psychiatric and neurological diseases; for the rapidly growing foetus and infant; and also for carcinogenesis by reducing DNA repair. Studies on children with severe inborn errors resulting in defective methyl group synthesis, support the theory that deficient methylation is one of the leading causes of demyelination.

The synthesis of glutathione is dependent on the trans-sulphuration of homocysteine. Glutathione is an important endogenous antioxidant. It protects many cellular components against oxidative damage and other types of injury. Glutathione also maintains α-tocopherol in its reduced form, either by a direct reaction or by a pathway involving ascorbate. Glutathione may also have protective vascular effects, possibly by interaction with nitric oxide.

Finally, certain forms of homocysteine itself are proposed to have oxidative effects and to react with proteins leading to protein damage.

**Why Homocysteine Levels Increase**

Plasma total homocysteine increases throughout life in both sexes. Before puberty, both sexes have low and similar levels (mean values of about 6 µmol/litre). During puberty, levels increase, more so in boys than in girls. At the same time, total homocysteine distribution starts to show a distortion in certain populations with more high levels occurring.

Throughout life, mean total homocysteine increases by between 3 µmol/litre and 5 µmol/litre. At the age of 40 to 42, mean values are about 11 µmol/litre and 9 µmol/litre in men and women, respectively.

After the menopause, the gender-related differences in total homocysteine diminish, but concentrations remain lower in women than in men. The gender disparity may be explained by hormonal status, greater muscle mass in men and gender-related lifestyle differences during pregnancy, total homocysteine concentrations are reduced by up to 50%. Higher plasma volume, or increased metabolic rate and glomerular filtration, and foetal homocysteine metabolism may be an explanation for this.

The higher total homocysteine concentrations seen in the elderly may be caused by many factors such as malabsorption owing to prevalent atrophic gastritis or insufficient nutritional supply of vitamins, lower nutritional intake, a slow-down of the metabolism, reduced kidney function and other physiological, age-related changes. Moreover, many drugs interact either by reducing the absorption of cofactors, or by increasing the catabolism of the vitamins. Certain diseases also influence the homocysteine metabolism. Nutritional and other lifestyle factors are important determinants of total homocysteine, and may explain of the observed variation between different populations.

Smoking, high alcohol intake and coffee consumption also interact by increasing the catabolism of vitamins or reducing the absorption of them. Several other lifestyle factors are also of importance for the metabolism of homocysteine.

Lack of physical exercise, obesity and even stress are also associated with hyperhomocysteinaemia. The plasma levels of total homocysteine are thus influenced by many factors (see Figure 2).

Several factors may therefore contribute to a patient’s hyperhomocysteinaemia, even if vitamin status, primarily of folate, vitamin B12 and B6, is a major determinant. Enzyme defects, disturbed...
distribution of the vitamins, which are actively transported by means of specific transport proteins and receptors, interaction with lifestyle factors, diseases and drugs, or a combination of these factors can thus impair homocysteine metabolism with various metabolic disturbances as a consequence. Increased total homocysteine levels are a sensitive marker of such disturbances.

Many of the factors causing hyperhomocysteinaemia, for instance, unhealthy lifestyle factors, can be eliminated. The diagnosis of hyperhomocysteinaemia could therefore be used as an incentive for the patient to opt for a healthier lifestyle.

**Efficacy of Homocysteine-lowering Treatment**

Supplementation with folic acid during the periconceptional period and pregnancy has been shown to substantially decrease the incidence of NTDs and other birth defects. It may also reduce the incidence of some pregnancy complications, such as spontaneous abortion.

Reduction of homocysteine levels has also been shown to have a positive impact on cognitive performance in elderly individuals with mild cognitive impairment, and to increase regional cerebral blood flow. However, early intervention seems crucial. Severe underlying neuronal and vascular damage is hardly likely to regress, although studies in animals suggest the possibility of reversibility of neuronal damage. Vitamin treatment of patients has also been demonstrated to influence the rate of progression of atherosclerosis, and to increase endothelium-dependent blood flow.

Prophylactic screening of homocysteine status in patients at risk and prophylactic vitamin supplementation can, based on a substantial amount of available data, be expected to have considerable impact on health. Continuing intervention trials involving over 70,000 subjects will definitely answer the question, to which extent such supplementation will affect the occurrence, recurrence or progression of potential homocysteine-related diseases.

**Recommended Reading**


Two recently published books can also be recommended:


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