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Cardiovascular diseases and homocysteine, a short summary of a long story.

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Nowadays, vascular disease is the leading cause of death and disability in the western world. According to the World Health Organisation report, 16.6 million people around the globe die of cardiovascular diseases each year. For example in 2001 the American Heart Association (AHA) reported that there were 7.2 million deaths from heart disease and 5.5 million from stroke. Another 15 million each year survive minor strokes and may use drugs for better life.

We should also remember that 60 million people with high blood pressure are at risk of heart attack, stroke and cardiac failure. To summarize the situation, cardiovascular diseases contributed in 2001 to nearly one third of global death. Cardiovascular disease risks factors in developing countries are the following:

- prevalence of high blood pressure, economic transition, urbanization, industrialization and globalization bring about lifestyle changes that promote stress and heart disease,
- tobacco (it generates approximately 30% of cardiovascular deaths worldwide),
- high cholesterol (estimated to cause about 4.4 million death and a level of less 5.0 mmol/l is suggested for both primary and secondary prevention of cardiovascular diseases),
- the global burden of diabetes in adults,
- overweight and obesity,
- and finally, excessive alcohol intake (near than 38% of men and 21% of women consume more than the recommanded daily benchmarks)(AHA).

A response to cardiovascular disease was found with the development of various therapeutic drugs corresponding to the diversity of the diseases, but this clinical care is costly and prolonged; we also have to note that cardiovascular disease affects individuals in their peak mid-life years, disrupting the future of the families dependent on them and undermining the development of nations by depriving them of workers in their most productive years (AHA).

On the other hand, there is another risk factor, hyperhomocysteinemia. Pioneers who first described this factor were Buty and du Vigneau in 1932; the association between elevated homocysteine levels and human disease was suggested in 1962 by Carson and Neil and in 1969 McCully described the vascular pathology in these patients (smooth muscle proliferation, progressive arterial stenosis, haemostatic changes).

Homocystein, an amino acid, precursor of cysteine and glutathione, is generated in almost all tissues in the human body and approximatively 80% is bound to proteins in human body and the remaining 20% is found in three forms: oxidized, mixed disulfide cysteine and a small amount of free homocysteine. The normal range of homocysteinemia is about 8.0 to 14.0 mmol/l for male subjects and 6.0 to 12.0 for female subjects. High levels of homocysteine in the body due to metabolic abnormalities (5,10 methylenetetrahydrofolate reductase deficiency, cystathionine beta synthase) can lead to the auto-oxidation of homocysteine and its convertion to toxic free radicals. So, we can find different forms of hyperhomocysteinemia: -

- moderate (16-30mmol/l),

- intermediate (31-100 mmol/l)
- and severe (> 100mmol/l).

The prevalence of hyperhomocysteinemia is 5% in the general population and 13-41% among patients with symptomatic atherosclerotic vascular disease. The mechanisms of homocysteine toxicity could be classify as endothelial dysfunction generation (impairment of nitric oxide production, over-production of reactive oxygen species, increased of the von Willebrand factor and thrombomodulin, increased tissue factor production), effects on coagulation factors, participation in oxidation stress, and the oxidation of low density lipoproteins.

Now we can identify the worst effects of high extracellular levels of homocysteine and its correlation with endothelin-1 defect (homocysteine decreases endothelin-1 expression by interfering with the AP-1 signalling pathway), and the possibility that L-homocysteine sulphinic acid and other acidic homocysteine derivatives are potent and selective metabolic glutamate receptor agonists. The growth effect of homocysteine on vascular smooth muscle cells may be mediated by a novel NMDA-like glutamate gated calcium ion channel receptor, a receptor with anatomic and physiological properties distinct from other NMDA receptors.

Homocysteine blood levels are affecting by age, sex (explained by the effects of sex hormones on homocysteine metabolism), smoking and genetic factors. Recently it has appeared that hyperhomocysteinemia may contribute to heart failure and results have shown that high homocysteine levels were associated with a risk of heart failure in both men and women but appeared to be more consistent in women than men (Vasan and colleagues). And while there is not strong evidence to suggest that lowering homocysteine levels is beneficial, we could say that people at high risk should be sure to get enough folic acid, from foods as leafy greens and fortified breakfast cereals, as well as two other B vitamins, B6 and B12. These vitamins are known to aid the breakdown of homocysteine in the body. Other diseases can be associated with hyperhomocysteinemia such neural tube defects, pernicious anaemia, renal impairment, hypothyroidism, malignancy, severe psoriasis, myocardial infarction or thrombogenesis.

Suggestions for further reading

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