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Editorial

Homocysteine research – where do we stand and where are we going?

The 4th Conference on Hyperhomocysteinemia was held in Saarbruecken, Germany from April 14 to 16, 2005. With the continual interest in hyperhomocysteinemia (HHcy), B-vitamin deficiency and related diseases, researchers, doctors and medical practitioners from around the world were inspired to attend the 4th Conference on Hyperhomocysteinemia, and to understand the progress that is being made in this field of research. More than 300 participants from 26 countries came together to exchange their experiences in the area of HHcy. A total of 40 guest speakers from 12 countries, from Europe and America, spoke about the latest developments and present knowledge of the different aspects of HHcy and related diseases. There is ongoing and increasing interest in HHcy, which might be partially explained by the fact that the medical areas that are affected by HHcy are still growing. The number of PubMed-listed articles regarding HHcy has increased markedly during the last decade, and 2 years ago, we organized the 3rd Conference on Hyperhomocysteinemia. In the meantime, many new results have expanded our knowledge of HHcy and strengthened its role as a risk factor for diseases. This gave us reason to organize the 4th Conference on Hyperhomocysteinemia.

The role of HHcy as a risk factor for cardiovascular disease was emphasized during the conference. This role has been supported by a few recent meta-analyses. Wald et al. outlined that lowering of homocysteine (Hcy) by 3 μmol/L is expected to reduce the risk of atherothrombotic vessel diseases (coronary vascular disease, stroke, venous thrombosis) by approximately 20% (1). A prompt decline in stroke mortality in the USA of 10–15% annually since 1998 has been reported, which is substantially higher than the annual decline before the era of folic acid fortification of grain products (2). Recent discord due to an apparent incongruity between results of the Swiss Heart and the FACIT trials regarding the efficiency of lowering the rate of restenosis after folate therapy has emphasized that the interpretation of different studies should be carried out with caution, otherwise misinterpretation may arise (3, 4). Moreover, factors such as the dose and duration of vitamin treatment, in addition to the stent used and the accompanying risk factors, may all potentiate or ameliorate the effect of folate on major adverse coronary events. The results of the Swiss Heart and FACIT trials are not contradictory; instead, they may even complement each other in the regard that high-risk patients profit from Hcy-lowering by vitamin therapy, which may significantly reduce major adverse coronary events (3). The relation of Hcy to chronic heart failure (CHF) is also a recent important aspect of HHcy and cardiovascular disease. Prospective studies on Framingham Study participants have confirmed that plasma Hcy is a major and independent risk factor for the development of CHF (5). Furthermore, Hcy has been related to clinical, echocardiographic, and laboratory parameters (N-terminal pro-brain natriuretic peptide, NT-proBNP) of CHF, suggesting a relation between Hcy and the severity of CHF (6).

HHcy has also been identified a risk factor for venous thrombosis in both retrospective and prospective studies. Oxidative stress is one important mechanism by which HHcy may increase the risk of recurrent venous thrombosis (7). In patients with a first episode of cerebral vein thrombosis (among other variables, such as folate and *MTHFR* mutation), HHcy has been associated with an increased risk of cerebral vein thrombosis, and this effect was even greater in women using oral contraceptives (8).

Approaches for correcting HHcy in patients with renal disease were reported, which provided evidence that Hcy can be normalized in patients with end-stage renal disease (ESRD) by intravenous administration of therapeutic dosages of B-vitamins (9) and N-acetylcysteine (10). However, it remains questionable whether normalization of plasma Hcy by vitamin therapy reduces the cardiovascular risk or improves hypomethylation in these patients (11). Further studies are warranted, which will hopefully provide more information on this aspect. Some recent studies reported that dialysis patients who had higher plasma Hcy had a better prognosis than those with lower Hcy. This is explained by the role of Hcy as a marker of the nutritional state and malnutrition is related to poor outcome in renal patients. This reverse epidemiology should not call into question the expected beneficial effects of Hcy-lowering treatment.

The relation between Hcy and hypomethylation has become a topic of utmost interest because hypomethylation is one important mechanism by which Hcy may be cytotoxic. Derangements in one-carbon metabolism may affect the integrity of the genome by altering DNA methylation patterns and/or causing elevated uracil insertion in DNA. Changes in DNA methylation are discussed in aging processes, cancer development and vascular disease. An interaction between folate and aging has been described in an animal model (12). In another animal model, vitamin B_{12} deficiency was also found to cause DNA hypomethylation, thereby representing a predisposition to cancer (13).

A relatively new but interesting aspect is the relation between Hcy and cognitive performance. A study in the stroke- and dementia-free Framingham Offspring Cohort (>2000 elderly people) has demon-

strated that Hcy is related to lower cognitive performance in elderly subjects, but not in younger adults (14). Prospective investigations in a normal aging population have indicated that HHcy is related to worse cognitive performance during a 6-year follow-up (15). In addition, it was found in cognitively normal elderly subjects that HHcy was independently associated with concurrent cognitive impairment, as measured by the Mini Mental State Exam (MMSE) (16).

The relation between osteoporosis and HHcy is a new and encouraging aspect in Hcy research, which may have practical consequences, especially for elderly people. van Meurs et al. reported an approximately two-fold higher risk for fractures in subjects in the highest age-specific quartile of Hcy concentrations (17). This association was found to be independent of bone mineral density and other risk factors for fracture. In post- and perimenopausal women, plasma Hcy concentration correlated with the bone resorption marker desoxypyridinoline cross-links (DPD), but not with the bone formation marker osteocalcin, indicating that HHcy may stimulate bone resorption (18). The effect of Hcy on osteoclast activity has been tested in vitro. Higher Hcy concentrations induced increased activity of tartrate-resistant acid phosphatase and cathepsin K, suggesting enhanced bone resorption, probably mediated by elevated osteoclast activity (19).

HHcy might be involved in pregnancy complications and poor pregnancy outcomes. Findings in Syrian pregnant women who developed preeclampsia demonstrate that elevated concentrations of Hcy, cystathionine and methylmalonic acid, which were very frequent in these patients, are indicative of poor nutritional status, which is a risk factor for preeclampsia (20). Reduced cellular vitamin B_{12} status in women who gave birth to a child with a neural tube defect (NTD) has been found, suggesting disturbed vitamin B_{12} metabolism in these mothers (21). Therefore, in addition to folate, vitamin B_{12} supplementation may further reduce the risk of NTDs. Moreover, elevated Hcy is associated with pre-term birth and low birth weight, and was also observed at higher prevalence in women with a history of miscarriage. These associations indicate the necessity for folic acid supplementation throughout pregnancy, and not just periconceptionally (22). More importantly, maternal vitamin B_{12} status is a major determinant of Hcy levels in newborns, and maternal concentrations of the metabolic markers predict the values in fetal blood at birth (23). These findings emphasize the importance of high maternal vitamin B_{12} status during pregnancy.

Hcy may adversely affect blood vessel walls by homocysteinylation of specific protein targets (albumin, transthyretin, and fibrinonectin), which may suffer from a loss of function and thus promote the progression of atherosclerosis. Protein homocysteinylation is also present in hemodialysis patients, with possible functional consequences in terms of protein function (24). Hcy-thiolactone is one highly reactive form of Hcy that may result in the formation of N-Hcy-protein adducts. Such adducts possibly function as neo-self antigens and induce an autoimmune response (25). It is hypothesized that N-Hcy-proteins may contribute to immune activation, an important modulator of atherogenesis.

Other intermediate products of Hcy metabolism have been related to vascular diseases and vessel wall properties. Some of these products are S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH) and 5-methyltetrahydrofolate (26). Recently, the lowering of free adenosine concentrations following an increase in Hcy has been proposed as a potential causal factor for HHcy. Findings in homocysteinuric patients have suggested that enhanced cellular adenosine uptake limits adenosine receptor stimulation and hence may contribute to the cardiovascular complications of this disease (27). NO synthesized from L-arginine by NO synthase is a potent vasodilator and anti-aggregant in the vascular wall. In vitro treatment of human endothelial cells with Hcy at higher concentrations led to endothelial NO synthase uncoupling through a reduction in intracellular tetrahydrobiopterin availability and thus to reduced NO formation (28).

The 4th Conference on Hyperhomocysteinemia gave an update on the present knowledge and state of Hcy research and provided information about the actual hot spots in this area. I am confident that the papers and discussions contributed to further progress in this field of science, above all in the practical sphere, in the diagnosis and treatment of patients. The course of the conference and the results allow us to be optimistic and will stimulate us to continue our efforts to make further progress in our field of research.

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