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Editorial

Homocysteine research: alive and kicking!

The first World Congress on Hyperhomocysteinaemia was held in Saarbruecken, Germany from June 5th to 9th, 2007. This congress was a highlight as it unified the 5th Conference on Hyperhomocysteinaemia in Saarbruecken with the 6th International Conference on Homocysteine Metabolism. This unification reflects our efforts to effectively exchange experiences of researchers in the field of homocysteine (HCY) from all over the world. The steadily increasing interest in research on hyperhomocysteinaemia is objectively demonstrated by the annually increasing number of PubMed listed publications. Over the last 10 years this increase was five-fold. With the continual interest in HCY research, B-vitamin deficiency and related diseases, researchers, doctors and medical practitioners from around the world were stimulated to attend the first World Conference on Hyperhomocysteinaemia. More than 400 participants from 47 countries and from all continents came together, to exchange their experiences in this research field.

The role of HCY as a risk factor of cardiovascular diseases is presently under debate. Despite the strong evidence for a causal relationship between hyperhomocysteinaemia and cardiovascular diseases, an open question in the causality issue remains; can HCY-lowering treatment reduce the incidence of cardiovascular diseases? Worldwide, approximately 52,000 people are currently included in various prevention trials to address this issue. These studies, reviewed by the B-Vitamin Treatment Trialists' Collaboration in this issue (1), are expected to be completed in 2011. Some secondary intervention trials have been completed meanwhile, VISP (2), NORVIT (3) and HOPE-2 (4). In the NORVIT study, 3749 patients with myocardial infarction were treated with B-vitamins over 3 years. The VISP study included 3860 stroke patients who were supplemented with low or high doses of B-vitamins for 2 years. In the HOPE-2 trial, 5522 patients suffered from vascular disease or diabetes and were treated over a period of 5 years with B-vitamins. However, these trials failed to show an improvement in cardiovascular end points. A serious problem of these secondary prevention trials is that treatment was not compared to non-treatment. Instead, these trials only compared conventional treatment versus conventional treatment plus vitamins. Patients with cardiovascular disease receive various medications, including ASS, statins and ACE inhibitors, of which some have proven to be effective in secondary prevention. This important confounder makes it difficult to find an additional or an independent effect for the vitamins. To avoid a type II error in this case, meaning the false declaration of B-vitamin treatment as ineffective, a very large number of participants must be included in randomised trials in order to demonstrate vitamin effects. For a risk reduction of 10%, 20% and 40%, respectively, the number of study participants must be at least 60,000, 12,000 and 3000, respectively (5). Another serious limitation of the current intervention trials is that the duration of these trials is insufficient to assure statistically valid results (3). Therefore, it is not surprising that these studies do not demonstrate positive results in terms of reduction of cardiovascular risk. Wald (5) expressed his doubt about the significance of these secondary prevention trials. Because of the lack of statistical power, these trials should not have been published as single trials, but only as meta-analyses. Other possible reasons for the lack of therapeutic effects are in some trials, amongst others, the beginning of folic acid fortification of grain products in the USA and Canada and the fact that vitamin B_{12} status and kidney function were not taken into consideration. In addition, in the HOPE-2, VISP and NORVIT studies, normohomocysteinaemia or normal vitamin status was considered as exclusion criteria. Last but not least, some intervention trials recruited patients shortly after a cardiovascular event, which is the critical period with the highest mortality and morbidity incidence independent of any medications. An improved patient selection should increase the statistical power of future studies.

The presenters of the results of the NORVIT intervention trial published in 2006 announced ''homocysteine is dead'' (3). However, an old proverb states that ''the condemned live longer''. This also holds true for HCY research, which is still alive and extends its importance steadily. A very recent meta-analysis by Wang et al. (6) and papers read at the World Congress on Hyperhomocysteinaemia (5, 7, 8) have contributed a great deal in clarifying this inconclusive situation. The meta-analysis by Wang et al. (6), which included eight randomised trials with approximately 16,841 patients, provided convincing evidence that lowering of plasma HCY by folic acid supplementation reduces the risk of stroke significantly by approximately 18%. The reduction of stroke risk was even higher when the treatment exceeded 36 months (–29%), the HCY-lowering was more than 20% (–23%), the patients had no stroke history (–25%) and the patients consumed no folic acid enriched grain products (–25%) (Table 1). The authors concluded that folic acid supplementation can effectively reduce the risk of stroke in primary and secondary prevention. This is in line with results from the USA and Canada, where food fortification with folic acid since 1998 has contributed to a decreased stroke risk (14). Since 1998, 13,000 less stroke deaths have been registered annually in the

Table 1 Relative risk for stroke and change in homocysteine concentration (6).

	HCY decrease, μmol/L	HCY change, %	Stroke events/total patients		RR (95% CI)
			Intervention	Control	
Toole et al. (2)	−2.3	−17.2	152/1877	148/1853	1.04 (0.84–1.29)
Liem et al. (9)	−2.6	−21.5	8/300	12/293	0.65 (0.27–1.57)
Lonn et al. (4)	−3.2	−26.2	111/2758	147/2764	0.76 (0.59–096)
Bonaa et al. (3)	−3.8	−29.0	49/1872	27/943	0.91 (0.58–1.45)
Zoungas et al. (10)	−4.7	−17.4	8/156	18/159	0.45 (0.20–1.01)
Wrone et al. (11)	−3.6	−10.9	19/342	8/168	1.17 (0.52–2.61)
Righetti et al. (12)	−15.1	−39.4	4/37	10/52	0.55 (0.19–1.62)
Mark et al. (13)	NR	NR	22/1657	35/1661	0.63 (0.37–1.07)

NR, not reported.

USA. The meta-analysis by Wang et al. (6) also underlines the role of the duration of treatment for a successful risk reduction. Only intervention studies lasting longer than 3 years have responded with a significant lowering of stroke risk. The mean observation period of the VISP and NORVIT study was only 2 and 3 years, respectively; only the HOPE-2 study lasted 5 years. Moreover, studies under 3 years do not improve their statistical power in meta-analyses. From studies with cholesterol lowering drugs, it is well known that longer observation periods are essential. The risk reduction in stroke risk by B-vitamins seems to be greater than in cardiovascular diseases. This was confirmed by Spence et al. (15) in an efficacy analysis of the VISP trial. Perspectives on this analysis are discussed in this issue (16). A prospective meta-analysis of the ongoing HCY-lowering trials which include approximately 50,000 patients will be available in some years from now. Final statements on the efficacy of B-vitamins in risk reduction regarding cardiovascular diseases should be postponed until the meta-analyses are published. The very promising data from the meta-analysis by Wang et al. (6) regarding reduction of stroke risk together with the valuable contributions presented at the World Congress on Hyperhomocysteinaemia have strongly stimulated and motivated researchers from around the world.

Another important current issue in HCY research deals with chronic heart failure (CHF), a new and very promising area. CHF is a major public health problem causing considerable morbidity and mortality (17). In the elderly population (>75 years), the prevalence of CHF exceeds 10% (18). Recently, plasma HCY has been suggested to be increased in CHF patients potentially representing an additional important risk factor of CHF (19). Experimental hyperhomocysteinaemia in rats caused increased BNP concentration in myocardial tissue, but also higher incidence of elevated plasma BNP level (20). In superfusion experiments utilising myocardial tissue, rising HCY concentrations in superfusion medium caused increasing BNP excretion (20). Thus, the results presented at the conference support a causal relationship between hyperhomocysteinaemia and CHF. Available data suggest that hyperhomocysteinaemia contributes to adverse cardiac remodelling characterised by interstitial and perivascular fibrosis resulting in increased myocardial stiffness (21). In addition, hyperhomocysteinaemia seems to affect the pump function of the myocardium. Therefore, hyperhomocysteinaemia might be an important aetiological factor in CHF.

In addition, a major topic at the congress was HCY as a risk factor for cognitive impairment, dementia and other neurodegenerative diseases (22). The potential improvement of cognitive function by means of HCY-lowering with B-vitamins has also been discussed (23). Epidemiological follow-up studies showed that plasma concentrations of HCY predict the risk of neurodegenerative diseases. Many neurotoxic effects of hyperhomocysteinaemia or vitamin deficiency are explained by hypomethylation of functional proteins or genes or oxidative stress (24). Furthermore, hypomethylation caused by hyperhomocysteinaemia and low B-vitamin status has been linked to key pathomechanisms in dementia. B-vitamin supplementation holds promise for preventing and reducing the risk of neurological damage. Patients with Parkinson disease, especially those receiving L-Dopa, had increased HCY and low serum folate (25). Other publications suggest associations between hyperhomocysteinaemia and multiple sclerosis (26), as well as epilepsy (27). Some studies even suggested a causal role of hyperhomocysteinaemia in epilepsy (28). In addition, hyperhomocysteinaemia is very common in elderly people and its prevalence is growing because of our rapidly aging population. All in all, it seems important to identify subjects with vitamin deficiency and to ensure sufficient vitamin intake for primary and secondary prevention of several neuropsychiatric disorders.

A further important aspect of HCY research is the relationship between hyperhomocysteinaemia and osteoporosis (29). Elderly people are again the most important risk group and identifying this risk factor might have marked clinical implications. Prospective clinical trials have linked high HCY plasma levels and low B-vitamin concentrations in adults with an increased risk of fragility fractures and osteoporosis (30, 31). Osteoporotic patients have low bone mass and deterioration of osseous micro-architecture, resulting in decreased bone strength and increased risk of fragility fractures (32). The special interest in hyperhomocysteinaemia as a risk factor for osteoporosis is, on the one hand, due to its high prevalence

in elderly people, and on the other hand, HCY can easily be modified by B-vitamin supplementation. Experimental hyperhomocysteinaemia in rats has confirmed a stimulated bone resorption and accumulation of HCY in bone tissue by collagen binding (33). In vitro experiments showed that HCY and low B-vitamin levels stimulated osteoclast activity and caused a shift towards bone resorption. The new data presented at the conference supports the hypothesis that hyperhomocysteinaemia (and possibly B-vitamin deficiencies) adversely affects bone quality by a stimulation of bone resorption and disturbance of collagen cross linking. Thus, a causal involvement of hyperhomocysteinaemia in osteoporosis is suggested.

DNA methylation is a major epigenetic modification of the genome that regulates gene expression. The relation between one-carbon metabolism and DNA methylation is an important issue that also attracts much scientific attention (34). Derangements in one-carbon metabolism may, on the one hand, affect the integrity of the genome by altering DNA methylation patterns, and on the other hand, cause defective DNA synthesis by increased uracil incorporation in DNA. Hypomethylation is one important mechanism by which HCY may be cytotoxic. Changes in DNA methylation are discussed in aging processes, cancer development and vascular disease (35). S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) are intermediate products of HCY metabolism playing a key role in methyl group transfer. SAM and SAH have been related to many diseases, such as atherosclerosis, renal diseases, neurological diseases and cancer (35). The determination of SAM and SAH provides more detailed information on possible effects on neurotransmitter formation, DNA synthesis and DNA methylation. The World Congress has clearly shown that we are now right at the beginning of understanding these processes and their relations to diseases.

In summary, the first World Congress on Hyperhomocysteinaemia provided an update on the present knowledge and state of HCY research worldwide. I am sure that the papers and discussions have contributed a great deal to further progress in this field of science. The organisers are convinced that this interdisciplinary field of research will gain more importance in the near future and will substantially contribute to public health. The new data that folic acid supplementation can effectively reduce the risk of stroke in primary and secondary prevention are encouraging and will influence the engagement in HCY research strongly. As a result of the congress, it has stimulated us to continue our efforts in making further progress in our favourite research field, hyperhomocysteinaemia.

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