Is Hyperhomocysteinemia an Important Risk Factor of Cardiovascular Disease?

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In the last couple of decades many studies have been carried out on the association of moderately high plasma levels of total homocysteine (tHcy) with coronary artery disease, cerebrovascular disease, peripheral artery disease and venous thromboembolism. Most studies showed a positive association between tHcy and thrombosis risk. However, despite this, many investigators are still skeptical about the importance of hyperhomocysteinemia as a thrombosis risk factor, because some important aspects of the association of hyperhomocysteinemia with cardiovascular diseases still need to be clarified.

In the following few lines I will try to explain why I consider hyperhomocysteinemia a proven risk factor for cardiovascular diseases and then I'll address the question of whether or not it is an important risk factor.

Is Hyperhomocysteinemia a Proven Cardiovascular Risk Factor?

Case-control, cross-sectional and prospective studies have clearly proven that there is a graded association between the plasma levels of total homocysteine (tHcy) and the risk for occlusive arterial and venous disease [1,2]. Despite this, hyperhomocysteinemia has not been universally accepted yet as an established cardiovascular risk factor. The skepticism of some physicians and investigators stems from the lack of proof that hyperhomocysteinemia causes cardiovascular diseases and that lowering tHcy reduces the cardiovascular risk (which actually sounds tautological, for the reasons explained below). However, the association between a risk factor and a disease is not necessarily causal [3-5]. By definition, risk factors are nothing more than statistical predictors of the risk for a disease. The demonstration of their causal association with that disease is strictly dependent on the demonstration, within proper randomized trials, that their modification alters the risk [5]. The logical consequence is that causality can be indisputably proven only for those risk factors that are modifiable. The universal acceptance as cardiovascular risk factors of age, male sex, and family history for premature atherosclerotic disease, which cannot be modified, implies that it is universally accepted that causality is not a criterion to be necessarily fulfilled by a risk factor. I do not see any good reason to make exceptions for hyperhomocysteinemia.

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As already mentioned, the evidence of the association of hyperhomocysteinemia with cardiovascular diseases is overwhelming. This association was demonstrated not only in case-control studies, but was also confirmed by the majority of prospective studies, especially those that enrolled patients at high cardiovascular risk [1]. Hyperhomocysteinemia fulfils all the minor criteria for causality [5], with the only exception of the so-called "biological plausibility", because we do not know yet the biological link between hyperhomocysteinemia and atherosclerosis and thrombosis. In vivo studies indicated that both chronic [6,7] and acute (induced by an oral methionine loading) [8-13] hyperhomocysteinemia impair the endothelium-dependent flow-mediated dilation of the brachial artery, but it is uncertain whether this effect is relevant and explains the association of hyperhomocysteinemia with atherogenesis and thrombogenesis. Be as it may, I believe that lack of biological plausibility does not necessarily imply the lack of a causal association between a risk factor and a disease: it may simply mirror our ignorance of the pathogenesis of that disease.

Further evidence of causality recently came from the demonstration of the association between cardiovascular risk and mutant 677T allele of the gene encoding for methylene-tetrahydrofolate reductase (MTHFR) [14,15], which is associated with decreased enzymatic activity and predisposes to hyperhomocysteinemia [16,17]. Finally, although it is true there is no demonstration yet that correction of mild/moderate hyperhomocysteinemia reduces the cardiovascular risk, one should not disregard the clear evidence that the very high cardiovascular risk of patients with homocystinuria is decreased by the supplementation of vitamins that lower their very high plasma tHcy levels [18].

Based on the above considerations, I think that hyperhomocysteinemia should be considered a proven cardiovascular risk factor, and that its causal role is not unlikely. A recent study in a Finnish populations, published only in abstract form, showed that hyperhomocysteinemia is also a useful risk factor, because it improves cardiovascular risk prediction modelling [19]

Is Hyperhomocysteinemia an Important Cardiovascular Risk Factor?

Hyperhomocysteinemia is not a major risk factor for cardiovascular disease. A recent meta-analysis showed that the strength of the association between homocysteine and the risk for ischemic heart disease or stroke is lower than that reported by previous summary analysis [2]. It showed that a 25% lower usual tHcy level (corresponding to about 3 $\mu\text{mol/L}$) was associated with an 11% lower risk for ischemic

heart disease and 19% lower stroke risk. Albeit modest, the relative risks were statistically significant, also after taking into account traditional cardiovascular risk factors. The 25% reduction in plasma tHcy levels that was considered in this meta-analysis is equivalent to the mean change in plasma tHcy concentration that is obtainable with folic acid supplementation [20]. If the ongoing clinical trials eventually show that decreasing tHcy with vitamin supplementation is indeed associated with a reduction in cardiovascular risk, then the potential implication for public health would still be very important, considering the high worldwide incidence of cardiovascular diseases.

An example of the impressive consequences on public health that treatment of hyperhomocysteinemia with vitamins could have comes from a recent report from the Centers for Disease Control and Prevention's National Center on Birth Defects and Developmental Disabilities in Atlanta, which was delivered during the 44th annual Conference on Cardiovascular Disease Epidemiology and Prevention of the American Heart Association in San Francisco in March 2004 [21]. In 1996, the United States Food and Drug Administration required grain products be fortified with folic acid to reduce the risk of neural tube defects in newborns. The researchers hypothesized that folic acid fortification might offer a secondary benefit of reducing serum tHcy concentrations in the population as a whole, which might lead to a decline in death rates due to cardiovascular disease and stroke. Fortification of flour with folic acid was shortly followed by a doubling of the average serum folate concentration, from 6.6 ng/mL to 15 ng/mL, and an average 14 percent reduction of the serum homocysteine concentration, from 9.6 $\mu\text{mol/L}$ to 8.3 $\mu\text{mol/L}$. The research team estimated that 31,000 stroke-associated deaths and 17,000 deaths related to ischemic heart disease may have been prevented each year since folic acid fortification. Overall, stroke-associated mortality was 10 to 15 percent lower in the three years after fortification (1999-2001), compared with the three years before fortification (1994-96). Before 1997, overall stroke mortality rates declined by about 1 percent per year, compared with 4.5 percent per year after 1997. Importantly, the decline in mortality associated with stroke showed a consistent pattern that ran across all genders and racial groups, with improvements for both men and women, whites and blacks. The accelerating improvement in death rates due to stroke and ischemic heart disease could not be explained by changes in other major risk factors, such as cigarette smoking, hypertension, diabetes and total serum cholesterol levels, many of which did not improve or worsen during the period studied.

If the promising results of this analysis will be confirmed by controlled studies, hyperhomocysteinemia will have to be considered a very important risk factor for cardiovascu-

lar diseases. Its importance will not derive from the strength of its association with the disease, but, rather, from the fact that its correction is easy, inexpensive and safe.

Should Patients with Hyperhomocysteinemia be Treated?

While awaiting the results of the ongoing clinical trials, should physicians screen their patients for hyperhomocysteinemia? Screening for plasma tHcy levels is not justified in healthy individuals at low cardiovascular risk, but it may be advisable in individuals at high risk due to previous cardiovascular events or other conditions [22,23]. Should the physician use tHcy measurement only to calculate the cardiovascular risk in his high-risk patients or also treat those with high tHcy levels? The easy answer, of course, would be: NO, because there is no evidence that treatment will decrease the cardiovascular risk of these patients, and the good physician must act according to Evidence-Based Medicine. However, I think that, in this case, the physician is facing a rather complex situation, which would give rise

to the following considerations: i) my patient has high tHcy levels, which are associated with a heightened cardiovascular risk and could be a marker of insufficient intake or abnormal utilization of some vitamins; ii) I know that by treating my patient with these vitamins I can easily, effectively and safely treat his/her hyperhomocysteinemia and his/her probable nutrition defect; iii) however, I do not know whether this treatment will also decrease my patient's risk for cardiovascular disease; iv) on the other hand, if my patient had much higher tHcy levels, similar to those found in patients with homocystinuria, I would be obliged to treat him/her with vitamins, because they dramatically and safely decrease the cardiovascular risk in these patients. I think that the good physician should at least share these considerations and concerns with the patient and reach with him/her a decision on how to proceed. As a (good) physician, I would not take decisions on this problem without informed consent of the patient; as a patient, I would certainly choose to take vitamins.

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