Revista Portuguesa de Cardiologia 41 (2022) 821–822

Portuguese Society of CARDIOLOGY

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Homocysteinemia and vascular disease: Where we stand in 2022

Homocisteinemia e doença vascular: Onde nos encontramos em 2022

R. Palma Reis

New Medical School and CHLN, Hospital Pulido Valente, Lisboa, Portugal

Available online 12 July 2022

The increased vascular risk of homocystinuria, a rare genetic disease that affects young children, is widely acknowledged. In the first description of the disease, referring to a intellectually disabled child who died at the age of eight due to a stroke, the autopsy described an occlusive vascular pathology that ''would only be seen in an elderly person''.[1] The international collaborative study on the natural history of homocystinuria, involving 629 patients with homocystinuria, defined thromboembolic complications as the main cause of death in these patients.[2]

McCully's theory of arteriosclerosis by homocysteinemia brought with it a new concept: the moderate elevation of homocysteine, such as that found in heterozygotes for homocystinuria, can result in an increased risk of vascular disease.[3–5] With moderate elevations of homocysteine, either homocystine, a large molecule that filters in the kidney and appears in the urine, composed of two linked molecules of homocysteine, or homocystinuria will not appear, and vascular disease should affect young adults, not children.

The homocysteine theory of atherosclerosis was studied in depth and proved at the end of the last century. Various national and international studies, involving thousands of patients, have shown that:

- In a normal population, homocysteinemia is higher in men than in women, and increases after menopause. In these circumstances, it can partially explain the gender differences in cardiovascular risk, as well as the increased vascular risk after menopause.[6]
- Homocysteinemia (Hcy) is higher in smokers, than in non-smokers.[7]
- Hyperhomocysteinemia (HHcy) is linked to myocardial infarction,[8,9] stroke[10] and peripheral vascular disease.
- The high prevalence of high Hcy levels in normal persons, as well as in vascular patients, excludes the heterozygosity for homocystinuria, a rare disease, as the cause of most of Hcy elevations.[11]
- Vitamin B deficiencies, in particular B6, B12 and folic acid, co-factors of methionine/homocysteine metabolism, were associated with an increase in Hcy levels.[12,13]
- The large COMAC study on homocysteinemia confirmed that Hcy risk is independent of conventional risk factors and enhances the risk.[14]
- High levels of Hcy are associated with worse prognosis after myocardial infarction.[15]

After defining Hcy risk, the control of Hcy plasma levels with B vitamin supplements is easy and possible. Folic acid can decrease HC levels by approximately 42%, B6 by 5% and B12 by 15%. The three elements together decrease Hcy levels by about 50%.[16]

Much more difficult to prove is the clinical benefit of reducing Hcy levels. We will need a large interventional study with thousands of patients at high cardiovascular risk (for example, patients with myocardial infarction) followed during a long period of 5 to 10 years. The high costs of the study, including the insurance policy, to support the use of generic and cheep medications (vitamins), mean that the study is not of interest to the pharmaceutical industry.

E-mail address: palma.reis@nms.unl.pt

https://doi.org/10.1016/j.repc.2022.06.005

In fact, from several studies by research groups, with different protocols and inclusion criteria, it has emerged that Hcy-lowering interventions with B vitamin supplements have failed to demonstrate clinical benefits in myocardial infarction patients, and presented a dubious or modest benefit in stroke patients.[17]

The lack of clinical benefit of B vitamin supplements can be explained by multiple arguments: clinical study selection based on the atherosclerotic disease are not adequate, inclusion criteria should be guided by the high levels of Hcy. Folic acid is already abundant in western diets, particularly in cereal enrichment with B vitamins and general supplementation is not useful. Folic acid can contribute to increasing the built-up of arterial plaque and folic acid and B12 can methylate vascular cell genes, which may also accelerate plaque growth.

Whatever the reason, the lack of clinical benefit from B vitamin treatment in HHcy led to a decrease in the enthusiasm for Hcy as a vascular risk factor. Consequently, world preventive efforts on atherosclerosis prevention were targeted toward more intense investment in known risk factors, with clearly proven efficacy of intervention, such as smoking cessation, lipid control, hypertension, diabetes, or physical activity.

With this in mind, the current issue of this journal presents a paper on the influence of pirfenidone (PFD) on vascular intimal injury caused by hyperhomocysteinemia.[18] Knowing that Hcy induces vascular intimal oxidative and inflammatory lesions, the authors tested an anti-fibrotic agent, PFD, to decrease these inflammatory alterations. In an animal study, comparing normally fed rabbits with rabbits fed with a methionine (precursor of Hcy) rich diet, the authors proved that Hcy induces significant alterations of endothelium, increasing neointimal area, with macrophage infiltration. The administration of PFD concomitantly with a methionine rich diet, decreased macrophage infiltration without changes in blood lipids or HC levels. The authors conclude that PDF can alleviate intimal hyperplasia and proliferation, by inhibiting inflammatory and Hcy-induced oxidative stress.

After the disappointment of Hcy treatment with B vitamin supplements, based on the rational of decreasing Hcy levels, this paper opens a potential new way to reduce Hhcy-associated vascular risk by decreasing the inflammatory effects of Hcy. The journey from animal to human studies is a long one, but the potential preventive effect of this kind of molecules is in existence.

In conclusion, high Hcy levels are at the very least a risk marker for atherosclerosis in different territories and increase atherosclerosis risk in primary and secondary prevention. Proving Hcy risk reversibility, Hcy will be an atherosclerotic risk factor.

A general vitamin supplement approach can effectively lower Hcy but failed to demonstrate this in clinical results. In these circumstances, vitamin supplementation can be reserved for a small population of patients with high levels of Hcy but after strict control of conventional risk factors, and which leads to indisputable clinical benefits.

New approaches to Hcy vascular risk are seductive but there is a long journey ahead between concept and animal effectiveness to human clinical randomized interventional trials confirming their safety and efficacy. This paper represents the first step on that long journey.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Mallory T. Case records of the Massachussets General Hospital. Case 19471. Marked cerebral symptoms following a limp of three months duration. N Engl J Med. 1933;209:1063–6.
2. Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystatione B-sinthase deficiency. Am J Hum Genet. 1985;37:1–31.
3. McCully KS, Wilson RB. Homocysteine theory of arteriosclerosis. Atherosclerosis. 1975;22:215–27.
4. Wilcken DEL, Reddy SG, Gupta VA. Homocysteinemia, ischemic heart disease, and the carrier state for homocystinuria. Metabolism. 1983;32:363–70.
5. Boers G, Smals A, Trijbels FJ, et al. Heterozygosity for homocystinuria in premature peripheral and cerebral occlusive arterial disease. N Engl J Med. 1985;313:709–15.
6. Palma Reis R, Azinheira J, Palma Reis H, et al. Influência do sexo e da menopausa nos níveis de homocisteinemia basal e após sobrecarga com metionina. Rev Port Card. 1999;18:155–9.
7. Palma Reis R, Azinheira J, Palma Reis H, et al. Influência do tabagismo na homocisteinemia basal e após sobrecarga. Rev Port Card. 2000;19:471–4.
8. Palma Reis R, Azinheira J, Palma Reis H, et al. A homocisteinemia como factor de risco de enfarte do miocárdio precoce - estudo de casos e controlos. Rev Port Card. 1994;13:119–24.
9. Palma Reis R, Azinheira J, Palma Reis H, et al. Homocisteinemia como factor de risco de enfarte do miocárdio - importância da idade e dos níveis da homocisteinemia. Rev Port Card. 1995;14:713–6.
10. Palma Reis R, Azinheira J, Palma Reis H, et al. A homocisteinemia como factor de risco de doença cerebrovascular precoce. Acta Méd Portuguesa. 1994;7:285–9.
11. Palma Reis R, Azinheira J, Palma Reis H, et al. Homocysteinemia after a methionine overload as a coronary artery disease risk factor - Importance of age and homocysteinemia levels. Coronary Artery Dis. 1995;6:851–6.
12. Palma Reis R, Azinheira J, Palma Reis H, et al. Influência dos níveis de B6, B12 e ácido fólico nos valores de homocisteinemia basal e após sobrecarga com metionina. Rev Port Card. 1998;17:57–61.
13. Killian Robinson, Kristopher Arheart, Helga Refsum, et al. Low circulating folate and vitamin B6: risk factors for stroke, peripheral vascular disease and coronary artery disease. Circulation. 1998;97:437–43.
14. Graham I, Daly L, Refsum H, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. J Am Med Assoc. 1997;227:1775–81.
15. Palma Reis R, Azinheira J, Palma Reis H, et al. Significado prognóstico da homocisteinemia após enfarte do miocárdio. Rev Port Card. 2000;19:581–5.
16. Ubbink JB, Vermaak WJH, Merwe A, et al. Vitamin requirements for the treatment of hyperhomocysteinemia in humans. J Nutr. 1994;124:1927–33.
17. Martí-Carvajal AJ, Solà I, Lathyris D, et al. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2017;8:CD006612, http://dx.doi.org/10.1002/14651858.CD006612.pub5. Published 2017 Aug 17.
18. Kong J, Deng Y. Pirfenidone alleviates vascular intima injury caused by hyperhomocysteinemia. Rev Port Cardiol. 2022;41:813–9.