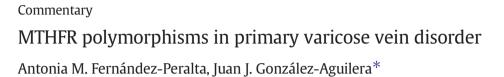
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Varicose veins occur commonly in the general population but, despite much research, the etiology of venous disease is still poorly understood. The pathogenesis of the vein dilatation remains obscure in spite of the evidence of a primary defect in the vein wall. A number of epidemiological studies have shown that, in addition to environmental factors, genetic mechanisms may play a role in determining susceptibility to vascular disease. In particular, abnormalities in the enzymes that control homocysteine metabolism have been shown to cause vascular disease (Sverdlova et al., 1998; Kim et al., 2007).

Wilmanns et al. (2015) present here a fundamental insight into the nature of primary varicose vein disease. They attempt to determine if the methylenetetrahydrofolate reductase polymorphisms (MTHFR C677T and A1298C) are implied in the morphology and types of complicated disease in patients with primary varicose veins. The C677T polymorphism is located in the catalytic domain of the protein, the binding site for the MTHFR co-factor Flavin adenine dinucleotide. This polymorphism is associated with an enhancement of the thermolability of the enzyme, a reduction of the activity, an increase of plasma homocysteine concentrations, and a decreased in plasma folate (Frosst et al., 1995). The second MTHFR polymorphism A1298C lies in the C-terminal end of the enzyme, the S-adenosylmethionine regulatory domain, and may result in a decrease of 40% in enzyme activity of the variant genotype (Weisberg et al., 2002). Both polymorphisms have been found to be implicated in colon cancer risk and the response to 5-FU chemotherapy, since MTHFR is implicated in the FU metabolism (Fernández-Peralta et al., 2010; Delgado-Plasencia et al., 2013). Also, these polymorphisms have been previously implicated in thrombotic disease (Milio et al., 2008; Wilmanns et al., 2011). Authors argued that different genetic origins may be the cause for the morphological types, trunk and perforator, of complicated and uncomplicated disease. In the study, the authors provide a hypothesis for the impact of MTHFR polymorphisms C677T and A1298C as hereditary components of primary varicose vein disease. They establish an interesting association: the axial trunk type morphology was almost exclusively associated with homozygosity (TT) or heterozygosity in C677T, while the perforator type morphology with homozygosity (CC) or heterozygosity in A1298C. Additionally, double heterozygosity CT (C677T) and AC (A1298C) are associated with the combined trunk and perforator phenotype. On the other hand, there is an increased risk of CEAP C3-6 complication from AA to CC genotype at the A1298C polymorphism.

MTHFR is an enzyme that is important in homocysteine metabolism. Therefore, alterations in the enzyme function (as seen in gene polymorphic variants) could lead to elevated levels of homocysteine, free radical formation, and endothelial damage. This could potentially lead to oxidative stress and dysfunctional endothelium. Although this paper suggests that there may be a link between MTHFR in the pathogenesis of varicose vein disease and its thrombotic complications, further studies should be conducted to confirm these associations in other series, in order to clarify how MTHFR influences the pathogenesis of varicose veins and the risk increase for developing the disease.

## Disclosure

The authors declared no conflicts of interest.

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