A Meta-Analysis of Plasma Homocysteine in Buerger's Disease

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Buerger's disease (BD) is a vascular inflammatory disease that commonly affects all three layers of small and medium arteries of upper and lower extremities in a progressive and segmental fashion; characteristically, BD develops in males, mostly smokers, within the 20 to 50 years age range. Claudication of feet, legs, arms or hands can be presenting signs that might evolve toward critical limb ischaemia, ulcerations and necrosis.¹

The pathogenesis of BD is multifactorial: from the haemostasis point of view, decreased fibrinolysis,² enhanced coagulation activation³ and tighter fibrin clots have been reported⁴; from the histology viewpoint there is increased expression of integrins and selectins that favour leucocyte adhesion on the endothelial lining, and from the functional point of view there is reduced flow mediated vasodilatation.⁵

Homocysteine (HC) is a sulphur amino acid, which can be either re-methylated to methionine or trans-sulphurated to cystathionine according to different genes coding for enzymes that control (the) two pathways: a polymorphism in the methylene tetrahydrofolate reductase (MTHFR) C677T gene is associated with decreased enzymatic activities allowing HC to reach toxic plasma levels that in turn promote thrombosis⁶ and vascular damage.⁷ We performed this

meta-analysis to evaluate whether plasma HC has any role in the vascular damage in BD.

We searched MEDLINE and EMBASE according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines⁸ from inception to December 2020 using the terms: ['Buerger disease' OR 'thromboangiitis obliterans'] and [homocysteine' OR 'hyperhomocysteinaemia'] and [methyltetrahydrofolate reductase].

We considered observational, cohort and/or case-control studies reporting the mean/median concentration of plasma HC and the MTHFR polymorphisms in BD patients and in controls from articles published in any language. We excluded case reports, reviews and records with no extractable data. The Newcastle Ottawa Quality Assessment Scale assessed the quality of the studies⁹; random effects meta-analyses for continuous outcomes estimated the standardised mean difference of HC between groups¹⁰ and Peto's odds ratio for rare events compared the prevalence of MTHFR TT between groups¹¹ (Comprehensive Meta-Analysis, BioStat, Englewood, New Jersey, United States). We could not assess publication bias as funnel plots are invalid with less than 10 articles in the meta-analysis.¹²

The search yielded 36 records that decreased to 29 after duplicate removal; once through with the relevancy screen,

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Plasma homocysteine in Buerger's disease and controls

A

Plasma homocysteine in Buerger's disease and smoking controls

B

Methylentetrahydrofolate reductase TT in Buerger's disease

C

Fig. 1 (A) Forest plot of studies investigating plasma homocysteine in Buerger's disease (BD) and controls (CTR). (B) Forest plot of studies investigating plasma homocysteine in Buerger's disease and smoking controls. (C) Forest plot of studies investigating the prevalence of the methylene-tetrahydrofolate reductase TT genotype in Buerger's disease and controls.

21 records were found eligible but only 7 articles met our inclusion criteria.^{13–19} HC was measured by high-performance liquid chromatography^{13,15} by enzyme-linked immunoassay^{16,18,19} and by fluorescent polarisation immune assay¹⁷; one study did not report the assay method.¹⁴ Median and ranges^{15,17} were converted to mean and standard deviation.²⁰ Three studies^{13,15,16} had two separate control groups made up of smokers and non-smokers: for the purpose of the meta-analysis, we averaged their HC concentration as other studies combined together smokers and non-smokers^{17,19} though only one article indicated the number of cigarettes smoked per year by all participants.¹⁵

The effect size (ES) of plasma HC from 193 BD patients and 428 controls favoured BD (►Fig. 1A) with low heterogeneity ($I^2 = 16.8\%$) that decreased ($I^2 = 11.7\%$) after exclusion of the study that did not report the method of HC assay.¹³ The ES of plasma HC from 61 BD patients and 57 smoking controls showed a lower heterogeneity ($I^2 = 11.4\%$) but a greatly reduced ES (►Fig. 1B); this implies an effect of smoking on plasma HC in the relevant group. On the other hand, the pooled prevalence of MTHFR TT from 236 BD patients and 288 controls^{14,21–24} was not significantly greater in BD patients than that in control participants (25% vs. 19%) (►Fig. 1C) and showed moderate heterogeneity ($I^2 = 56.7\%$, $p = 0.056$); removal of the study with the lowest number of participants¹⁴ changed slightly the prevalence (24.2% vs. 19.7%, $p = 0.9$) and the heterogeneity ($I^2 = 41\%$, $p = 0.16$).

Despite the paucity of the available studies, an inherent limitation of our meta-analysis, the resulting data are consistent with an involvement of plasma HC in BD, but this is unlikely to be genetically driven as we did not find an increased prevalence of the common homozygous MTHFR C677T genotype in the BD populations where this genotype was investigated, whereas other genes of the HC pathway have not been searched for in BD.

However, the increased oxidative and nitrative stress that accompanies BD,^{25–27} whether or not supported by smoking,²⁸ may inhibit cystathionine β synthase,²⁹ the first enzyme in the trans-sulphuration pathway that catalyses HC to cystathionine; indeed, this enzyme is susceptible also to disulphide redox inhibition³⁰ perpetuating the elevated HC that via one route maintains a high level of oxidative stress³¹ and via another sustains vascular damage⁷: in this sense, elevated plasma HC is more an effect of the inflammation that accompanies BD and less likely to be a primary cause of BD. However, attempts to reduce HC seem intuitive: this might be accomplished via the administration of antioxidant agents, which may release cystathionine β synthase from its inhibition, rather than by the administration of the B vitamins that are cofactors in the metabolic pathways of HC.

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Conflict of Interest

None declared.

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