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

Mira Merashli1 Tommaso Bucci2 Daniele Pastori3 Pasquale Pignatelli3 Alessia Arcaro4 Fabrizio Gentile4 Vincenzo Marottoli5 Paul R.J. Ames6,7

1 Department of Rheumatology, American University of Beirut, Beirut, Lebanon
2 Department of General Surgery, Surgical Specialties and Organ Transplantation “Paride Stefanini,” Sapienza University of Rome, Rome, Italy
3 Prima Clinica Medica, Atherothrombosis Centre, Department of Clinical, Internal Medicine, Anaesthesiology, & Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy
4 Department of Medicine & Health Sciences ’V.Tiberio’, University of Molise, Campobasso, Italy
5 Multimedica SRL, Naples, Italy
6 Immune Response and Vascular Disease Unit, CEDOC, Nova University Lisbon, Lisbon, Portugal
7 Department of Haematology, Dumfries Royal Infirmary, Dumfries, United Kingdom

Address for correspondence Paul R.J. Ames, MD, MSc, PhD, FRCPath, Department of Haematology, Dumfries Royal Infirmary, Dumfries, United Kingdom (e-mail: paxmes@aol.com).

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 'thromboangioiitis obliterans'] and ['homocysteine' OR 'hyperhomocysteinemia'] and [methylentetrahydrofolate 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,
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.
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.\(^1\) 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 428 controls favoured BD ($I^2 = 0.9\%$) 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 nitritative stress that accompanies CD,\(^2\)–\(^7\) whether or not supported by smoking,\(^8\) may inhibit cystathionine β synthase,\(^9\) the first enzyme in the trans-sulphuration pathway that catalyses HC to cystathionine; indeed, this enzyme is susceptible also to disulphide redox inhibition\(^10\) perpetuating the elevated HC that via one route maintains a high level of oxidative stress\(^11\) and via another sustains vascular damage;\(^7\) 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.

**References**


