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The *MTHFR* 677C→T polymorphism, blood pressure and riboflavin: a 4-year follow-up study

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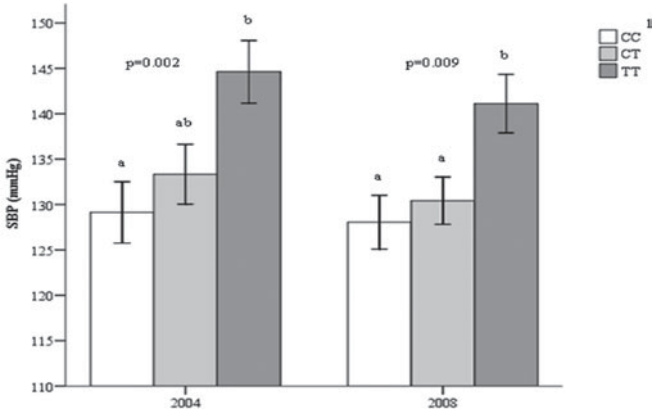
High blood pressure (BP) affects up to 40% of the UK population and is a major risk factor for CVD and stroke in particular. A common polymorphism (677C→T) in the gene encoding the enzyme methylenetetrahydrofolate reductase (MTHFR), produces an enzyme with decreased activity *in vivo*, and has recently been associated with hypertension[1]. Riboflavin, in the form of FAD, is required as a cofactor for MTHFR and supplementation has been shown to correct impaired MTHFR activity in those homozygous for the polymorphism (TT genotype)[2]. Recent work at our centre reported that the elevated BP observed in CVD patients with the TT genotype was highly responsive to riboflavin supplementation (1.6 mg/d/16 weeks)[3]. The aim of the current study was to follow-up the original cohort to investigate the impact of this polymorphism on BP over time, and to confirm the BP-lowering effect of riboflavin specifically in those with the TT genotype. After new ethical approval was sought and granted, 83 out of the original 181 patients (with known *MTHFR* genotypes) agreed to participate in this follow-up. In addition, those with the TT genotype (*n* 31) were invited to participate in a riboflavin cross-over design intervention (1.6 mg/d/16 weeks) where the 2004 treatment groups were reversed.

At the follow-up, and similar to observations in 2004, patients with the TT genotype compared to those with CC and CT genotypes had significantly higher systolic BP, with a similar trend noted for diastolic BP. This was observed despite the fact that the majority of the cohort was taking antihypertensive drugs and, in line with NICE guidelines, the number of antihypertensive drugs prescribed had increased over the 4-year period. Also, a combined 2004 and 2008 analysis showed that riboflavin intervention resulted in a significant decrease in both systolic (−9.2 mmHg, SD 12.8, $P = 0.001$) and diastolic (−6 mmHg, SD 9.9, $P = 0.003$) BP.



Differences between genotype groups at each time-point determined by one-way ANOVA with superscript letters indicating significant differences ($P<0.05$) by Tukey *post-hoc* test.

[1]CC (wild-type), CT (heterozygous) and TT (homozygous) genotypes for the MTHFR 677 C→T polymorphism.

The finding that the *MTHFR* 677 TT genotype remained a significant risk factor for hypertension despite major changes in drug management over this time period strengthens the evidence advocating this polymorphism as a genetic risk factor for hypertension. Moreover, riboflavin administration at a dietary level offers a novel, low-cost and low-risk treatment for hypertension in a genetically predisposed group. These findings could have important implications for the management and prevention of hypertension worldwide given that the prevalence of this polymorphism is 10–12% in Western populations and can be as high as 32% in some.

1. Heux *et al*. (2004) *Hypertens Res* **27**, 663–667.
2. McNulty *et al*. (2006) *Circulation* **113**, 74–80.
3. Horigan *et al*. (2010) *J Hypertens* **28**, 478–486.