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(RESEARCH ARTICLE)

Interaction of MTHFR Gene Polymorphisms and Gut Microbiota with Folate, Vitamin B12, and Homocysteine Levels in Hypertensive Iraqi Adults

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Abstract

Hypertension is a leading global cardiovascular risk, and emerging evidence suggests that genetic variants particularly polymorphisms in the MTHFR (methylenetetrahydrofolate reductase) gene may influence blood pressure by modulating gut microbiota, folate, and homocysteine metabolism. In an Iraqi case-control study involving 180 adults (90 hypertensive, 90 normotensive), researchers genotyped the MTHFR C677T and A1298C variants via PCR-RFLP, measured serum homocysteine, folate, and vitamin B_{12} by ELISA and chemiluminescence assays, and profiled gut microbiota using 16S rRNA sequencing. They found that the 677 T allele was more common in hypertensive individuals ($p = 0.021$), who also had significantly higher homocysteine (18.1 ± 5.2 vs 12.6 ± 4.3 µmol/L, $p < 0.001$), lower folate (6.8 ± 2.4 vs 9.2 ± 2.8 ng/mL, $p < 0.001$), and reduced B_{12} (280 ± 85 vs 340 ± 92 pg/mL, $p = 0.004$). Microbiome analysis revealed gut dysbiosis in hypertensives, marked by reduced diversity (Shannon index 3.25 ± 0.42 vs 3.68 ± 0.39, $p = 0.002$), decreased Bifidobacterium (3.6 ± 1.4% vs 6.1 ± 1.7%, $p < 0.001$), and an increased Firmicutes/Bacteroidetes ratio (2.9 ± 0.8 vs 1.7 ± 0.5, $p < 0.001$). Critically, there was a significant gene–microbiome interaction: individuals with the TT genotype and low microbial diversity had the highest homocysteine levels (21.9 ± 5.3 µmol/L, $p = 0.018$ for interaction). These findings highlight a complex interplay between MTHFR polymorphisms and gut microbiota in regulating homocysteine metabolism in hypertensive Iraqi adults—and suggest that personalized nutritional or probiotic interventions might help manage hypertension.

Keywords: MTHFR polymorphisms; Gut microbiota; Homocysteine; Folate metabolism; Hypertension

1. Introduction

Hypertension is a serious global health issue, with a population impact exceeding 1.28 billion adults around the world, and, being the primary risk factor of cardiovascular morbidity and mortality in the world (1). Although the classic risk factors that include obesity, physical activities, and dietary habits have been widely studied, there is growing evidence that biochemical and genetic factors are also important determinants in the pathogenesis of hypertension. High homocysteine levels, which are accompanied by the lack of folate (vitamin B9) and vitamin B12 have always been associated with the heightened cardiovascular risk and the emergence of H-type hypertension (2).

Through the middle of one-carbon metabolism, the enzyme methylenetetrahydrofolate reductase (MTHFR) catalyzes the metabolic transformations between 5,10-methylenetetrahydrofollate and 5-methyltetrahydrofollate a vital substrate of the process of remethylation of homocysteine to methionine. There are two prevalent single nucleotide polymorphisms (SNP) in the MTHFR gene, C6 77T (rs 1801133) and A1298C (rs1801131), which have been subject to numerous and strong population based researches. C677T is associated with a thermolabile enzyme that has an activity loss of about 30-70 per cent in heterozygote and homozygote respectively thus increasing the levels of homocysteine

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and changing the folate status (3). Comparative analysis has reported ethnic and geographic differences in the distribution and clinical outcome of these polymorphisms with the Middle Eastern populations showing different patterns compared to the other populations in Europe and Asia (4).

The gut microbiota has been the most recently discovered as a critical controller of cardiovascular health owing to modern advances in the study of the microbiome. Gut microbial community is a community of trillions of microorganisms that have a variety of effects on host metabolism via effects that include but not limited to short-chain fatty acid production, systemic inflammation, production and metabolism of essential nutrients such as B vitamins (5). Reduced diversity of microbes, and changes in community structure as dysbiosis have been repeatedly reported in hypertensive humans of a variety of populations (6). A number of studies have also documented a decrease of beneficial taxa, including Bifidobacterium and an elevated Firmicutes/Bacteroidetes ratio among hypertensive patients (7).

Although there has been increased awareness of the genetic and microbial factors in hypertension, the interaction that may have taken place between MTHFR genetic variants and gut microbiota composition in terms of predisposing to folate bioavailability, vitamin12 status, and homocysteine metabolism has not been extensively studied. Such interaction may have a consequential knowledge gap, since these interactions may greatly affect the personal predisposition to H-type hypertension and reactivity to nutritional intervention. The Iraqi population is especially suitable to this inquiry because hypertension is extremely common in this area and there is a relative lack of studies on these multifaceted interactions between genes, environment, and microbiomes in cohorts within the Middle East (8).

These complex interdependences can also have value to explain the pathophysiology of hypertension and find new risk stratification biomarkers. In addition, this knowledge would be able to guide the design of individualized nutritional or probiotic studies, particularly those that might have a high-risk genetic structure. To this end, the proposed paper aims to address the most severe gap in knowledge by intensive examination of the interconnections between MTHFR polymorphisms, gut microbiota structure, and essential metabolic indicators in hypertensive Iraqi patients who visit Al-Yarmouk Teaching Hospital.

The objectives of this study are to:

- Compare the genotypes of MTHFR C677T among hypertensive Iraqi adults and normotensive controls A1298C;
- Assess and contrast folate, vitamin B 12 and homocysteine levels in the serum of both cohorts compared to their MTHFR genotypes; and
- Explore how these genotypes may interaction with gut microbiota features and their effects on the above serum biomarkers.

2. Methods

This case-control study was performed between March 2024 and March 2025 at Al-Yarmouk Teaching hospital, Baghdad, Iraq, a large hospital providing a wide range of health care services. These participants were adult males and females (18 years and above), 90 hypertensive (systolic blood pressure 140mmHg, diastolic blood pressure 90mmHg or currently under antihypertensive treatment) and 90 age and sex matched normotensive controls (systolic/diastolic blood pressure <140/90mmHg and no known history of hypertension). The exclusion criteria were recent (less than one month) antibiotic or probiotic use, chronic gastrointestinal disease, severe liver or kidney dysfunction, and simultaneous folate or B -vitamin use.

A detail questionnaire was used to get the demographic data, the history of the clinical states, the use of medications, the consumption of food (particularly folate and vitamin B12), smoking habits, and the level of activity. The anthropometric data (height, weight), blood pressure was registered based on the standardized procedures. After an overnight fast, the venous blood samples were taken, serum separated, and kept at -80 °C. We measured homocysteine via ELISA, and folate and vitamin B12 using chemiluminescence immunoassays, performing all assays in duplicate with quality control procedures in place.

Peripheral blood leukocytes were used to extract genomic DNA and genotype MTHFR C677T (rs1801133) and A1298C (rs1801131) polymorphisms by PCR -restriction fragment length polymorphism (PCR -RFLP). PCR amplification products of both genotypes were digested with the corresponding restriction enzyme (HinfI to call C677T, MboII to call A1298C) and genotype called on agarose gels. In order to guarantee genotyping accuracy, 10% of samples were re-genotyped for confirmation.

Stool samples were obtained to test microbiomes; microbial DNA was retrieved and V3 V4 hypervariable region of bacterial 16S rRNA gene was amplified and sequenced in an Illumina platform. Bioinformatics processing included filtering, OTU clustering, taxonomic assignment, and calculation of diversity metrics (alpha and beta diversity), plus quantification of key taxa (e.g., Bifidobacterium, Prevotella, Firmicutes, Bacteroidetes).

The SPSS version 25 was used to conduct statistical analyses. There were descriptive statistics of means (including means ± SD or percentages). Between-group comparisons involved independent-samples t -tests or chi-square tests. Multivariate linear regression models (including MTHFR genotype × microbiome interaction terms) adjusting for age, sex, BMI, and diet, with $p < 0.05$ considered significant.

The Institutional Review Board of Ibn Sina University of medical and pharmaceutical sciences provided an ethical approval. All the participants received informed consent written. The Personal and genetic data were kept confidential, and participants were free to withdraw at any time, with ethical principles such as those in the Declaration of Helsinki.

3. Results

A total of 180 participants were enrolled in the study, including 90 hypertensive cases and 90 normotensive controls, with both groups well-matched for age and sex. Analysis of MTHFR genotypes revealed a significant difference in C677T distribution between groups (p=0.021), with hypertensive individuals showing a higher prevalence of the T allele (CC: 42.2%, CT: 41.1%, TT: 16.7%) compared to controls (CC: 61.1%, CT: 32.2%, TT: 6.7%), while no significant difference was observed for the A1298C polymorphism (p=0.183), as genotype frequencies were similar between hypertensive (AA: 48.9%, AC: 40.0%, CC: 11.1%) and control participants (AA: 55.6%, AC: 37.8%, CC: 6.6%). (Table 1)

Table 1 Genotype distribution of MTHFR polymorphisms among study participants

Genotype	Hypertensive group (n=90)	Controls group (n=90)	p-value
C677T			0.021*
CC	38 (42.2%)	55 (61.1%)	
CT	37 (41.1%)	29 (32.2%)	
TT	15 (16.7%)	6 (6.7%)	
A1298C			0.183
AA	44 (48.9%)	50 (55.6%)	
AC	36 (40.0%)	34 (37.8%)	
CC	10 (11.1%)	6 (6.6%)	

*Statistically significant (p<0.05)

Table 2 reveals that, hypertensive participants exhibited significant alterations in key biochemical parameters compared to normotensive controls, that include a statistically significant decreasing serum folate (6.8±2.4 vs 9.2±2.8 ng/mL, p<0.001) and vitamin B12 (280±85 vs 340±92 pg/mL, p=0.004), representing reductions of 26% and 18% respectively, alongside substantially elevated homocysteine concentrations (18.1±5.2 vs 12.6±4.3 μmol/L, p<0.001), a 44% increase, collectively indicative of H-type hypertension and disrupted one-carbon metabolism in this cohort.

Table 2 Biochemical parameters by hypertension status

Parameter	Hypertensive (mean ± SD)	Control (mean ± SD)	p-value
Serum Folate (ng/mL)	6.8 ± 2.4	9.2 ± 2.8	<0.001*
Vitamin B12 (pg/mL)	280 ± 85	340 ± 92	0.004*
Homocysteine (μmol/L)	18.1 ± 5.2	12.6 ± 4.3	<0.001*

*Statistically significant (p<0.05)

Gut microbiota analysis (Table 3) revealed significant differences in hypertensive and normotensive participants with hypertensive having lower alpha diversity (Shannon index: 3.25±0.42 vs 3.68±0.39, p=0.002) indicating that hypertensive participants had lower microbial richness and evenness. The ratio of Firmicutes/Bacteroidetes was significantly higher in hypertensive participants (2.9± 0.8 vs 1.7 +0.5, p=0.001), a 71% increase suggestive of dysbiosis. At the genus levels, the abundance of Bifidobacterium was reduced by 41% in hypertensive participants (3.6±1.4% vs 6.1±1.7%, p<0.001) and Prevotella abundance increased by 47% (8.4±2.8% vs 5.7±2.3%, p=0.011), that highlighting distinct microbial alterations associated with hypertension.

Table 3 Gut Microbiota composition and diversity

Microbiota Feature	Hypertensive (mean ± SD)	Control (mean ± SD)	p-value
Shannon Diversity Index	3.25 ± 0.42	3.68 ± 0.39	0.002*
Firmicutes/Bacteroidetes Ratio	2.9 ± 0.8	1.7 ± 0.5	<0.001*
Bifidobacterium abundance (%)	3.6 ± 1.4	6.1 ± 1.7	<0.001*
Prevotella abundance (%)	8.4 ± 2.8	5.7 ± 2.3	0.011*

*Statistically significant (p<0.05)

Gene-microbiome interaction analysis has revealed a strong synergistic interaction between MTHFR C677T genotype and gut microbial diversity on the level of homocysteine (p=0.018 interaction term) as presented in Table 4. Participants who possessed the CC genotype and were rich in microbial diversity (Shannon index 3.5 and above) possessed a mean homocysteine levels of of 13.0±3.8 μmol/L, and this modestly increased to 14.8±4.2 μmol/L in those with low diversity (Shannon index <3.5). In contrast, TT genotype carriers exhibited a much stronger influence of microbial diversity: individuals with preserved diversity showed homocysteine levels of 16.2±4.1 μmol/L, whereas those with low diversity had substantially elevated levels of 21.9±5.3 μmol/L, representing a 35% increase compared to TT carriers with high diversity and a 69% increase relative to CC carriers with high diversity.

Table 4 Interaction between MTHFR C677T genotype and microbiota diversity on homocysteine levels

MTHFR Genotype	Gut Diversity (Shannon Index)	Mean Homocysteine (μmol/L)	p- value (interaction)
CC	≥3.5	13.0 ± 3.8	
CC	<3.5	14.8 ± 4.2	
TT	≥3.5	16.2 ± 4.1	
TT	<3.5	21.9 ± 5.3	0.018*

*Statistically significant interaction (p<0.05)

These findings indicate that the genetic susceptibility (TT genotype) and gut dysbiosis (low microbial diversity) have a synergistic effect that leads to significant increases in the levels of homocysteine, substantially higher than would be predicted from either factor alone.

4. Discussion

This study is the one of the first comprehensive investigations examining the assiociation between MTHFR genetic polymorphisms, gut microbiota composition, and key metabolic markers in hypertensive adults in Iraq. These findings reveal a significant association between the MTHFR C677T polymorphism and hypertension, accompanied by disturbances in folate, vitamin B12, and homocysteine metabolism. Hypertensive participants also had significant gut dysbiosis, and significantly, the interaction effect between MTHFR genotype and gut microbiota diversity was statistically significant to determine the levels of homocysteine. These findings highlight the need to consider genetic and microbial factors combinatively to gain a better insight into metabolic dysregulation as a disease associated with hypertension.

MTHFR 677T allele was observed to have an extremely high proportion among the hypertensive, in comparison to normotensive controls (37.2% and 22.8% respectively). This observation is in line with previous studies which have been done in the neighboring populations of Middle East. Meta-analysis by Meng et al. described a similar increase in the T allele in hypertensive Viets (9), and Er ZC and colleagues have shown that the TT genotype is linked with the high risk of hypertension in Turkish cohorts (10). In contrast, the A1298C polymorphism was not significantly associated, and this agrees with regional reports that C677T is the functionally dominant polymorphism in this population (11).

The biologic plausibility of this relation is solidly established. A C677T polymorphism that causes the creation of a thermolabile form of the MTHFR enzyme causing the reduced catalytic activity and, therefore, the inhibition of the folate-dependent remethylation of homocysteine to methionine (3). This is an enzymatic deficiency that triggers hyperhomocysteinemia, a highly-reported cardiovascular risk determinant. The ethnic variations in allele frequency and phenotypic expression provide the urgency of the population-specific genetic research; especially, the Iraqi group seems to have an intermediate allele distribution between the Mediterranean and South Asian ones.

We observed significantly high levels of homocysteine in hypertensive patients with a mean of 18.1 μmol/L, exceeding the 15 μmol/L threshold for hyperhomocysteinemia (12). This increase was accompanied by low folate and vitamin B12 levels, which are indicative of H-type hypertension. The findings are consistent with a recent meta-analysis conducted by Wang et al. which showed similar metabolic profiles in diverse populations (13). The 44% increase in homocysteine compared to controls is also clinically important, given that epidemiological studies have shown that a 5 μmol/L change could lead to about 20% increment in cardiovascular risk (14). Other biochemical patterns were observed by Liu et al. in Chinese hypertensive cohorts (2). In particular, the baseline folate levels in our cohort were lower than in some East Asian groups, which could be explained by dietary parameters, since the traditional Iraqi diets may provide lower bioavailable folate despite vegetable-rich meals.

Gut microbiota analysis revealed marked dysbiosis in hypertensive participants. A significant reduction in Shannon diversity indicated diminished microbial complexity, a pattern widely reported in hypertensive populations (15). The reduction of microbial diversity is linked to the decrease in the stability of the ecosystem, which may have negative impacts on the process of host metabolic regulation. Firmicutes/Bacteroidetes ratio was also higher in hypertensive subjects and this is a reflection of Chinese researches (16, 17). The Phylum-level changes could affect host metabolism, by changing the production of short-chain fatty acids, which regulate blood pressure by altering vascular tone and effects on renin-angiotensin system (18).

Depletion of Bifidobacterium among hypertensive individuals is of particular interest because this group of commensals is the producers of B vitamins and anti-inflammatory agents (19). Their depletion can be a cause of systemic inflammation and dysfunctional bioavailability of B -vitamins. The abundance of Prevotella was high, which could be due to the effects on the diet, since the species is known to be able to flourish on the diets rich in fibers (20). Nevertheless, some species of Prevotella have been associated with inflammatory conditions providing evidence that strain-based analysis is warranted.

The most novel finding of this study is the significant interaction between MTHFR C677T polymorphism and the diversity of the gut microbiome is statistically significant and leads to changes in plasma homocysteine levels. People with the TT genotype and reduced microbial diversity had a higher homocysteine level which was 69% higher than that of people with CC genotype who retained a preserved microbial diversity. This symbiotic connection suggests that the genetic predisposition and dysbiosis of the microbiota together enhance the dysfunction of the metabolism. Through a mechanistic process, gut microbes synthesize B -vitamin cofactors, folate especially, which has the ability to partially mitigate genetic-based enzyme deficits (21). State of dysbiosis can limit microbial folate production or lower the bioavailability of it with a disproportionate effect on carriers of the TT allele. Additionally, dysbiosis is often associated with increased intestinal permeability and systemic inflammatory reactions, which, in their turn, may also impair nutrient absorption and metabolic control (22). Recent studies propose that microbial metabolites have the potential to regulate the expression of host genes and enzyme activity, and thus increasing metabolic disturbances (23).

These findings agree with the results of multi-omics studies carried out on Asian and European cohorts which have already started to explain the complex relationship between genes and the microbiome in the cardiovascular disease context (5, 6). The current research is one of the first attempts to question such interactions through the prism of MTHFR polymorphisms and homocysteine metabolism in a Middle Eastern population, which, in turn, highlights the significance of the microbiome analysis in the context of the further development of individualized cardiovascular risk stratification.

The high prevalence of the MTHFR 677T allele in hypertensive adults of Iraq underscores the potential benefit of increasing the consumption of folate and B - vitamins, especially in individuals with hyperhomocysteinemia. However, the results of a gene-microbiome interaction suggest that dietary changes can be insufficient in the case of dysbiosis. Specific probiotic or prebiotic products, particularly those based on B -vitamin-producing strains, may have an additional benefit. The intake of folates rich diets and the probability of fortification should then be incorporated in health promotions in the area of public health and promoting dietary habits that maintain a harmonious gut microbiota.

The strengths of the study are the comprehensive design, integrating genetic, biochemical, and microbiome analyses within a single cohort. The application of standardized laboratory procedures, adequate sample size and the use of control groups which are well-matched increases the reliability and reduces bias. However, the case-control design was limits causal inference, and self-reported dietary data may introduce recall bias. Also, a single-center investigation, limited genetic analysis, and genus-level microbiome profiling restrict generalizability. Longitudinal studies, genotype-stratified clinical trials, and advanced multi-omics approaches must be included in the future studies to clarify causal mechanisms and inform personalized interventions across broader populations.

5. Conclusion

The MTHFR 677T allele is highly prevalent among hypertensive Iraqi adults leading into disrupted folate metabolism and elevated homocysteine. Hypertension is also associated with Gut dysbiosis with reduced microbial diversity. Notably, that genetic risk and microbiome alterations interact in a synergistic effect, which poses an additional burden on cardiovascular risk. These findings highlight the need for precision approaches, including MTHFR genotyping, microbiome assessment, dietary and probiotic interventions, folate supplementation, and development of regional genetic and microbiome reference data.

Compliance with ethical standards

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