Review Article

Methylenetetrahydrofolate reductase (MTHFR) polymorphisms in andrology—a narrative review

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Background and Objective: Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme involved in folate metabolism and one-carbon metabolism. MTHFR gene polymorphism affects enzyme activity. MTHFR gene polymorphism is closely related to many human diseases, such as cardiocerebrovascular diseases, diabetes, neural tube defects (NTDs), tumors, and so on. In the field of Andrology, MTHFR gene polymorphism may be associated with male infertility and erectile dysfunction (ED), and there is a possibility of treating male infertility and ED by supplementing with folic acid. However, its exact pathophysiologic mechanism is not fully understood. We sought to obtain a robust understanding of the interactions between MTHFR gene polymorphism, oxidative stress, DNA methylation, hyperhomocysteinemia (HHcy), male infertility, and ED.

Methods: We performed a non-systematic literature review using the PubMed database to identify articles specifically related to MTHFR, male infertility and ED.

Key Content and Findings: Our literature review on MTHFR gene polymorphism in male infertility patients indicates a significant association between C677T gene polymorphism and male infertility. There is limited literature on the correlation between ED and MTHFR gene polymorphism, and there are two different conclusions, related and unrelated. More clinical data are needed to clarify the conclusion. There is a possibility of using folic acid supplementation to treat male infertility and ED, especially for patients with thymine-thymine (TT) genotype. Future research is necessary to further understand the relationship between MTHFR gene polymorphism and male infertility and ED.

Conclusions: Our literature review on MTHFR gene polymorphism in male infertility patients indicates a significant association between C677T gene polymorphism and male infertility. Folic acid supplementation can improve sperm quality. The correlation between MTHFR gene polymorphisms and ED is questionable and needs to be confirmed by more clinical data. MTHFR gene polymorphisms are associated with homocysteine (Hcy) levels, which affects vascular endothelial function and may be related to the development of vascular ED (VED). Folic acid supplementation improves International Index for Erectile Function (IIEF) questionnaire scores in ED patients in whom phosphodiesterase 5 inhibitor (PDE5i) alone is ineffective.

Keywords: Methylenetetrahydrofolate reductase gene polymorphism (MTHFR gene polymorphism); DNA methylation; hyperhomocysteinemia (HHcy); male infertility; erectile dysfunction (ED)

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Introduction

Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme involved in the folate cycle and one-carbon metabolism. Its main function is to convert 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF). MTHFR, as a carrier of one carbon unit within cells, participates in the synthesis of purines and pyrimidines, providing methylation for the synthesis of DNA, RNA, and proteins. At the same time, MTHFR acts as a methylation donor and uses vitamin B12 as a coenzyme to demethyl serum homocysteine (Hcy) under the catalysis of methionine synthase, maintaining normal levels of serum Hcy. *Figure 1* illustrates the biochemical pathways affected by MTHFR polymorphisms.

A large number of studies have shown that MTHFR gene polymorphism is closely related to many human diseases, such as cardiocerebrovascular diseases (1), diabetes (2), neural tube defects (NTDs) (3), tumors (4-6), Alzheimer's disease (7), etc. (8). In the field of andrology, MTHFR gene polymorphism is associated with male infertility and erectile dysfunction (ED) (9,10).

The MTHFR gene has more than 20 single nucleotide polymorphisms, with the most common being C677T and A1298C. The cytosine (C) at position 677 of the MTHFR gene is replaced by thymine (T), resulting in a highly conserved transition from alanine to valine. This missense mutation can lead to a decrease in enzyme activity and heat tolerance of MTHFR. Research reports that compared to the cytosine-cytosine (CC) genotype, the enzyme activity in the cytosine-thymine (CT) genotype decreased by 30%, while in the thymine-thymine (TT) genotype, the enzyme activity decreased by 70%. The enzyme activities corresponding to A1298C gene polymorphism are AA100%, AC83%, and CC61%, respectively (11).

In recent years, a large number of studies have confirmed that hyperhomocysteinemia (HHcy) (12), reactive oxygen species (ROS) induced oxidative stress (13), abnormal DNA methylation (14), and other factors affect sperm quality and are risk factors for male infertility. The folate cycle and carbon cycle disorders caused by MTHFR gene mutations are associated with many risk factors for male infertility. Therefore, MTHFR gene polymorphism may affect male fertility. The MTHFR gene polymorphism affects the folate cycle and one carbon cycle, leading to Hcy accumulation, abnormal DNA methylation, and decreased antioxidant capacity, ultimately affecting sperm quality and causing male infertility (15).

HHcy is considered one of the most important cardiovascular risk factors. HHcy directly affects endothelial cells, affects endothelial function, and increases the risk of cardiovascular disease by reducing the production of endothelial nitric oxide (16). Meanwhile, HHcy damage to endothelial cells may interfere with penile blood supply or other erection mechanisms (17), leading to the occurrence of ED. Epidemiological studies on ED have shown that ED is closely related to cardiovascular disease (18), endothelial dysfunction is a shared aetiological factor of ED and cardiovascular disease (19), therefore HHcy may be a new risk factor for ED (20).

As the field of andrology continues to see progress in new diagnostic and therapeutic technologies, we sought to obtain a robust understanding of the interactions between MTHFR gene polymorphism, oxidative stress, DNA methylation, HHcy, male infertility, and ED. To this end, herein, we provide a narrative review of the contemporary literature in this area of interest. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-153/rc).

Methods

A comprehensive literature search was performed in the PubMed database, without a limit on dates of publication. The following search terms were employed: "MTHFR gene polymorphism", "DNA methylation", "HHcy", "male infertility", and "ED". Emphasis was placed on studies that reported semen analyses, sperm diagnostics, and molecular assessment. Articles were selected based on quality and relevance. A wide range of animal and human studies were reviewed. The search strategy summary is outlined in *Table 1*.

Results

MTHFR gene polymorphism and male infertility

Correlation

A meta-analysis included 59 studies on MTHFRC677T and 28 studies on MTHFRA1298C to analyze the correlation between MTHFR gene polymorphism and male infertility. This study suggests that MTHFRC677T is associated with an increased risk of male infertility in the Asian region. MTHFRA1298C is not significantly associated with the risk of male infertility (21). In addition, Aliakbari *et al.* found through meta-analysis that both MTHFR polymorphisms

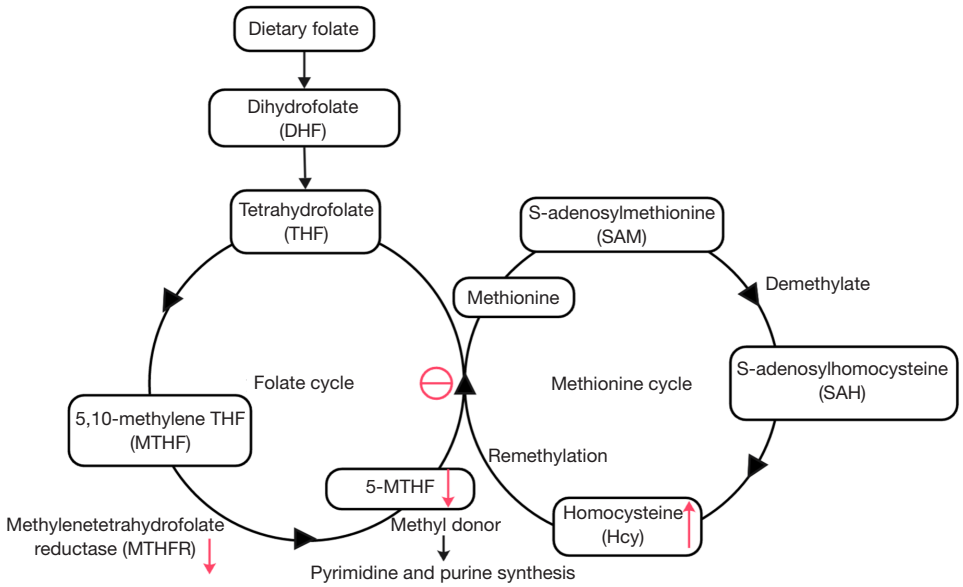

Figure 1 Folate cycle and methionine cycle.

Table 1 The search strategy summary

Items	Specification
Date of search	February 21, 2024
Database searched	PubMed
Search terms used	"MTHFR gene polymorphism", "DNA methylation", "HHcy", "male infertility", and "ED"
Timeframe	Between 2000 and 2023
Inclusion criteria	English and Chinese language studies were included. Peer-reviewed published articles were prioritized
Selection process	Each author was independently involved in literature search. The primary author (Z.X.) reviewed all included articles

Relevant important references are listed in *Table 2*. MTHFR, methylenetetrahydrofolate reductase; HHcy, hyperhomocysteinemia; ED, erectile dysfunction.

are significantly associated with the risk of male infertility. When stratified by race, a significant association between C677T and male infertility was observed in Asians and Caucasians, while only Asians were observed to have a risk of male infertility in A1298C (22). Based on extensive research, the MTHFRC677T gene polymorphism is significantly associated with male infertility in Asian populations, while the correlation between MTHFRA1298C and male infertility needs further confirmation. This may be because mutations in the C677T gene have a more significant impact on enzyme activity than mutations in the A1298C gene. In addition, the differences between Asians and Caucasians may be related to regional dietary habits involving folic acid. Research has shown that Asians have lower folate concentrations and higher plasma Hcy concentrations (23). The study found that the homozygous 677TT and combined heterozygous 677CT/1298AC groups had the highest percentage of patients with elevated blood Hcy levels and >15 μmol/L (57.8% and 18.8%, respectively) (24).

Infertile males have a higher rate of DNA fragmentation in their sperm compared to normal fertile males (25). Damaged sperm DNA integrity can lead to an increased rate of early spontaneous abortion in spouses. A study

Table 2 Relevant important references

Author(s)	Title	Journal	Year
Han LJ, He XF, Ye XH (21)	Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and male infertility risk: An updated meta-analysis	*Medicine (Baltimore)*	2020
Aliakbari F, Pouresmaeili F, Eshghifar N, *et al.* (22)	Association of the MTHFR 677C>T and 1298A>C polymorphisms and male infertility risk: a meta-analysis	*Reprod Biol Endocrinol*	2020
Wu W, Shen O, Qin Y, *et al.* (23)	Methylenetetrahydrofolate reductase C677T polymorphism and the risk of male infertility: a meta-analysis	*Int J Androl*	2012
Clément A, Amar E, Brami C, *et al.* (24)	MTHFR SNPs (Methyl Tetrahydrofolate Reductase, Single Nucleotide Polymorphisms) C677T and A1298C Prevalence and Serum Homocysteine Levels in >2100 Hypofertile Caucasian Male Patients	*Biomolecules*	2022
Colacurci N, De Leo V, Ruvolo G, *et al.* (25)	Recombinant FSH Improves Sperm DNA Damage in Male Infertility: A Phase II Clinical Trial	*Front Endocrinol (Lausanne)*	2018
Liu Y, Zhang F, Dai L (26)	C677T polymorphism increases the risk of early spontaneous abortion	*J Assist Reprod Genet*	2019
Xin Z, Han N, Jin H (27)	Correlation analysis of age and MTHFR C677T polymorphism with sperm motility and sperm DNA integrity	*Cell Mol Biol (Noisy-le-grand)*	2023
Safarinejad MR, Shafiei N, Safarinejad S (28)	Relationship between genetic polymorphisms of methylenetetrahydrofolate reductase (C677T, A1298C, and G1793A) as risk factors for idiopathic male infertility	*Reprod Sci*	2011
Xie C, Ping P, Ma Y, *et al.* (29)	Correlation between methylenetetrahydrofolate reductase gene polymorphism and oligoasthenospermia and the effects of folic acid supplementation on semen quality	*Transl Androl Urol*	2019
Martínez Duncker Rebolledo E, Chan D, Christensen KE, *et al.* (30)	Sperm DNA methylation defects in a new mouse model of the 5,10-methylenetetrahydrofolate reductase 677C>T variant and correction with moderate dose folic acid supplementation	*Mol Hum Reprod*	2024
Clement A, Amar E, Clement P, *et al.* (31)	Hyperhomocysteinemia in hypofertile male patients can be alleviated by supplementation with 5MTHF associated with one carbon cycle support	*Front Reprod Health*	2023
Huang WJ, Lu XL, Li JT, *et al.* (32)	Effects of folic acid on oligozoospermia with MTHFR polymorphisms in term of seminal parameters, DNA fragmentation, and live birth rate: a double-blind, randomized, placebo-controlled trial	*Andrology*	2020
Safarinejad MR, Safarinejad S, Shafiei N (33)	Role of methylenetetrahydrofolate reductase gene polymorphisms (C677T, A1298C, and G1793A) in the development of early onset vasculogenic erectile dysfunction	*Arch Med Res*	2010
Bai S, Li MZ, Wan YY, *et al.* (34)	Association between MTHFR c.677C>T variant and erectile dysfunction among males attending fertility clinic	*Asian J Androl*	2024
Šerý O, Šrámková T, Klempová J, *et al.* (35)	The relationship between the C677T polymorphism of the MTHFR gene and serum levels of luteinizing hormone in males with erectile dysfunction	*Neuro Endocrinol Lett*	2012
Lombardo F, Sgrò P, Gandini L, *et al.* (36)	Might erectile dysfunction be due to the thermolabile variant of methylenetetrahydrofolate reductase?	*J Endocrinol Invest*	2004
Lombardo F, Tsamatropoulos P, Piroli E, *et al.* (37)	Treatment of erectile dysfunction due to C677T mutation of the MTHFR gene with vitamin B6 and folic acid in patients non responders to PDE5i	*J Sex Med*	2010
Wang CH, Huang YF (38)	Hyperhomocysteinemia and erectile dysfunction: an update	*Zhonghua Nan Ke Xue*	2011

showed significant differences in the distribution frequency of the MTHFRC677T genotype and alleles between males who experienced early spontaneous abortion in spouses and those who had normal fertility. For cases of spontaneous abortion, the distribution frequency of CT and TT genotypes is higher. The scholar believes that MTHFR can affect sperm DNA integrity by affecting DNA methylation, leading to an increase in early spontaneous abortion rates in spouses (26). However, another study showed that age has a negative impact on sperm motility and sperm DNA integrity. Age is positively correlated with DNA Fragmentation Index (DFI) and negatively correlated with forward sperm motility. However, the MTHFRC677T polymorphism does not affect sperm forward motility or DNA integrity (27).

Research has found that men with alleles 677T, 1298C, and 1793G have significantly increased serum Hcy and decreased folate levels. There is a positive correlation between serum folate concentration and sperm density, forward sperm motility, and normal sperm morphology (28). Xie *et al.* believe that MTHFRC677T gene mutations and high Hcy concentrations are risk factors for oligoasthenozoospermia (29).

Treatment

Martínez Duncker Rebolledo and colleagues evaluated DNA methylation in sperm of mice with different MTHFRC677T genotypes by constructing a low enzyme activity MTHFR677TT mouse model and using bisulfite pyrophosphate sequencing and whole genome bisulfite sequencing. Compared with 677CC mice, 677TT mice showed lower levels of sperm methylation. Supplementing with folic acid (10 mg/kg diet) increased sperm methylation and partially corrected changes in sperm DNA methylation in TT genotype mice (30). Male infertility caused by decreased MTHFR enzyme activity may be due to low levels of sperm DNA methylation, and supplementation with folic acid can partially correct this low methylation.

A clinical intervention experiment has shown that 5-MTHF is very effective in reducing circulating Hcy. Patients with Hcy levels >15 μmol/L received a 3-month micronutrient combination therapy containing 5-MTHF (a downstream product of the MTHFR enzyme). The Hcy level of the patient decreased from an average of 27.4 μmol/L to an average of 10.7 μmol/L. Statistical analysis found that the 677TT genotype and the combined heterozygous 677CT/1298AC genotype accounted for 77.9% of patients with elevated Hcy (31). This indicates that the T allele is a risk factor for high Hcy. In these patients with low fertility, treatment with micronutrients including 5-MTHF can reduce Hcy. In the combined treatment of oligospermia patients with folic acid supplementation, it was found that there were differences in the therapeutic effect of folic acid supplementation among male infertility patients of different genotypes. Daily supplementation of 0.8 mg folic acid improved the sperm concentration of TT genotype oligospermia patients better than other genotypes (29). This means that there is a possibility of personalized folate supplementation therapy for patients with different genotypes. A randomized controlled clinical trial found that taking folic acid 0.8 mg daily for 3 months significantly improved semen parameters in patients with the MTHFR677TT genotype compared to patients receiving placebo. The MDA in semen and sperm DNA fragmentation rate in patients with the MTHFR677TT genotype were significantly reduced at the end of treatment. These studies indicate that male infertility patients receiving folic acid supplementation therapy can significantly reduce serum Hcy levels and improve sperm quality, especially for oligozoospermia patients (32).

Discussion

Methylation and demethylation play important roles in the production of germ cells. The correct methylation of DNA ensures appropriate chromatin concentration in the sperm head, enabling sperm maturation and its ability in fertilization and post-fertilization events (39). In male mouse testes, the activity of MTHFR is five times higher than that of other organs, and its inactivation leads to HHcy, decreased methylation ability, and sperm arrest caused by low DNA methylation in sperm. Mutations in the MTHFR gene are the cause of decreased MTHFR enzyme activity in sperm cells, leading to decreased availability of methionine and decreased DNA methylation (40).

ROS-induced oxidative stress plays a crucial role in infertility cases (41). Human sperm is particularly susceptible to oxidative stress, as they gradually lose their ability to repair DNA damage from male germ cells to mature sperm (42). Recent data indicate that oxidative stress in sperm not only has a negative impact on DNA integrity but also has a negative impact on the dynamics of epigenetic reprogramming. This may damage the father's genetic and epigenetic contributions to developing embryos, and affect embryo development and embryo quality. The incidence rate of 30–80% of infertile men is caused by oxidative stress and the decline of semen's total antioxidant capacity (43). The antioxidant function of folic acid is one of

the possible mechanisms for improving semen parameters and pregnancy outcomes. There is ample evidence to support the fact that antioxidant supplements, especially combinations of antioxidant intake, can effectively improve semen parameters in men with low fertility (44).

Hcy is a cytotoxic byproduct of S-adenosylhomocysteine hydrolysis, produced by the release of methyl groups from the universal methylation effector S-adenosylmethionine to receptor targets. It inhibits the methylation process, and its elevation is associated with various disease states (45), ultimately being both a cause and a result of oxidative stress (46).

MTHFR gene polymorphism and ED

Correlation

Safarinejad *et al.* found that compared to normal individuals, patients with early-onset vascular ED (VED) had higher serum Hcy levels (12.29±2.32 *vs.* 9.82±2.35 μmol/L, P=0.001) (33). According to subgroup analysis of ED severity (mild, moderate, and severe), severe VED patients had higher serum Hcy levels compared to mild VED patients (13.48±2.51 *vs.* 11.21±2.32 μmol/L, P=0.001). Through ratio analysis, individuals with the MTHFR677TT genotype and the 677TT+1298AC combination genotype had a 3.16- and 3.89-fold increased risk of developing VED, respectively. This suggests that MTHFR polymorphism may be associated with the risk of early-onset VED.

Research has found that there is a significant difference in International Index for Erectile Function-5 (IIEF-5) scores between MTHFR677TT males and MTHFR677CC males, and the overall score of 677TT is lower, indicating that males with this genotype are more prone to developing ED. The correlation between MTHFRC677T polymorphism and the severity of ED was analyzed using logistic regression, and it was found that there is a positive correlation between MTHFR677TT polymorphism and the risk of severe ED (IIEF-5 score less than 11) (34). However, the conclusion drawn by Šerý and others is that the C677T polymorphism of the MTHFR gene is not directly related to ED, but it exhibits a relationship between this polymorphism and plasma luteinizing hormone (LH) levels. The plasma LH levels in CC genotype patients are significantly higher than those in CT and TT genotype patients (35). At present, most scholars agree that HHcy is a risk factor for endothelial damage and the occurrence of ED, but the correlation between MTHFR gene polymorphism and ED still needs further research.

Treatment

Lombardo *et al.* reported a patient with the TT genotype of MTHFR who developed refractory ED caused by vasoactive phosphodiesterase 5 inhibitor (PDE5i) without apparent cause. After taking 5 mg of folic acid and 1,000 μg of vitamin B12 daily for 1 month, the patient resumed treatment with 50 mg of sildenafil and achieved satisfactory treatment results (36). A clinical study of 75 ED patients found that. There are differences in baseline values of Hcy and folate among patients with different genotypes. Patients with TT genotype exhibit high levels of Hcy and low levels of folate. After receiving treatment with sildenafil citrate for 2 months, all patients who did not respond to treatment will receive a combination of sildenafil, vitamin B6, and folic acid for 6 weeks. The experimental results showed that all 18 patients who did not respond to monotherapy exhibited high levels of Hcy and low levels of folate. After combination therapy, the IIEF questionnaire improved in 16 cases (88.9%). Their blood Hcy and folate levels showed significant differences before and after treatment (37). HHcy in homozygous patients with C677T mutations may interfere with the erection mechanism, leading to ED. In cases of HHcy associated with low folate levels, treatment with PDE5i alone may fail. Therefore, some scholars believe that the treatment of ED patients with high Hcy should first reduce Hcy levels by using folic acid alone or in combination with vitamin B6 or B12, followed by PDE5i treatment (38). Most scholars believe that HHcy may interfere with blood supply, leading to ED.

Discussion

At present, there are few articles on the correlation between MTHFR gene polymorphism and ED, and the conclusions are mixed, more clinical research data are needed to explore the correlation. HHcy directly affects vascular endothelial cells by reducing the production of endothelial nitric oxide, affecting vascular endothelial function and increasing the risk of cardiovascular diseases. At the same time, HHcy injury to vascular endothelial cells may interfere with penile blood supply or other erectile mechanisms, and thus lead to the occurrence of ED. Folic acid supplementation can significantly reduce the Hcy level in ED patients, and combined folic acid supplementation is a suitable choice for ED patients with PDE5i refractory.

Discussion

The MTHFRC677T gene polymorphism is an important factor affecting enzyme activity. MTHFR is involved in the human folate cycle and carbon metabolism, and a decrease in enzyme activity can lead to abnormal DNA protein methylation, accumulation of serum Hcy, and a decrease in folate levels. Further damage to the integrity of sperm DNA, obstacles to sperm development, and a decrease in sperm antioxidant stress capacity can affect sperm quality, leading to infertility. In addition, the accumulation of serum Hcy damages endothelial cells affects endothelial function, and increases the risk of cardiovascular disease. May interfere with the blood supply to the penis, leading to the occurrence of VED.

Insufficient folic acid during pregnancy increases the risk of NTDs in offspring while supplementing folic acid can greatly reduce the risk (47). Since 2009, China has widely adopted large-scale folic acid supplementation (0.4 mg folic acid tablets) as the main strategy for preventing NTDs (48). Many reproductive centers in hospitals have strategies to guide personalized folic acid supplementation for pregnant women by detecting MTHFR gene polymorphisms, to reduce pregnancy-related diseases and birth defects. In terms of male reproductive health, personalized supplementation of folic acid by detecting MTHFR gene polymorphism to help treat male infertility and ED seems to be a feasible solution.

For male infertility patients and ED patients with MTHFRC677T gene mutations, supplementing folic acid therapy with routine treatment is a more comprehensive treatment method. Being able to simultaneously increase serum folate levels and reduce blood Hcy levels is beneficial for the patient's cardiovascular system. However, different scholars have different opinions on the type and dosage of folic acid. Some scholars believe that a small dose of 0.8 mg folic acid significantly improves sperm quality in TT genotype patients (29), while others have found that high-dose folic acid supplementation can lead to the accumulation of unmetabolized Hcy and oxidative stress (49). Therefore, some scholars believe that physiological doses of 5-MTHF (800 μg) instead of high-dose folic acid (5 mg) for treatment, it avoids the potential adverse effects of unmetabolized folic acid syndrome (50), which is suspected to lead to immune dysfunction and other adverse pathological effects, such as cancer (especially colorectal and prostate cancer). However, some scholars believe that the MTHFR C677T polymorphism is not related to the pregnancy rate or outcome of women receiving assisted reproduction and supplementing with sufficient synthetic folate (51), indicating that simple supplementation with cheaper and easier to obtain folate, rather than expensive 5-MTHF, seems appropriate.

Our review of the literature on MTHFR-associated male diseases indicates that MTHFR gene polymorphisms are associated with male infertility, especially the C677T gene polymorphism, which has a strong effect on enzyme activity, and the correlation between MTHFR gene polymorphisms and ED is questionable and needs to be confirmed by more clinical data. MTHFR gene polymorphisms affect sperm quality, but the exact pathophysiological mechanisms are not fully understood. Folic acid supplementation can improve sperm quality, and MTHFR gene polymorphisms are associated with Hcy levels, which affects vascular endothelial function and may be related to the development of VED. Folic acid supplementation improves IIEF questionnaire scores among ED patients on whom PDE5i alone is ineffective. Future studies are necessary to further understand the relationship between MTHFR gene polymorphisms and male infertility and ED as well as to explore the mechanism of folic acid supplementation in the treatment of male infertility and ED.

Conclusions

Our literature review on MTHFR gene polymorphism in male infertility patients indicates a significant association between C677T gene polymorphism and male infertility. Folic acid supplementation can improve sperm quality. The correlation between MTHFR gene polymorphisms and ED is questionable and needs to be confirmed by more clinical data. MTHFR gene polymorphisms are associated with Hcy levels, which affects vascular endothelial function and may be related to the development of VED. Folic acid supplementation IIEF questionnaire scores in ED patients in whom PDE5i alone is ineffective.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-153/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-153/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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