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MTHFR Gene Methylation and Diabetes Mellitus Type2: Unraveling the Interplay and Clinical Significance - A Systematic Review

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Abstract:

Type 2 diabetes mellitus (T2DM) is a prevalent condition influenced by genetic and environmental factors, leading to various complications such as retinopathy, nephropathy, neuropathy, cardiovascular events, atherosclerosis, and increased susceptibility to infections. This systematic review examines the relationship between methylenetetrahydrofolate reductase (MTHFR) gene methylation and T2DM, emphasizing its clinical significance and complications. MTHFR gene variants, particularly the C677T polymorphism, have been associated with an elevated risk of T2DM, especially in Asian populations. Methylation patterns within the MTHFR gene, in combination with specific genetic variations, have been linked to metabolic parameters and the development of microvascular complications in individuals with diabetes. Understanding the impact of MTHFR gene methylation on T2DM pathogenesis can aid in risk assessment, diagnosis, and personalized treatment strategies. The review discusses the underlying mechanisms by which MTHFR gene methylation may contribute to diabetes pathophysiology, as well as its potential implications for risk assessment and diagnosis. Moreover, further investigation is needed to explore the potential of MTHFR gene methylation as an early detection marker for assessing complications and enhancing diagnostic strategies of T2DM. The review emphasizes the need for further research to gain a comprehensive understanding of the intricate relationship between MTHFR gene methylation and diabetes. Additionally, exploring the potential of MTHFR gene methylation as an early detection marker for complications and improving diagnostic strategies in T2DM warrants further investigation.

Keywords: MTHFR gene, Methylation, Diabetes mellitus, Pathophysiology, SNPs

Introduction

Type 2 diabetes mellitus (T2DM) is a rapidly expanding noncommunicable disease worldwide, characterized by a combination of various factors and a complex genetic background. T2DM imposes a significant burden on public health, leading to various complications and significantly impacting morbidity and mortality rates. Notably, individuals of South Asian descent demonstrate a heightened genetic susceptibility to developing type 2 diabetes mellitus (T2DM). Among the South Asian countries, India, in particular, has a significant proportion of individuals affected by T2DM, accounting for approximately one out of every six cases worldwide (Shitomi-Jones, et al., 2023).

Type 2 diabetes mellitus (T2DM) is primarily influenced by both genetic and environmental factors. Early prediction plays a crucial role in timely diagnosis and the prevention of complications. The complications associated with T2DM encompass retinopathy, nephropathy, neuropathy, cardiovascular events (such as heart attacks and strokes), atherosclerosis, and susceptibility to infections. The clinical manifestations of T2DM can be mild or go unnoticed for many years. However, if left untreated, it can lead to chronic complications such as retinopathy, nephropathy, neuropathy, heart attacks, strokes, atherosclerosis, and increased susceptibility to infections (Elqadi et al., 2021). Hence gene polymorphism analysis in diabetic patients can be a valuable tool for assessing the risk of developing diabetes. Although genetic factors are not the sole determinant of diabetes, understanding the role of gene polymorphisms can aid in predicting an individual's risk and implementing appropriate preventive measures or interventions. Ongoing research and advancements in genetic testing hold promise for improving risk assessment and personalized approaches to diabetes management in the future.

The enzyme methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism and converts 5,10 methylenetetrahydrofolate to methylenetetrahydrofolates, which are necessary as co-substrates in the conversion of homocysteine to methionine. A specific single nucleotide polymorphism (SNP), rs1801133 or MTHFR C677T, has been identified in the MTHFR gene located on chromosome 1 (1p36. 3). This SNP results in reduced MTHFR enzyme activity due to an amino acid change from alanine to valine position 222 (A222V). As a consequence, this impairment can lead to increased levels of circulating homocysteine (Hcy). The enzyme methylenetetrahydrofolate reductase (MTHFR) plays a crucial role in folate metabolism. One of its important functions is converting 5,10 methylenetetrahydrofolate to methylenetetrahydrofolates, which are necessary as co-substrates in the conversion of homocysteine to methionine (Raghubeer & Matsha 2021). Thus the alteration of this pathway may lead to higher levels of circulating homocysteine (Hcy). Elevated homocysteine levels have been associated with various health conditions, including cardiovascular diseases, neural tube defects, and pregnancy complications. It is important to note that the impact of the MTHFR C677T SNP on health outcomes is complex (Elqadi et al., 2021, Yuan et al., 2020).

The specific genetic variation known as the MTHFR C677T polymorphism has been linked to a number of diseases, including cardiovascular events like heart attacks and strokes, lung and breast cancers, infertility, and type 2 diabetes mellitus (T2DM). To better understand how this polymorphism relates to the risk of developing T2DM, a meta-analysis study was conducted by Meng et al. in 2019. The findings revealed a significant association between the MTHFR C677T polymorphism and T2DM, particularly among Asian populations. This suggests that individuals carrying this genetic variant may face a higher likelihood of developing T2DM compared to those who do not have this particular polymorphism.

The increasing prevalence of type 2 diabetes mellitus (T2DM) worldwide necessitates the identification of high-risk individuals for early intervention. Genetic polymorphisms, along with environmental factors, contribute to the development of T2DM. Further research involving larger global populations is needed to deepen our understanding of the molecular mechanisms underlying T2DM and identify more precise biomarkers for early risk identification (Li, et al., 2020).

DNA methylation is a fundamental epigenetic mechanism that regulates gene expression and has been implicated in the development of various diseases. Methylenetetrahydrofolate reductase (MTHFR) plays a critical role in providing methyl groups for DNA methylation. Notably, several studies have reported a significant association between genetic polymorphisms of the MTHFR gene and an increased risk of diabetes. However, the specific relationship between epigenetic changes within the MTHFR gene and the development of diabetes, as well as its complications, remains to be fully elucidated. Further research is warranted to comprehensively understand the impact of MTHFR gene methylation on diabetes pathogenesis and its potential implications for diagnosis, treatment, and prevention strategies (dos Santos Nunes et al., 2017).

This review comprehensively explores the interplay between methylenetetrahydrofolate reductase (MTHFR) gene methylation and diabetes mellitus type 2 (T2DM), shedding light on its clinical significance and complications. By synthesizing existing evidence, the review contributes to our understanding of the role of MTHFR gene methylation in T2DM development, progression, and potential as an early detection marker. The findings emphasize the need for further research to fully elucidate the complex relationship

between MTHFR gene methylation and T2DM, ultimately paving the way for improved management and prevention of T2DM.

Complications of T2DM: Role of MTHFR

The MTHFR enzyme plays a crucial role in folate metabolism, influencing the conversion of dietary folate into essential methyl group donors. Various studies have investigated the clinical significance of MTHFR gene polymorphisms and their impact on different aspects of health, particularly in relation to type 2 diabetes mellitus (T2DM) and its complications (Nithya et al., 2017). This discussion highlights the relationship between MTHFR gene variants and metabolism in the context of T2DM, renal impairment, myocardial infarction, and coronary artery disease. Additionally, the influence of MTHFR gene methylation on diabetes-related cardiac fibrosis and the association between MTHFR polymorphisms and T2DM-related complications are explored.

Type 2 diabetes mellitus (T2DM) is a major public health problem, and inadequate folic acid intake has been linked to an increased risk of T2DM. Folate, as a methyl group donor, plays a vital role in DNA stability and cellular processes. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in folic acid metabolism and DNA synthesis. The C677T polymorphism of the MTHFR gene has been extensively studied and found to significantly decrease MTHFR activity. Recent meta-analysis results suggest a significant association between the MTHFR C677T polymorphism and T2DM, especially in Asian populations. However, further well-designed, large-scale studies are necessary to validate and explore this relationship in more depth. (Meng et al., 2019)

The relationship between a specific gene polymorphism (MTHFR C677T) is associated with impaired enzyme activity, increased homocysteine levels, and the progression of renal impairment in patients. Two hundred hypertensive patients and 200 healthy controls were considered in the study of Elsaid et al., (2021). The study found that patients with the TT genotype had higher levels of homocysteine and urinary albumin creatinine ratio (UACR) compared to those with the CC genotype. Carrying the T allele was associated with a higher risk of hypertension and early renal impairment. The study suggests that the genetic variant and hyperhomocysteinemia may contribute to the rapid progression of renal impairment in young hypertensive patients. Thus the study proved that lowering homocysteine levels may potentially reduce renal impairment in hypertensive patients.

The MTHFR gene variants have been found to play a role in the pathophysiology of myocardial infarction (MI) in diabetic patients. These genetic variations affect the metabolism of folate and homocysteine, leading to impaired homocysteine clearance and elevated levels. Increased homocysteine levels contribute to endothelial dysfunction and worsen the risk of cardiovascular disease, including MI. The MTHFR C677T (rs1801133) polymorphism, particularly the T/T homozygous genotype, has been associated with a higher risk of MI in the presence of diabetes. Understanding the role of MTHFR gene variants in the pathogenesis of MI can aid in identifying potential therapeutic targets for this condition (Mallhi et al., 2023).

Diabetes cardiac fibrosis is a complex complication of diabetes that involves several factors, such as inflammation, aging, abnormal metabolism, and altered gene transcription. One critical cellular event contributing to this condition is the pyroptosis of cardiac fibroblasts (CFs). Pyroptosis is a specific type of cell death associated with inflammation. The development of diabetes cardiac fibrosis is also influenced by abnormal epigenetic modifications, which play a role in controlling CFs pyroptosis and the overall progression of the disease. The study of Sun et al., (2022) proved that regulation of MTHFR through DNA methylation, particularly mediated by DNMT3A (DNA methyltransferase 3A), plays a critical role in diabetes-related cardiac fibrosis by suppressing MTHFR due to DNA methylation. This suppression is driven by increased levels of DNMT3A, an enzyme responsible for adding methyl groups to the DNA of the MTHFR gene. As a result, the decreased expression of MTHFR leads to negative effects on the heart.

The relationship between methylation patterns of the methylenetetrahydrofolate reductase (MTHFR) gene, specific genetic variations (C6TT7 and A1298C polymorphisms), and metabolic, inflammatory, and oxidative stress parameters related to microvascular complications in diabetic patients. The hypermethylated methylation profile, particularly in conjunction with the 1298AA genotype, was

associated with higher levels of glycemia, total cholesterol, and LDL cholesterol in diabetic individuals. These results highlight the potential influence of methylation patterns and genetic variations on the development of microvascular complications in diabetes (Santana Bezerra et al., 2019).

Type 2 diabetes mellitus (T2DM) is a prevalent form of diabetes characterized by chronic complications affecting multiple organs. Notable correlations were observed between these polymorphisms and T2DM-related complications, specifically stroke (CVA), nephropathy, high LDL cholesterol, and triglyceride levels. These findings suggest that MTHFR polymorphisms can serve as risk markers for these complications in T2DM patients, enabling timely intervention. MTHFR is involved in folate metabolism, and its variants (C677T and A1298C) can lead to decreased enzyme activity (Yagmour et al., 2022). The association between these polymorphisms and T2DM varies among different ethnic populations as per the study of Chehadeh et al., 2016.

The study of Diniz et al., (2021) revealed a significant association between physical activity level and the methylation profile of the MTHFR gene in patients with type 2 diabetes mellitus (T2DM). Insufficient physical activity was linked to a partially methylated pattern of the MTHFR gene promoter, suggesting a potential role in the development of microvascular complications. No significant associations were found with nutritional status. These findings emphasize the importance of regular physical activity in T2DM management, as it may influence gene methylation and potentially impact patient outcomes.

The significant association between global DNA methylation and the NOS3 rs1799983 polymorphism suggests that gene-epigenetic mechanisms involving NOS3 may contribute to the development of vascular complications in diabetes, even in individuals with well-managed metabolic control. These findings underscore the crucial role of epigenetics in unraveling the intricate interplay between genetic factors and environmental influences in the onset and advancement of type 2 diabetes (Matsha et al., 2016).

Conclusion

In summary, the systematic review aimed at a comprehensive analysis of the relationship between methylenetetrahydrofolate reductase (MTHFR) gene methylation and diabetes. The review highlights the importance of understanding this interplay for risk assessment, diagnosis, and personalized treatment strategies in the context of type 2 diabetes mellitus (T2DM). The findings suggest that MTHFR gene methylation may contribute to the pathogenesis of T2DM and its complications, with the MTHFR C677T polymorphism being a significant genetic variant associated with increased risk. The review calls for further research to fully elucidate the complex mechanisms underlying this relationship and explores the potential clinical implications of MTHFR gene methylation as a biomarker for T2DM management and prevention.

Abbreviations

T2DM: Type 2 diabetes mellitus

MTHFR: Methylenetetrahydrofolate reductase

SNP: Single nucleotide polymorphism

Hcy: Homocysteine

MI: Myocardial infarction

CFs: Cardiac fibroblasts

DNMT3A: DNA methyltransferase 3A

LDL: Low-density lipoprotein

CVA: Cerebrovascular accident (stroke)

NOS3: Nitric oxide synthase 3

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