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Gene–diet interactions and the risk of type 2 diabetes mellitus and metabolic syndrome

Interações gene–dieta e o risco de diabetes tipo 2 e síndrome metabólica

Interacciones gene–dieta y el riesgo de desarrollar diabetes mellitus tipo 2 y síndrome metabólico

Diolina Gonçalves da Silva[1], Rodrigo da Silva Santos[1], Angela Adamski da Silva Reis[1].

ABSTRACT

Objective: To analyze the factors associated with individual responses related to gene–diet interactions and to understand the role of precision nutrition in the development of personalized nutritional strategies. **Literature review:** Metabolic Syndrome consists of a cluster of risk factors that increase susceptibility to several alterations in cellular metabolism, with Type 2 Diabetes Mellitus being one of the main metabolic disorders associated with this condition. Given the complexity of this syndrome, Precision Nutrition, also referred to as predictive nutrition, has emerged as a promising approach for the prevention and management of metabolic diseases. This strategy is based on the development of individualized nutritional recommendations grounded in specific biological and environmental characteristics, integrating genomic information, dietary patterns, and levels of physical activity. Scientific evidence indicates that genetic variants in genes such as *FTO*, *MTHFR*, *APOE*, *LEP*, *LEPR*, *TCF7L2*, *GST*, *ACE*, and *PPARγ* are associated with the development of metabolic syndrome. The interaction between these genetic variants and environmental factors, particularly hypercaloric diets rich in lipids and sodium, significantly contributes to the increased risk of developing this syndrome. **Final considerations:** Precision nutrition, by integrating genetic, metabolic, and environmental information, has the potential to improve strategies for the prevention and treatment of Type 2 Diabetes Mellitus and Metabolic Syndrome, enabling more effective and personalized nutritional interventions.

Keywords: Diabetes mellitus, Precision nutrition, Genetic polymorphisms, Metabolic syndrome, Diet therapy.

RESUMO

Objetivo: Analisar os fatores associados às respostas individuais decorrentes das interações gene-dieta e compreender o papel da nutrição de precisão no desenvolvimento de estratégias nutricionais personalizadas. **Revisão bibliográfica:** A Síndrome metabólica corresponde a um conjunto de fatores de risco que aumentam a suscetibilidade a diversas alterações no metabolismo celular, sendo o Diabetes Mellitus tipo 2 um dos principais distúrbios metabólicos associados a essa condição. Diante da complexidade dessa síndrome, a Nutrição de precisão, também denominada nutrição preditiva, surge como uma abordagem promissora para a prevenção e o manejo dessas doenças metabólicas. Essa estratégia baseia-se na elaboração de recomendações nutricionais individualizadas, fundamentadas em características biológicas e ambientais

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específicas, integrando informações genômicas, padrões alimentares e níveis de atividade física. Evidências científicas indicam que variantes genéticas em genes como *FTO*, *MTHFR*, *APOE*, *LEP*, *LEPR*, *TCF7L2*, *GST*, *ACE* e *PPARγ* estão associadas ao desenvolvimento da síndrome metabólica. A interação entre essas variantes genéticas e fatores ambientais, especialmente dietas hipercalóricas ricas em lipídios e sódio, contribui significativamente para o aumento do risco de desenvolvimento dessa síndrome. **Considerações finais:** A nutrição de precisão, ao integrar informações genéticas, metabólicas e ambientais, apresenta potencial para aprimorar estratégias de prevenção e tratamento do Diabetes Mellitus tipo 2 e da Síndrome metabólica, permitindo intervenções nutricionais mais eficazes e personalizadas.

Palavras-chave: Diabetes mellitus, Nutrição de precisão, Polimorfismos genéticos, Síndrome metabólica, Dietoterapia.

RESUMEN

Objetivo: Analizar los factores asociados a las respuestas individuales derivadas de las interacciones gen–dieta y comprender el papel de la nutrición de precisión en el desarrollo de estrategias nutricionales personalizadas. **Revisión bibliográfica:** La Síndrome metabólico consiste en un conjunto de factores de riesgo que aumentan la susceptibilidad a diversas alteraciones del metabolismo celular, siendo la Diabetes mellitus tipo 2 uno de los principales trastornos metabólicos asociados a esta condición. Dada la complejidad de este síndrome, la Nutrición de precisión, también denominada nutrición predictiva, surge como un enfoque prometedor para la prevención y el manejo de las enfermedades metabólicas. Esta estrategia se basa en el desarrollo de recomendaciones nutricionales individualizadas fundamentadas en características biológicas y ambientales específicas, integrando información genómica, patrones alimentarios y niveles de actividad física. Evidencias científicas indican que variantes genéticas en genes como *FTO*, *MTHFR*, *APOE*, *LEP*, *LEPR*, *TCF7L2*, *GST*, *ACE* y *PPARγ* están asociadas con el desarrollo del síndrome metabólico. La interacción entre estas variantes genéticas y factores ambientales, especialmente dietas hipercalóricas ricas en lípidos y sodio, contribuye significativamente al aumento del riesgo de desarrollar este síndrome. **Consideraciones finales:** La nutrición de precisión, al integrar información genética, metabólica y ambiental, presenta un gran potencial para mejorar las estrategias de prevención y tratamiento de la Diabetes mellitus tipo 2 y del Síndrome metabólico, permitiendo intervenciones nutricionales más eficaces y personalizadas.

Palabras clave: Diabetes mellitus, Nutrición de precisión, Polimorfismos genéticos, Síndrome metabólico, Dietoterapia.

INTRODUCTION

Metabolic Syndrome consists of a cluster of risk factors that increase susceptibility to various alterations in cellular metabolism, with insulin resistance being the primary disturbance. This syndrome is multifactorial, involving dietary, genetic, and environmental factors. The presence of obesity and genetic alterations contributes significantly to the development of insulin resistance (FAHED G, et al., 2022). Type 2 Diabetes Mellitus (T2DM) is one of the main metabolic disorders associated with metabolic syndrome. It is characterized by elevated blood glucose levels, insulin resistance, and the influence of genetic predisposition (HARRIETER J and RODEN M, 2023).

The global prevalence of diabetes has increased significantly due to the rising consumption of highly caloric foods, particularly ultra-processed products rich in saturated fats and sugar. Reduced physical activity during leisure time and increased sedentary behavior contribute to a positive energy balance, in which caloric intake exceeds energy expenditure, further exacerbating the incidence of the disease. The growing prevalence of T2DM is closely associated with economic development, lifestyle changes, unhealthy dietary patterns, and increasing obesity rates. As a chronic condition, T2DM can lead to several complications, including diabetic retinopathy, neuropathy, nephropathy, and cardiovascular diseases (ZHENG L, et al., 2025).

Advances in omics technologies have enabled the emergence of new scientific fields, making it possible to better understand the genetic basis underlying interindividual responses to dietary intake. In T2DM, insulin secretion and action must meet metabolic demands, requiring precise regulation of the molecular mechanisms involved. Dysfunction of pancreatic β-cells leads to decreased insulin production, while α-cells increase glucagon secretion, resulting in reduced glucose uptake by tissues and skeletal muscles and subsequent hyperglycemia. In addition to genetic predisposition, environmental and epigenetic interactions also contribute to the increasing prevalence of T2DM (KIANI AK, et al., 2022).

Diet is a fundamental component of health, directly influencing gene expression and metabolic pathways. Moreover, genome-wide association studies (GWAS) have significantly advanced the understanding of T2DM by identifying genetic variants associated with the disease. These variants, particularly single nucleotide variants (SNVs), interact with micro- and macronutrients, altering metabolic and molecular pathways and thereby affecting biochemical processes within cells (FUCHSBERGER C, et al., 2016).

Additionally, genetic analyses have identified more than 100 loci associated with an increased risk of developing T2DM. Most of these variants are linked to pancreatic islet development, glucose sensing, insulin secretion, synthesis, signaling, or resistance, while others are associated with obesity and inflammatory processes (KARADERI T, et al., 2015). Beyond genetic variants, gene–diet interactions are also modulated by epigenetic mechanisms, which influence gene expression without altering the DNA sequence. Processes such as DNA methylation, histone modification, and regulation by non-coding RNAs are affected by dietary intake, particularly by nutrients that act as methyl donors. A deficiency in these nutrients may impair normal epigenetic regulation, leading to abnormal gene expression patterns associated with chronic diseases such as T2DM (MALCOMSON FC and MATHERS JC, 2017).

Given this complexity, Precision Nutrition, also referred to as predictive nutrition, has emerged as a promising approach for the prevention and management of T2DM. This field of medicine aims to propose personalized nutritional recommendations based on individual characteristics and environmental factors, integrating genomic information, dietary patterns, and levels of physical activity (TEBANI A and BEKRI S, 2019). From this perspective, the present review aims to analyze the factors associated with individual responses to gene–diet interactions and to explore the role of precision nutrition in the development of personalized nutritional strategies.

LITERATURE REVIEW

One of the key concepts in Precision Nutrition is nutrigenetics, which focuses on understanding the interaction between genetic variants and nutrient metabolism (TEBANI A and BEKRI S, 2019). This scientific field aims to adapt dietary recommendations to individual genetic variations using genetic analysis tools such as genome-wide association studies (GWAS). The application of GWAS has led to a growing body of research aimed at elucidating gene–environment interactions involved in the development of chronic diseases, such as Type 2 Diabetes Mellitus (T2DM), as well as identifying single nucleotide variants (SNVs) that may inform personalized dietary recommendations. GWAS methodologies are designed to map genetic markers, allowing the characterization of the relationship between genetic variants and individual susceptibility to insulin resistance through the analysis of interaction pathways between SNVs and nutritional factors (ZEINALIAN R, et al., 2022).

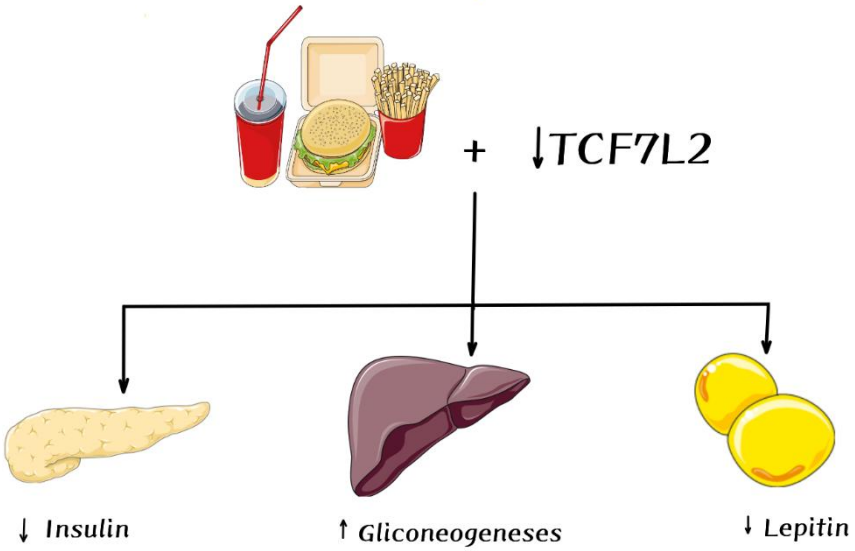
GWAS analyses that incorporate dietary factors related to T2DM phenotypes have helped identify several genes associated with disease susceptibility and progression, particularly those involved in energy and lipid metabolism. Among these genes, *CAPN10* was the first to be associated with T2DM through genomic scanning. This gene encodes calpain-10, a protein involved in insulin vesicle release. Following glucose metabolism, the increase in ATP promotes depolarization of the cell membrane by closing ATP-sensitive potassium channels, which allows an influx of calcium ions into the cell (HATTA AT, et al., 2018). This cascade activates calpain-10, which cleaves proteins from the N-ethylmaleimide-sensitive soluble fusion protein (SNARE) family, thereby facilitating insulin exocytosis. Variants such as rs5030952, rs2975762, rs3792267, and rs2975760 in the *CAPN10* gene are associated with elevated blood glucose levels and an increased risk

of T2DM (MISHRA KC, et al., 2024). Functionally, calpain-10 deficiency impairs SNARE protein cleavage, reducing the stimulus for insulin release (PÂNICO P, et al., 2014). The association of *CAPN10* variants with lifestyle habits and environmental exposures has been linked to susceptibility to T2DM. The interaction between variants in this gene and environmental factors, such as a sedentary lifestyle and diets rich in lipids, increases the likelihood of developing the disease. In this context, precision nutrition emerges as a promising strategy to improve prevention approaches (FAROOQI H, et al., 2025).

In addition to *CAPN10*, another gene involved in glucose metabolism and relevant to precision nutrition in T2DM is *TCF7L2*. This gene encodes transcription factor 7-like 2, a key regulator of glucose homeostasis through its role in insulin synthesis and processing, maintenance of pancreatic islets, and production of glucagon-like peptide-1 (GLP-1). In pancreatic β-cells, TCF7L2 interacts with β-catenin to form a complex that facilitates insulin secretion. In intestinal cells, this interaction also stimulates GLP-1 production (DEL BOSQUE-PLATA L, et al., 2021).

In hepatocytes, elevated insulin levels stimulate the activity of the β-catenin/TCF7L2 complex, contributing to the repression of hepatic gluconeogenesis. In adipocytes, this same complex is activated by insulin and promotes the expression of the leptin gene, which induces satiety and enhances insulin signaling through the phosphorylation of insulin receptor substrates (IRS) (DEL BOSQUE-PLATA L, et al., 2021). Variants such as rs7903146 and rs12255372 in the *TCF7L2* gene, when combined with a high-calorie diet, are associated with disturbances in glucose homeostasis and impaired insulin secretion. Altered expression or function of TCF7L2 reduces insulin release, stimulates gluconeogenesis, and inhibits leptin production, ultimately contributing to insulin resistance (HUANG Z, et al., 2018) (**Figure 1**). Additionally, individuals carrying the rs7903146 SNV in the *TCF7L2* gene showed improved anthropometric parameters when consuming omega-3-rich foods, such as fish, which helped reduce insulin resistance (BHORI M, et al., 2021).

Figure 1 - The association of a hypercaloric, lipid-rich diet with reduced TCF7L2 expression promotes decreased insulin secretion, increased gluconeogenesis, and reduced leptin release. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0. (https://creativecommons.org/licenses/by/4.0/).



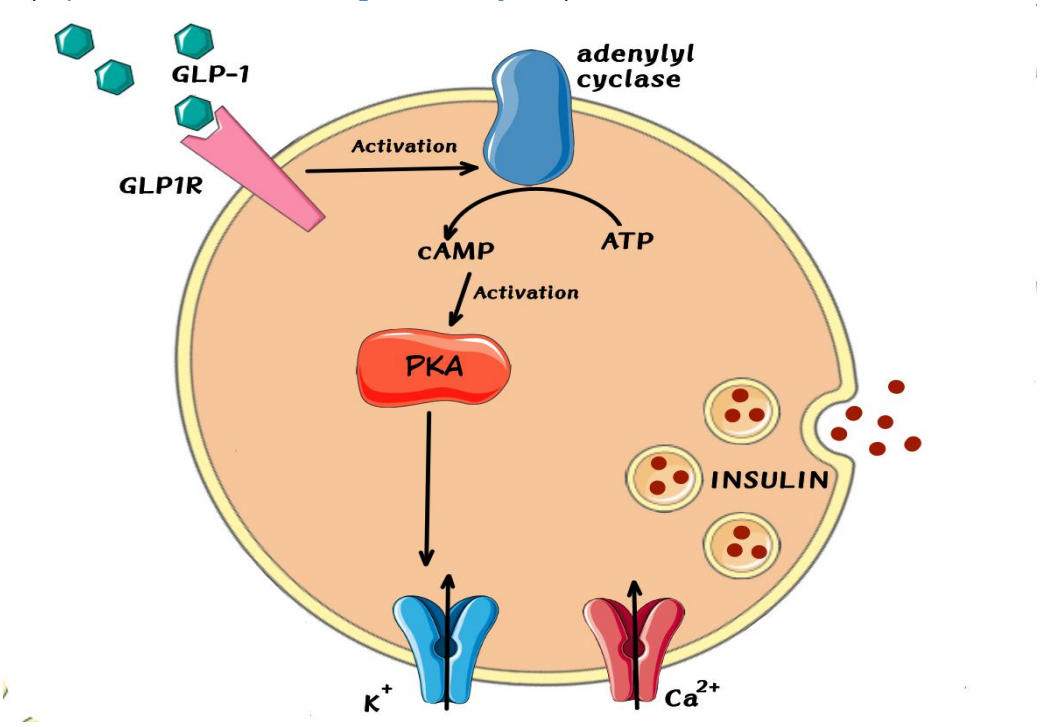
Source: Silva DG, et al., 2026.

Within the TCF7L2 pathway, GLP-1 stimulated by this gene also plays a key role in understanding gene–nutrition interactions. GLP-1 acts by stimulating insulin secretion and inhibiting glucagon release. The interaction of GLP-1 with its receptor (GLP1R), encoded by the GLP1R gene, promotes the activation of G proteins, which subsequently stimulate adenylate cyclase, an enzyme responsible for catalyzing the formation of cyclic adenosine monophosphate (cAMP) (FRANCIS L and BUTLER MG, 2025).

The interaction of cAMP with protein kinase A (PKA) increases intracellular potassium and calcium fluxes, thereby promoting the exocytosis of insulin-containing vesicles (**Figure 2**). Single nucleotide variants (SNVs) such as rs6923761, rs3765467, rs1820, and rs1042044 in the *GLP1R* gene can alter receptor conformation and reduce its affinity for GLP-1, leading to reduced insulin secretion and contributing to the development of Type 2 Diabetes.

Additionally, adherence to a grain-rich diet among individuals homozygous for the mutant allele has been associated with an increased risk of developing Type 2 Diabetes. In contrast, among patients carrying SNVs in *GLP1R*, a plant-rich diet was associated with improved dietary regulation and lower blood glucose levels (BHORI M, et al., 2021).

Figure 2 - GLP-1 binds to its receptor, GLP1R, stimulating the production of cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A (PKA), which increases potassium and calcium influx, promoting the exocytosis of insulin-containing vesicles. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0. (https://creativecommons.org/licenses/by/4.0/).

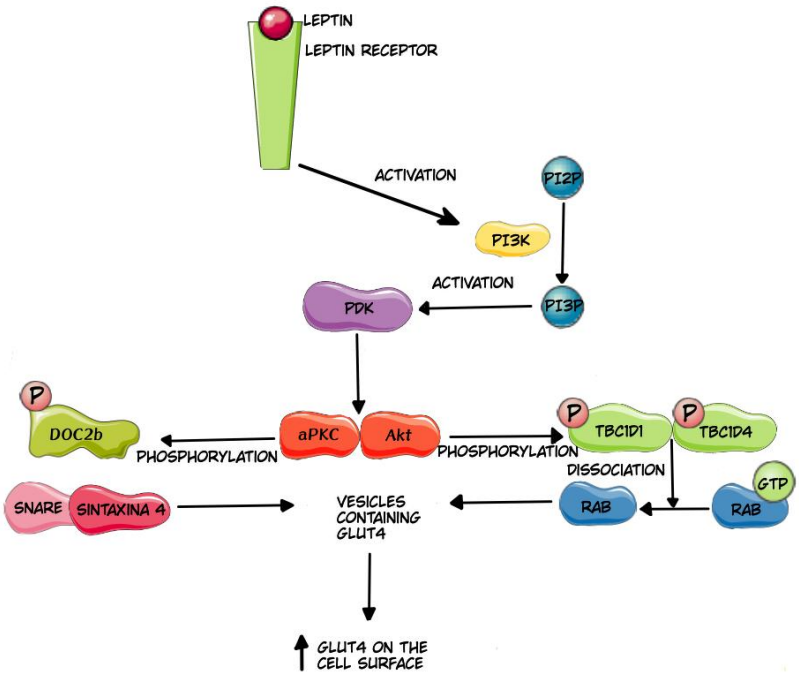


Source: Silva DG, et al., 2026.

Together with GLP-1, leptin signaling also contributes to the regulation of metabolic processes associated with Metabolic Syndrome and Type 2 Diabetes Mellitus by controlling appetite and energy balance. Leptin is a hormone that acts on the hypothalamus to reduce appetite, promote satiety, and increase energy expenditure (GENCHI VA, et al., 2021).

When leptin binds to its receptor, it activates Janus kinase (JAK), which phosphorylates tyrosine residues on the receptor. This activation triggers phosphatidylinositol 3-kinase (PI3K), which catalyzes the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3). As PIP3 levels increase, the enzyme phosphoinositide-dependent kinase (PDK) is activated. This activation subsequently stimulates two key signaling proteins: atypical protein kinase C (aPKC) and protein kinase B (Akt). These proteins promote the translocation of GLUT4-containing vesicles to the plasma membrane by regulating Rab GTPase activity and facilitating interactions with components of the SNARE complex, including syntaxin-4. As a result, glucose transporters are inserted into the membrane, allowing glucose uptake by the cell (FRIEDMAN JM, 2019).

Figure 3 - Binding of leptin to its receptor activates PI3K, leading to the activation of PDK and stimulating the translocation of GLUT4-containing vesicles to the plasma membrane. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0. (https://creativecommons.org/licenses/by/4.0/).



Source: Silva DG, et al., 2026.

Leptin secretion is influenced by body mass, nutritional status, and insulin concentration. Serum leptin levels decrease during fasting and increase with adequate nutrition, contributing to cellular glucose uptake through the translocation of GLUT4 transporters. Variants in the genes encoding leptin (LEP) and its receptor (LEPR) are intrinsically linked to Metabolic Syndrome due to their association with obesity. Mutations in the LEP gene may lead to defective leptin secretion, inactive leptin synthesis, or the absence of circulating leptin (WABITSCH M, et al., 2015).

Mutations in the LEPR gene can result in a truncated receptor lacking transmembrane and intracellular domains. Individuals carrying the mutant allele often experience rapid weight gain early in life, progressing to obesity with excessive fat deposition in the trunk and limbs (FAROOGI IS and O'RAHILLY S, 2014). The G2548A (rs7799039) and Q223R (rs1137101) variants in *LEP* and *LEPR*, respectively, are among the most frequently reported. Individuals with the AA and RR genotypes are often associated with high-calorie, high-fat dietary patterns. Based on these findings, nutrigenetics and pharmacogenetics have emerged as valuable tools for the management of individuals carrying these genetic variants (PRIMO D, et al., 2020).

Considering these genetic influences, therapeutic strategies such as nutrigenetics and pharmacogenetics have been explored. In pharmacogenetics, daily subcutaneous injections of human leptin in patients with low circulating leptin concentrations have proven effective for promoting weight loss, reducing appetite and food intake, and increasing postprandial satiety. In nutrigenetics, the analysis of the patient's genotype profile is essential for determining the most appropriate dietary strategy. Consequently, patients carrying the rs7799039 and rs1137101 variants should carefully evaluate their dietary lipid intake (FRIEDMAN JM, 2019).

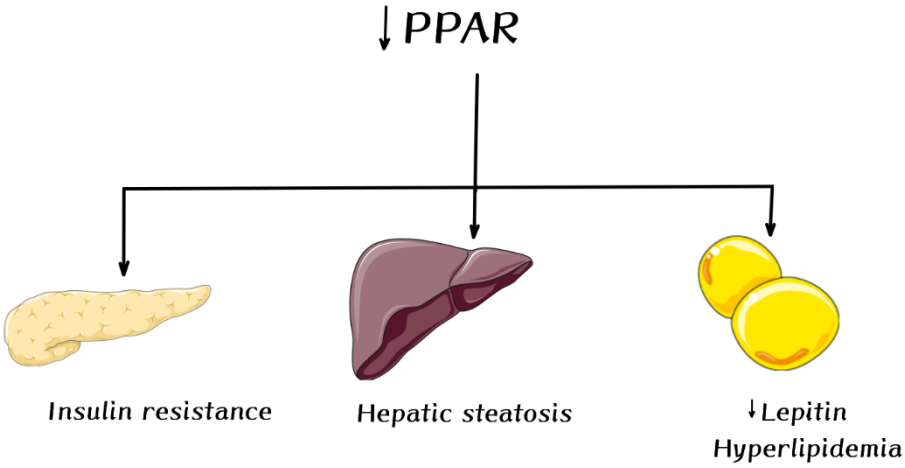
In addition to hormonal regulation, lipid transport mechanisms also play a central role in energy metabolism associated with the development of Metabolic Syndrome. Dietary lipids are transported in the bloodstream by cholesterol and lipoproteins, forming chylomicrons that deliver lipids to peripheral tissues. The remaining chylomicrons are processed in the liver to form very-low-density lipoproteins (VLDL), which interact with apolipoprotein E (ApoE) to regulate lipid distribution and maintain lipid homeostasis (CHEN L, et al., 2019).

Variants of the *APOE* gene, when combined with a high-fat diet, are associated with metabolic syndrome due to their role in lipid metabolism. ApoE isoforms influence cholesterol absorption, synthesis, and lipoprotein production. Individuals carrying the ApoE4 isoform tend to present higher total and LDL cholesterol levels, and their serum lipid response to diet varies according to genotype, highlighting the importance of personalized dietary strategies (KHALIL YA, et al., 2021).

Furthermore, it is important to highlight the role of *PPARγ* gene variants in lipid metabolism. The peroxisome proliferator-activated receptor gamma (PPARγ), encoded by the *PPARγ* gene, is a transcription factor involved in the regulation of inflammation and energy homeostasis and has also been associated with metabolic syndrome. PPARγ negatively regulates pro-inflammatory genes and promotes the release of free fatty acids from circulating lipoproteins while also stimulating their uptake, thereby increasing lipid storage (ZOU H, et al., 2023).

PPARγ acts in adipocytes by stimulating the secretion of adipokines such as adiponectin and leptin, which enhance insulin sensitivity in peripheral tissues. In addition, PPARγ modulates the expression of genes related to lipid mobilization, transport, and storage, including lipoprotein lipase (LPL) and the fatty acid transporter CD36 (**Figure 4**) (JANINE C and RANJITHA KUMARI BD, 2015).

Figure 4 - Reduced expression of PPARγ is associated with increased insulin resistance, hepatic steatosis, reduced leptin secretion, and hyperlipidemia. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0. (https://creativecommons.org/licenses/by/4.0/).



Source: Silva DG, et al., 2026.

Variants in the *PPARγ* gene are associated with hyperlipidemia, insulin resistance, and hepatic steatosis. The rs1801282 variant, in particular, is associated with reduced transcriptional activity of the mutant PPARγ protein due to its lower affinity for DNA compared with the wild-type protein. A Spanish study evaluated the association between a low-calorie Mediterranean diet combined with physical exercise and the rs1801282 variant of *PPARγ*, showing that individuals carrying the mutant allele experienced less weight loss than those with the wild-type genotype (STIENSTRA R, et al., 2007). On the other hand, a Finnish study showed that individuals carrying the same mutant allele experienced greater weight loss after following a low-fat, high-fiber diet compared with those carrying the wild-type allele (GARAULETE M, et al., 2011). These findings suggest a possible interaction between diet and the *PPARγ* variant in the regulation of body weight.

In addition to pathways related to energy and lipid metabolism, precision nutrition has highlighted the importance of the combined analysis of genetics and nutrition in several other metabolic pathways. Among these, the vitamin B9 metabolic pathway, the renin–angiotensin–aldosterone system, and the oxidative stress pathway stand out. The vitamin B9 pathway refers to the set of molecular mechanisms associated with the metabolism of this vitamin in the body, from its absorption to its intracellular processing (CARBONI L, 2022).

The renin-angiotensin–aldosterone system represents one of the principal mechanisms responsible for the regulation of blood pressure (SCHÜLER R, et al., 2017). Finally, the oxidative stress pathway encompasses the mechanisms responsible for maintaining cellular redox balance, and its disruption leads to an imbalance between oxidant and antioxidant factors (ALNASSER SM, 2024).

With regard to vitamin B9 metabolism, the *MTHFR* gene has been shown to be highly relevant in the analysis of gene–nutrition interactions in patients with Type 2 Diabetes Mellitus. The *MTHFR* gene encodes the enzyme methylenetetrahydrofolate reductase, which participates in the metabolic pathway of vitamin B9. Vitamin B9, found in legumes, green leafy vegetables, liver, and other foods, is ingested in its polyglutamate form and absorbed as monoglutamate. It is subsequently converted into 5-methyltetrahydrofolate (5-MTHF), which can also be synthesized endogenously. The production of 5-MTHF occurs through the reduction of 5,10-methylenetetrahydrofolate (5,10-MTHF) by the enzyme methylenetetrahydrofolate reductase. 5-MTHF acts as a methyl donor in homocysteine metabolism, facilitating its conversion into methionine in a reaction catalyzed by the enzyme methionine synthase (MTR), which is dependent on vitamin B12 (CARBONI L, 2022).

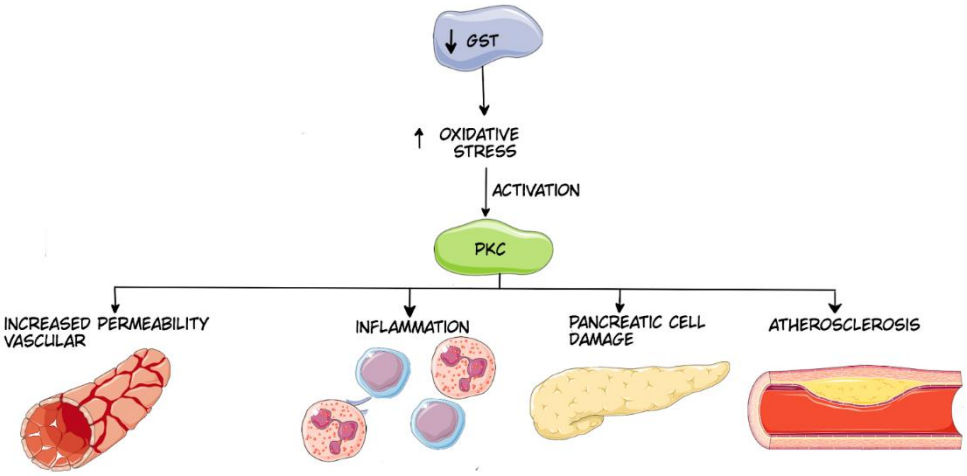
The combination of a diet deficient in vitamins B9 and B12 with the presence of the rs1801133 variant leads to the production of a less active form of the MTHFR enzyme due to the substitution of alanine with valine at position 222. This reduction in enzymatic activity favors the accumulation of homocysteine. Hyperhomocysteinemia promotes endothelial damage through the generation of reactive oxygen species (ROS) derived from the thiol groups present in homocysteine. This oxidative stress promotes lipid peroxidation and increases susceptibility to atherogenesis in affected tissues, contributing to the microvascular and macrovascular complications commonly observed in Type 2 Diabetes Mellitus (GUAN H, et al., 2020).

Regarding the renin–angiotensin–aldosterone system, one of the main genetic factors involved in Metabolic Syndrome is an insertion/deletion variant in the Alu region of intron 16 of the *ACE1* gene, which encodes angiotensin-converting enzyme 1 (ACE1). This variant is associated with ACE1 enzyme levels, with individuals homozygous for the deletion allele expressing higher serum ACE1 concentrations linked to hypertension, hyperglycemia, obesity, and hypertriglyceridemia (XI B, et al., 2012). A high-calorie diet rich in saturated fats may further increase ACE1 levels, and excessive sodium intake combined with the deletion allele can intensify increases in blood pressure. These findings highlight the importance of integrating genetic analysis with nutritional strategies in the development of effective treatments (SCHÜLER R, et al., 2017).

In addition to these factors, oxidative stress is also associated with the pathophysiology of Metabolic Syndrome. It results from an imbalance between free radical production and antioxidant defense capacity. Among the enzymes involved in antioxidant defense, glutathione S-transferase (GST) plays a key role by catalyzing the nucleophilic attack of reduced glutathione on reactive electrophiles (ALNASSER SM, 2024). Changes in GST activity can increase oxidative stress and contribute to the development of diabetes, mainly through the activation of protein kinase C (PKC) (RANIERE R, et al., 2018).

PKC reduces nitric oxide synthesis and promotes the expression of chemokines and inflammatory cytokines, the migration of smooth muscle cells from the arterial wall to the vascular intima, the formation of foam cells that initiate atherosclerosis, and the production of free radicals that damage pancreatic β-cell islets, thereby impairing insulin secretion (ENGIN A, 2024) (**Figure 5**). The *GST* gene presents several genetic variations that give rise to different enzyme isoforms, including the *GSTP1* variant, which has been strongly associated with the development of diabetes. The substitution of adenine with guanine at position 105 results in an enzyme with reduced activity, increasing cellular susceptibility to damage caused by free radicals. In addition, a high-calorie diet rich in ultra-processed foods disrupts redox mechanisms, increasing oxidative stress and contributing to cellular damage (RANIERE R, et al., 2018).

Figure 5 - Reduced GST levels are associated with increased oxidative stress, which promotes vascular permeability, inflammation, pancreatic β-cell damage, and the progression of atherosclerosis. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0. (https://creativecommons.org/licenses/by/4.0/).



Source: Silva DG, et al., 2026.

FINAL CONSIDERATIONS

Precision nutrition is a promising approach for the prevention and management of multifactorial diseases by considering individual genotypic and phenotypic characteristics. As discussed, the identification of genetic variants associated with increased risk enables the implementation of predictive nutrition strategies through personalized dietary recommendations. Variants in the *FTO*, *MTHFR*, *APOE*, *LEP*, *LEPR*, *TCF7L2*, *GST*, *ACE*, and *PPARγ* genes are among those most strongly linked to Metabolic Syndrome, making them important targets for studies on gene-diet interactions.

The presence of the rs9939609 variant in the FTO gene has been associated with reduced weight gain when combined with adherence to a Mediterranean diet. Regarding the insertion/deletion variant in the *ACE* gene, its interaction with excessive sodium consumption contributes to increased blood pressure. In addition, individuals carrying the rs1801282 variant in the *PPARγ* gene who follow a low-fat, high-fiber diet have shown greater weight loss. Therefore, this field of research may contribute to the prevention and treatment of multifactorial diseases such as Type 2 Diabetes Mellitus and Metabolic Syndrome.

In summary, precision nutrition represents an important scientific and clinical advance, demonstrating that there is no universal diet suitable for all individuals, but rather personalized dietary strategies that can improve health, prevent disease, and optimize therapeutic outcomes. In this context, the evidence presented in this review suggests that improvements in dietary patterns particularly the inclusion of bioactive compounds capable of interacting with metabolic pathways and the immune system may contribute to reducing the prevalence of these conditions.

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