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REVIEW ARTICLE

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The impact of macro- and micronutrients on metformin anti-diabetic activity: a systematic review

Asif Jan[1,2*], Mashal Khattak[1], Syed Shaukat Ali[3], RahatUllah[4,5], Muhammad Tahir[6,7], JunYa Kaimori[8], Waheed Ali Shah[1], Rani Akbar[9]

[1] Department of Pharmacy, University of Peshawar, Peshawar 25000, Pakistan.
[2] District Headquarter Hospital (DHQH) Charsadda, Charsadda 24430, Pakistan.
[3] Department of Pharmacy, University of Malakand, 23060, Pakistan.
[4] Department of Pharmaceutical Sciences, OU College of Pharmacy, University of Oklahoma Health Sciences, 1110 N, Stonewall Avenue, Oklahoma City, Oklahoma, 73117, USA.
[5] Neuroregernation and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
[6] Molecular Neuropsychiatry & Development (MiND) Lab, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto 43964, ON, Canada.
[7] Institute of Medical Science, University of Toronto, Toronto 43964, ON, Canada.
[8] Department of Health and Nutrition, Otemae Univeristy, 2-1-88 Otemae, Chuo-ku, Osaka city, Osaka 540-0008, Japan.
[9] Department of Pharmacy, Abdul Wali Khan University Mardan 23200, Pakistan.

*Corresponding author: Dr Asif Jan. Department of Pharmacy, University of Peshawar, Peshawar 25000, and District Headquarter Hospital (DHQH) Charsadda, Charsadda 24430, Pakistan.
Phone: +92301-5940602.
E-mail: asif.research1@gmail.com

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Abstract

Introduction: Type 2 Diabetes Mellitus (T2DM) affects over 537 million individuals worldwide, with cases expected to rise to 783 million by the year 2045. Metformin is the primary treatment, but its efficacy varies due to dietary influences. Growing evidence suggests that macro- and micronutrients interact with metformin, influencing its therapeutic effects. However, these interactions remain poorly understood. This review aims to bridge this knowledge gap by synthesizing recent findings on metformin-nutrient interactions to inform optimized therapeutic and dietary strategies. **Objective:** The objective of this systemic review is to investigate the impact of macro- and micronutrients on metformin anti-diabetic activity. **Methods:** This systematic review adheres to PRISMA guidelines, focusing on systematic reviews, meta-analyses, and experimental studies from PubMed, Scopus, and Web of Science. The research was carried out from September to October 2024. The studies were evaluated for quality using the GRADE tool and the risk of bias was assessed using the Cochrane tool. **Results and conclusion:** 132 research studies were identified and subjected to an eligibility assessment. After a careful evaluation, 33 studies were included in this systematic review. The Cochrane tool used for assessing the risk of bias revealed that 22 studies had a high risk of bias, while 24 studies failed to meet the GRADE criteria. Most of the studies showed homogeneity in their findings, with X^2=85.7%>50%. It was concluded that high saturated fat intake reduces metformin's effect alternatively, nutrients like leucine enhance metformin efficacy through mechanisms involving the AMPK pathway, promoting lipid oxidation and glycemic improvements. Micronutrients such as calcium, magnesium, and potassium play essential roles in glucose metabolism and insulin signaling. These minerals are absorbed through OCT1 transporters, the same transport pathway used by metformin for cellular uptake. Clinical trials have demonstrated that adequate dietary intake of these micronutrients stabilizes blood glucose levels when combined with metformin. In conclusion, it is suggested that dietary composition should be an integral component of T2DM management for patients on metformin therapy.

Keywords: Diabetes Management. Metformin. Nutrient Interactions. Glycemic Control. Pharmacogenetics. Nutrigenetics.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a multifactorial metabolic disorder that presents with chronic hyperglycemia, insulin resistance, and progressive dysfunction of beta-cells of the pancreas, which leads to impaired/decreased insulin secretion. It is a condition that affects millions globally and is often accompanied by a range of comorbidities, including cardiovascular disease, obesity, and dyslipidemia **[1]**.

Metformin, a biguanide, remains one of the most widely prescribed drugs for T2DM management due to its well-established ability to improve insulin sensitivity, reduce hepatic glucose production, and lower blood glucose levels through multiple mechanisms. The drug primarily works by activating AMP-activated protein kinase (AMPK), which regulates various metabolic pathways to decrease glucose production in the liver and enhance glucose uptake in peripheral tissues, such as muscle and adipose tissue **[2]**.

Although metformin is widely used and effective, individual responses to the drug can vary significantly. This variability in drug response is driven by several factors, such as genetic differences, body composition, and physiological characteristics. Therefore, a thorough understanding of metformin's pharmacokinetics (absorption, distribution, metabolism, and excretion), pharmacodynamics, and its interaction with various nutrients is crucial for optimizing its role in personalized treatment strategies **[3,4]**.

Recent studies have shown that dietary composition can significantly modulate the effectiveness of metformin therapy. Macronutrients, such as fats, carbohydrates, and proteins, play an important role in regulating the absorption and pharmacokinetics of metformin. High-fat and high-carbohydrate diets, for example, can alter the gut microbiome, which in turn affects the absorption and efficacy of metformin by modifying the composition and activity of intestinal bacteria. These microbiota-mediated changes can influence the bioavailability of metformin, potentially leading to either suboptimal or enhanced therapeutic outcomes **[5]**.

Furthermore, macronutrient intake can influence the activation of AMPK, a key signaling molecule that mediates the effects of metformin in various tissues. The interaction between diet and AMPK activation presents a mechanism through which dietary composition could either augment or diminish metformin effects on blood glucose control **[6]**. In addition to macronutrients, micronutrients such as calcium, magnesium, and potassium are also critical in modulating metformin pharmacodynamics. These micronutrients influence drug transporters, specifically the organic cation transporter 1 (OCT1), which facilitates the uptake of metformin into hepatocytes. Variations in the expression and activity of these transporters, influenced by dietary factors, may further affect metformin's bioavailability and its overall therapeutic response **[7]**. This suggests that personalized dietary interventions could play a pivotal role in optimizing metformin efficacy in the management of T2DM.

Moreover, the integration of nutrigenetics and pharmacogenetics has opened new avenues in understanding the genetic factors that influence individual responses to metformin. Genetic variations in specific genes, such as SLC22A1, which encodes OCT1, have been shown to affect the pharmacokinetics of metformin. Polymorphisms in these genes can lead to variations in transporter function, ultimately impacting metformin absorption, distribution, and clearance from the body. These genetic variations, when combined with dietary factors, highlight the need for a more individualized approach to T2DM management, where both genetic makeup and diet are considered in treatment decisions **[8-10]**.

Precision medicine approaches that incorporate genetic, dietary, and pharmacological factors are essential for developing tailored therapies that can optimize drug efficacy and minimize side effects. Such approaches could be pivotal in improving the management of T2DM, particularly for individuals who experience suboptimal responses to standard metformin therapy.

This review aimed to explore in detail the complex interactions between dietary components and metformin pharmacology, providing insights into how personalized nutrition strategies, when integrated with pharmacogenetic information, can enhance the therapeutic outcomes of metformin while addressing the inherent variability in T2DM management.

Methods

Study Design

This systematic review adhered to internationally recognized frameworks for conducting systematic reviews, specifically following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The PRISMA framework is accessible at http://www.prisma-statement.org (accessed on 10/10/2024). To ensure methodological rigor, the review also followed the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews)

criteria. Additional information about AMSTAR-2 can be found at https://amstar.ca/ (accessed on 10/10/2024).

Search Strategy and Search Sources

The literature search was conducted between September to October 2024, and relevant studies were identified through an extensive search in three key electronic databases: PubMed, Scopus, and Web of Science. The search strategy incorporated a combination of keywords and phrases related to the scope of the review, including ("Metformin" AND "Diabetes Mellitus Type 2") AND ("Macronutrients" OR "Micronutrients") AND "Drug-Nutrient Interactions". Boolean operators were used to refine search queries and ensure comprehensive retrieval of relevant articles. Following the database search, titles and abstracts of identified records were screened for eligibility based on pre-defined inclusion criteria. Studies were selected if they explored the interaction between metformin and dietary components (macronutrients or micronutrients) or examined their effects on glycemic control, lipid metabolism, and other metabolic markers in patients with Type 2 Diabetes Mellitus. The full-text articles deemed potentially relevant were collected for this in-depth review.

Study Quality and risk bias

Studies were classified into high, moderate, low, or very low categories based on factors like risk of bias, precision, and consistency. Systematic reviews and Meta-analyses were given preference followed by randomized clinical trials whereas editorials, case reports, and short communications were considered lower-quality articles/studies, as assessed using the GRADE framework. The risk of bias was determined using the Cochrane tool, with the Funnel Plot (which compares sample size to effect size) and Cohen's d test applied for analysis.

Results and Discussion

Summary of Findings

As a corollary of the literature search system, 132 articles were identified and assessed for inclusion in this review. Ultimately, 33 of the 52 shortlisted studies were selected to contribute to the findings of this systematic review. These selected studies demonstrated moderate to high quality (Figure 1), based on the evaluation of their scientific evidence. This assessment considered the study types, including meta-analyses, expert consensus, randomized clinical trials, and prospective and observational studies. The identified biases did not undermine the scientific validity of the studies. Using the GRADE framework, most studies showed homogeneity in their findings, with X^2=85.7%>50%. According to the Cochrane risk-of-bias tool, 22 studies were categorized as having a high risk of bias, while 24 did not align with GRADE or AMSTAR-2 criteria.

Figure 1. Flowchart showing the process of selection of articles.

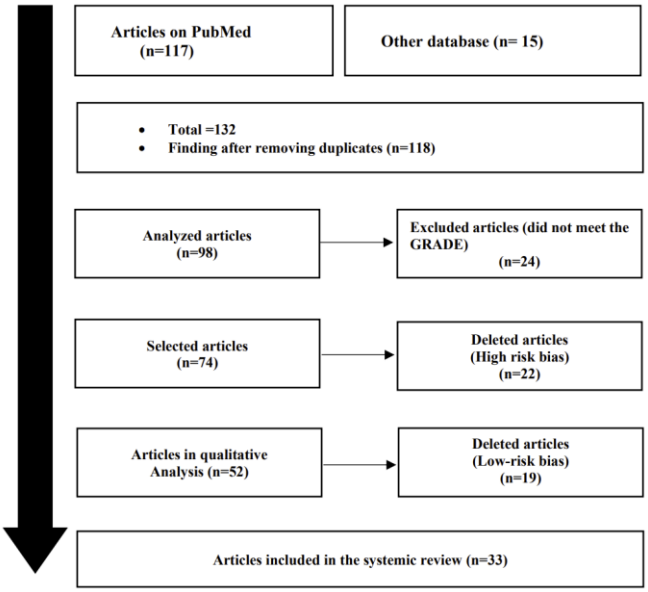
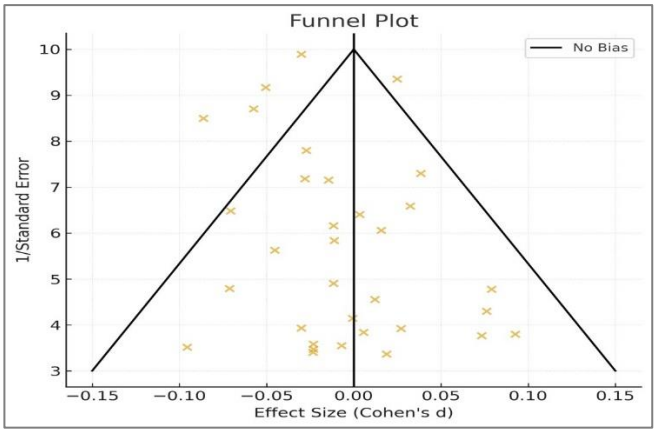


Figure 2 shows the risk of bias analysis using a Funnel Plot, which evaluates the Effect Size (Magnitude of the difference) based on Cohen's Test (d). Sample precision, expressed as the inverse of the standard error (1/Standard Error), was also analyzed. The graph displayed a symmetrical distribution, indicating no substantial risk of bias. This symmetry was evident across studies with smaller sample sizes (lower precision), located at the bottom of the graph, and studies with larger sample sizes (higher precision), positioned at the top.

Figure 2. The funnel plot, shows that studies have no risk of bias which is displayed at the bottom of the graph. The studies with high confidence and strong recommendations are located at the top (n=33 studies).



Source: Own authorship.

Major Clinical Outcomes

Macronutrient Effects on Metformin Efficacy

High-Fat Diet

High-fat diets, particularly those high in saturated fats, have been associated with reduced metformin efficacy. These diets exacerbate insulin resistance, a hallmark of T2DM, by impairing the activation of AMP-activated protein kinase (AMPK), which is critical for metformin's glucose-lowering effects. AMPK activation helps to inhibit hepatic gluconeogenesis and enhance peripheral glucose uptake, but high-fat intake suppresses this pathway, reducing the drug's therapeutic benefits **[11,12]**. Clinical studies have shown that individuals consuming high-fat diets exhibit elevated fasting glucose levels and reduced postprandial glycemic control compared to those adhering to low-fat diets. In animal models, chronic high-fat feeding reduced hepatic AMPK activation and increased lipid accumulation, worsening glycemic parameters. This is particularly concerning for T2DM patients, as dietary fat intake can directly counteract the pharmacological mechanisms of metformin **[13-15]**. Additionally, high-fat diets disrupt gut microbiota and indirectly impair glucose metabolism and insulin sensitivity, further attenuating the drug effects.

Role of Amino Acids

Amino acids, particularly branched-chain amino acids like leucine, have demonstrated the potential to enhance metformin action by activating the AMPK/Sirt1 signaling pathway. Leucine has been found to stimulate lipid oxidation and reduce hepatic fat accumulation, which synergistically complements metformin's therapeutic effects. These mechanisms are particularly relevant for individuals with co-morbid conditions such as non-alcoholic fatty liver disease (NAFLD), a common occurrence in T2DM patients **[16,17]**.

Preclinical studies in rodent models revealed that leucine supplementation alongside metformin significantly reduced hepatic steatosis, inflammation markers, and circulating triglycerides compared to metformin alone **[18]**. Similarly, arginine has been shown to improve endothelial function and reduce oxidative stress, enhancing insulin sensitivity **[19,20]**. These findings suggest that dietary amino acid supplementation could be a viable strategy to amplify metformin metabolic benefits, particularly in individuals with complex metabolic profiles.

Micronutrient Effects on Metformin Efficacy

Calcium, Magnesium, and Potassium

Micronutrients such as calcium, magnesium, and potassium play crucial roles in glucose metabolism and insulin signaling. These minerals are absorbed through OCT1 transporters, the same transport pathway used by metformin for cellular uptake. Clinical trials have demonstrated that adequate dietary intake of these micronutrients stabilizes blood glucose levels when combined with metformin, highlighting a pharmacodynamic interaction **[21-24]**.

For instance, calcium has been linked to enhanced insulin secretion and beta-cell function, while magnesium improves insulin receptor sensitivity and reduces systemic inflammation. Potassium has been implicated in the regulation of glucose-stimulated insulin secretion. In populations with low dietary intake of these minerals, metformin efficacy may be reduced due to insufficient OCT1-mediated transport activity **[22,24]**. Genetic polymorphisms in the gene encoding OCT1 transporter significantly influence metformin pharmacokinetics. Variants such as rs628031 (408Val) have been associated with altered drug absorption and therapeutic outcomes. Individuals carrying loss-of-function OCT1 alleles tend to exhibit reduced cellular uptake of metformin, resulting in reduced glycemic control **[25,26]**.

The interaction between these polymorphisms and dietary micronutrients adds another layer of complexity. For example, individuals with specific OCT1 variants may require higher dietary intake of calcium and magnesium to achieve sufficient drug transport and therapeutic efficacy. These findings underscore the potential of integrating pharmacogenetic testing with personalized dietary interventions to optimize T2DM management.

Effect of Gut Microbiota on Metformin Efficacy

The gut microbiota plays a pivotal role in modulating the therapeutic effects of metformin. The drug alters the composition of gut microbiota, promoting the growth of beneficial bacterial strains such as *Akkermansia muciniphila* and *Bifidobacterium*, which are involved in carbohydrate metabolism and anti-inflammatory pathways. These changes contribute to improved glucose tolerance, reduced systemic inflammation, and enhanced insulin sensitivity. Dietary patterns further influence these microbiota-mediated effects **[27-29]**. High-fiber diets, for instance, amplify metformin's benefits by increasing the production of short-chain fatty acids (SCFAs) such as butyrate, which improve gut barrier integrity and glucose metabolism. In contrast, high-fat diets disrupt microbial diversity and increase the abundance of pathogenic bacteria, counteracting the positive effects of metformin **[30]**.

Emerging evidence suggests that prebiotic and probiotic interventions can enhance metformin efficacy by restoring gut microbiota balance **[31-33]**. For

example, supplementation with inulin or resistant starch has been shown to increase SCFA production and improve glycemic control in T2DM patients on metformin therapy. These findings highlight the gut microbiota as a critical intermediary in nutrient-metformin interactions and a potential target for dietary interventions.

Conclusion

This review highlights the complex interplay between dietary factors and metformin pharmacokinetics and pharmacodynamics, providing insights for optimizing Type 2 Diabetes Mellitus management. Macronutrients, micronutrients, genetic variants, and gut microbiota collectively influence metformin efficacy, emphasizing the potential of personalized dietary interventions. Diets high in saturated fats impair AMPK activation, diminishing metformin glucose-lowering effects, while amino acids like leucine enhance AMPK activity, improving glycemic control. Micronutrients such as calcium, magnesium, and potassium modulate metformin pharmacokinetics through interactions with OCT1 transporters; with genetic polymorphisms like SLC22A1 rs628031 further influencing drug absorption and efficacy. These findings suggest that personalized dietary recommendations based on genetic profiles could enhance therapeutic outcomes. Tailored nutrition strategies can mitigate dietary risks, enhance beneficial interactions, and optimize metformin therapy for improved glycemic control.

Clinical Implications and Future Directions

The findings of this review have significant clinical implications, suggesting that dietary composition should be an integral component of T2DM management for patients on metformin therapy. Long-term, randomized controlled trials are needed to validate the efficacy of personalized dietary interventions and to establish evidence-based guidelines for integrating diet, genetics, and pharmacology in T2DM care. Additionally, exploring the role of sex-specific differences and age-related changes in nutrient-metformin interactions could further refine these recommendations.

Challenges and Limitations

Despite the promising potential of personalized dietary approaches, several challenges remain. The variability in dietary habits across populations and the lack of standardized protocols for assessing nutrient-metformin interactions pose significant barriers to implementation. Furthermore, while genetic testing is becoming more accessible, integrating such tools into routine clinical practice requires significant resources and infrastructure. Addressing these challenges will be essential for translating the findings of this review into real-world applications.

CRediT

Author contributions: **Conceptualization -** Asif Jan, Mashal Khattak, Syed Shaukat Ali, RahatUllah, Muhammad Tahir, Jun-Ya Kaimori, Waheed Ali Shah, Rani Akbar; **Data curation-** Asif Jan, Mashal Khattak, Syed Shaukat Ali, RahatUllah, Muhammad Tahir, Jun-Ya Kaimori, Waheed Ali Shah, Rani Akbar; **Formal Analysis -** Asif Jan, Mashal Khattak, Syed Shaukat Ali, RahatUllah; **Investigation-** Asif Jan, Mashal Khattak, Syed Shaukat Ali, RahatUllah, Muhammad Tahir; **Methodology-**Muhammad Tahir, Jun-Ya Kaimori, Waheed Ali Shah, Rani Akbar; **Project administration-** Asif Jan; **Supervision-** Asif Jan; **Writing-original draft-** Asif Jan, Mashal Khattak, Syed Shaukat Ali, RahatUllah, Muhammad Tahir, Jun-Ya Kaimori, Waheed Ali Shah, Rani Akbar; **Writingreview & editing-** Asif Jan, Mashal Khattak, Syed Shaukat Ali, RahatUllah, Muhammad Tahir, Jun-Ya Kaimori, Waheed Ali Shah, Rani Akbar.

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Ethical Approval

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Informed Consent

Not applicable.

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Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate[@].

Peer Review Process

It was performed.

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