REVIEW ARTICLE
Iran J Allergy Asthma Immunol
February 2026; 25(1):1-15.
DOI:10.18502/ijaai.v25i1.20431

Metformin in Diabetes Management and Immune Modulation: A Comprehensive Review

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Received: 6 June 2025; Received in revised form: 9 July 2025; Accepted: 25 July 2025

ABSTRACT

Metformin is a primary treatment for type 2 diabetes (T2D), well-known for its ability to lower blood glucose levels through both AMP-activated protein kinase (AMPK)-dependent and -independent pathways. Recent evidence suggests that metformin also possesses immunomodulatory properties, indicating its potential as a therapeutic agent that extends beyond metabolic regulation. This review summarizes the current understanding of metformin's dual roles in managing diabetes and modulating the immune system. It also explores the underlying mechanisms, clinical implications, and potential directions for future research.

Keywords: Clinical trials; Diabetes mellitus type 2; Innate immunity; Metformin; NLRP3 protein

INTRODUCTION

Type 2 diabetes (T2D) is the most common form of diabetes mellitus. It is primarily characterized by insulin resistance, beta cell dysfunction, and increased glucose production by the liver. Patients with T2D are generally more susceptible to infections than those without diabetes, likely due to a weakened immune system.[1] Research has confirmed decreased innate immune responses, which are associated with factors such as cytokines, low levels of complement C4, and impaired functions of polymorphonuclear cells and monocyte-derived macrophages. These impairments include reduced chemotaxis, phagocytosis, and killing abilities.

However, no deficiencies in adaptive immunity have been observed.[2,3]

The pathogenicity of microorganisms tends to increase in high-glucose environments. This phenomenon is attributed to the enhanced adherence of microorganisms to diabetic cells by carbohydrate-receptor complexes. Evidence suggests that better disease management can improve these effects.[3] Additionally, some studies have linked decreased C4 protein levels, resulting from high consumption in T2D, to renal or vascular complications.[4]

The inability to regulate blood sugar levels leads to increased serum levels of inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8), which are produced by mononuclear cells and neutrophils.[5] Additionally, elevated levels of glycosylated proteins and lipids contribute to the worsening of the disease.[6] Reduction in plasma levels of zinc (Zn) impairs lymphocyte responses, decreases the secretion of inflammatory cytokines, and hinders cell chemotaxis.[7]

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Patients also experience a decreased oxidative capacity to produce free radicals.[8] High blood sugar levels and their consequent excretion in urine increase the risk of microbial infections. This risk may stem from the saturation of complement receptors (CR), such as CR3, by microbial secretory factors, which can prevent opsonization and phagocytosis.[1,2] For these reasons, identifying a drug that effectively regulates the immune response and reduces the risk of microbial infections has become a primary objective in immune research.

Metformin (dimethyl biguanide) is identified as a first-line treatment for T2D; it reduces gluconeogenesis and enhancing insulin sensitivity.[9]

Metformin is a biguanide derivative from the plant *Galega officinalis*. About 50 years ago, it was established as highly effective in managing T2D. Historical reports indicate that some goats that consumed this plant died due to severe hypoglycemia. This effect was primarily attributed to guanidine, which originates from the plant and reduces insulin resistance.

Metformin effectively lowers both fasting and post-meal glucose levels by inhibiting glucose production in the liver, reducing glucose absorption in the intestines, and enhancing glucose uptake and utilization by peripheral tissues. However, the specific pharmacodynamic properties of metformin-such as the exact role of AMP-activated protein kinase (AMPK), its effects on gut microbiota,[10] anti-aging effects,[11] anti-cancer effects,[12] and cardioprotective effects[13]-have remained unclear for many years and continue to be a subject of debate.

This medication also possesses immunomodulatory properties, and these diverse mechanisms could effectively contribute to the development of new antidiabetic medications.[9] This study examines the immunological effects of metformin in both laboratory settings and clinical phases involving diabetic patients.

METHODS

This study explores the molecular mechanisms underlying the action of metformin, as identified in both in vivo and in vitro research. It also reviews relevant clinical trials. The information was collected from reputable sources such as Web of Science, PubMed, Medline, Google Scholar, and the Cochrane Library, using keywords including "Metformin and Type 2 Diabetes," "transcription factor, metformin," and "metformin cell signaling."

Mechanisms of Metformin Function

Metformin works through several mechanisms to help regulate blood sugar levels, including a decrease in glucose production in the liver, improved insulin sensitivity, enhanced uptake of glucose by muscle cells, and decreased absorption of glucose from the intestines. Together, these actions make metformin an effective treatment for managing T2D.

Metabolic Effects

The metabolic effects of metformin primarily occur through the activation of AMPK and the modulation of mitochondrial respiration.

Metformin inhibits complex I of the mitochondrial respiratory chain, specifically NADH: ubiquinone oxidoreductase. This action reduces ATP production and increases the AMP/ATP ratio (Figure 1).

The activation of AMPK leads to a cascade of metabolic effects that promote energy conservation and, in some contexts, inhibit anabolic processes. These are summarized as below:

1. Improved Uptake of Glucose in Muscle and Fat Tissue

AMPK plays a crucial role in enhancing the transport of the Glucose Transporter type 4 (GLUT4) protein to the cell membrane in muscle and fat tissues. This process increases glucose uptake from the bloodstream. When AMPK is activated, it helps reduce insulin resistance in these tissues, allowing glucose to enter cells more easily and lowering blood sugar levels. This mechanism is especially important for individuals with insulin resistance, such as those who are obese and diabetic. Notably, metformin works by enhancing glucose uptake without requiring additional insulin secretion.[14]

2. Reduced Hepatic Gluconeogenesis

Metformin helps lower glucose production in the liver by inhibiting key enzymes involved in the gluconeogenesis pathway, especially phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). PEPCK plays a crucial role in converting oxaloacetate into phosphoenolpyruvate, which is a rate-limiting step in gluconeogenesis. When metformin activates AMPK, it represses transcription factors like Forkhead Box Protein O1 (FoxO1) and cAMP responsive element-

binding protein (CREB) that typically promote the expression of the *PEPCK* gene. As a result, reduced levels of PEPCK limit the liver's ability to synthesize glucose from non-carbohydrate sources, such as lactate, glycerol, and amino acids.[15,16]

Glucose-6-phosphatase plays a crucial role in converting glucose-6-phosphate (G6P) into free glucose during the final step of gluconeogenesis and glycogenolysis. When metformin activates AMPK, it leads to the suppression of hepatocyte nuclear factor 4α (HNF4α), which is a transcription factor that regulates the expression of the *glucose-6-phosphatase* gene. This reduction in glucose-6-phosphatase activity causes G6P to be trapped within hepatocytes, preventing its release into the bloodstream.[16]

3. Increase Glycolysis

Metformin enhances glycolysis in the liver through mechanisms involving phosphofructokinase-2 (PFK-2). When activated, AMPK phosphorylates and activates PFK-2. This enzyme acts as a potent allosteric activator for phosphofructokinase-1 (PFK-1), leading to a significant increase in the rate of glycolysis. The product fructose-2,6-bisphosphate (F2,6BP) not only promotes glycolysis but also inhibits gluconeogenesis. Hexokinase 2 (HK2), which is responsible for converting glucose to glucose-6-phosphate, is primarily expressed in tissues such as skeletal muscle and adipose tissue. However, the effect of metformin on HK2 is indirect and is mediated by AMPK.[17]

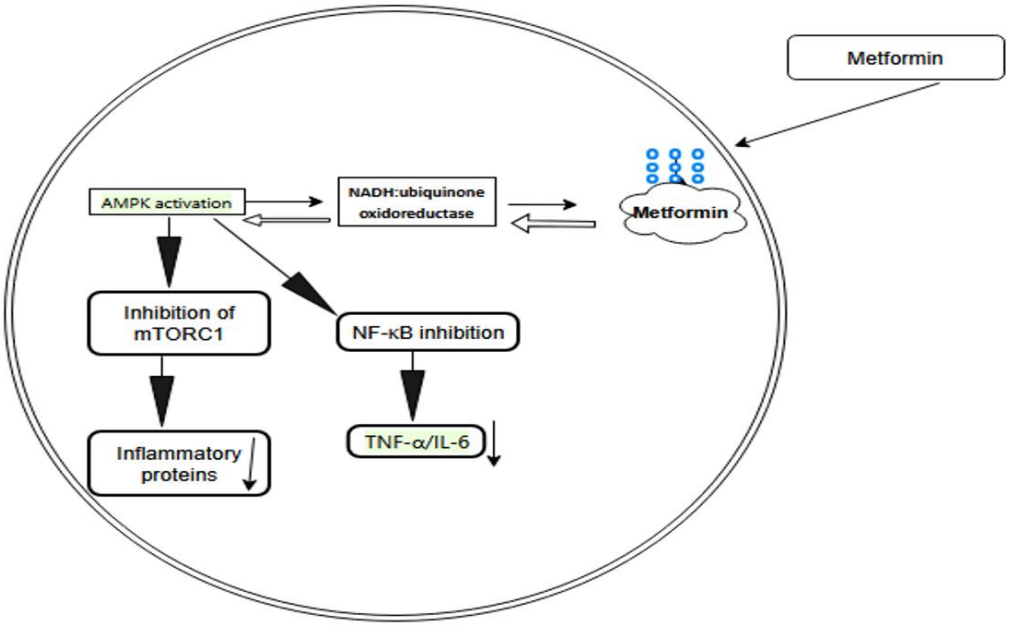

Figure 1. Metformin reduces the production of cytokines (TNF-α and IL-6) and inflammatory mediators (NF-κB: Nuclear factor kappa B) by enhancing cellular metabolism and activating the respiratory chain enzyme complex pathway. (NADH: nicotinamide adenine dinucleotide hydrogenase, mTOR: mammalian target of rapamycin complex 1, and AMPK: Adenosine 5'-monophosphate-activated protein kinase).

4. Enhanced Fatty Acid Oxidation and Reduced Lipid Synthesis

Metformin not only enhances insulin sensitivity but also decreases fat accumulation in skeletal muscle. It promotes the oxidation of fatty acids while reducing the synthesis of triglycerides. In the presence of metformin, several genes associated with acyl-CoA synthesis and fatty acid oxidation are upregulated, while genes related to lipolysis are downregulated. This combination of effects contributes to weight loss.[18]

5. Increase Mitochondriogenesis

Mitochondrogenesis is the process of producing new mitochondria, which is crucial for maintaining cellular function, especially in energy-demanding cells such as those found in the liver, muscles, and nerves. Factors

like diabetes and aging can impair the effectiveness of this process. Research has shown that metformin can enhance mitochondrogenesis by activating AMPK and triggering intracellular signaling pathways mediated by silent mating-type information regulation 1 (SIRT1) and mammalian target of rapamycin complex 1 (mTOR). The effects of metformin on mitochondrogenesis are dose-dependent and can vary based on the duration of use and the specific type of cells involved. This process involves the activation of various nuclear and mitochondrial genes, including the transcription factor peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which is activated by metformin. Additionally, regular physical activity and a balanced diet play significant roles in promoting mitochondrogenesis.[19]

6. Regulation of Autophagy

Mitophagy, or selective mitochondrial autophagy, is a crucial mechanism for maintaining mitochondrial quality control, which removes dysfunctional mitochondria under normal physiological conditions. However, factors such as aging, diabetes, and certain liver diseases can impair mitophagy. One important pathway for mitophagy involves AMPK and its downstream target, Unc-like autophagy 51 (ULK1). This pathway has emerged as a vital factor in promoting mitophagy in response to mitochondrial and energy stresses.[20] In an in vivo study , researchers investigated the combined effects of exercise and metformin in treating T2D by targeting the AMPK/ULK1 autophagy pathway. The findings indicated that both exercise and metformin improved insulin sensitivity. Additionally, the ubiquitin-proteasome system was activated, leading to protein degradation and muscle atrophy through the AMPK/ULK1 autophagy degradation pathway.[21]

AMPK-independent Effects

Impact on Neuropeptides

Metformin alters gut microbiota composition of the and increases the production of metabolites, especially short-chain fatty acids (SCFAs) such as butyrate, acetate, and valerate. The rise in SCFAs is associated with reduction in fasting insulin levels.[10] These metabolites stimulate the secretion of GLP-1 and PYY in individuals with T2D. Enhanced GLP-1 and PYY signaling activates afferent vagal pathways, conveying satiety signals to the brain and improving energy intake regulation..[22]

Immune Modulation Pathways

Anti-inflammatory Functions

Nuclear factor kappa B (NF-κB)

The nuclear factor kappa B (NF-κB) pathway plays a central role in the expression of inflammation-related genes, including cytokines, chemokines, and inflammatory enzymes, is significant. Metformin exerts an inhibitory effect on the AMPK-mediated NF-κB pathway, thereby reducing inflammation (Figure 2).[23]

Additionally, metformin may suppress this pathway by inhibiting mitochondrial reactive oxygen species (ROS), which are known activators of NF-κB.[23]

NLRP3

The NLRP3 inflammasome is responsible for producing pro-inflammatory cytokines, including IL-1β and IL-18, in response to factors such as uric acid crystals, ROS, and infections. Metformin has been shown to inhibit this inflammasome, which may be relevantfor managing metabolic diseases, (e.g., type 2 diabetes) as well as inflammatory diseases (e.g., arthritis) (Figure 3).[24,25] Under stress conditions, factors such as mtDNA leakage into the cytosol, cathepsin release, and extracellular potassium contribute to NLRP3 activation, and metformin can attenuate these pathways.. Additionally, metformin accelerates the ubiquitination process of NLRP3,[26] which leads to a reduction in the synthesis of inflammatory mediators such as TNF-α, IL-6, IL-1β, IL-18, and monocyte chemoattractant protein-1 (MCP-1).[27] (Considering these findings, metformin is emerging as a potential treatment not only for metabolic diseases such as diabetes but also for autoimmune diseases. Further documentation is provided below.

Regulation of Immune Cells

Innate Immunity

Metformin can shift macrophage polarization from a pro-inflammatory state (M1) to an anti-inflammatory state (M2).[26] This transition helps reduce tissue inflammation and promotes healing. Furthermore, metformin inhibits neutrophil activity and enhances the secretion of IL-10 from M2 macrophages. It also decreases the accumulation and activity of neutrophils and DCs by inhibiting mTORC1 during acute inflammatory responses, such as sepsis or ischemia-reperfusion injury (Figure 4).[28]

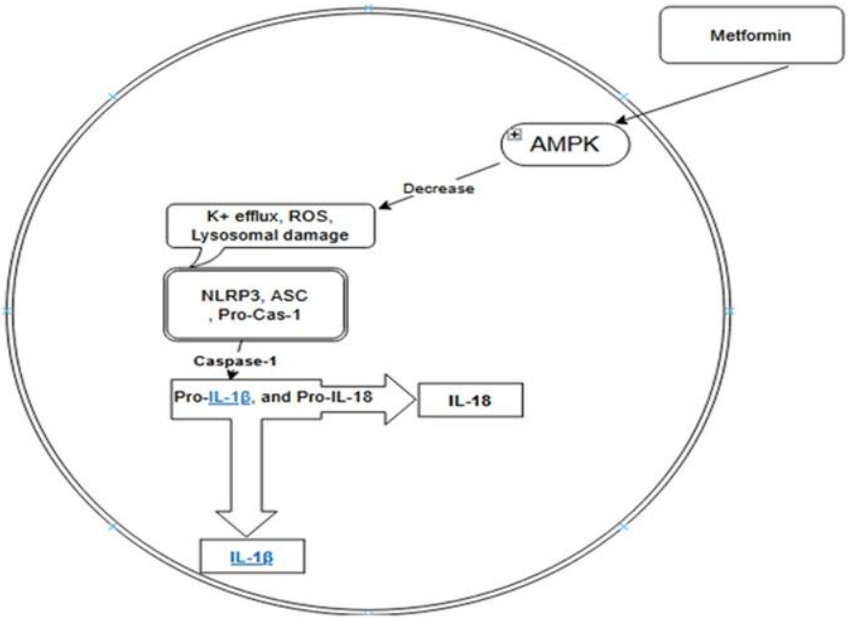

Figure 2. This illustrates the effect of Metformin on the expression of NF-κB genes through the AMPK pathway. (AMPK: AMP-activated protein kinase, ROS: Reactive Oxygen Species, NLRP3: NLR family pyrin domain containing 3, ASC: apoptosis-associated speck-like protein).

Acquired immunity

Modulation of T cell differentiation

Research has demonstrated that inhibiting glycolysis suppresses the development of T_H1 and T_H17 cells while promoting the production of regulatory T cells (Tregs).[29] In diabetic patients, metformin enhances Treg production and inhibits T_H1 and T_H17 cells by activating AMPK. Additionally, by inhibiting mTOR, metformin not only prevents differentiation into T_H17 cells but also favors differentiation into Treg cells. The oxidative stress commonly found in T2D creates a favorable environment for the differentiation of T lymphocytes into T_H1 and T_H17 cells, and this environment can be modulated by metformin (Figure 5).[30]

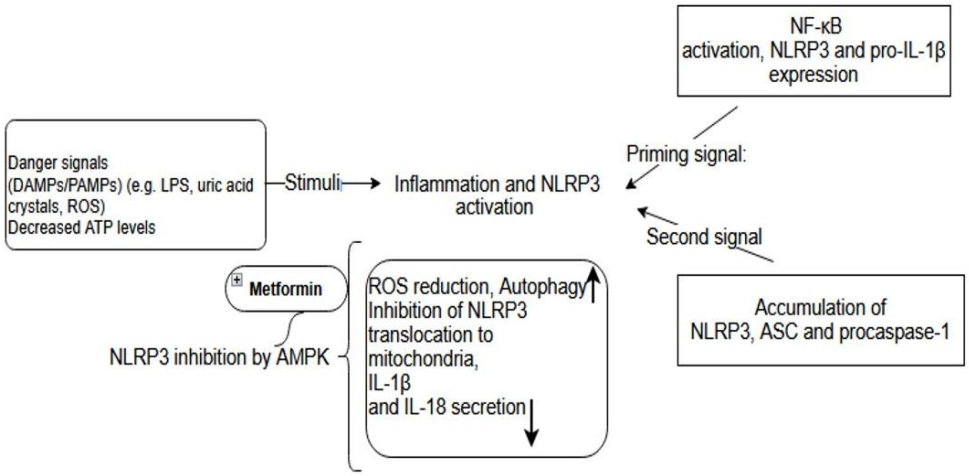

Figure 3. This schematic diagram shows the effects of metformin on immune cells, which lead to increased autophagy and inhibition of the NLRP3 pathway. (DAMPs: Damage-Associated Molecular Patterns; PAMPs: Pathogen-Associated Molecular Patterns; LPS: Lipopolysaccharide)

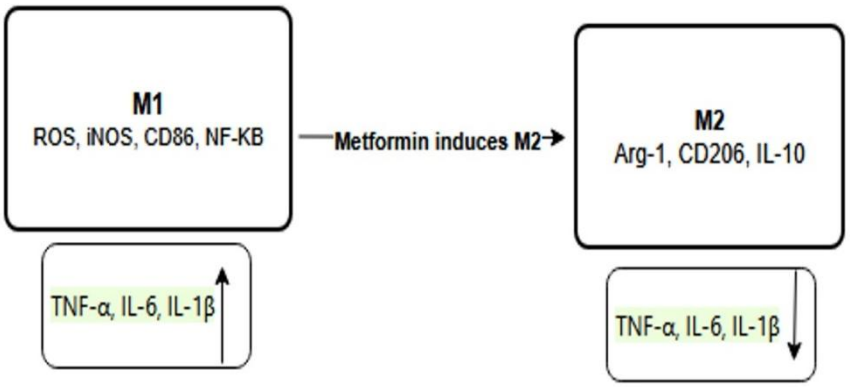

Figure 4. The inhibitory effect of metformin on pro-inflammatory macrophages is demonstrated. (M1 and M2 macrophages; iNOS: Inducible Nitric Oxide Synthase; Arg 1: the enzyme arginase 1)

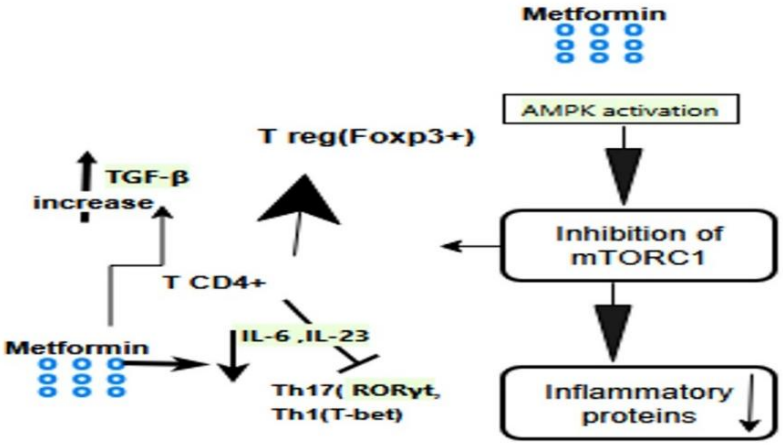

Figure 5. The mechanism by which metformin influences T cell differentiation is illustrated. (TGF-β: Transforming Growth Factor beta; RORγt: Retinoic Acid Receptor-related Orphan Receptor gamma t; Foxp3; Forkhead box protein P3; T-bet: T-box transcription factor)

The impact on B cell function

Metformin influences B-cell- dependent immune responses through several mechanisms. It activates the enzyme AMPK, which inhibits the mTOR pathway-essential for cell growth and proliferation.[31] This inhibition leads to a decrease in metabolic activity, particularly glycolysis, which is crucial for B-cell activation and proliferation. Additionally, metformin hinders the differentiation of B cells into plasma cells and reduces antibody production, highlighting its significance in managing autoimmune diseases like lupus.[32]

Moreover, metformin inhibits the transcription factor NF-κB and decreases inflammatory cytokines levels. This reduction lowers the expression of co-stimulatory molecules such as CD80 and CD86 on the surface of B lymphocytes. Consequently, this process disrupts the ability of B lymphocytes to function as antigen presenters to T lymphocytes, preventing excessive activation of immune responses in autoimmune diseases.[33]

There is evidence that metformin impacts mucosal immunity by affecting B lymphocytes, in part through changing the gut microbiome composition. Studies indicated that this effect of metformin is associated with reduced antibody production, especially in autoimmune diseases such as rheumatoid arthritis (RA) Diagram.[34]

Several clinical trials utilizing metformin for metabolic and immunological purposes in diabetic patients are summarized in Table 1.

Table 1. Clinical trials showing the effects of metformin on diabetes.

Author, year, Ref	Clinical trial	Result
Hyer et al. (2025) [35]	Women with gestational diabetes	Metformin is a viable for preventing fetal macrosomia in women with gestational diabetes.
He et al. (2021) [36]	Patients newly diagnosed with T2DM	As compared with insulin injection, early treatment with sitagliptin + metformin in T2DM produced non-inferior outcomes.
Saha et al. (2020)[37]	Newly diagnosed with T2DM	HbA1c, FBS, and blood sugar 2 hours highly decreased in sitagliptin+metformin group.
He et al (2021)[38]	Newly diagnosed with T2DM	Sitagliptin-metformin in T2DM with severe hyperglycaemia showed better outcomes in glycaemic remission compared with glimepiride.
Nguyen et al (2021)[39]	T2DM	The metformin effect on Glucose level reduction was lower compared with sulfonylurea and sitagliptin.
Song et al (2014)[40]	T2DM	Metformin + Sitagliptin is effective in the treatment of T2DM complicated with NAFLD.
Skandalis et al (2012)[41]	T2DM with Bullous pemphigoid (BP)	Blood Pressure was an adverse event of the metformin + gliptin combination therapy in T2DM.
Soliman et al (2012)[42]	T2DM with kidney transplant	Insulin+glargine resulted in a weight gain (0.8 kg).
Memon et al (2022)[43]	T2DM	Metformin monotherapy compared with sitagliptin achieved more complications such as nausea, vomiting, diarrhea, and headache.
Ke et al (2014)[44]	T2DM	Insulin combined with metformin could help to reduce insulin daily doses during Continuous Subcutaneous Insulin Infusion (CSII).
Billings et al (2017)[45]	Maturity-Onset Diabetes of the Young (MODY)	After one year of taking metformin, improved beta-cell function was more closely associated with the frequency of the rs3212185 allele (hepatocyte nuclear factor 4 alpha (HNF-4α)).
Sam et al (2017)[46]	Obese children with insulin resistance	A Solute Carrier Family 22 Member 1 (SLC22A1) genotype did not significantly affect metformin pharmacokinetics.
Jack et al (2018)[47]	T2DM	Novel evidence for associations of common and rare variants in Pre-MRNA Processing Factor 31 (PRPF31), Carboxypeptidase A6 (CPA6), and signal transducer and activator of transcription 3 (STAT3) with metformin response.
Pearson et al (2003)[48]	Diabetes caused by Hepatocyte Nuclear Factor 1 Alpha (HNF-1α) mutations or T2DM	HNF-1α diabetes had a 5.2-fold greater response to gliclazide than to metformin and 3.9-fold greater response to gliclazide than those with T2DM. They had a strong insulin secretory response to tolbutamide, and more insulin sensitive than those with T2DM.
Pedersen et al (2024)[49]	T2DM	Circulating Fibroblast Activation Protein (FAP) activity decreased and gene and protein expression of β-klotho, Fibroblast growth factor receptor 1c (FGFR-1c), and pFGFR1c in adipose tissue after metformin.
Konopka et al (2019)[50]	T2DM	Metformin attenuated whole-body insulin sensitivity and VO2max after Aerobic Exercise Training (AET).
Ciaraldi et al (2002)[51]	T2DM	Insulin-stimulated whole-body glucose disposal rates (20%) increased, weight-stable, leptin unchanged, adipocyte size decreased, and GLUT1 and GLUT4 in adipocytes unaltered after Metformin take.

AET: Aerobic Exercise Training; CPA6: Carboxypeptidase A6; CSII: Continuous Subcutaneous Insulin Infusion; FAP: Fibroblast Activation Protein; FBS: Fasting Blood Sugar; FGFR-1c: Fibroblast growth factor receptor 1c; GLUT1: Glucose Transporter type 1; GLUT4: Glucose Transporter type 4; HbA1c: Hemoglobin A1c; HNF-1α: Hepatocyte Nuclear Factor 1 Alpha; HNF-4α: Hepatocyte nuclear factor 4 alpha; MODY: Maturity-Onset Diabetes of the Young; NAFLD: Non-alcoholic fatty liver disease; PRPF31: Pre-MRNA Processing Factor 31; SLC22A1: Solute Carrier Family 22 Member 1; STAT3: Signal transducer and activator of transcription 3; T2DM: Type 2 Diabetes Mellitus.

Metformin → AMPK activation → [Glycolysis ↓ | Fatty acid oxidation (FAO ↑)] → mTOR inhibition → B cell hypoactivation

Metformin → Regulatory B cells (Breg) ↑ + Cytokines ↓ → Immune tolerance

Metformin → Glycemic control + Microbiota → Reduced inflammation → B cell stabilization

Diagram. Metformin can decrease inflammatory cytokines, increase anti-inflammatory cytokines, and improve B cell function for mucosal immunity.

Evidence From Clinical Studies Linking Metformin to Safety Outcomes

1. Related to Diabetes

Reducing the risk of infections, particularly in the urinary and respiratory tracts of patients with T2D, can be achieved indirectly by managing and controlling blood sugar levels. Scientific evidence indicates that chronic hyperglycemia hampers the function of white blood cells, such as neutrophils and macrophages, leading to an increased likelihood of infections. Therefore, administering metformin, which helps improve HbA1c levels, can enhance the function of these white blood cells and subsequently reduce the incidence of infections.[52,53]

Some studies have shown that metformin regulates the activity of macrophages and T lymphocytes by activating the AMPK enzyme. This regulation may help prevent the severity of bacterial or viral infections, including COVID-19, in patients with diabetes.[54] Furthermore, these studies confirm that metformin usage in individuals with T2D reduces the risk of cardiovascular diseases. These findings highlight metformin's anti-inflammatory properties, its ability to reduce neutrophil counts, its role in increasing intracellular pH to combat viral infections, and its interference with the endocytotic cycle.[54]

Lactic Acidosis

Although evidence is limited, some clinical trials involving patients with T2D who also had cardiovascular and renal disorders indicated that metformin is safe and has minimal side effects.[55] Additionally, there have been case reports and epidemiological studies suggesting a risk of lactic acidosis in patients with impaired renal function, liver failure, or severe hypoxia after taking metformin. For patients with T2D who experience renal failure, impaired renal function can lead to the accumulation of metformin, which is associated with lactic acidosis.[56] In these studies, the primary outcomes-mortality and the progression of kidney disease-were significantly reduced in users of metformin. However, the risk of lactic acidosis, a secondary outcome related to metformin use, remained unchanged.[57] In line with this, Biradar et al (2010) examined the incidence of lactic acidosis in patients aged 65 and older who were hospitalized in the intensive care unit and had impaired renal function. They found that gastrointestinal symptoms, known as metformin-associated lactic acidosis (MALA), were predominant in these patients and significantly correlated with increased morbidity and mortality.[58] Some studies have indicated that 20% to 30% of diabetic patients taking metformin experience gastrointestinal effects such as nausea, diarrhea, abdominal pain, and anorexia. In these patients, there is a significant increase in bile salt circulation, while the absorption of these salts is reduced. Metformin appears to decrease bile salt reabsorption in the ileum, which leads to higher bile salt concentrations in the colon and the development of digestive disorders.[59,60]

Vitamin B12 Deficiency

There is evidence that the use of metformin is associated with reduced absorption of vitamin B12, which may increase the risk of neuropathy or megaloblastic anemia. A 2019 study involving 1 111 patients with T2D found that serum vitamin B12 levels decreased significantly in those taking metformin at doses greater than 1 500 mg daily for more than six months. Specifically, for every 1 mg increase in the daily metformin dose, there was a corresponding decrease of 0.142 pg/mL in vitamin B12 levels. This suggests that metformin may inhibit the intestinal absorption of vitamin B12.[61]

Additionally, serum homocysteine levels in these patients were negatively correlated with vitamin B12 levels, which could represent a risk factor for cardiovascular disease. The amino acid homocysteine plays an essential role in DNA methylation and various intracellular reactions involving vitamin B12.

Consequently, elevated homocysteine levels are associated with an increased risk of cardiovascular disease, cognitive impairment, cancers such as breast cancer, and chronic kidney disease.[62,63]

Immunity During Pregnancy

Increased blood sugar levels during pregnancy can lead to complications such as macrosomia (high fetal weight greater than 4 000 grams) and neonatal hypoglycemia. The use of metformin to manage gestational diabetes helps to maintain fetal health and reduce pregnancy-related complications. Metformin works by improving insulin sensitivity and decreasing glucose production in the liver, which helps regulate maternal blood sugar levels.[64]

Fluctuations in maternal blood sugar can result in neonatal hypoglycemia after birth. However, maintaining stable glucose levels with metformin can significantly reduce this risk. Additionally, metformin may enhance the immunity of newborns. Research involving women with polycystic ovary syndrome (PCOS) found that metformin use did not lead to an increase in congenital abnormalities or other fetal complications.[65] There is also evidence suggesting that a daily dose of 2 000 mg of metformin can effectively prevent weight gain in pregnant women with diabetes who have PCOS.[66]

2. Exploring Conditions Beyond Diabetes: Autoimmune and Inflammatory Diseases

Obesity and metabolic syndrome, which can be linked to hyperglycemia, dyslipidemia, and inflammation, are significant risk factors for osteoarthritis (OA). Treatment of these conditions may influence the progression of OA.[67] Recent research emphasizes the role of metformin as a modulator of inflammatory and metabolic factors. This medication may be beneficial in managing synovitis, preventing joint destruction, and reducing cartilage degradation in patients with RA and OA.[68]

Metformin, known for its anti-inflammatory and antioxidant properties, shows potential as a therapeutic agent for autoimmune diseases. However, clinical trials investigating its effectiveness are limited. For instance, in the case of multiple sclerosis, metformin is currently undergoing phase II trials, with the outcomes of these studies yet to be determined. Recent findings indicate promising results when metformin is combined with IFNβ-1a for treating multiple sclerosis, as it appears to positively affect the oxidative stress marker MDA.[69] Additionally, some clinical trials have explored the use of metformin for immunological purposes in non-diabetic patients with arthritis, as referenced in Table 2.

3. Effects of Metformin in Diabetic Patients with COVID-19

Evidence suggests that the combination of metformin, insulin, and corticosteroids may effectively prevent severe COVID-19 in patients with T2D.[81] However, some cohort studies examining the relationship between metformin use and susceptibility to COVID-19 have not found a significant link. In fact, the severity of symptoms in type 2 diabetic patients taking metformin was similar to that in individuals not using the medication.[82]

Studies involving diabetic patients with COVID-19 have explored the protective role of metformin. These studies highlighted several beneficial effects, including the regulation of the immune system, the renin-angiotensin system, and the function of dipeptidyl peptidase 4 (DPP4).[83] Metformin was found to activate ACE2, which is the primary receptor for COVID-19, in respiratory epithelial cells via AMPK signaling, thereby reducing viral adhesion.[83] Additionally, it decreased the attachment of COVID-19 to DPP4 on T cells and helped modulate the immune response.[84]

Metformin's immunometabolic effects, specifically through glycolysis and mitochondrial oxidation in inflammatory cells, contributed to a diminished severity of the immune response against the virus. Furthermore, it reduced platelet aggregation and the risk of thrombosis.[54,83] Among type 2 diabetic patients with COVID-19 who were treated with metformin, hematological indicators such as C-reactive protein (CRP) showed a significant decrease compared to those not using metformin, highlighting its anti-inflammatory effects in this population.[85]

Several studies focusing on T2D and COVID-19 are summarized in Table 3.

Table 2. Clinical trials examining the effects of metformin on arthritis.

Author, year, Ref	Clinical trial	Result
Abdalla et al (2021)[70]	Rheumatoid arthritis (RA)	The levels of TNF-α, IL-1β, IL-6, IL-17A, NF-κB, TGF-β1, MDA, Anti-CCP and IGF-IR expression by metformin decreased compared with that of healthy individuals.
Zhang et al (2023)[71]	RA	The serum HMGB1 and cytokine levels declined with the metformin take.
Pan et al (2025)[72]	OA with overweight or obesity.	The use of metformin for the treatment of symptomatic knee OA is supported in overweight or obese individuals.
Halabitska et al (2025)[73]	OA and impaired glucose tolerance (IGT)	Metformin led to improvements in inflammatory markers and lipid profiles. However, BMI increased.
Alimoradi et al (2025)[74]	OA	Metformin increased miR-451 expression levels simultaneously with pain reduction. Additionally, BCL-2 and CXCL16 decreased.
Karim et al (2024)[75]	OA with diabetes	Metformin improves hand-grip strength (HGS), physical performance, and gut permeability in OA patients.
Aiad et al (2024)[76]	OA	Metformin reduced serum levels of Cartilage Oligomeric Matrix Protein (COMP), C-terminal cross-linked telopeptide of type I collagen (CTX-1), and IL-1β.
Dong et al (2023)[77]	OA (grade 3)	Metformin inhibited microRNA-34a while promoting SIRT1 expression in OA chondrocytes.
Alimoradi et al (2023)[78]	OA	Metformin attenuated symptoms of OA with a high-risk genotype of wild genotype (CC) of Bcl-2, and wild allele (G) of CXCL16.
Guangfeng et al (2022)[79]	OA	Metformin may slow the knee cartilage volume loss in OA patients.
Lu et al (2018)[80]	OA with diabetes	Metformin take decreased the joint replacement candidate of OA patients.

Anti-CCP, anti-cyclic citrullinated peptide; BCL-2, B-cell lymphoma 2; BMI, body mass index; COMP, Cartilage Oligomeric Matrix Protein; CTX-1, C-terminal cross-linked telopeptide of type I collagen; CXCL16, C-X-C motif chemokine ligand 16; HGS, hand-grip strength; HMGB1, high mobility group box 1; IGT, impaired glucose tolerance; IGF-IR, insulin-like growth factor I receptor; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-17A, interleukin-17A; MDA, malondialdehyde; miR-451, microRNA-451; NF-κB, nuclear factor kappa B; OA, osteoarthritis; RA, rheumatoid arthritis; SIRT1, sirtuin 1; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor alpha.

Table 3. Studies examining both type 2 diabetes (T2D) and COVID-19.

Author, year, Ref	Method (sample)	Result
Almengló et al (2021)[86]	Epicardial and subcutaneous fat biopsies were used for RNA expression analysis by real-time PCR of ACE1, ACE2, and ADAM17	The highest ACE2 levels were found in patients with diabetes and obesity. ACE1 and ACE2 levels were not upregulated by antidiabetic treatment (metformin).
Ghany et al (2021)[87]	A retrospective cohort study conducted on elderly COVID-19 patients	Metformin (1000 mg/day) decreased the mortality rate of elderly COVID-19 patients.
Hardin et al (2022)[88]	A 78-year-old male with T2DM and a mild COVID-19	An FBS and hemoglobin A1C (HbA1C) were recorded as 403 mg/dL and 11% respectively. The link between viral symptoms and exacerbation of T2DM was shown.
Heald et al (2022)[89]	Cross-sectional study of T1DM or T2DM with COVID-19 infection.	There was a protective effect of metformin in individuals with T2DM.
Ouchi et al (2022)[90]	Cohort study of diabetic patients with COVID-19 who used metformin.	Users of insulin, combined with metformin or dipeptidyl peptidase-4 inhibitor (IDPP4) alone had higher risk.
Vordoni et al (2021)[91]	A diabetic patient with acute kidney injury, metformin-associated lactic acidosis, and COVID-19	Lactic acidosis is a relatively rare complication of metformin use.

ACE1, angiotensin-converting enzyme 1; ACE2, angiotensin-converting enzyme 2; ADAM17, ADAM metallopeptidase domain 17; HbA1C, hemoglobin A1c; IDPP4, dipeptidyl peptidase-4 inhibitor; PCR, polymerase chain reaction; RNA, ribonucleic acid; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

CONCLUSIONS

Metformin, once considered the first-line treatment for T2D, is now prescribed with caution due to concerns about its potential cytotoxicity in diabetic patients with kidney complications. Many of the drug's effects-such as regulating energy balance, reducing glucose production in the liver, enhancing insulin sensitivity, and modulating inflammation-are particularly relevant in the context of viral infections like COVID-19, as they are linked to the AMPK pathway. The various effects of metformin connect metabolic balance and immune response, indicating its therapeutic potential extends beyond merely controlling blood glucose levels.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

Not applicable.

AI ASSISTANCE DISCLOSURE

Not applicable.

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