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Beyond Glycemia: Metformin's Anti-Inflammatory, Antioxidant, and Immunomodulatory Properties in Chronic Diseases: A Narrative Review

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ABSTRACT

For more than sixty years, metformin (1,1-dimethylbiguanide hydrochloride) has been the most frequently prescribed drug for mitigating blood glucose levels and is the most important treatment for individuals newly diagnosed with type 2 diabetes mellitus (T2DM). The primary effect of metformin is to directly suppress hepatic gluconeogenesis and improve insulin sensitivity. However, metformin also promotes insulin release via an indirect mechanism that involves increasing the levels of glucagon-like peptide-1 (GLP-1). Recent investigations have underscored the broader therapeutic potential of metformin in chronic diseases associated with inflammation. This study aims to explore the properties of metformin beyond blood sugar reduction in chronic diseases by examining indicators related to inflammation and immunity. The anti-inflammatory and antioxidant mechanisms of metformin involve both AMP-activated protein kinase (AMPK)-dependent and -independent pathways. AMPK mediates the anti-inflammatory and antioxidant effects of metformin by regulating the activity and levels of NF-κB, NLRP3, inflammatory cytokines, NRF2, as well as oxidative and antioxidant markers. In addition, other roles of metformin that contribute to reducing the incidence of T2DM and chronic complications, including cardiovascular diseases, cerebrovascular diseases, nephropathy, retinopathy, neuropathy, autoimmune diseases, neurodegenerative diseases, and cancer, include direct inhibition of mitochondrial ROS, inhibition of mTORC1, modulation of gut microbiota, GDF15 upregulation, and regulation of innate and adaptive immunity.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic inflammatory condition marked by a progressive decline in insulin production by pancreatic beta cells, along with diminished insulin sensitivity. This condition progresses over time and may give rise to severe complications such as cardiovascular and cerebrovascular diseases, as well as nephropathy, retinopathy, and neuropathy (1, 2). Metformin (1,1-dimethylbiguanide hydrochloride) has remained the leading medication for mitigating blood sugar for more than six decades and is the most important treatment for individuals newly diagnosed with T2DM. Metformin was first produced in 1922, and its initial use for attenuation of blood glucose levels was reported in 1929. Metformin is currently consumed daily by over 200 million subjects with T2DM globally, either alone or in conjunction with sulfonylureas or dipeptidyl peptidase-4 inhibitors (3). The primary action of metformin is to directly suppress hepatic gluconeogenesis and improve insulin sensitivity. However, metformin also boosts insulin secretion through an indirect pathway involving elevated levels of glucagon-like peptide-1 (GLP-1). (4, 5). Recent studies emphasize the broader therapeutic potential of

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metformin in chronic diseases associated with inflammation. As a result, in addition to reducing the diabetic complications mentioned above, this drug could also serve a role in the debarment of neurodegenerative diseases, autoimmune diseases, and cancer. This underscores the clinical significance of metformin's anti-inflammatory properties (6). The goal of this investigation is to assess metformin's broader therapeutic effects beyond blood sugar reduction in chronic diseases by examining indicators related to inflammation and immunity

Methods

This article is a narrative review. A comprehensive examination was carried out on the PubMed, MeSH, Scopus, and Google Scholar to locate studies pertinent to the evaluation. Most of the studies examined were published between 2015 and 2025. The keywords used were T2DM, metformin, AMPK, NF-κB, NLRP3, IL-1β, IFN-γ, TNF-α, ICAM-1, VCAM-1, TLR4, NRF2, GSH, SOD, GPx, HO-1, ROS, MDA, SIRT-1, GDF15, macrophage, neutrophils, adaptive immunity, innate immunity. Approximately 70 articles were evaluated, with around 54 selected for the final analysis.

Mechanisms of Metformin's Anti-Inflammatory Effects

AMPK Dependent Pathways

AMP-activated protein kinase (AMPK) plays an essential role in mediating both the metabolic and anti-inflammatory actions of metformin. As a cellular energy sensor, AMPK promotes the entry of glucose into skeletal muscle and fat cells via glucose transporter 4 (GLUT4) (7). Metformin acts on the electron transport chain by suppressing complex I, leading to an elevated AMP/ATP ratio and triggering AMPK activation (8).

AMPK, NF-κB, NLRP3, and inflammatory agents

Through various mechanisms, AMPK exerts inhibitory effects on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). AMPK can halt the IκB kinase (IKK) complex, which is vital for activating NF-κB. By suppressing the phosphorylation and destruction of IκBα mediated by IKK, AMPK aids in maintaining the cytoplasmic retention of NF-κB, thereby forbidding its movement into the nucleus (9). In a study published by Cameron et al. Metformin prohibited IKK activity at mouse hepatocytes (10).

AMPK blocks the translocation of NF-κB p65 from the cytosol into the nucleus, thereby mitigating the transcription of pro-inflammatory genes (11). In hypoxic conditions, AMPK suppresses the JNK pathway, which subsequently stops NF-κB from becoming activated. In ischemia-reperfusion injury, this process is particularly noteworthy because activating AMPK attenuates the secretion of inflammatory cytokines(12).

The NOD-like receptor protein 3 (NLRP3) inflammasome is crucial for the processing and release of mature forms of interleukin-1 beta (IL-1β) and IL-18 (13). AMPK obstacles the activity of caspase-1 in the NLRP3 inflammasome. Consequently, it not only attenuates the expression of IL-1β and IL-18 by lowering NF-κB activity but also mitigates the secretion of these cytokines by inhibiting NLRP3 (14). Yang and colleagues declared that metformin (200 mg/kg/day for 8 weeks) mitigated the expression levels of mTOR, NLRP3, caspase-1, IL-1β, and the N-GSDMD fragment of Gasdermin-D (GSDMD-N) in diabetic mice. Following NLRP3 inflammasome activation, GSDMD-N serves a vital function in driving the pyroptosis process (15). Han et al. showed under normal glucose levels, metformin markedly lowered the baseline secretion of IL-1β, interferon gamma (IFN-γ), and tumor necrosis factor-α (TNF-α) in trophoblast cell line (Sw.71). Moreover, metformin markedly suppressed the generation of IL-8 under hyperglycemic conditions (16). According to a randomized controlled trial (RCT) reported by Aiad et al., 12 weeks of metformin therapy (500 mg/day) in patients with obesity-related knee osteoarthritis (OA) led to a significant reduction in serum IL-1β levels (17). Furthermore, in patients with ulcerative colitis (UC), taking 1000 mg of metformin daily for six months led to downregulation of TNF-α, signal transducer and activator of transcription 3 (STAT-3), and intracellular adhesion molecule-1 (ICAM-1). ICAM-1 is a chemokine. STAT-3 activates macrophages and T lymphocytes, which subsequently results in the generation of pro-inflammatory cytokines (18). In a clinical trial reported by Kruszelnicka et al., a notable reduction in circulating levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) was observed in T2DM patients taking 1655 mg/day of metformin for at least 12 months (19).

AMPK is involved in macrophage polarization by facilitating the shift of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype via NF-κB inhibition (20). Moreover, in macrophages, AMPK attenuates the expression of the pro-inflammatory marker C-C chemokine receptor 2 (CCR2), partly by haltering NF-κB (21). In a study conducted by Cahova and colleague, the

expression of TNF-α, IL-1β, CCR2, and toll-like receptor 4 (TLR4) was notably mitigated in high-fat diet (HFD) rats after receiving metformin at 150 mg/kg for 10 weeks (22). The TLR4 receptor is a member of the toll-like receptor family, which serves as an example of pattern recognition receptors (PRR). It activates NF-κB and NLRP3 (23).

One of the pathways through which AMPK hinders NF-κB activation, mitigates oxidative stress, and improves insulin sensitivity involves the phosphorylation and subsequent blocking of acetyl-CoA carboxylase (ACC) activity, along with fatty acid production. Fatty acids promote inflammation, oxidative stress, and insulin resistance through the activation of protein kinase C (PKC) (24, 25).

AMPK, NRF2, and antioxidants

As a key transcription factor, NRF2 is vital for controlling how cells respond to oxidative stress. In the nucleus, NRF2 interacts with antioxidant response elements (AREs), leading to the upregulation of several antioxidant genes, including glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), and catalase. In typical circumstances, NRF2 resides in the cytoplasm and is marked for breakdown by Kelch-like ECH-associated protein 1 (KEAP1). When oxidative stress occurs, changes in reactive oxygen species (ROS) concentrations cause NRF2 to detach from KEAP1. This permits NRF2 to shift to the nucleus and upregulate its target genes. Furthermore, NRF2 upregulates phase II enzymes involved in detoxification, which assist in the metabolism and removal of harmful substances, thereby further reducing cellular damage (26-28). AMPK directly phosphorylates NRF2 at specific residues, promoting its movement into the nucleus and boosting its transcriptional activity. Moreover, the activation of AMPK disarranges the interaction between KEAP1 and NRF2, stabilizing NRF2 and enabling its accumulation in the nucleus. Furthermore, AMPK can upregulate NRF2 by activating transcription agents like forkhead box O3 (FOXO3) or peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), further elevating antioxidant defenses (29, 30).

Fan et al. stated metformin mitigated the neurogenesis damage and neurocognitive impairments caused by sevoflurane in the developing rat brain by upregulating NRF2 (31). Singh et al. declared that metformin notably attenuated malondialdehyde (MDA) in T2DM patients after one month of metformin treatment. In contrast, the levels of SOD substantially decreased. MDA is a crucial indicator of oxidative stress and lipid peroxidation (32). In a study by Naghdi et al., intake of metformin at doses of 300 and 500 mg/kg in diabetic rats led to normalization of MDA levels and betterment the activities of CAT, SOD, and GPx (33).

AMPK activates sirtuin-1 (SIRT-1), which deacetylates NRF2 and enhances its activity (29). SIRT-1, an NAD-dependent histone deacetylase, is crucial for protecting cells from ROS. The relationship between SIRT-1 and NF-κB is mutually regulatory. By removing acetyl groups from the p65 subunit, SIRT-1 suppresses NF-κB activity. Conversely, NF-κB halters SIRT-1 activity and expression by elevating ROS levels and promoting proinflammatory factors like IFN-γ (34, 35). Apart from its ability to combat oxidative stress and inflammation that lead to attenuation in the incidence of chronic diseases, SIRT-1 also raises insulin secretion by downregulation of uncoupling protein-2 (UCP-2) (35). In a study reported by de Kreutzenberg et al., intake of metformin 1500 mg/day for eight weeks raised insulin sensitivity and upregulated the SIRT-1 gene and protein in subjects with prediabetes (36).

AMPK-Independent Pathways

Direct Inhibition of Mitochondrial ROS

Metformin hinders excessive activation of the electron transport chain and attenuates ROS production by halting mitochondrial complex I (37). The NLRP3 protein senses ROS in the mitochondria, triggering its oligomerization and inflammasome assembly. Therefore, metformin inhibits NLRP3 by reducing mitochondrial ROS levels (38).

mTOR Suppression

Metformin can hinder the mammalian target of rapamycin complex 1 (mTORC1) pathway in an AMPK-dependent and -independent manner (39, 40). Metformin lowers the overactivation of T-cells, immune reactions, and production of inflammatory agents by suppressing mTORC1 (41). This mechanism implies that metformin could contribute to both the prevention and reduction of cancers as well as autoimmune conditions including rheumatoid arthritis, lupus, and multiple sclerosis (42).

Modulation of Gut Microbiota

Metformin might positively alter gut microbial composition through an increase in the relative abundance of bacteria that produce anti-inflammatory short-chain fatty acids (SCFAs). Additionally, metformin decreases the prevalence of pro-inflammatory bacterial

species in the gut (43). In studies involving animals, metformin raised the gut levels of Akkermansia spp., which generate short-chain fatty acids, and this change correlated with diminished adipose tissue inflammation. (44).

GDF15 Upregulation

Growth differentiation factor 15 (GDF15) is a stress-responsive cytokine belonging to the transforming growth factor-beta (TGF-β) superfamily. This cytokine, also referred to as macrophage inhibitory cytokine-1 (MIC-1), is secreted in response to cellular stressors like inflammation, tissue damage or metabolic stress (45). Metformin agitates GDF15 secretion mainly in the intestine and distal kidney (46). In a study published by Coll et al., metformin increased GDF15 expression in mice, and this upregulation was responsible for the drug's positive effects on energy homeostasis and body weight (47). Furthermore, Gao et al stated that blood GDF15 levels substantially aroused after consumption of metformin for 4 months in patients with T2DM (48).

Immunomodulatory Effects of Metformin

Innate Immunity

Metformin promotes polarization of macrophages from M1 subtype to M2 via AMPK, which lowers inflammatory immune responses. Jing et al. demonstrated that metformin taking for 7 weeks in high fat-fed mice improved obesity-related inflammation by altering macrophage polarization (49). During the initial stages of innate immunity, neutrophils perform a critical function. Activated neutrophils can release neutrophil extracellular traps (NETs), consisting of chromatin and antimicrobial proteins, via a form of non-apoptotic cell death called NETosis (50). Excessive NETosis may lead to tissue injury and worsen pathological conditions. Menegazzo et al. showed the administration of metformin in prediabetic individuals for 8 weeks resulted in a reduction of NET components, including elastase, proteinase-3, histones, and double-stranded DNA, compared to patients with T2DM who received insulin or dapagliflozin (51).

Adaptive Immunity

CD8+ T cells or cytotoxic T cells are a subset of lymphocytes that serve a critical function in the immune response. Metformin raises the production and stability of CD8+ T cells through the activation of fatty acid oxidation within these cells, uncovering a new mechanism for boosting immune (52). Finisguerra et al. declared that metformin protected murine and human CD8+ T cells from apoptosis mediated by hypoxia (53). T helper-1 (Th1) cells secrete IFN-γ, which is crucial for fighting intracellular pathogens such as viruses and specific bacteria. Th1 cells increase macrophage function, facilitating phagocytosis and the elimination of pathogens. Th17 cells play a role in inflammation and, similar to Th1 cells, are associated with various autoimmune and inflammatory conditions. They attract neutrophils to areas of infection. It was shown, metformin mitigates the number of Th1 and Th17 cells. Tregs (regulatory T cells) represent a specialized group of T lymphocytes that are crucial for sustaining immune homeostasis and hindering autoimmune diseases. Park et al. stated Th17 cells that were treated with metformin transitioned into Treg cells (54).

Conclusion

Based on studies conducted on cells, animals, and humans, in addition to mitigating hepatic gluconeogenesis and increasing insulin secretion and sensitivity, metformin can hinder or mitigate the incidence of T2DM and its chronic complications, including cardiovascular diseases, cerebrovascular diseases, nephropathy, retinopathy, and neuropathy, due to its anti-inflammatory, antioxidant, and immunomodulatory properties. Furthermore, because of these effects beyond glucose metabolism, metformin is also involved in averting autoimmune diseases, neurodegenerative diseases, and cancer in patients with T2DM. Of course, more original studies need to be conducted to determine the anti-inflammatory, antioxidant, and immunomodulatory properties of metformin in preventing complications of chronic diseases.

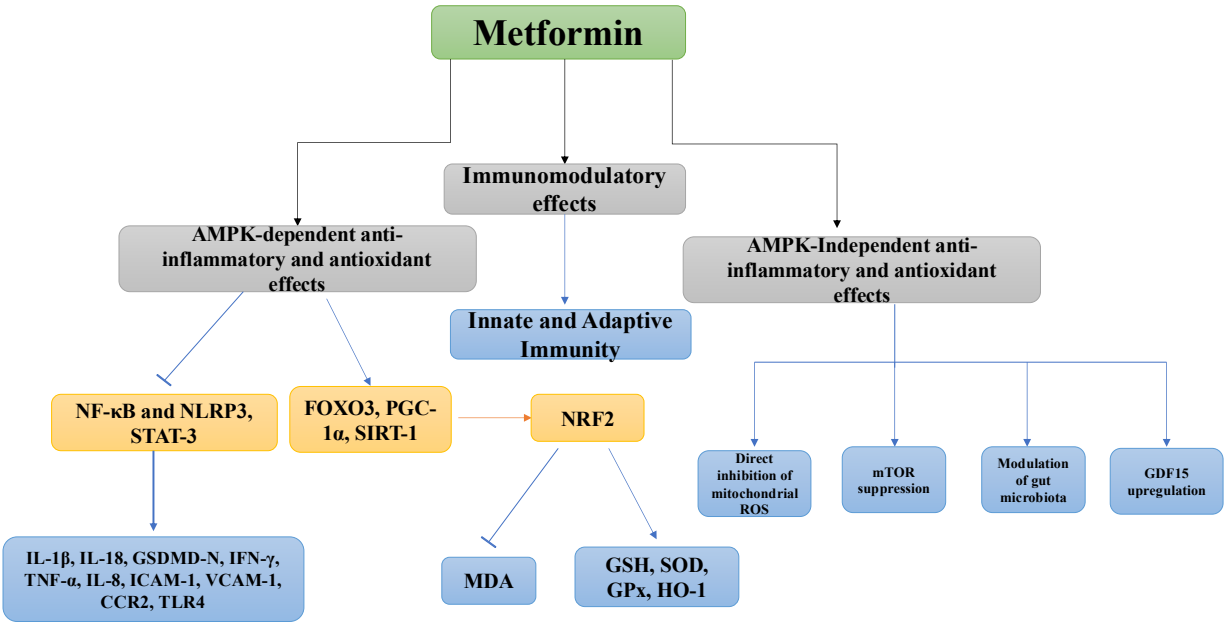

Fig.1. Metformin's roles beyond glucose metabolism in reducing chronic disease incidence. In addition to its direct effect on glucose metabolism, metformin declines the incidence of T2DM and other chronic diseases through both anti-inflammatory and antioxidant effects, which are dependent and independent of AMPK and immunomodulatory effects. STAT-3: signal transducer and activator of transcription 3, FOXO3: forkhead box O3, PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha, SIRT-1: sirtuin-1, NRF2: nuclear factor erythroid 2-related factor 2, GDF15: growth differentiation factor 15.

Abbreviations

T2DM: Type 2 diabetes mellitus, GLP-1: Glucagon-like peptide-1, AMPK: AMP-activated protein kinase, GLUT4: Glucose transporter 4, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, NLRP3: NOD-like receptor protein 3, IL-1β: Interleukin-1 beta, GSDMD-N: N-GSDMD fragment of Gasdermin-D, IFN-γ: Interferon gamma, TNF-α: Tumor necrosis factor-α, Sw.71: Trophoblast cell line, OA: Osteoarthritis, UC: Ulcerative colitis, STAT-3: Signal transducer and activator of transcription 3, ICAM-1: Intracellular adhesion molecule-1, sVCAM-1: soluble Vascular cell adhesion molecule-1, CCR2: C-C chemokine receptor 2, TLR4: Toll-like receptor 4, HFD: High-fat diet, PRR: Pattern recognition receptors, ACC: Acetyl-CoA carboxylase, PKC: Protein kinase C, NRF2: Nuclear factor erythroid 2-related factor 2, AREs: Antioxidant response elements, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, HO-1: Heme oxygenase-1, KEAP1: Kelch-like ECH-associated protein 1, ROS: Reactive oxygen species, FOXO3: Forkhead box O3, PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, MDA: Malondialdehyde, SIRT-1: Sirtuin-1, UCP-2: Uncoupling protein-2, mTORC1: Mammalian target of rapamycin complex 1, SCFAs: Short-chain fatty acids, GDF15: Growth differentiation factor 15, TGF-β: Transforming growth factor-beta, MIC-1: Macrophage inhibitory cytokine-1, NETs: Neutrophil extracellular traps, Th1: T helper-1, Tregs: Regulatory T cells.

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