World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Benign outcomes of metformin for various diseases: A review

SANTHOSH G [1,*], NITHISHWAR M [1] and FATHIMA BASHEERA M [2]

[1] *Doctor of Pharmacy, Department of Pharmacy practice, Arulmigu kalasalingam college of Pharmacy, Virudhunagar, Tamilnadu, India – 626126.*
[2] *Assistant Professor, Department of Pharmacy Practice, Arulmigu kalasalingam college of Pharmacy, Virudhunagar, Tamilnadu , India – 626126.*

World Journal of Advanced Research and Reviews, 2023, 20(01), 278–286

Publication history: Received on 23 August 2023; revised on 01 October 2023; accepted on 04 October 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.20.1.2036

Abstract

Metformin is the most popularly prescribed first-line drug in the management of type 2 diabetes mellitus. Metformin exerts different effects such as anti- hyperglycemic effect, analgesic effect in the management of musculoskeletal pain and anti-depressant effect in depression management, cardio protective and neuroprotective effects in the cardiovascular system and central nervous system. Nrf2 is the factor responsible for enhancing the anti-oxidative effects of metformin. Metformin exerts its anti-proliferative effect through the suppression of tumor development and modifies the surroundings of the tumor.

Keywords: Metformin; Diabetes mellitus; AMPK activation; Pain management; PCOS; Depression.

1. Introduction

1.1. Definition

Metformin is a desirable anti hyperglycemic agent in use for T2DM [9]. As an oral biguanide derivative, it decreasing the production of hepatic glucose and absorption of gastrointestinal glucose [30].

1.2. Introduction

Metformin (1, 1-dimethylbiguanide) directly exerts its action on the central nervous system. Metformin is safe to use, not expensive, and highly tolerated in T2DM so it is in use as a first-line anti-diabetic drug [69]. The other name of metformin is Glucophage as it is responsible for the inhibition of an increase in insulin sensitivity peripherally. The reduction in resistance of insulin occurs by elevating the insulin receptors numbers and enhancing the uptake of glucose by tissues [70]. Metformin in comparison with other biguanides produces a desirable effect and the lactic acidosis risk is rare [44].

1.3. Synthetic genesis of metformin

From the perennial plant, Galega officinalis the guanidine-based medications were extracted. The other common names are French Lilac and Goat's Rue. The indications for the herb are an increase in the frequency of micturition and thirst [44].

* Corresponding author: G. SANTHOSH

1.4. Nature of metformin

Synthetically metformin consists of a hydrophilic base, at a physiological PH this comes under cationic species. Metformin has weak properties of passive diffusion and lipophilicity so it is dependent on organic cation transporters (OCTs) these are highly expressed in the potential targets of metformin including adipose tissue, liver, and muscle. [56]

1.5. Key functions of metformin

Metformin works by decreasing intestinal glucose absorption, improving peripheral glucose uptake, lowering fasting plasma insulin levels, and increasing insulin sensitivity, which results in a reduction of blood glucose concentrations without causing overt hypoglycemia [47]. The positive reversal effects of metformin are metabolic dysfunction mediated by corticosterone behaviors induced by depression and lipopolysaccharide in connection with the pathways related to glutamatergic neurotransmission and inflammation. [55]. via the non-neuronal and neuronal mechanisms which stimulate the 5-hydroxytryptamine release in turn the secretion of insulin increases [57]. Full-length use of metformin reduces the risk of Total Knee Arthroplasty (TKA) because of the dose-dependent effect of metformin and it has the ability to regulate and make the lipopolysaccharide-stimulated pro-inflammatory responses weaken in the macrophages and monocytes [19, 20].

1.6. Dosage recommendation

The initial dose of metformin therapy is 500 mg BD. The recommended maximum daily metformin dose is 2,500 mg with 500 mg tablets TID as divided doses [30].

1.7. Pharmacokinetics of metformin

Metformin on oral administration disseminates to most of the tissues but the absorption in the small intestine is partial and the maximum luminal concentration of metformin absorption occurs in the gastrointestinal tract. A single dose of 1.5g in 3 hours. The peak plasma concentration is 18mM and about 20hr is the mean plasma half-life of metformin [41].

1.8. Establishment of metformin XR

On OD administration of Metformin XR the active drug is released via polymers that are hydrated after fluid uptake prolongs the time of gastric residence this makes the drug absorption slow in the upper gastrointestinal tract. The Metformin XR has better tolerability and compliance increase with olanzapine [43, 64].

2. Diverse mechanism of action of metformin

2.1. AMPK activation

Upon activation by metformin upregulates the expression of pCREB, histone acetylation, and BDNF promotor [3]. Activation by metformin results in suppression of lipogenic transcription factor (SREBP-1) expression. Metformin exerts its action on hepatocytes resulting in phosphorylation and in turn inhibits the acetyl-CoA carboxylase responsible for the rate-limiting step in lipogenesis [48]. In mPFC neurons metformin recovers the cognitive function through AMPK activation [5].

2.2. Analgesic effect

Metformin mediates its analgesic effect via AMPK activation resulting in the inhibition of the mTOR (mammalian target of rapamycin) pathway. AMPKα2 subunit is responsible for supporting metformin anti-nociceptive activity. Metformin decreases the nociceptor agitation and mechanical allodynia through the inhibition of mTOR signals [2]. Metformin provides anti-nociceptive activity via partial opioidergic pathways activation. mTORC1 inhibition by suppression of Rag GTPases45 and increase of REDD1 expression in a p53-dependent manner and it is AMPK independent this results in prevention of opioid tolerance [47,24]. The various mechanism employing AMPK activators results in the reduction of neuronal agitation by reducing the voltage-gated potassium channels and inhibition of voltage-gated sodium channels phosphorylation as well as decreasing the unforced oscillations of Ca2+ [6]. Metformin reduces the expression of Transient Receptor Potential Ion Channel and ASIC3 [15].

2.3. Antidepressant effect

In Lipopolysaccharide-induced depression, metformin decreases the release of presynaptic glutamate and also it may involve the insulin receptor pathway [32]. Metformin in connection with the serotonin system elevates the bioavailability of serotonin via several pathways involving the tryptophan/kynurenine system [59].

2.4. Anti-hyperglycemic effect

Metformin decreases cortisol secretion and Adreno corticotropic hormone through many pathways such as the pro-opiomelanocortin pathway or liver X receptor α or AMP-activated protein kinase [34]. Metformin directly inhibits the DPPIV and leads to weight loss and reduction in food intake by increasing the levels of GLP-1 in plasma. Metformin works independently on glucose metabolism and signaling of insulin by AMPK-dependent mechanism this increases the ß amyloid in the cells. [43, 66].

2.5. Anti – proliferative effect

Metformin provides its anti-proliferative effects by blocking the induction of cell cycle arrest at the G1 phase this reduces the cyclin E2F1 and D1 and inhibits the cell expansion. Metformin also has the ability to inhibit Akt and MAPK. Aromatase activity and aromatase mRNA are reduced by metformin via suppressing the P1.3 specific transcripts and (PII) promoter [3]. Metformin suppresses tumor development by reducing its survival, and growth and prevents metastasis of the tumor by modifying the tumor surroundings by means of apoptosis, autophagy, and activation of p53, inflammatory response, DNA damage, and reduction in the generation of ROS [46]. Other effects of metformin in cancer include elevation in the CD8 (+) tumor-infiltrating lymphocyte numbers, inhibits the synthesis of pro inflammatory cytokines, and decreases in angiogenesis and lipogenesis [47]. Metformin stimulates late the PPARs (peroxisome proliferator-activated receptors [35, 61].

2.6. Anti-oxidative effect

Metformin's anti-oxidative effects are determined by Nrf2 (nuclear factor erythroid 2-related factor) a transcriptional factor on activation that manages the multiple antioxidant gene expression this occurs in an AMPK-dependent manner [59].

2.7. Effect on oxidative stress

Metformin has the ability to reduce the levels of glycation end products and malondialdehyde and increase the activity of superoxide dismutase in serum resulting in the inhibition of diabetes-induced oxidative stress [22]. In cells, oxidative stress is inhibited by metformin through the elimination of senescent cells and by promoting the restoration of mTOR. It also blocks the adenylate cyclase responsible for the production of glucagon-induced cAMP [50]. p38 MAPK phosphorylation outcome is the testosterone-induced stress which is the main cascade of oxidative stress it is inhibited by metformin [54].

2.8. Neuroprotective effect

Metformin provides neuroprotection in opposition to the MPTP neurotoxic effects by elevating the levels of BDNF in substantia nigra through the inhibition of synuclein phosphorylation [62].

2.8.1. CAD

The vasoactive effects of metformin are produced by means of AMP-activated protein kinase activation. The action involves the phosphorylation of endothelial nitric oxide synthase located at the serine 177 in human aortic endothelial cells in the endothelial isoform [9]. Via endothelial nitric oxide synthase-dependent pathway, metformin promotes ischemia-induced revascularization for cardio protection [40].

2.8.2. Alzheimer's disease.

Metformin stimulates the protein phosphatase 2A activity and increases the tau protein dephosphorylation in an AMPK-independent manner [45].

2.8.3. PCOS

The positive actions of metformin include restoration of the hypothalamus–pituitary–ovarian function results in the progesterone and oestradiol balance from corpus luteum and granulosa cells as well as a reduction in the levels of insulin due to oxidation of glucose in the endometrial tissues [52].

2.8.4. Osteoarthritis

Metformin inhibits TNF-α via the AMPK pathway by blocking the IL-6 release leads to ossification inhibition and reduces the osteogenic-specific markers [11]. Activation of SIRT3/PINK1/Parkin results in the mTORC1 pathway downregulation [19].

2.8.5. Dercum's disease

Metformin enhances the apolipoprotein E effect responsible for nerve renewal after peripheral nerve impairment. Metformin as a treatment for Dercum's disease influences the lines of P-endorphin as well as inflammatory cytokines and adipokines. [1)].

2.8.6. Erectile dysfunction

Direct action by decreasing the sympathetic nerve activity or producing indirect action on the blood pressure and reduces the levels of prostate-specific antigen [12].

3. Targets of metformin

3.1. Mitochondrial respiratory chain complex 1

Mitochondrial respiratory chain complex 1 is the main target of metformin its inhibition is employed in the hepatic gluconeogenesis independent regulation besides stimulating changes in the redox state and cellular energy state [31].

3.2. AMP/ATP ratio

Metformin inhibits the complex I of the mitochondrial respiratory chain in order to increase the AMP/ATP ratio through enhancement of the shift from aerobic to anaerobic glycolysis [14]. AMP: ATP ratio is employed in the activation of AMPK (heterotrimer AMP-activated protein kinase), which plays a vital role in cellular metabolism [17].

3.3. Gastrointestinal tract

Play a vital role in supporting the action of metformin regulates the recirculation of bile acid and promotes the glucose-lowering gut incretin hormone glucagon-like peptide-1 (GLP1) secretion. And gut microbiota is involved in both the therapeutic and adverse effects of metformin [31].

Table 1 Utilities of metformin treatment

SI.no.	Disease	Effects
1.	PCOS	Metformin produces ant estrogenic effects by reducing the levels of estrogens and testosterone in the blood. In breast cancer treatment metformin produces the anti-cancer effect by prevention of cancer evolution via controlling the rate of tumour progenitor cell increase. [3]. In PCOS women metformin treatment increases the pain pressure threshold without influencing the plasma β-endorphin concentration and increases the SHBG levels. [4]. Metformin increases gonadal activity leads to proper ovary functioning and regular menstrual cycle and exerts its action on steroidogenesis and exerts a beneficial effect in endometriosis [8, 23]. Metformin enhances menstruation by reducing subcutaneous adipose tissue and BMI and also promotes the development of follicles as well as insulin resistance [10]. Metformin decreases the prevalence and seriousness of virilism, and acne and alters infertility [38]. Metformin normalizes ovarian steroidogenesis reduces the circulating levels of testosterone, and androstenedione, and increases the activity of adrenal enzymes along with metabolically active hormones such as ghrelin, leptin, and resistin which involve in the enhancement of reproductive physiology. Additionally, metformin increases the response to gonadotropins [52, 67]. Metformin along with D-chiro-inositol exerts positive action in restoring the quality of oocytes and reducing the follicular fluid proteins oxidative damage [53].
2.	DIABETES	Beta-endorphin enhances metformin's insulin-sensitizing effects [7]. Metformin controls the production of endogenous glucose which determines the fasting plasma glucose concentrations [13]. Metformin lowers the levels of HRQoL [27]. The combination of sulfonylurea with metformin reduces the risk of dementia in T2DM patients [60].
3.	GOUT	Metformin reduces cell death through the inhibition of mTOR signalling [11].

4.	AUTOIMMUNE DISEASE	Metformin treatment is shown to be efficacious in ankylosing spondylitis [11].
5.	OSTEOARTHRITIS	Metformin produces disease-altering properties in knee osteoarthritis such as pain reduction, chondroprotection, and immunomodulation [16]
6.	MOOD DISORDER	Metformin presence decreases the risk of developing de novo mood disorder [35].
7.	DEPRESSION	Metformin exerts its neuroactive effect on pathways related to depression including axonal regeneration and neurotrophins [39].
8.	CAD	Metformin treatment lowers the risk of vascular disease development due to high levels of PAI-1 [68].

4. Therapeutic union of metformin with other drugs

The combination of metformin with sulfonylurea enhances the control over glycemic as well as increases the sensitivity of insulin. Also, it is better in comparison with monotherapy of metformin. [30, 33, 58]. Metformin, meloxicam, and pioglitazone along with NSAID therapy improve the symptoms of OA. [18, 21, 26]. The combination of medroxyprogesterone acetate in addition to metformin improves the clinical manifestation of endometrial hyperplasia [12]. Metformin and a small dose of spironolactone combination result in an antidepressant effect in an efficacious manner along with an increase in adherence to the medication without any adverse events [25, 70]. Sitagliptin and metformin union results in the enhancement of the function of fasting β-cell [28]. The beneficial effects of metformin and ascorbic acid combination include alterations of monoamine transmission, depression markers, control of the rate of diabetes and depressive behavior along with a notable decrease in adrenal weights and levels of corticosterone in plasma [34]. Fluoxetine and metformin combination therapy results in an increase in plasticity, and alterations in mood by fluoxetine and metformin influence the profile of metabolism leading towards improvement by affecting the major electrophysiological activity particularly the dorsal hippocampus in order to produce the antidepressant effect [36]. And milnacipran and metformin combination therapy produce also produce an anti-depressant effect [37]. A combination of aripiprazole and metformin decreases the weight gain related to SGA [65].

5. Applications of metformin

- Metformin influences the ceramides responsible for cell differentiation, and cellular signalling by modifying its effects thus the outcome is the prevention of myoblast senescence [40, 49].
- Metformin exerts its action by decreasing the levels of TGs, ALT, AST, GGTs, LDL-C, free fatty acids, and alkaline phosphatase and enhances the metabolism of lipoproteins [43, 63].
- Metformin exerts action on the intracellular growth of mycobacterium tuberculosis by inhibiting the TGF-β-induced NADPH oxidase 4 expression via AMPK mediation [29].
- Metformin use reduces the tPA antigen levels leading to a decrease in maximal ST-segment depression [9].
- HoloTCII is a marker to monitor the status of cobalamin in metformin users [42].

5.1. Demerit of metformin use

Metformin on withdrawal produces more side effects and increases the risk to develop depression as comorbidity [51].

6. Conclusion

Metformin is used to improvise the clinical manifestations of various diseases such as polycystic ovarian syndrome, coronary artery disease, autoimmune diseases, and neurodegenerative diseases. The most important thing to note is metformin is safe, and has better tolerability as well as compliance. Provides the required therapeutic effect based on the indications without producing unwanted effects. Metformin in combination with other drugs produces synergistic effects resulting in the desired therapeutic outcome. But metformin on discontinuation leads to the development of depression. Over all metformin has maximum beneficial effects and minimum side effects.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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