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The Potential Role of Metformin as a Weight Loss Drug in Non-Diabetic Individuals: A Comprehensive Review

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ABSTRACT

Recent clinical research studies evaluated metformin's potential effects as a weight-reducing drug in non-diabetic individuals despite its glucose-lowering effects. Metformin reduces weight by acting on the appetite regulatory pathways, peripheral fat metabolism, and averse unfavorable fat storage. Clinical recent findings indicated that individuals maintain weight with the help of lifestyle modifications and bariatric surgery. However, metformin's clinical efficacy on weight loss helped the individuals overcome overweight and obesity complications. Metformin alters the hypothalamic physiology, including insulin and leptin sensitivity. Furthermore, metformin regulates the circadian rhythm changes and gastrointestinal physiology by affecting food intake and regulating fat oxidation, storage fat in the liver, muscles, and adipose tissues. Research also indicated other appetite suppressing medications such as topiramate, lorcaserin, and phentermine along with metformin also seems logical but clinical data reported that their weight loss results are lacking. However, more detailed research on how metformin induces weight loss in non-diabetic individuals and the prescription of other pharmacological interventions is needed.

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Introduction

According to scientific reports, it is estimated that 78 million individuals and 12.5 million adolescents are obese and overweight globally. Clinical findings indicated that obesity and overweight are major health concerns; 2.8 million deaths per year worldwide are reported, leading to the prevalence of cardiovascular complications, type-2 diabetes, and cancer (1). Randomized controlled trials (RCTs) and other research studies showed that lifestyle modifications, proper diet are effective in weight loss, maintain body weight, and metabolic health. However, some individuals need pharmacological therapy to manage overweight and obese complications (2). Metformin is a first-line drug designed to lower glucose levels. It is mainly recommended by the "American Diabetes Association (ADA)" for T2DM patients, pre-diabetic individuals, and one cardiovascular disease risk factor, including hypertension. Studies reported its effective role in reducing weight in non-diabetic individuals who are obese and overweight (3). Several mechanisms have been reported by which the metformin effectively improves the glycemic control in obese individuals that involves lowering hepatic glucose production, blocking gastrointestinal glucose absorption,

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enhancing peripheral insulin sensitivity (4). In some research studies, weight loss by metformin in non-diabetic individuals is considered a favorable side effect. Studies reported the metformin reduces weight with the help of appetite regulatory pathways and shows influences on adiposity and gut-derived signals (5).

This current review focuses on the recent shreds of evidence describing how metformin interacts with fat metabolic and circadian rhythm pathways and reduces weight. Lastly, the clinical findings of metformin's combined effect with exercise and other anti-obesity drugs or medications for obesity-related comorbidities are discussed.

Literature review

1. Search Strategy

This is a narrative and a comprehensive review in order to obtain an overview of the metformin role s weight loss drug in non-diabetic individuals. Literature search was done by using PubMed articles in English with the following search terms: metformin, drug, non-diabetic individuals, pathophysiology, biochemical pathways, and microbiome. Previous studies were critically studied, analyzed and reviewed then ll the relevant data were summarized in this narrative review. All the authors drafted and discussed the manuscript and agreed on the final version.

2. Metformin, as an anti-obesity drug

Current evidence reported the metformin's efficacy as an anti-obesity drug in non-diabetic patients. Studies showed that within the first three years of the double-blinded randomized controlled trial, about 1700mg/day, the metformin dosage caused an effective "weight loss of approximately 2.9 kg vs. 0.42kg in the placebo group" (Cicero, Tartagni, and Ertek 2012). One previous study reported that the weight loss effect by metformin was persisted for up to eight years. Hence, these clinical findings suggested that metformin treatment promoted two to five kg weight loss up to one year in non-diabetic individuals (6). Another previous study indicated a 2000mg/day dosage of metformin-induced 3 kg weight loss for three months in obese individuals with or without exercise (7).

Scientific studies indicated that combined therapy of metformin with the diet had grabbed attention in the scientific community. This combined effect is significant because high glycemic carbs may cause gastrointestinal (GIT) discomfort by metformin. In addition, research shreds of evidence in this field of study are required to investigate the effects of metformin that low carbohydrate diets cause effective weight loss (8). However, recent research work showed that metformin's lower doses of approximately 1000 to 1500 mg/day are considered a potent anti-obesity medication in people with the polycystic ovarian syndrome (PCOS) and psychiatric disorders that are primarily associated with weight gain, insulin resistance and this evidence supporting the fact that metformin drug is considered an effective weight loss medication approach in non-diabetic patients (9)(figure 1).

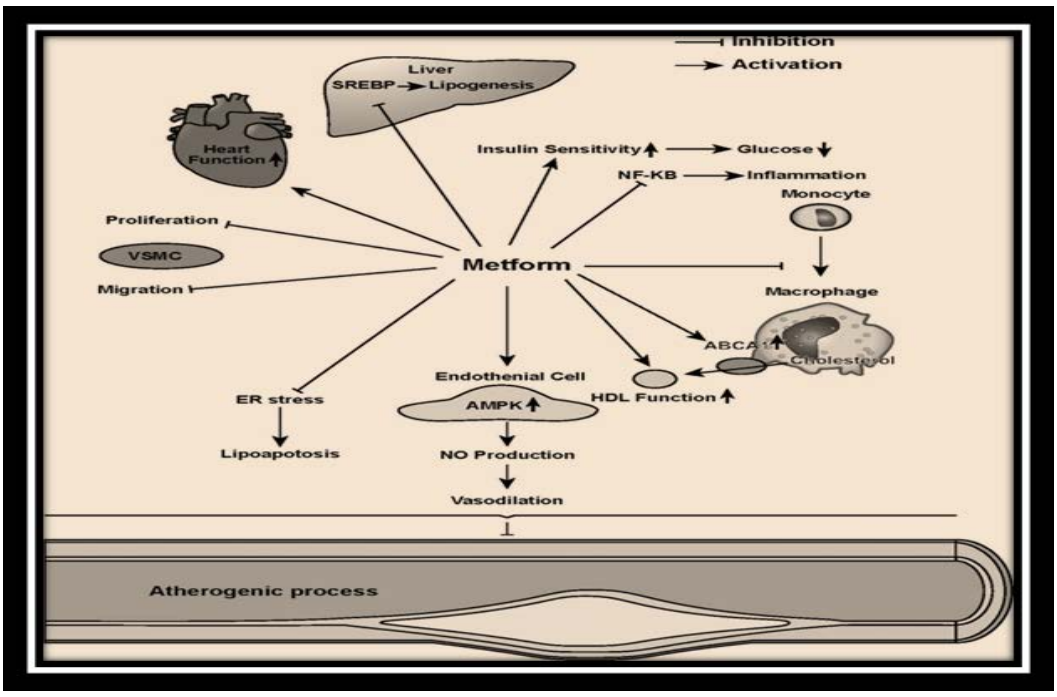

Figure 1: Weight loss mechanisms by metformin in non-diabetic individuals

2-1 Weight loss mechanisms by metformin in non-diabetic individuals

Studies showed that metformin improves weight loss by decreasing food intake, but daily energy expenditure changes are not reported yet. Moreover, previous research studies have observed reduced meal size during the metformin treatment, on the other hand, meal number gradually reduces with time. These altering meal pattern observations are significant because they better understand the potential brain regions affected by metformin (3) (table 1).

Table 1: Metformin and its effects on different biochemical pathways for weight loss.

Sr. No.	Study	Results	References
1.	Metformin and CNS regulation	metformin regulates intake of food by influencing appetite regulatory pathways	(11)
2.	Metformin and Adiposity sensors	stimulates the anorectic signaling mechanisms in the hypothalamic region, and causes a reduction in hunger	(15)
3.	Gut-mediated signals inducing satiety	co-prescription of "metformin with DPP-IV inhibitors (a GLP-1 receptor agonist)" is given to the patients, weight loss glycemic control is increased	(18)
4.	The Action of Metformin to Increase Fat Metabolism	Metformin causes an increase in "AMPK activity" in the skeletal muscles. This activity enhances GLUT-4 transporters, hexokinase II, and mitochondrial biogenesis	(20)
5.	Effect of Metformin on Circadian Rhythm	metformin treatment amplified the expression of "adipose-derived circadian locomotor output cycles kaput (CLOCK), brain and muscle aryl hydrocarbon receptor nuclear translocator-line 1 (BMAL1), and period (PER) 2" after AMPK is activated	(23)
6.	Metformin and Microbiome	Metformin therapy in rats was found to alter the gut microbiota and increase the number of bacteria that metabolize SCFA	(21)

2-2 Central nervous system (CNS) regulation

The brain's hypothalamic region is highly innervated by neurons that play an essential role in regulating feeding and meal patterns; metformin may directly affect the individual's feeding behavior. Studies reported that metformin reduces the consumption of food by decreasing the "orexigenic peptides, neuropeptide Y (NPY), and agouti-related protein (AgRP)" in the hypothalamic region. It is indicated that metformin excites the interaction between insulin and AMPK (adenosine monophosphate-activated kinase) in the liver, adipose tissues, and skeletal muscles (10).

Research findings reported that it is effective that metformin regulates the anorectic effects by modifying the hypothalamic AMPK. Ghrelin (hunger hormone), an orexigenic hormone, is secreted from the stomach in response to lower blood/glucose levels. Ghrelin promotes hunger by increasing neuropeptide Y and agouti-related protein neural activity via adenosine monophosphate-activated kinase AMPK (2). This relation between elevated ghrelin weight loss is described by the fact that metformin blocks the ghrelin-induced stimulation of the AMPK pathway.

Metformin also increases the STAT3 signaling cascade in the hypothalamic region of the brain and inhibits the expression of neuropeptide-Y NPY and AgRP thus, highlighting that metformin regulates intake of food by influencing appetite regulatory pathways (11).

2-3 Adiposity sensors

Leptin, an adipocyte-derived hormone, plays a pivotal role in the regulation of energy balance. It also neutralizes the effect of ghrelin, a hormone that enhances food intake. Leptin is involved in improving energy usage by directly binding to the obesity receptor b and inhibiting AMPK action in the hypothalamus, which reduces the expression of NPY and AgRP (12). It also carries out the activation of STAT3 in the NTS, which affects the hypothalamus by producing anorectic effects. Metformin plays a significant role in regulating food intake by directly influencing the adipose-brain axis's signaling mechanisms, mainly due to its fat mass-reducing characteristic (13).

The reduced circulation of leptin levels and enhanced expression of leptin receptors indicate metformin's role in improving leptin sensitivity. This causes a decrease in AMPK action in the hypothalamus. In addition, clinical reports demonstrated an increase in the mammalian target of rapamycin (mTOR) due to metformin, which induces appetite suppression. mTOR acts as a downstream target for AMPK and is involved in facilitating the expression of leptin. These findings support the suggestion of adipose signals acting as secondary messengers, which can induce food intake by metformin (14).

Metformin is also involved in increasing insulin sensitivity. Insulin regulates adiposity by acting as a signal for energy status. Hyperinsulinemia can cause a decrease in blood glucose levels. This leads to stimulating specific neuronal pathways, which induce an increase in eating and reduce satiety. This characteristic counteracts with metformin-insulin relation mentioned above (12). Also, insulin mainly acts as an anabolic hormone. It induces the storage of fat in peripheral tissues. However, it also shows the anorectic effects of leptin by binding to its receptors present in the hypothalamus and cause the suppression of AMPK. Insulin resistance in the brain is also related to obesity, i.e., higher the resistance, higher is the AMPK activity, and lower the presence of pro-opiomelanocortin (POMC) in the hypothalamus (15).

Therefore, a decrease in insulin resistance leads to an improvement in appetite regulation. In addition, it helps enhance the "glucose-specific changes" during appetite regulation, stimulates the anorectic signaling mechanisms in the hypothalamic region, and causes a reduction in hunger. Due to its ability to enhance leptin sensitivity in the hypothalamus as well as improving insulin sensitivity in the whole body by 20-30%, it can be assumed that other signals involved in the regulation of food intake in the brain, e.g., peptide tyrosine (PYY), cholecystokinin (CCK), GLP-1, among others can also be stimulated by metformin (12).

2-4 Gut-mediated signals inducing satiety

As a reaction to food intake, the production of a hormone called GLP-1 (Glucagon-like peptide-1) occurs in the L-cell of the GIT. This hormone is also produced in the brain stem, mainly in the NTS cell bodies. GLP-1 specifically causes a reduction in the appetite due to its action on the vagal afferent nerves that extend towards NTS and causes a direct decrease in AMPK activity in the hypothalamus, which in turn increases the POMC levels. As a result, gastric motility is slowed down by high GLP-1 levels. This causes a considerable reduction in the carbohydrate absorption and circulation of glucose (16).

A study conducted on rats involving the transection of their midbrains to examine neural pathways leading from hindbrain to hypothalamus revealed that the NTS's sole activity is not enough to decrease food intake by and leptin and GLP-1. These outcomes strongly suggest that other phenomena like neural and circulating factors possibly help food intake regulation (17).

Furthermore, mettformin elevates the level of GLP-1 either by inhibiting dipeptidyl peptidase-IV (DPP-IV), an enzyme involved in the degradation of GLP-1, or by causing an alteration in muscarinic receptors gastrin-releasing peptide related pathways. This activity of metformin possibly causes the reduction of hunger as well as carbohydrate absorption. In addition, variations in the gut microbiota induced by metformin can also be partially responsible for enhanced GLP-1 levels (18). Enterocytes are directly affected by metformin, and it decreases the glucose uptake from the intestines to blood circulation. It is also involved in regulating energy homeostasis and insulin activity by changing the gut's immune signaling. Therefore, as metformin has no direct effect on PYY and CCK, an enteroendocrine mechanism involving enhanced levels of GLP-1 and some possible alterations in the gut can bring about a significant change in body weight (17).

Previous reports showed that when co-prescription of "metformin with DPP-IV inhibitors (a GLP-1 receptor agonist)" is given to the patients, weight loss glycemic control is increased (18).

2-5 The Action of Metformin to Increase Fat Metabolism

Metformin is also involved in fat metabolism in addition to its potential role in weight loss. Metformin plays a vital role in decreasing the levels of circulating lipids as well as hepatic lipid concentration. After metformin treatment, a reduction in hepatic steatosis occurs, showing consistency with the fat oxidation due to AMPK and lipogenesis reduction (19).

A metabolic pathway is stimulated when AMPK is activated, which initiates phosphorylation of "acetyl-CoA carboxylase (ACC)," which leads to the reduction of "malonyl-CoA levels" and elevation in activity of "carnitine palmitoyltransferase-1" to increase fat oxidation in mitochondria. Furthermore, AMPK also causes inhibition of lipogenic gene expression of certain enzymes in the liver, reducing lipids' storage. These enzymes include fatty acid synthase, 3-hydroxy-3-methylgutaryl-CoA reductase, and acetyl-CoA carboxylase (ACC) (20).

According to research studies, inactivation of thyroid hormone receptor-4 in an AMPK-related manner occurred due to metformin activity, which caused the reduction in expression of stearoyl-CoA desaturase 1 (SCD1). This enzyme plays a vital role in forming monounsaturated species of ceramide and diacylglycerol during the metabolism of saturated fatty acids. Therefore, reduced levels of this enzyme primarily caused reduction in fat mass and elevation in insulin sensitivity, that ultimately leads to the enhanced oxidation of lipids and reduced lipogenesis (17,20).

Metformin activity on fat metabolism can also be affected by exercise. A recent report showed that improvement in the glycemic control, liver diacylglycerol content and de novo lipogenesis decreases when metformin is given. Skeletal muscle plays a vital role in glucose uptake due to insulin stimulation, and the main enzyme involved in the regulation of energy metabolism is AMPK. Metformin causes an increase in "AMPK activity" in the skeletal muscles. This activity enhances GLUT-4 transporters, hexokinase II, and mitochondrial biogenesis (21).

During exercise, the body relies on fats as a source of energy as compared to rest conditions. AMPK activity in skeletal muscles is the key mechanism to increase this consumption of lipids. Overweight individuals with a healthy body were given metformin for 7-10 days, enhancing lipids' oxidation. However, exercise intensities varied in these individuals. Therefore, it presented a possibility of improving fat usage in skeletal muscles due to metformin (2).

Although the long-lasting effects of metformin may be uncertain about fuel adaptations during exercise training, it is partially involved in the inhibition of cardiorespiratory fitness and oxidation of fats in pre-diabetic adults. Therefore, for proper prevention of diabetes, further studies need to be done to elaborate on the roles of metformin in skeletal muscles during exercise (7).

2-6 Effect of Metformin on Circadian Rhythm

Homeostatic mechanisms concerning meal size influence food intake. Studies reported that environmental factors, social gatherings, and diurnal rhythms majorly control the number of meals. The circadian system mainly controls the feeding behavior in a person. This rhythm is made of a central clock and oscillators in the brain and peripheral tissues respectively (22).

Circadian rhythm is also associated with obesity and type 2 diabetes progression. In another study, it is reported that metformin treatment amplified the expression of "adipose-derived circadian locomotor output cycles kaput (CLOCK), brain and muscle aryl hydrocarbon receptor nuclear translocator-line 1 (BMAL1), and period (PER) 2" after AMPK is activated (23).

Additionally, metformin is also involved in enhancing the leptin levels and stimulating AMPK activity in skeletal muscles and the liver, as reported in a study. Activation of an enzyme known "liver casein kinase 1-a and skeletal muscle casein kinase 1-e" is associated with these results. It is strongly suggested the role of metformin in altering the circadian clock pathways which led to energy metabolism regulation. Further clinical study on chronotherapy will help understand and discover more options for the treatment of obesity-related diseases (2, 24).

2-7 Metformin and Microbiome: A Future Perspective

Metformin buildup in the gastrointestinal tract is expected to affect epithelial brush border metabolism and those of the gut's diverse bacterial flora. Multiple factors are assumed to be playing both causal and correlative impacts in the distribution of microbial flora among obese and non-obese populations (25). The obesity syndrome phenotype is adversely linked with several prevalent multiple intestinal species. Ackermansia treatment improves metabolic characteristics in mice, and metformin enhances the relative abundance of Ackermansia, according to studies (26).

One study showed that Metformin treatment caused alterations in phyla Bacteroides and Firmicutes (27). A decline in bacteria that generate short-chain fatty acids acetate and butyrate, for example, are being studied as critical signaling metabolites that influence hepatic gluconeogenesis as well as fatty acid metabolism. Increases in SCFAs are considered to lead towards lower hepatic gluconeogenesis, lower adipocyte release of free fatty acids, and appetite suppression via the incretin system (28).

Metformin therapy in rats was found to alter the gut microbiota and increase the number of bacteria that metabolize SCFA (21). Furthermore, in a rat model of T2D, metformin-mediated changes in intestinal Lactobacillus sp. have also been demonstrated to lower hepatic glucose production by restoring average intestinal glucose sensing and expression of sodium-glucose cotransporter-1 (SGLT1) (29).

Human studies have shown that it has a positive impact on the microbiota. According to a new double-blind, randomized control research, metformin dramatically changed the relative abundance of various bacterial strains. Stool samples were given to mice, who showed improved metabolic parameters and increased expression of the bacterial genes involved in "SCFA metabolism" after receiving metformin treatment (30)

These findings raise the intriguing possibility that metformin's beneficial effects, including its weight-loss effects, result from a changed microbiome.

Conclusion

Studies reported that metformin is considered a viable and effective pharmacological approach for weight loss in overweight and obese people via neuronal appetite pathways and fat metabolism

regulatory pathways. Clinical studies suggested that metformin in combination with exercise or other weight loss drugs promote weight loss. Research also indicated other appetite suppressing medications such as topiramate, lorcaserin, and phentermine along with metformin also seems logical and clinical data reported that these drugs gained FDA approval and their results and effects in obese people are robust.

Moreover, future research work is required to evaluate multiple metformin doses on the appetite mechanism of action to understand how metformin effectively reduces weight in non-diabetic and obese individuals.

Conflict of Interest

There is no conflict of interest.

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