How Does Metformin Work in the Treatment of Obesity? A Review

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Abstract. The rising prevalence of obesity is associated with a higher risk of developing cardiovascular diseases. Because it can induce weight loss, metformin, a long-used drug for treating diabetes, is used as an off-label medication for the treatment of obesity. However, the mechanism underlying this effect of metformin is unclear, especially in people without diabetes. This review discusses the recent evidence on the mechanisms of action of metformin in the treatment of obesity. Articles related to the topic were identified using search engines such as PubMed, ScienceDirect, and Google Scholar. We included articles that were published in English between January 1, 2015, and June 30, 2021. The ability of metformin to induce weight loss may involve several mechanisms: the neurohormonal pathway, the metabolic pathway, or gut microbiome activity. The most recent evidence relates to the effects of metformin on the gut microbiome. Metformin may inhibit the growth of non-butyrate-producing bacteria—such as Escherichia coli—and may promote the growth of butyrate-producing bacteria. Butyrate increases insulin sensitivity, thereby lowering insulin level and suppressing appetite via the incretin system. Several hypotheses regarding metformin's antiobesity effects have been proposed, but further investigations are needed, especially on the effectiveness and tolerability of metformin for euglycemic people with obesity.

Keywords: Obesity · Metformin · Off-Label Medication

1 Introduction

Obesity is a metabolic disease whose prevalence has been increasing each year. Obesity is also a risk factor relating to the increasing prevalence of noncommunicable diseases such as cardiovascular disease, cancer, diabetes, and others [1]. More than 1.9 billion adults (39%) worldwide were considered to be overweight in 2016, and 650 million of these were considered to be obese (13%) [2]. According to the 2018 national data, the prevalence of obesity among Indonesian adults is 21.8% and had increased from 14.8% in 2013 [3].

Weight loss has been shown to reduce the incidence of comorbid diseases associated with obesity and overweight such as type 2 diabetes and cardiovascular diseases. However, no monotherapy is effective for treating obesity, and the management of obesity and

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overweight include low caloric diet, physical activity, antiobesity agents, and/or surgery (in certain cases) [4, 5].

Several medications have been approved as antiobesity agents. Two agents are most frequently prescribed in Indonesia: orlistat and diethylpropion. Orlistat is an antiobesity agent that acts by inhibiting lipase in the stomach and pancreas, which causes hydrolysis and inhibition of triglyceride absorption, therefore reducing fat uptake by the body [6]. Some trials have concluded that orlistat is effective for losing and maintaining weight loss [7]. Orlistat also improves insulin sensitivity and low serum glucose level. However, the use of orlistat can induce unpleasant side effects, and gastrointestinal side effects such as fatty/oily stool, fecal urgency, increased defecation, frequent flatus, and flatus with discharge are the main reasons for discontinuation of orlistat use [7]. Diethylpropion, a sympathomimetic agent, acts as an antiobesity agent by reducing appetite in the central nervous system [8]. A randomized controlled trial (RCT) showed that diethylpropion use of 50 mg twice daily induced an average weight loss of 9.8% within 6 months [9]. Diethylpropion is indicated only for short-term use because of its high potential for side effects and abuse. The known side effects of diethylpropion are dry mouth, increased pulse and blood pressure, insomnia, constipation, and other sympathomimetic effects [8].

In addition to these drugs, other drugs that are not indicated for obesity are suspected of having antiobesity effects and are used as off-label medications. Metformin is a biguanide drug often prescribed in the treatment of type 2 diabetes [10]. The favorable side effect of metformin—weight loss—has attracted the attention of researchers who have explored its efficacy as an antiobesity agent. Igel et.al. Considered this medication as "an old therapy that deserved a new indication for the treatment of obesity" [11]. A cross-sectional study with 100 participants with diabetes who underwent treatment with metformin found that 44% experienced weight loss [12]. The potency of metformin as an antiobesity agent was also studied in people without diabetes. A preclinical study showed that the administration of a combination of meniran (Phyllanthus niruri Linn.) water extract and metformin controlled weight gain and decreased the Lee index in rats [13].

A study in Iran included 36 obese women without diabetes reported a greater reduction in body mass index (BMI) in the metformin group, who received metformin twice per day and ate a low-calorie diet for 2 months, compared with 16 participants who received a placebo and ate a low-calorie diet. The reductions in BMI were 4.5% and 2.6%, respectively [14]. Abrori et al. found that slow-release metformin was more effective in inducing weight loss than regular metformin in obese people [4]. A recent retrospective cohort study reported that the use of metformin monotherapy as an adjunct to lifestyle modifications in patients with obesity was associated with clinically meaningful weight loss in those with type 2 diabetes or prediabetes and those without either condition [15].

Despite the evidence supporting an antiobesity effect of metformin, the mechanisms of action remain elusive. This review summarizes the recent evidence from the literature on the mechanisms of action of metformin in the treatment of obesity.

2 Method

Articles related to the topic were identified using search engines such as PubMed, ScienceDirect, and Google Scholar. Keywords used were "obesity" and "metformin". In line with the aim of this review we included articles that were published in English between January 1, 2015, and June 30, 2021.

3 Result and Discussion

3.1 Pathophysiology of Obesity

Obesity is a complex disorder involving appetite regulation and energy metabolism that can be controlled by several biological factors [1]. Genetic factors are involved in the development of this disease. Physiologically, obesity is defined as a state of abnormal or excessive accumulation of fat in adipose tissue that can interfere with health [5]. The World Health Organization defines obesity as excessive fat accumulation that might impair health and is diagnosed at a BMI $\geq$ 30 kg/m2. However, considering the differences between ethnic groups, the WHO Western Pacific Region recommends a BMI cutoff point of $\geq$ 25 kg/m2 for the Asian population.

Obesity starts as an imbalance between caloric intake and expenditure. The excess calories are stored as triglycerides in fat cells in adipose tissue, especially in adipose organs such as subcutaneous fat, visceral and pelvic fat, and the perimuscular, perivascular, and periosteal areas. This fat accumulation eventually results in weight gain. Excess fat deposits can lead to metabolic syndrome, which includes dyslipidemia and insulin resistance, processes that can lead to adverse physiological effects without intervention [4, 5, 16]. Excess energy intake that is not balanced by expenditure over the long term can lead to weight gain and obesity [16].

Excess energy is stored in adipocytes as triglycerides, which are broken down into free fatty acids and then transported in plasma to sites where they are metabolized. Over a period of time, the increased free fatty acid level leads to lipid accumulation in the liver and skeletal muscle, which stimulates lipolysis, glycogenolysis, gluconeogenesis and, finally, hyperglycemia [17].

Obesity is also accompanied by increased numbers of macrophages and other immune cells in adipose tissue, in part because of tissue remodeling in response to apoptosis of adipocytes. These immune cells secrete proinflammatory cytokines, which contribute to the insulin resistance and elevated free fatty acid level that often accompany obesity [17, 18].

3.2 Pharmacology of Metformin

Metformin is a biguanide drug that acts as an antihyperglycemic agent to improve glucose tolerance by lowering both basal and postprandial plasma glucose levels. Metformin is widely prescribed as a first-line pharmacological treatment for type 2 diabetes. Metformin works by inhibiting hepatic glucose output through gluconeogenesis and glycogenolysis inhibition; therefore, the liver is considered to be the main site of

metformin action [10, 19]. One hypothesis is metformin administration results in the activation and phosphorylation of AMP-activated protein kinase (AMPK) in the liver and skeletal muscle, which then causes a wide range of pharmacological effects such as stimulation of fatty acid oxidation, inhibition of cholesterol and triglyceride synthesis, and stimulation of glucose uptake into skeletal muscle [10, 19].

Another hypothesis proposed of the mechanism of action of metformin is its action in the gut mucosa. One study suggested that the gut is likely to be at least as important as the liver in the role of metformin in the management of type 2 diabetes [10]. About 50% of metformin is absorbed by the gut, and the concentration of the remaining unabsorbed metformin is 30–300 times higher in the gut mucosa than in the plasma. An experimental study of animals found that the remaining metformin has a wide range of effects including delayed intestinal glucose absorption, augmented lactate production by enterocytes, increased secretion of gastrointestinal hormones or peptides containing glucagon-like peptide 1, increased bile acid metabolism, and potential effects on intestinal microbiota [10, 20].

3.3 Mechanisms by Which Metformin Promotes Weight Loss

Several mechanisms has been proposed to explain how metformin can lead to weight loss; these involve the neurohormonal pathway, metabolic pathway, and gut microbiome activity.

3.3.1 Neurohormonal Pathway

A study of diabetic mice administered oral metformin reported an increase in the concentration of the drug in the cerebrospinal fluid, which suggests that metformin can penetrate the blood–brain barrier and enter the hypothalamus. The hypothalamus is highly innervated by neurons that regulate feeding and appetite, and it is possible that metformin can directly affect these neurons. As mentioned above, metformin acts through the activation and phosphorylation of AMPK in the liver, which results in inhibition of hepatic glucose production. Metformin appears to stimulate weight loss by acting in the hypothalamus to reduce food intake by decreasing the expression of the orexigenic peptides, neuropeptide Y and agouti-related protein (AgRP), and increasing the expression of POMC [11, 21].

Metformin has also been shown to increase leptin sensitivity in the hypothalamus, as indicated by lower circulating leptin level and elevated leptin receptor expression, which later reduce AMPK activity and thereby exert an anorectic effect [7, 22].

3.3.2 Metabolic Pathway

Metformin acts by increasing insulin sensitivity. Increased insulin sensitivity has been hypothesized to alleviate postprandial hypoglycemia, which may lessen hypoglycemia-induced hunger and carbohydrate craving, thereby reducing food intake and eventually lowering blood glucose level. Reduced blood glucose level may also be caused by decreased intestinal glucose absorption and inhibition of gluconeogenesis, which ultimately contribute to weight loss. Moreover, by increasing fat oxidation and decreasing lipid production, the low blood glucose state reduces lipid deposition in the liver and

skeletal muscle. These mechanisms may explain the potential mechanism by which metformin assists in weight loss [22, 23].

3.3.3 Gut Microbiome Activity

Another mechanism underlying the effects of metformin involves its influence on the gut microbiome [15]. A different pattern of gut flora has been found in individuals with obesity and/or prediabetes compared with individuals without obesity or prediabetes. For example, the gut flora appears to be in a state of dysbiosis in people with obesity and/or prediabetes. Obesity and type 2 diabetes mellitus are associated with a lack of diversity in the gut microbiome [24]. Certain bacteria that produce short-chain fatty acids (SCFAs), such as acetate and butyrate, are found in smaller amounts in the gut of people with obesity.

The gut flora is thought to be affected by the accumulation of metformin in the gastrointestinal tract [21]. Metformin can alter the gut microbiome by inhibiting the growth of nonbutyrate-producing bacteria (such as Escherichia coli) and increasing the growth of butyrate-producing bacteria (such as Akkermansia muciniphila) in people with prediabetes and obesity, which may restore the normal balance. The growth of butyrate-producing bacteria increases the amount of butyrate, which is then absorbed into the circulation where it improves insulin sensitivity along with metformin and ultimately lowers insulin level [24].

Metformin treatment in rats was found to modulate gut microbiota and increase the number of SCFA-metabolizing bacteria. Increased SCFAs are thought to contribute to decreased hepatic gluconeogenesis, reduced FFA release from adipocytes, and suppression of appetite via the incretin system [21].

4 Conclusion

Metformin is frequently used off-label as a treatment for obesity. This review has summarized the recent findings that reveal metformin's mechanism of actions in weight management. Despite the hypotheses to explain how metformin assists in weight loss in people with obesity, further research is needed to provide the evidence base for the use of metformin for treating obesity.

Author's Contribution. MSS collected the data, analyzed the findings and drafted the manuscript. RR designed the concept of the study, analyzed the results and worked on the manuscript writing. Both authors agreed with the final version.

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