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COMMENTARY

Effects of metformin on blood glucose levels and bodyweight mediated through intestinal effects

Biguanides, including metformin, are drugs with a long history. They have been used to treat patients with type 2 diabetes since the 1960s. However, biguanides have not been widely used since the 1970s when one of the biguanides, phenformin, was found to cause lactic acidosis. The United Kingdom Prospective Diabetes Study (UKPDS) showed that metformin not only had hypoglycemic action equivalent to sulfonylureas and insulin, but also significantly lowered mortality and the incidence of cardiovascular disease compared with sulfonylureas or insulin treatment[1], while exerting a cardioprotective effect that lasted 10 years after the study ended[2]. Metformin is also inexpensive. For these reasons, metformin is currently the first-line drug in the A Consensus Report "Management of Hyperglycemia in Type 2 Diabetes" by the American Diabetes Association/the European Association for the Study of Diabetes[3].

Metformin mainly acts on the liver and inhibits mitochondrial respiratory chain complex I, leading to an increased intracellular adenosine monophosphate (AMP)/adenosine triphosphate ratio. As a result, AMP-activated protein kinase (AMPK), an energy sensor, is activated to inhibit gluconeogenesis[4]. Recently, it was reported that metformin exerts an AMPK-independent inhibitory effect on gluconeogenesis by suppressing glucagon signaling in the liver[5]. In skeletal muscle, AMPK activation by metformin facilitates the transport of glucose transporter 4, one of the glucose transporters, to the surface of the cell membrane, leading to increased glucose uptake[6]. Thus, metformin lowers blood glucose levels by inhibiting gluconeogenesis and improving insulin sensitivity without facilitating insulin secretion (Figure 1). Because of these mechanisms of action, metformin characteristically does not increase bodyweight or the frequency of hypoglycemia when used alone.

Metformin also acts on various organs other than the liver and muscle. The intestine is considered to be a target organ of metformin, and it has long been known that metformin suppresses glucose absorption in the small intestine. Recently, it was reported that metformin contributes to the improvement of blood glucose levels by altering intestinal flora[7]. Metformin also increases the secretion of glucagon-like peptide-1 (GLP-1), an incretin, from enteroendocrine L cells by activating AMPK in the intestine[8]. Increased GLP-1 secretion not only leads to the improvement of blood glucose levels, but also contributes to weight suppression through appetite suppression in patients with type 2 diabetes. Coll *et al.*[9] showed in a human study that metformin increases the blood concentration of growth differentiation factor 15 (GDF15) in a dose-dependent manner. GDF15 acts on the feeding center in the brain to decrease appetite, causing weight loss[10]. Because the GDF15 level in the blood is increased in response to stress and tissue injury, it has been suggested that high levels of GDF15 are associated with the weight loss observed in patients with many chronic diseases, such as cancer. Furthermore, it was reported that mice deficient for glial cell-derived neurotrophic factor receptor alpha-like (GFRAL), which is the receptor for GDF15, become bulimic under stress conditions, and are resistant to anorexia and weight loss induced by chemotherapy. Coll *et al.*[9] showed that metformin induces GDF15 gene expression in the intestine and kidney in mice, and increased blood levels of GDF15 decrease bodyweight and increase energy consumption through glial cell-derived neurotrophic factor receptor alpha-like GFRAL in high-fat diet-fed mice.

Thus, metformin acts in a multifaceted manner on blood glucose levels and bodyweight through many organs, and the elucidation of various mechanisms of action is expected to progress in the future.

DISCLOSURE

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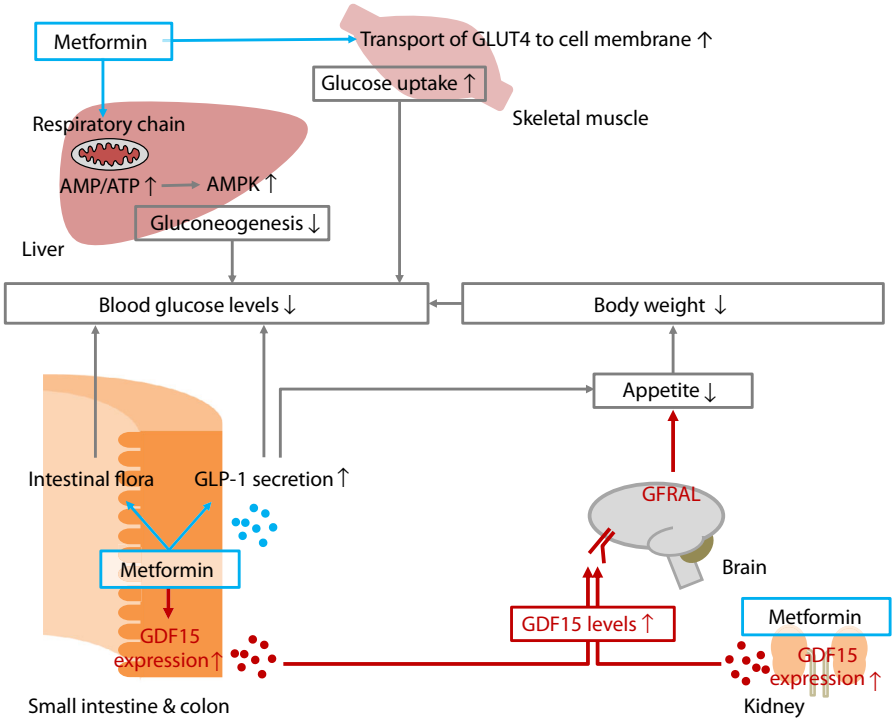

Figure 1 | Mechanisms by which metformin reduces blood glucose levels and bodyweight. Metformin lowers blood glucose levels by inhibiting gluconeogenesis and increasing insulin sensitivity. Metformin also acts on the intestine, and reduces blood glucose levels and body weight by various mechanisms. AMP, adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; GDF15, growth differentiation factor 15; GFRAL, glial cell-derived neurotrophic factor receptor alpha-like; GLP-1, glucagon-like peptide-1; GLUT4, glucose transporter 4.

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