Review Article

The Role of SGLT 2 Inhibitor in the Therapy of Obesity

Abstract

Obesity is an abnormal or excessive fat accumulation that presents a risk to health, including hypertension, stroke, kidney disease, atherosclerosis, type 2 diabetes mellitus, heart disease, and sleep apnea. Obesity can be caused by various aetiology, such as genetics, lifestyle, psychology, treatment, and more. Treatment of obesity is needed to prevent these further complications. According to various studies, SGLT 2 inhibitor has shown effectiveness in losing weight. This review article aims to describe the effectiveness and safety of SGLT 2 inhibitors in the treatment of obesity. It is expected SGLT 2 inhibitor can be considered in the administration of therapy in patients with obesity.

Keywords: Obesity, SGLT 2 inhibitor, Weight loss

1. Introduction

Obesity is a condition where body fat accumulates abnormally or excessively which presents a health risk. In Asia Pacific, obesity isdefined as a body mass index (BMI) over 25 kg/m^2. Various complications may present from obesity including hypertension, stroke, kidney disease, atherosclerosis, type 2 diabetes mellitus, heart disease, and sleep apnea. Furthermore, obesity can affect individual economies and psychosocial factors.[1–4]

According to World Health Organization (WHO), in 2006 it was reported that more than 650 million adults were obese and 124 million children aged 5-19 years were obese. Based on the data distribution, obesity is no longer a health problem in developed countries, but also a problem in developing countries. In Indonesia, the prevalence of obesity has shown an increase from 14,8% in 2013 to 21,8% in 2018.[5,6]

Obesity can be caused by disturbances in the central regulation that regulates appetite. This regulation is called the brain-gut axis, while in normal conditions the signal from the gut including ghrelin, neuropeptideyy (PYY), cholecystokinin (CCK), *glucagon-like peptide* (GLP-1) and some mechanoreceptor by distention, pancreas by insulin, and adipokine hormones such as adiponectin and leptin. These signals are integrated into the hypothalamus to regulate energy balance. The melanocortin leptin pathway is activated via the leptin receptor (LEPR) and insulin receptor (INSR) on the surface of arcuate nucleus neurons.[7]

Furthermore, the signal is divided into 2 feedback groups, pro-opiomelanocortin and cocaine and amphetamine-related transcript neurons (POMC/CART) that regulate anorexigenic peptides and the other group regulates the production of orexigenic peptides such as agouti-related peptide (AGRP) and neuropeptide-Y (NPY).After the post-translational process occurs through pro-convertase 1 & 2 (PC1 & PC2), it produces the hormones α- β- and γ-melanocyte stimulating hormone (MSH) and β- endorphins.AGRP dan

α-MSH binds to the melanocortin-4 receptors (MC4R) on the paraventricular nucleus in the hypothalamus. Figure 1[7]

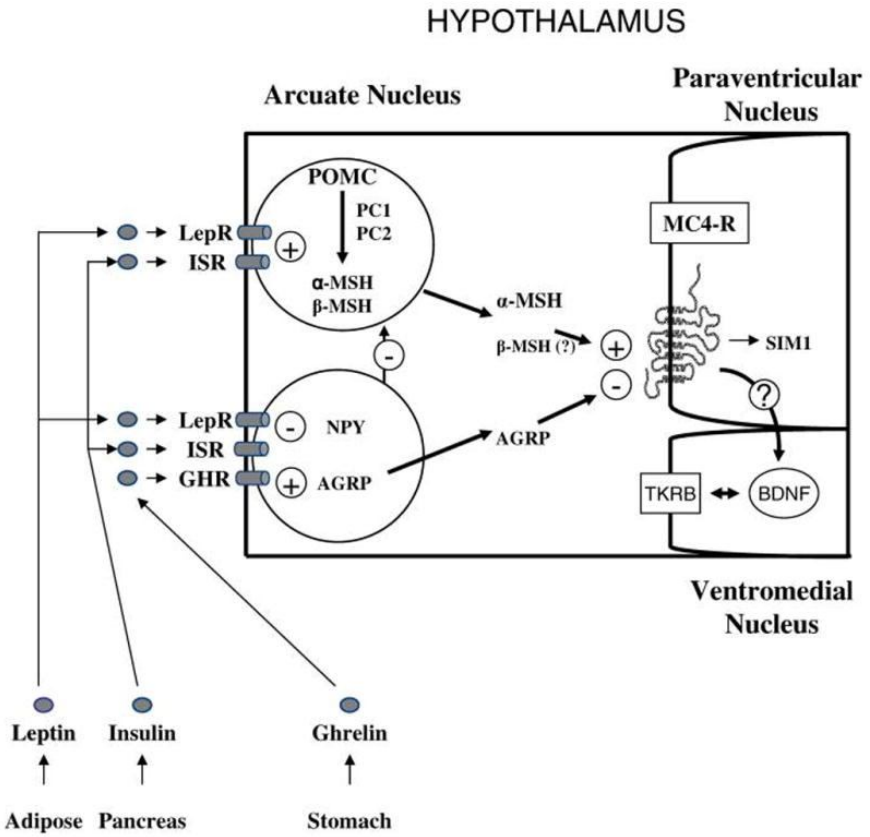

Figure 1. Melanocortin Leptin pathway[7]

Genetic mutations in these pathways can affect appetite and weight disorders, such as the LEP and LEPR genes which encode leptin and receptors. If mutations occur in these genes can lead to leptin and receptor deficiencies resulting in satiety disorders, hyperphagia and obesity.LEPR disorders can also interfere with thyroid hormone function, growth, puberty and fertility. Mutations in POMC lead to hypoglycaemia in neonates, red patches of hair and hyperphagia in late childhood.MC4R mutations cause satiety disorders and are reported to be the triggers for obesity, metabolic syndrome and hypertension in children. Deficiency of PC1 & PC2 can trigger obesity accompanied by growth, gonadotropic, intellectual and developmental disorders.[8–11]

In addition to disruption of central regulation, obesity can be caused by lifestyles, such as high consumption of fast food, high sugar and fat dietary, skipping breakfast, less physical activity, and sedentary behaviour. These lifestyles can lead to increased storage of fat in adipose above normal capacity. [12–14]

In diagnosing obesity, several factors such as lifestyle, mental disorders, medical history, neuroendocrine and genetics must be considered. Lifestyle histories such asdietary, physical activity, sedentary behaviour, and circadian rhythm. Medication history including antidepressant (*selective serotonin reuptake inhibitor*/SSRI), antipsychotic, corticosteroid, insulin and sulfonylurea, beta blocker, alpha-blocker, and proton pump inhibitorcan be

contributed to weight gain. Family history of obesity, growth and developmental history before 5 years old such as hyperphagia, intellectual disorder, hearing and vision disorder, and extremity raises the suspicion of a genetic disorder. Neuroendocrine disorders such as Cushing syndrome, thyroid disorder, polycystic ovarian syndrome (PCOS), and growth hormone deficiency. Mental disorders such as depression, binge eating, and other eating disorder can contribute to obesity. [15]

Obesity is diagnosed based on BMI calculations of more than 25 kg/m^2 based on Asia Pacific or more than 30 kg/m2 based on WHO. BMI measures a body'sheight and weight, then calculates the ratio of body weight in kilograms divided by height in meters squared. Several other measurements can be used in diagnosing obesity such as waist circumference and skin folds.However, the results of these examinations are influenced by other factors such as the distribution of fat and skeletal muscle. [16–18]

The increased storage of fat in adipose causes adipose tissue to release several proteins such as adipokines, resistin, leptin, and tumor necrosis factor-α (TNF-α) which play a role in the emergence of complications in obesity. Adipokine cause activation of the sympathetic nervous system, which in turn activates the renin-angiotensin-aldosterone system (RAAS) which causes an increase in blood pressure.In addition, leptin resistance can lead to hyperleptinemia which can trigger the sympathetic nervous system, resulting in hypertension.There is an increase in sodium reabsorption in the kidney causing impaired excretion of water and salt also resulting in hypertension. Furthermore,hypertension can reduce the glomerular filtration rate (GFR) causing chronic kidney disease. [19,20]

Insulin resistance occurs in obese patients due to several factors including chronic systemic inflammation caused bythe excessive release of hormones that activate pro-inflammatory adipose tissue leading to insulin resistance in the liver and periphery, adipocyte dysfunction, oxidative stress, endothelial reticulum stress, degeneration, hypoxia, and genetic disorders that induce insulin resistance, resulting in further type 2 diabetes mellitus. Increasedlevels of *non-esterified fatty acids* (NEFA) in obesity can cause insulin resistance and decreased functions of pancreatic beta cells. Dysfunction of pancreatic beta cells causes dysregulation of blood glucose levels resulting in type 2 diabetes mellitus. [21–23]

Several adipokines initiate and promote systemic inflammation such as leptin, resistin, retinol-binding protein 4 (RBP4), angiopoietin-like protein-2 (AngptL-2), IL-6 and monocyte chemoattractant protein (MCP-1), associate with endothelial dysfunction, hypercoagulation, and insulin resistance plays a role in the occurrence of atherosclerosis.Hyperleptinemia increases inflammation through its potent chemoattractant properties of monocyte/macrophage cells, thereby releasing mediators TNFα, IL-6, and MCP-1, and increasing the expression of adhesion molecules VCAM-1, ICAM-1 and E-selectin causing monocytes to be attracted to the endothelium, increasing vascular permeability, and formed atheroma formation. In addition, leptin can cause the production of reactive oxygen species (ROS) leading to endothelial dysfunction and interfering with nitric oxide (NO) function, resulting in vasoconstriction and thrombosis.Leptin can also cause disturbances in myocardial relaxation which trigger atherosclerotic heart disease. Several other adipokines play a role in atherosclerosis, such as adiponectin, resistin, adipocyte fatty acid binding protein (A-FABP), omentin-1, and chemerin.[24,25]

In addition to heart disease, stroke disease can also develop through the further process of atherosclerosis, while free fatty acids are still being hydrolysed and transported to the periphery, this will increase body fat and increase the release of adipokines and hormones that activate pro-inflammatory causes this process to continue. Furthermore, there is an increase in NF kB activity, which causes chronic inflammation to continue and accelerates atherogenesis and increases in MAP kinase activity which causes impair glucose metabolism. This process can develop and contribute to the occurrence of complications such as stroke, myocardial infarction.[26]

Accumulation of fat causes collapsesin obese patients, especially in the upper airways, which can lead to obstructive sleep apnea (OSA).It is also triggered due to stimulation of the sympathetic nervous system, inflammation, endothelial dysfunction, hypoxia and oxidative stress which correlate between obesity and OSA.Furthermore, OSA can cause sleep and hormonal disturbances, especially melatonin, resulting in circadian rhythm disturbances. Together with excessive intake may predispose to type 2 diabetes mellitus and metabolic syndrome.In addition, OSA can cause activity disturbances due to excessive sleepiness during the day.OSA can lead to other diseases such as hypertension, insulin resistance, cardiovascular disease, dyslipidemia, and others due to oxidative stress, inflammation, and metabolic dysregulation.[27,28]

Comprehensive obesity management is necessary to prevent complications. According to the European Guideline of Obesity 2015, managementof obesity includesweight loss, maintenance and prevention of weight regain, and lifestyle changes such as diet and physical activity.In addition, obesity managementcannot only focus on reducing body weight but also improves waist circumstance, body composition, maintains fat-free mass and reduces fat mass. Several treatments can be done such as diet, physical activity, diet, medicine, cognitive therapy and surgery. [29]

Medication therapy is recommended for individuals with obesity accompanied by co-morbidities, such as hypertension, type 2 diabetes mellitus, and OSA. Various types of drugs are used, for example, orlistat, lorcaserin, topiramate, bupropion and liraglutide. However, sodium-glucose cotransporter-2 inhibitors (SGLT 2 inhibitors) have shown promising results in weight loss.This article aims to describe the effectiveness and safety of SGLT-2 inhibitors in the treatment of obesity. [29]

2. Glucose Physiology in Kidney

In 24 hours, an estimated 180 g of glucose is filtered at a 180 L/day GFR. Glucose is completely reabsorbed in the proximal tubule via the SGLT cotransporter enzymes, SGLT 1 and SGLT 2 in the S1, S2 and S3 segments of the proximal tubule in the kidney. First, glucose passes through the atypical membrane and enters the cell via the SGLT so the glucose accumulates inside the cell and carries out intracellular metabolism. Second, glucose leaves the cell towards the plasma across the basolateral membrane facilitated by GLUT2.In addition, there is a Na+/K+ pump on the basolateral membrane to move sodium from the intracellular to the plasma. Figure 2 [30,31]

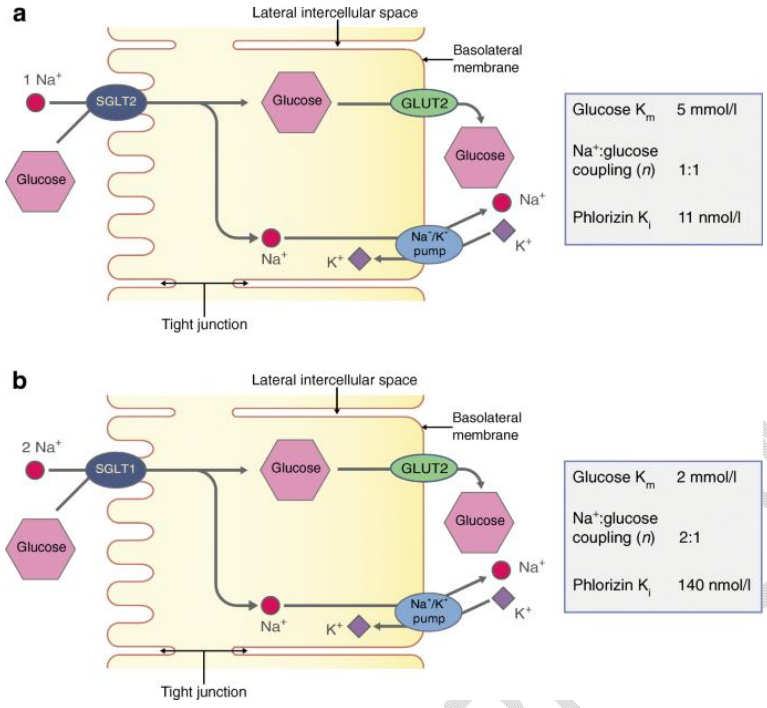

Figure 2. The Process of Glucose Reabsorption in the Kidney's Proximal Tubule[31]

SGLT 2 is produced in the proximal tubule of the kidney, while SGLT 1 is produced in the further part of the proximal tubule of the kidney and small intestine which plays another role in glucose absorption in the intestine. SGLT 2 is focused on the S1 and S2 segments of the proximal tubule, whereas SGLT1 is on the S3 segment of the proximal tubule and in the membrane of mature enterocytes at the brush border.SGLT 2 is focused on the S1 and S2 segments of the proximal tubule, while SGLT1 is on the S3 segment of the proximal tubule and in the membrane of mature enterocytes at the brush border.[32,33]

3. SGLT 2 vs SGLT 1

SGLT 1 is encoded by SLCA1, while SGLT 2 is encoded by SLC5A2. SGLT 1 has a high affinity, but a low capacity for glucose absorption. Normally, about 10% of glucose is filtered by SGLT1. While SGLT 2 has a low affinity, but a high capacity for glucose absorption and accounts for approximately 90% of filtered glucose reabsorption.[32,34,35]

Several studies reported the differences in SGLT 2 and SGLT 1 mutations. SGLT2 mutations cause glucosuria due to impaired reabsorption of glucose in the kidney, but hyperglycaemia does not occur. In addition, SGLT 3 expression has been reported, but it remains unclear. Whereas SGLT 1 and SLC5A1 mutations, congenital malabsorption of glucose and galactose occurs, especially in neonates, causing severe diarrhoea, malabsorption, dehydration, and death. This is because SGLT 1 has a function to absorb glucose and galactose in the small intestine resulting in malabsorption of glucose and galactose.[36,37]

Currently, SGLT 2 inhibitors have been recognized and applied in the treatment of type 2 diabetes mellitus and also included in the Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus in Indonesia in 2021, but not with SGLT 1 inhibitors. SGLT 1 inhibitors are still in doubt because of the "double-edged sword" effect, which has

the advantage of lowering blood sugar levels by inhibiting glucose absorption in the intestine and glucosuria, the effect of cardiac protection by inhibiting ROS production. However, SGLT 1 inhibitors have effects in the form of osmotic diarrhoea, correction of hypoglycaemia which is hampered due to impaired absorption of glucose in the intestine and ketoacidosis.[38–41]

4. SGLT 2 inhibitor

Apart from the effect of lowering blood glucose levels, SGLT 2 inhibitors have several other benefits such as improving lipid profiles, reducing albuminuria, and reducing systolic blood pressure. Cardioprotective effect due to natriuresis that lowers plasma volume, increasing haematocrit, so blood pressure can be lowered. Other effects include reducing the production of inflammatory cytokines from adipose tissue,reducing oxidative stress and AGES. [42,43]

Chronic hyperinsulinemia can lead to increased HPA axis activity, resulting in more cortisol being produced. Increased cortisol in plasma may develop into impaired glucose intolerance and metabolic syndrome, due to increased gluconeogenesis and adipose tissue lipolysis, and inhibits glucose uptake in muscle. Tofogliflozin has been confirmed that can reduce serum ACTH and cortisol levels, which concluded that SGLT 2 inhibitors influence the HPA pathway. Although the mechanism is still unclear. Several drugs have been reported to have a lowering effect on leptin levels, such as empagliflozin and dapagliflozin. However, the mechanisms are also not fully understood.[44,45]

SGLT 2 inhibitor has an antihypertension effect, although this effect is still unclear. Maybe due to decreased reabsorption of sodium, about 30-60% more sodium is excreted. Reduced levels of sodium in the plasma, causing a decrease in cardiac afterload, lead to improvements in atrial and ventricular coupling and cardiac efficiency. [46]

SGLT 2 inhibitors have been reported to show improvement in patients with heart failure by improving hemodynamics, improving myocardial energy supply, and the sympathetic and parasympathetic nervous systems. SGLT 2 inhibitor reduces intravascular volume, blood pressure, and sympathetic reflex and excessive neurohormonal regulation of intravascular volume and blood pressure without increasing heart rate. Ketone bodies which are useful as an energy source for the heart and the production of adenosine triphosphate (ATP) in the heart muscle also increased. SGLT 2 inhibitors also improve ejection fraction function and reduce infarctsize. In addition, SGLT 2 inhibitors reduce sympathetic nerve activity by inhibiting the vagus nerves in the liver at the rostral raphe pallidus, combined with a good oxygen supply to the myocardium and cardiac preload afterload by simply decreasing sympathetic activity and heart rate.[47]

Anti-inflammation effect of SGLT 2 inhibitor, especially against atherosclerosis. SGLT 2 inhibitor can reduce the inflammatory molecules in plasma, such as TNF-α, monocyte chemoattractant protein 1 (MCP-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), VCAM-1, intercellular adhesion molecule 1 (ICAM-1), IL-1β, and IL-6. Dapagliflozin shows that can reduces infiltration and induces M2 macrophages as a precursor to the development of atherosclerosis.[48]

SGLT2 inhibitors have another benefit in lowering uric acid levels in hyperuricemia patients by reducing urate reabsorption. Urate is reabsorbed in the S1 proximal tubule of the

kidney and excreted in the S2 segment. In the S1 segment, urate is reabsorbed via the URAT1 and GLUT9b transporters on the apical membrane and GLUT 9a transporters on the basolateral membrane. SGLT 2 inhibitor can suppress GLUT 9b, so it can inhibit urate from being reabsorbed and increase muscle excretion through urine.[49,50]

Uric acid is a pro-inflammatory mediator. La Grotta, et al study shows that SGLT-2 inhibitors can be lowering Il-6 levels, possibly mediated by decreased levels of uric acid and insulin. It can reduce low-grade inflammations, that contributed to cardiovascular events and microvascular complications. [51]

5. SGLT 2 Inhibitor in The Treatment of Obesity

The effect of weight loss is reported as an effect of SGLT 2 inhibitors, where glucose is excreted in the urine around 60-100g/day causing wasted calories.Glucose and insulin levels in the blood tend to be lower, causing the body's metabolism to shift to fat metabolism through the process of gluconeogenesis, suppress glucose oxidation, increased lipolysis, and increased fat oxidation, also ketogenesis. This leads to a further reduction in fat mass and body weight. [52]

Adipocyte function is also restored through SGLT2, causing a decrease in levels of leptin, visfatin, plasminogen activator inhibitor-1, increased adipocyte levels, and supports the process of lipolysis so that visceral fat is reduced. Apart from that, weight loss can also be caused by reduced fluid in the body due to the mechanism of reducing glucose.[53]

Various types of SGLT 2 inhibitor drugs have been reported to show promising results in weight loss, such as dapagliflozin, empagliflozin, canagliflozin, and ipragliflozin. Administration of 5 mg dapagliflozin per day for 28 weeks can reduce body weight by 2.8 kg. Administration of 25 mg empagliflozin per day for 24 weeks can reduce body weight by 2,2 kgand when combined with dietary restrictions of 360 kcal per day, it can reduce body weight by up to 5.7 kg. Administration of ipragliflozin 50 mg ipragliflozin per day before or after breakfast for 24 weeks can reduce body weight by 2,6 kg. In addition, waist circumference decreased by 2.9 cm and body fat mass decreased by 1.9 kg. [54–56]

Combination therapy between SGLT 2 inhibitors and other classes of anti-diabetic has drugs shown promising results. Administration of canagliflozin 100 mg or 300 mg per day combined with metformin 2000 mg per day for 104 weeks, both resultedin weight loss of 3.6 kg. The combination of 10 mg dapagliflozin per day and metformin 850 mg twice per day for 1 year, has been shown to reduce body weight by 6,9 kg and reduce waist circumference by 4,7 cm. This amount is greater than the monotherapy between dapagliflozin or metformin alone.[57,58]

The combination of 50 ipragliflozin per day and metformin and pioglitazone for 24 weeks, has been shown to reduce body weight by 6,9 kg, BMI by 0,6 kg/m^2, and waist circumference by 3,2 cm. The combination of 10 mg dapagliflozin per day with exenatide 2 mg once a week for 24 weeks can reduce body weight by 4,48 kg. In addition, blood glucose levels and systolic blood pressure also showed improvement. [59,60]

Several case reports reported that the combination of SGLT 2 inhibitors with liraglutide showed weight reduction and improvement of other metabolic parameters. The combination of 3 mg liraglutide per day with 10 mg dapagliflozin per day and 850 mg metformin 3 times a

day, has been shown to reduce body weight by 6,7 kg in 8 months of treatment. Another case report in which the combination of liraglutide with canagliflozin 100 mg daily and metformin 1 g 3 times daily resulted in a weight loss of 20.2 kg within 6 weeks. In addition, the weight loss of the combination of liraglutide 1.8 mg per day and dapagliflozin 10 mg per day showed a weight loss of 73.5 kg within 1 year of therapy. Furthermore, other metabolic parameters, including HbA1c showed improvement.[61,62]

The combination of SGLT 2 with other drugs, 300 mg canagliflozin with 15 mg phentermine once a day which is an amine sympathomimetic drug. Mechanism by stimulating satiety through upregulation of serotonin, norepinephrine and dopamine. The combination for 26 weeks showed a weight loss of 7.3 kg.The combination for 26 weeks showed a weight loss of 7.3 kg. [63]

6. Safety of SGLT 2 inhibitor

In general, SGLT 2 inhibitors are considered safe and well-tolerated. Common side effects from the use of other anti-diabetic drugs such as hypoglycaemia are reported to be quite low in the use of SGLT 2 inhibitors because SGLT 2 inhibitors do not trigger insulin release and interfere with glucose synthesis.However, there are some side effects of SGLT 2 inhibitors in general such as yeast infection in the urinary tract, dehydration and orthostatic hypotension, especially in the elderly.In addition, it was reported the occurrence of euglycemic diabetic ketoacidosis (DKA). Urinary tract infection is a common side effect because increased glucose levels in the urine can facilitate the growth of microorganisms. [64]

DKA euglycemic occurs due to decreased blood glucose levels and increased synthesis of ketone bodies due to the breakdown of free fatty acids and increased glucagon which causes lipolysis and ketogenesis in the liver.Hypotension occurs due to the mechanism of SGLT 2 inhibitors which reduce volume through osmotic diuresis and natriuresis. However, the euglycemic state of DKA is rare and occurs mainly in type 1 diabetes mellitus patients who are combined with dapagliflozin, and in those who reduce insulin doses to anticipate hypoglycaemia.But this situation causes an increase in the production of ketone bodies. Patients with type 2 diabetes using SGLT 2 inhibitors are still allowed with good monitoring to prevent the occurrence of DKA.[65,66]

Anotherside effect has been reported by combination therapy of canagliflozin with metformin, such as self-discontinuation, decreased GFR, kidney failure, and generalized pruritus. The combination of dapagliflozin with exenatide has been reported several side effects such as nasopharyngitis, headache, decreased appetite, urinary tract infection, injection marks, digestive symptoms such as nausea, vomiting, diarrhoea, dyspepsia, constipation and abdominal pain, and injection area (such as mass, pruritus, erythema, etc) [60]

Several side effect from the combination of canagliflozin and phentermine has been reported such as yeast urinary tract infection, osmotic diuresis (such as dry mouth, thirst, polyuria), psychiatric adverse effects such as anxiety, insomnia and stress also been reported. Increased heart rate, tachycardia and palpitations were also reported.[63]

7. Conclusion

Obesity is a condition where body fat accumulates abnormally or excessively which presents a health risk. Management of obesity needs to be carried out in a comprehensive manner starting with diet, physical activity, medication and others to prevent complications.Several studies reported that the use of SGLT 2 inhibitors can effectively reduce body weight through their mechanism of eliminating glucose in the body. In addition, SGLT 2 inhibitors are considered safe and several side effects can be considered. It is expected that SGLT 2 inhibitors can be considered in the administration of pharmacological therapy in obese patients

References

[1] Purnell J. Definitions, Classification, and Epidemiology of Obesity. South Dartmouth: Endotext; 2018.

[2] Lim JU, Lee JH, Kim JS, Hwang Y Il, Kim TH, Lim SY, et al. Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J COPD 2017;12:2465–75. https://doi.org/10.2147/COPD.S141295.

[3] Fruh SM. Obesity: Risk factors, complications, and strategies for sustainable long-term weight management. J Am Assoc Nurse Pract 2017;29:S3–14. https://doi.org/10.1002/2327-6924.12510.

[4] Lam BC, Lim AL, Chan S, Yum MS, Koh NY, Finkelstein E. The impact of obesity: a narrative review. Singapore Med J 2023;64:163. https://doi.org/10.4103/singaporemedj.smj-2022-232.

[5] WHO. Obesity and overweight. World Heal Organ 2021.

[6] Kementerian Kesehatan RI. Laporan Riskesdas 2018. Lemb Penerbit Balitbangkes 2018.

[7] Thaker V V. Genetic And Epigenetic Causes Of Obesity. Adolesc Med State Art Rev 2017;28:379–405.

[8] Funcke J-B, von Schnurbein J, Lennerz B, Lahr G, Debatin K-M, Fischer-Posovszky P, et al. Monogenic forms of childhood obesity due to mutations in the leptin gene. Mol Cell Pediatr 2014;1:1–8. https://doi.org/10.1186/s40348-014-0003-1.

[9] Nunziata A, Funcke JB, Borck G, Von Schnurbein J, Brandt S, Lennerz B, et al. Functional and Phenotypic Characteristics of Human Leptin Receptor Mutations. J Endocr Soc 2019;3:27–41. https://doi.org/10.1210/js.2018-00123.

[10] Hilado MA, Randhawa RS. A novel mutation in the proopiomelanocortin (POMC) gene of a Hispanic child: Metformin treatment shows a beneficial impact on the body mass index. J Pediatr Endocrinol Metab 2018;31:815–9. https://doi.org/10.1515/jpem-2017-0467.

[11] Burnett LC, Leduc CA, Sulsona CR, Paull D, Rausch R, Eddiry S, et al. Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi

syndrome. J Clin Invest 2017;127:293–305. https://doi.org/10.1172/JCI88648.

[12] Kerkadi A, Sadig AH, Bawadi H, Thani AAM Al, Chetachi W Al, Akram H, et al. The relationship between lifestyle factors and obesity indices among adolescents in Qatar. Int J Environ Res Public Health 2019;16:1–15. https://doi.org/10.3390/ijerph16224428.

[13] Cha E, Akazawa MK, Kim KH, Dawkins CR, Lerner HM, Umpierrez G, et al. Lifestyle habits and obesity progression in overweight and obese American young adults: Lessons for promoting cardiometabolic health. Nurs Heal Sci 2015;17:467–75. https://doi.org/10.1111/nhs.12218.

[14] Tchernof A, Després JP. Pathophysiology of human visceral obesity: An update. Physiol Rev 2013;93:359–404. https://doi.org/10.1152/physrev.00033.2011.

[15] van der Valk ES, van den Akker ELT, Savas M, Kleinendorst L, Visser JA, Van Haelst MM, et al. A comprehensive diagnostic approach to detect underlying causes of obesity in adults. Obes Rev 2019;20:795–804. https://doi.org/10.1111/obr.12836.

[16] Khanna D, Peltzer C, Kahar P, Parmar MS. Body Mass Index (BMI): A Screening Tool Analysis. Cureus 2022;14:1–6. https://doi.org/10.7759/cureus.22119.

[17] Nuttall FQ. Body mass index: Obesity, BMI, and health: A critical review. Nutr Today 2015;50:117–28. https://doi.org/10.1097/NT.0000000000000092.

[18] Han TS, Sattar N, Lean M. Assessment of obesity and its clinical implications. Br Med J 2006;333:695–8.

[19] Shariq OA, Mckenzie TJ. Obesity-related hypertension: A review of pathophysiology, management, and the role of metabolic surgery. Gland Surg 2020;9:80–93. https://doi.org/10.21037/gs.2019.12.03.

[20] Hall JE, Do Carmo JM, Da Silva AA, Wang Z, Hall ME. Obesity-Induced Hypertension: Interaction of Neurohumoral and Renal Mechanisms. Circ Res 2015;116:991–1006. https://doi.org/10.1161/CIRCRESAHA.116.305697.

[21] Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes, Metab Syndr Obes 2014;7:587–91. https://doi.org/10.2147/DMSO.S67400.

[22] Wondmkun YT. Obesity, insulin resistance, and type 2 diabetes: Associations and therapeutic implications. Diabetes, Metab Syndr Obes 2020;13:3611–6. https://doi.org/10.2147/DMSO.S275898.

[23] Johnston LW, Harris SB, Retnakaran R, Giacca A, Liu Z, Bazinet RP, et al. Association of NEFA composition with insulin sensitivity and beta cell function in the Prospective Metabolism and Islet Cell Evaluation (PROMISE) cohort. Diabetologia 2018;61:821–30. https://doi.org/10.1007/s00125-017-4534-6.

[24] Henning RJ. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. Am J Cardiovasc Dis 2021;11:504–29.

[25] Yoo HJ. Adipokines as a novel link between obesity and atherosclerosis. World J Diabetes 2014;5:357. https://doi.org/10.4239/wjd.v5.i3.357.

[26] Quiñones-Ossa GA, Lobo C, Garcia-Ballestas E, Florez WA, Moscote-Salazar LR, Agrawal A. Obesity and Stroke: Does the Paradox Apply for Stroke? Neurointervention 2021;16:9–19. https://doi.org/10.5469/neuroint.2020.00108.

[27] McFarlane SI. Obstructive sleep apnea and obesity: implications for public health. Sleep Med Disord Int J 2017;1:1–15. https://doi.org/10.15406/smdij.2017.01.00019.

[28] Kuvat N, Tanriverdi H, Armutcu F. The relationship between obstructive sleep apnea syndrome and obesity: A new perspective on the pathogenesis in terms of organ crosstalk. Clin Respir J 2020;14:595–604. https://doi.org/10.1111/crj.13175.

[29] Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. Obes Facts 2015;8:402–24. https://doi.org/10.1159/000442721.

[30] Gronda E, Jessup M, Iacoviello M, Palazzuoli A, Napoli C. Glucose metabolism in the kidney: Neurohormonal activation and heart failure development. J Am Heart Assoc 2020;9:1–11. https://doi.org/10.1161/JAHA.120.018889.

[31] Ghezzi C, Loo DDF, Wright EM. Physiology of renal glucose handling via SGLT1 , SGLT2 and GLUT2 Online Mendelian Inheritance in Man. Diabetologia 2018;1:2087–97.

[32] Rieg T, Vallon V. Development of SGLT1 and SGLT2 inhibitors. Diabetologia 2018;61:2079–86. https://doi.org/10.1007/s00125-018-4654-7.

[33] Wright EM. Basic Science for Clinicians SGLT2 Inhibitors : Physiology and Pharmacology 2021;2:2027–37.

[34] Ly JP, Onay T, Sison K, Sivaskandarajah G, Sabbisetti V, Li L, et al. The Sweet Pee Model for Sglt2 Mutation. J Am Soc Nephrol 2011;22:113–23. https://doi.org/10.1681/ASN.2010080888.

[35] Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: Therapeutic implications. Diabet Med 2010;27:136–42. https://doi.org/10.1111/j.1464-5491.2009.02894.x.

[36] Seidelmann SB, Feofanova E, Yu B, Franceschini N, Claggett B, Kuokkanen M, et al. Genetic Variants in SGLT1, Glucose Tolerance, and Cardiometabolic Risk. J Am Coll Cardiol 2018;72:1763–73. https://doi.org/10.1016/j.jacc.2018.07.061.

[37] Ma M, Long Q, Chen F, Zhang T, Lu M, Wang W, et al. Nutrition management of congenital glucose–galactose malabsorption. Medicine (Baltimore) 2019;98:e16828. https://doi.org/10.1097/md.0000000000016828.

[38] Soelistijo S. Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia 2021. Jakarta: 2021.

[39] Tsimihodimos V, Filippas-Ntekouan S, Elisaf M. SGLT1 inhibition: Pros and cons. Eur J Pharmacol 2018;838:153–6. https://doi.org/10.1016/j.ejphar.2018.09.019.

[40] Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. N Engl J Med 2017;377:2337–48. https://doi.org/10.1056/nejmoa1708337.

[41] Koepsell H. The Na+-D-glucose cotransporters SGLT1 and SGLT2 are targets for the

treatment of diabetes and cancer. Pharmacol Ther 2017;170:148–65. https://doi.org/10.1016/j.pharmthera.2016.10.017.

[42] Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol 2020;17:761–72. https://doi.org/10.1038/s41569-020-0406-8.

[43] Pittampalli S, Upadyayula S, Hema ;, Mekala M, Lippmann S. Risks vs Benefits for SGLT2 Inhibitor Medications Health care providers should carefully assess patients with diabetes mellitus before prescribing sodium-glucose cotransporter 2 inhibitor medications and monitor for adverse effects 2018:45–8.

[44] Janssen JAMJL. New Insights into the Role of Insulin and Hypothalamic-Pituitary-Adrenal (HPA) Axis in the Metabolic Syndrome. Int J Mol Sci 2022;23. https://doi.org/10.3390/ijms23158178.

[45] Szekeres Z, Sandor B, Bognar Z, Ramadan FHJ, Palfi A, Bodis B, et al. Clinical Study of Metabolic Parameters, Leptin and the SGLT2 Inhibitor Empagliflozin among Patients with Obesity and Type 2 Diabetes. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms24054405.

[46] Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic to Transl Sci 2020;5:632–44. https://doi.org/10.1016/j.jacbts.2020.02.004.

[47] Kubota Y, Shimizu W. Clinical Benefits of Sodium–Glucose Cotransporter 2 Inhibitors and the Mechanisms Underlying Their Cardiovascular Effects. JACC Asia 2022;2:287–93. https://doi.org/10.1016/j.jacasi.2022.03.009.

[48] Scisciola L, Cataldo V, Taktaz F, Fontanella RA, Pesapane A, Ghosh P, et al. Anti-inflammatory role of SGLT2 inhibitors as part of their anti-atherosclerotic activity: Data from basic science and clinical trials. Front Cardiovasc Med 2022;9. https://doi.org/10.3389/fcvm.2022.1008922.

[49] Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. Diabetes, Obes Metab 2019;21:1291–8. https://doi.org/10.1111/dom.13670.

[50] Suijk DLS, van Baar MJB, van Bommel EJM, Iqbal Z, Krebber MM, Vallon V, et al. SGLT2 Inhibition and Uric Acid Excretion in Patients with Type 2 Diabetes and Normal Kidney Function. Clin J Am Soc Nephrol 2022;17:663–71. https://doi.org/10.2215/CJN.11480821.

[51] La Grotta R, de Candia P, Olivieri F, Matacchione G, Giuliani A, Rippo MR, et al. Anti-inflammatory effect of SGLT-2 inhibitors via uric acid and insulin. Cell Mol Life Sci 2022;79:273. https://doi.org/10.1007/s00018-022-04289-z.

[52] Pratama KG, Tandarto K, Hengky A. Weight Loss Effect of Sodium-Glucose Cotransporter-2 (Sglt2) Inhibitors in Patients With Obesity Without Diabetes: a Systematic Review. Acta Endocrinol (Copenh) 2022;18:216–24. https://doi.org/10.4183/aeb.2022.216.

[53] Pan R, Zhang Y, Wang R, Xu Y, Ji H, Zhao Y. Effect of SGLT-2 inhibitors on body composition in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. PLoS One 2022;17:1–13. https://doi.org/10.1371/journal.pone.0279889.

[54] Kinoshita T, Shimoda M, Nakashima K, Fushimi Y, Hirata Y, Tanabe A, et al. Comparison of the effects of three kinds of glucose-lowering drugs on non-alcoholic fatty liver disease in patients with type 2 diabetes: A randomized, open-label, three-arm, active control study. J Diabetes Investig 2020;11:1612–22. https://doi.org/10.1111/jdi.13279.

[55] Sargeant JA, King JA, Yates T, Redman EL, Bodicoat DH, Chatterjee S, et al. The effects of empagliflozin, dietary energy restriction, or both on appetite-regulatory gut peptides in individuals with type 2 diabetes and overweight or obesity: The SEESAW randomized, double-blind, placebo-controlled trial. Diabetes, Obes Metab 2022;24:1509–21. https://doi.org/10.1111/dom.14721.

[56] Kawata T, Iizuka T, Iemitsu K, Takihata M, Takai M, Nakajima S, et al. Ipragliflozin Improves Glycemic Control and Decreases Body Fat in Patients With Type 2 Diabetes Mellitus. J Clin Med Res 2017;9:586–95. https://doi.org/10.14740/jocmr3038w.

[57] Leiter LA, Yoon KH, Arias P, Langslet G, Xie J, Balis DA, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: A randomized, double-blind, phase 3 study. Diabetes Care 2015;38:355–64. https://doi.org/10.2337/dc13-2762.

[58] Cheng L, Fu Q, Zhou L, Fan Y, Liu F, Fan Y, et al. Dapagliflozin, metformin, monotherapy or both in patients with metabolic syndrome. Sci Rep 2021;11:1–5. https://doi.org/10.1038/s41598-021-03773-z.

[59] Han E, Lee YH, Lee BW, Kang ES, Cha BS. Ipragliflozin additively ameliorates non-alcoholic fatty liver disease in patients with type 2 diabetes controlled with metformin and pioglitazone: A 24-week randomized controlled trial. J Clin Med 2020;9:1–14. https://doi.org/10.3390/jcm9010259.

[60] Lundkvist P, Sjöström CD, Amini S, Pereira MJ, Johnsson E, Eriksson JW. Dapagliflozin once-daily and exenatide once-weekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. Diabetes, Obes Metab 2017;19:49–60. https://doi.org/10.1111/dom.12779.

[61] Chua MWJ. High-Dose Liraglutide and SGLT2 Inhibitor: A Promising Combination. Clin Pract 2022;12:1–7. https://doi.org/10.3390/CLINPRACT12010001.

[62] Jayasinghe KNU, Greener VJ, Feher MD. Combining SGLT2 inhibitor and GLP-1 agonist: Exaggerated weight loss in a morbidly obese patient with type 2 diabetes. Br J Diabetes Vasc Dis 2016;16:138–9. https://doi.org/10.15277/bjd.2016.092.

[63] Hollander P, Bays HE, Rosenstock J, Frustaci ME, Fung A, Vercruysse F, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: A randomized clinical trial. Diabetes Care 2017;40:632–9. https://doi.org/10.2337/dc16-2427.

[64] Scheen AJ. An update on the safety of SGLT2 inhibitors. Expert Opin Drug Saf 2019;18:295–311. https://doi.org/10.1080/14740338.2019.1602116.

[65] Mascolo A, Di Napoli R, Balzano N, Cappetta D, Urbanek K, De Angelis A, et al. Safety profile of sodium glucose co-transporter 2 (SGLT2) inhibitors: A brief summary. Front Cardiovasc Med 2022;9. https://doi.org/10.3389/fcvm.2022.1010693.

[66] Zhang L, Tamilia M. Euglycemic diabetic ketoacidosis associated with the use of a sodium-glucose cotransporter-2 inhibitor. Cmaj 2018;190:E766–8. https://doi.org/10.1503/cmaj.171319.