The Role of SGLT 2 Inhibitor in the Therapy of Obesity

Giovanno Sebastian Yogie [a*], Darren Gosal [b], Yohanes Firmansyah [a] and Alexander Halim Santoso [c]

[a] *Faculty of Medicine, Tarumanagara University, Jakarta, Indonesia.*
[b] *Faculty of Medicine, Hasanuddin University, Makasar, Indonesia.*
[c] *Department of Clinical Nutrition, Tarumanagara University, Jakarta, Indonesia.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Review Article

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.

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*Corresponding author: Email: giovannousa@gmail.com;

1. INTRODUCTION

Obesity is a condition where body fat accumulates abnormally or excessively which presents a health risk. In Asia Pacific, obesity is defined 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 the 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, neuropeptide yy (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 Fig. 1 [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, it 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 hypoglycemia 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].
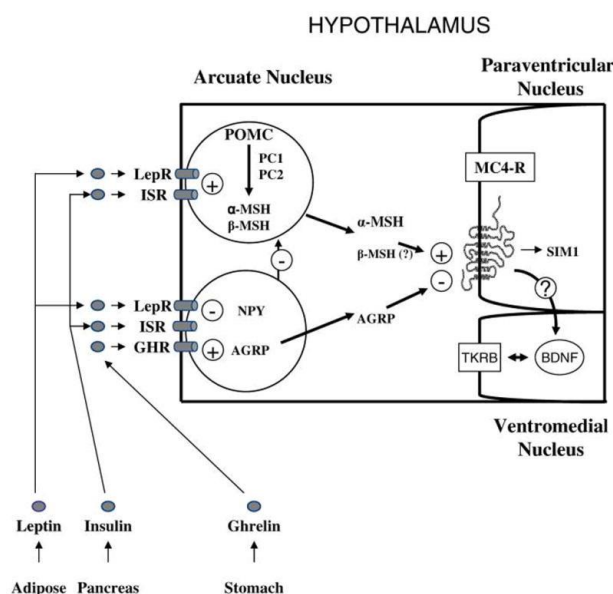

Fig. 1. Melanocortin Leptin pathway [7]

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 behavior. 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 as dietary, physical activity, sedentary behavior, and circadian rhythm. Medication history including antidepressant (*selective serotonin reuptake inhibitor*/SSRI), antipsychotic, corticosteroid, insulin and sulfonylurea, beta blocker, alpha-blocker, and proton pump inhibitor can 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 disorders 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's height 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 by the 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. Increased levels 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 hydrolyzed 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 collapses in 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, management of obesity includes weight loss, maintenance and prevention of weight regain, and lifestyle changes such as diet and physical activity. In addition, obesity management cannot 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].
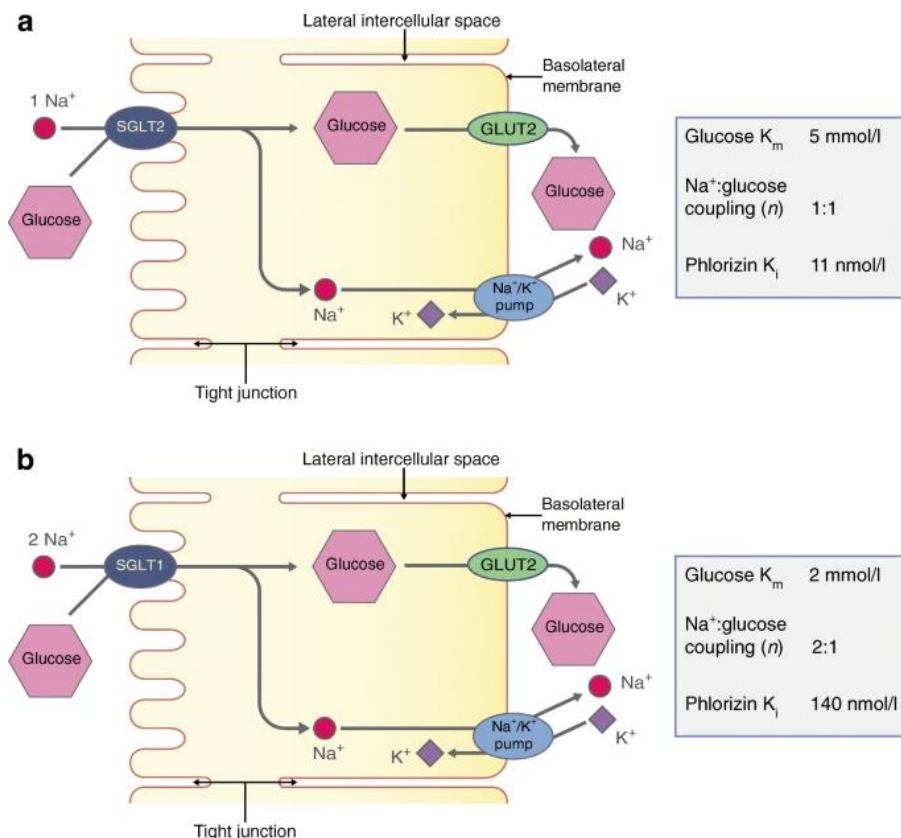
2. GLUCOSE PHYSIOLOGY IN KIDNEY

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

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 Fig. 2 [30,31].

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 hyperglycemia 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 diarrhea, 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 included in the Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus in Indonesia 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 can develop osmotic diarrhea, delayed correction of hypoglycemia due to impaired glucose absorption 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 hematocrit, 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 to 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 infarct size. 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 reduce 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 kg and 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 resulted in 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 mg 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. [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 hypoglycemia 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 hypoglycemia. 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].

Another side 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, diarrhea, 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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