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EFFECTIVENESS OF SGLT2 INHIBITORS IN GLYCEMIC CONTROL, WEIGHT LOSS, BLOOD PRESSURE REDUCTION, CARDIOPROTECTIVE AND RENOPROTECTIVE EFFECTS: REVIEW

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a type of diabetes mellitus caused by decreased insulin secretion and is characterized by hyperglycemia. 90% of all DM cases in the world are T2DM. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the newest antidiabetic agents to treat T2DM. Seven monotherapy agents are available in Europe, America, and Japan. Combination therapy can be given concurrently with metformin HCl, saxagliptin, linagliptin, or sitagliptin phosphate. The mechanism of action of SGLT2 inhibitors is related to glycosuria. The inhibition of glucose re-absorption by SGLT2 inhibitors occurs in the renal tubules. A review was conducted on the SGLT2 inhibitors in lowering blood glucose and other activities on this occasion. This review begins with a literature search on the Pubmed database using the keywords "effectiveness of SGLT2 inhibitors", "SGLT2 inhibitors," and "efficacy of SGLT2 inhibitors for type 2 diabetes mellitus". SGLT2 inhibitors are proven to effectively fight against glycemia, reduce weight, blood pressure, uric acid, risk of death from cardiovascular disease, and protect the kidneys. The effect is obtained based on the measurement of the clinical parameters of each condition.

***Keywords**: Diabetes mellitus, empagliflozin, SGLT2 inhibitors*

INTRODUCTION

One public health problem with long and short-term complications is diabetes mellitus [1][2]. According to the American Diabetes Association (ADA), diabetes is a complex group of chronic metabolic diseases and requires medical treatment that incorporates multifactorial risk reduction strategies beyond glycemic [3]. Diabetes mellitus (DM) can develop into quite serious complications such as heart disease, stroke, blindness, kidney failure, and nervous disorders if not treated properly [4]. In general, diabetes mellitus is divided into 4 types, namely type 1 DM (T1DM), type 2 DM (T2DM), gestational DM, and DM with other causes. Diabetes mellitus is caused by dysfunction of pancreatic beta cells, where insulin is produced, which is T1DM. In contrast, T2DM is caused by the body experiencing insulin resistance or lack of insulin [4].

Based on data from the Ministry of Health of the Republic of Indonesia in 2018, Indonesia is the sixth country with the most people with diabetes after China, India, the United States, Pakistan, Brazil, and Mexico. In Indonesia, the number of people with diabetes is around 10.3 million people aged 20-79 years [5].

Efforts to prevent or delay the risk of complications to help maintain the patient's quality of life can be made with diabetes treatment itself. Sodium-glucose cotransporter 2 (SGLT2) inhibitor is a promising breakthrough for the treatment of diabetes (Yu et al., 2017). SGLT2 inhibitors can inhibit glucose reabsorption and help excrete large amounts of glucose through the urine. This SGLT2 inhibitor effectively treats DM by regulating blood glucose levels almost without side effects [7].

SGLT2 inhibitors are classified into several types, namely SGLT2 inhibitors derived from C-glucoside, O-glucoside, N-glucoside, and non-glucoside. SGLT2 inhibitor derivatives have different chemical stability. All C-glucoside products SGLT2 inhibitors have better chemical and metabolic stability than O-glucoside derivatives. This is why most researchers are interested in C-glucoside. Dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, leusogliflozin and tofogliflozin are C-glucoside derivatives. The purpose of this review is to examine the effectiveness of the C-glucoside-derived SGLT2 inhibitor group as both antidiabetic and other activities. [7].

RESEARCH METHODS

Review writing begins with the collection of journals to be reviewed. The journals used are from the PubMed database, published 2016-2021. The keywords used in this search are "effectiveness of SGLT2 inhibitors", "SGLT2 inhibitors," and "efficacy of SGLT2 inhibitors for type 2 diabetes mellitus". The journals are then screened by title and abstract, followed by a conceptual review, and finally, a complete journal review. This journal review is written based on all the journals reviewed in their entirety.

RESULTS AND DISCUSSION

A literature search was carried out using the keywords “effectiveness of SGLT2 Inhibitor”, “SGLT2 inhibitor,” and “efficacy of SGLT2 inhibitor for diabetes mellitus type 2” in the PubMed database published in 2016-2021. The screening

process for titles and abstracts left 50 articles, and after a review of the abstracts, 35 journals that were considered relevant for the study were obtained.

DM cases are predicted to continue to grow from time to time [4]. The increase in DM cases causes an increase in the incidence of various other cases. DM can be a risk factor for the development of various other diseases, including chronic kidney disease (CKD), stroke, blindness, hypertension, nerve disorders, and heart failure. [3][9][10]. In addition, DM can also cause pregnancy complications and complications in children associated with an accelerated risk of nephropathy, retinopathy, and nerve damage [4].

SGLT 2 INHIBITOR THERAPY

Currently, there are many agents available that can control blood glucose levels, both in solid and injectable forms, with limited use due to side effects. Among the sulfonylureas, glimepiride, metformin, or insulin have side effects of hypoglycemia, weight gain, gastrointestinal side effects, and fluid retention [8][11]. This case triggered the discovery and development of new drugs that became a breakthrough in DM therapy, namely SGLT2 inhibitors [12]. There have been many studies that have proven the effectiveness of SGLT2 inhibitors in cases of T2DM. Several SGLT2 inhibitors have completed phase III clinical trials and are still in clinical trials. SGLT2 inhibitors that have been approved for use based on data from the European Medicines Agency (EMA), Food and Drug Administration (FDA), and the Ministry of Health, Labor and Welfare (MHLW) can be seen in Table 1 for SGLT2 inhibitors in single preparations and Table 2 for combined preparations SGLT2 inhibitors with other antidiabetics

Table 1. Single-stock SGLT2 inhibitors approved by EMA, FDA, and MHLW

Name of the Drug	Trade Name	Manufacturer	Distribution Permission Status			Reference
			EMA	**FDA**	**MHLW**	
Canagliflozin	Invokana®	Janssen-Cilag International NV	November 2013	March 2013	-	[8][9]
Dapagliflozin	Farxiga®	AstraZeneca	November 2012	Januar 2014	-	[8][9]
Empagliflozin	Jardiance®	Boehringer Ingelheim	May 2014	August 2014	-	[8][9]
Ertugliflozin	Steglatro®	Merck and Pfizer	March 2018	December 2017	-	[8][9]
Sotagliflozin	Zynquista®	Guidehouse Germany	April 2019	December 2018	-	[8][10]
Ipragliflozin	Suglat®	Astellas, Kotobuki Pharmaceutical	-	-	January 2014	[11]
Luseogliflozin	Lusefi®	Taisho Pharmaceutical Holding	-	-	March 2014	[12]

Table 2. SGLT2 inhibitor preparations in combination with other antidiabetics that have been approved for circulation by the EMA, FDA, and MHLW

Name of the Drug	Trade Name	Sponsor	Status			Reference
			EMA	FDA	MHLW	
Canagliflozin; Metformin	Vokanamet (EMA) ® Invokamet (FDA) ®	Janssen-Pharm	April 2014	September 2016	-	[8][9]
Dapagliflozin; Metformin	Xigduo XR®	AstraZeneca	December 2017)	Oktober 2014; Juli 2017	-	[8][9]
Dapagliflozin; Saxagliptin HCl	Qtern®	AstraZeneca	July 2016	February 2017; May 2019	-	[8][9]
Empagliflozin; Linagliptin	Glyxambi®	Boehringer Ingelheim	November 2016	January 2015	-	[8][9]
Empagliflozin; Metformin	Synjardy®	Boehringer Ingelheim	May 2015	August 2015	-	[8][9]
Empagliflozin; Linagliptin; Metformin HCl	Tryjardy XR®	Boehringer Ingelheim	January 2020	-	-	[9]
Ertugliflozin; Metformin HCl	Segluromet®	Merck Sharp Dohme	March 2018	December 2017	-	[8][9]
Ertugliflozin; Sitagliptin Phosphate	Steglujan®	Merck Sharp Dohme	March 2018	December 2017	-	[8][9]

MECHANISM OF ACTION OF SGLT2 INHIBITOR

The discovery of congenital diseases to impaired glucose control in the kidneys and excreted glucose in the urine became a concept in inhibiting glucose reabsorption. The mechanism of action of SGLT2 inhibitors is related to glycosuria. Increased calorie loss and glucose excretion through urine is the mechanism of work of SGLT2 inhibitors. Renal glucose reabsorption by the SGLT2 protein is the main pathway in glucose reabsorption [13]. Decreased glucose re-absorption by SGLT2 inhibitors occurs in the renal tubular system [14].

T2DM treatment with inhibitor SGLT2 is ideal because the SGLT2 protein can reabsorb 90% of filtered glucose as a drug target. Glucose reabsorption with serum glucose concentration in normal kidneys is at the threshold of 180 mg/dL. SGLT2 inhibitors can reduce the point to 120 mg/dL [15][16]. The work of SGLT2 inhibitor is not dependent on insulin because this drug works on the kidneys. Inhibition of glucose reabsorption leads to a decrease in glucose levels in the blood. The amount of urinary glucose excretion (UGE) is associated with the severity of hyperglycemia. The more severe hyperglycemia, the greater the amount of UGE. The mechanism indicates a low risk of hypoglycemia [17]. SGLT2 inhibitors may also increase the sensitivity of pancreatic incretin β [18].

EFFECTS ON GLYCEMIA

The effectiveness of SGLT2 inhibitors against glycemia in T2DM patients has been widely studied. Based on the results of many studies that have proven that SGLT2 inhibitors have high energy in glycemia. A study reported that SGLT2 inhibitors significantly lowered fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) [19]. The results also parallel the research conducted by Rodbard et al. and Pratley et al. [20][21]. T2DM patients with regular kidney function show decreased HbA1c and lower blood plasma glucose [22]. FPG and HbA1c are laboratory blood parameters in diagnosing diabetes and prediabetes [23]. FPG and HbA1c levels decrease indicates that SGLT2 inhibitors effectively treat glycemia.

SGLT2 inhibitors decrease total cholesterol, triglycerides, and cholesterol/HDL-C levels [13][24]. The rating assessment examines screening complications in newly diagnosed T2DM patients [23]. The results of the Sasaki et al. study also stated that SGLT2 inhibitor is effective on glycemia with decreased fasting immunoreactive insulin (F-IRI) and fasting C-peptide immunoreactivity (F-CPR) [24].

EFFECT ON WEIGHT

SGLT2 inhibitors are also effective in weight loss. Studies conducted in America, Asia, and Australia proved the effects of weight loss [19]-[24]. Jabbour et al. in 2018 established that there was no significant weight loss difference in both 28 weeks and 52 weeks [14]. The difference in doses affects weight loss due to the administration of this drug. Higher doses (dapagliflozin, canagliflozin, and ertugliflozin) provide more significant weight loss [14][25][21].

There was no correlation between weight loss and changes in HbA1c levels. SGLT2 inhibitors are responsible for mechanisms in weight loss itself. Failure of calories through glucose in the urine (UGE) can cause weight loss [24]. The research is in line with the report provided by Jabbour et al. excret al. [14], Fioretto et al. [19], Takashima et al. [26], and Zhou et al. [27]. This weight loss is not affected by kidney function [28]. Karg et al. reported the mechanism of weight loss caused by diuresis osmotic and natriuresis due to the administration of SGLT2 inhibitor [29]. Normalization of volume in the body due to such treatment can induce weight loss [30].

EFFECT ON BLOOD PRESSURE

Based on Tables 3, 4, 5, and 7, inhibitor SGLT2 and lowering blood glucose and weight can also lower blood pressure. SGLT2 inhibitor is primarily able to lower *Systolic Blood Pressure* (SBP) [19]. The study is in line with the results reported by Jabbour et al. [14], Zou et al. [27], and Dharmalingam et al. [13]. Other studies gave similar results on administering SGLT2 inhibitor (Canagliflozin) 100 mg or 300 mg [20].

Unlike the results of previous studies, Karg et al. reported that the decrease in blood pressure was not only in systolic but also in his diastolic blood pressure (DBP) [31]. The report was proven with the same results from the Takashima et al. reported [26]. Although the rate of decline given is not as large as at systolic. A decrease in diastolic blood pressure was also obtained from the Zhou et al. study results [27]. SGLT2 inhibitors provide a blood pressure-

lowering effect independent of kidney function [32]. Inhibition of glucose reabsorption in proximal tubule cells in the same direction as the blockade of sodium reabsorption as a glycosuria mechanism of SGLT2 inhibitors. A decrease in blood pressure in either systolic or diastolic is caused by diuresis osmotic natriuresis [30]. A drop in blood pressure can also be caused by weight loss and a reduction in arterial stiffness [33].

EFFECT ON URIC ACID

One of the risk factors for cardiovascular is hyperuricemia [34]. Hyperuricemia is also considered a role in CKD develop development [35]. In Table 4, Okada et al. proved a decrease in serum uric acid in T2DM patients using SGLT2 inhibitors (empagliflozin). The results were obtained with post *hoc* analysis from the SACRA study. The patient's age becomes one-factor dedetermines the decrease in uric acid levels. Decreased uric acid levels in patients ≥75 years provided a more significant reduction than in patients <75 years. After declines in the administration of this drug, the decrease was ± 0.77 mg/dL in patients aged ≥75 years and ±0.62 mg/dL in patients <75 years [36]. Serum uric acid occurs due to increased glucosuria, causing uric acid to train the renal tubules [37].

EFFECTS ON CARDIOVASCULAR (CV)

Diabetes can lead to an increased risk of death due to cardiovascular causes (CV). In addition to being affected by blood pressure, another cause is abnormal levels of kidney sodium. Sodium levels are caused by increased salt intake from food [38]. SGLT2 inhibitors also protect against disease risk. These results are proven in research conducted by sports activity changes Monteiro Pettitt et al. Based on this study, there was no significant difference in each patient's age out means. However, patients aged <65 years showed a reduced risk of death on a CV. It is also in line with the case of heart failure treatment. There were differences in outcomes in death patients from all causes and the incidence of worsening neuropathy. In these cases, ages 65 to <75 years of age provides a more significant decrease [39].

SGLT2 inhibitors could lower the heart rate, a CV parameter in one study. The decrease in heart rate is more significant at night than during the day [36]. The same results were also shown by a report from Verma et al. in PATIENTS CABG *(coronary artery bypass graft)* [40]. Decreased death cases from cardiovascular disease are associated with a decrease in blood pressure, both systolic and diastolic, due to the administration of SGLT2 inhibitor [40]. Decreased sodium levels in the body also affect cases of cardiovascular death [31].

EFFECT ON THE KIDNEY

Cases of diabetes that increase, causing the incidence of CKD also increased. DM is a risk factor for CKD [19]. SGLT2 inhibitors are effective at lowering cases of CKD. However, the administration of SGLT2 inhibitor in patients with a history of kidney disorders should be highly considered due to specific mechanisms. SGLT2 inhibitors have a protective effect on the kidneys. There was a decreased infiltration rate in the glomerulus (eGFR) in a study conducted by Fiorett et al. in 2018. The eGFR value obtained showed a considerable reduction in the 4th week [19].

Research conducted by Takashima et al. (2018) confirmed that SGLT2 inhibitors could protect against the risk of nephropathy. In addition to the decrease in eGFR, there is also a decrease in UACR (Urine *Albumin-to-creatinine ratio).* The UACR occurs due to a reduction in intraglomeric pressure. The study also mentioned a decrease in L-FABP *(liver-type free acid-binding protein).* L-FABP is a marker for seeing changes in the tubulointerstitial. The increase in L-FABP is due to various pressures on the proximal tubules of the kidneys that can induce the expression of the L-FABP gene. SGLT2 inhibitor will reduce L-FABP to prevent damage to the tubulointerstitial [26].

Increased hematocrit also occurred in patients treated with SGLT2 inhibitors. Increased hematocrit will provide more oxygen to the tissues, so the SGLT2 inhibitor can help heal various tubular injuries. An increase in hemoglobin also occurs to contributes to the maintenance of GFR. SGLT2 inhibitors have also been shown to treat NAG *(N-acetyl-β-d-glucosaminidase),* AST *(aspartate aminotransferase),* ALT *(alanine aminotransferase),* and γ-GTP *(γ-glutamyl transpeptidase),* meaning it can provide kidney protection [26].

The effect of SGLT2 inhibitors on various clinical parameters gycemialed, weight loss, decreased blood pressure, cardiovascular, and kidney can be seen in Tables 3-7. Each table displays data from one type of drug.

Table 3. Effects of a single or combination dapagliflozin on various clinical parameters related to DM, weight, and blood pressure

Year	Research Subjects	CountryCountry	Changes in Clinical Parameters Value	Reference
2018	321 DMT2 and CKD patients	United States	HbA1c : 0,34% ↓ Weight: 1.25g ↓ FPG : 0,9 mmol/L ↓ SBP : 3,1 mmHg ↓ eGFR : - Week 4: 4.90 mL/min/↓ - Week 12: 4.75↓ - Week 24: 2.49↓ - Week to >27: 0.621↓	[19]
2018	695 patients	The United States and Europe	**Single dapagliflozin** - Week 28 :↓1,39% - Week 52 : ↓1,23%	[14]

			FPG : - Week 28 : ↓2,73 mmol/L - Week 51 : ↓2,21 mmol/L PPG 2 jam : - Week 28 : ↓3,39 mmol/L - Week 52 : ↓3,31 mmol/L Weight : - Week 28 : ↓2,22 kg - Week 52 : ↓2,28 kg SBP : - Week 28 : ↓1, eight mmHg - Week 52 : ↓2, seven mmHg **Combination exenatide QW + Dapagliflozin** HbA1c : - Week 28 : ↓1,98% - Week 52 : ↓1,75% FPG : - Week 28 : ↓7,17 mmol/L - Week 52 : ↓6,66 mmol/L PPG 2 jam : - Week 28 : ↓4,88 mmol/L - Week 52 : ↓4,58 mmol/L Weight : - Week 28 : ↓3,55 kg - Week 52 : ↓3,31 kg SBP : - Week 28 : ↓4, three mmHg - Week 52 : ↓4, 5 mmHg	
2018	59 DMT2 patients	German	HbA1c : 0,05 ↓ Weight : 0, kg ↓ FPG : 18 m/dL ↓ PPG : 24 m/dL ↓ SBP : 4 mmHg ↓ DBP : 2 mmHg ↓ Heart rate: 0,9 bpm	[31]

Table 4. Effects of Empagliflozin on various clinical parameters related to DM, Weight, gout, kidney disease, and cardiovascular disease.

Year	Research Subjects	Country	Changes in Clinical Parameters	Reference

2018	40 DMT2 patients	Japan	HbA1c : 0,4% ± 0,7 (p<0,05). ↓ Weight : 0,9 kg/m^2 ±0,4 ↓ SBP : 3, one mmHg ±2,0 ↓ DBP : 1, six ± 1,0 ↓ UACR : 83 mg/GC ↓ L-FABP : 65% NAG : 3% β2MG : 27% AST : 3U/L ↓ ALT : 3 UL ↓ γ-GTP : 7,5 U/L ↓ Haemoglobin : 0,8 ±1,7 g/dL	[26]
2017	Two thousand patients with grouping: 155 patients (6.7%) had a history of CV, 1433 (62.0%) patients with a history of hypertension, 945 (40.9%) patients who were taking statins, 1727 (74.7%) patients who had 0 – 1 CV risk factor and 586 patients (25.3%) had ≥2 CV risk factors.	Asian, United State	**History of CVD Disease** HbA1c : - 100 mg : ↓0,85% - 300 mg : ↓0,98% Weight : - 100 mg : ↓2,7 kg - 300 mg : ↓3,0 kg SBP : - 100 mg : ↓5,5 mmHg - 300 mg : ↓4,9 mmHg **Without CVD History** HbA1c : - 100 mg : 0,85% - 300 mg : ↓1,05 Weight : - 100 mg : ↓2,5 kg - 300 mg : ↓3,1 kg SBP : - 100 mg : ↓4,2 mmHg - 300 mg : ↓5,0 mmHg **History of Hypertension** HbA1c : - 100 mg : ↓0,72% - 300 mg : ↓1,01% Weight : - 100 mg : ↓2,7 kg - 300 mg : ↓3,2 kg	[25]

			SBP : - 100 mg : ↓4,3 mmHg - 300 mg : ↓5,0 mmHg **Without history, three hundred ta a third of hypertension** HbA1c : - 100 mg : ↓0,87% - 300 mg : ↓1,09% Weight : - 100 mg : ↓2,2 kg - 300 mg : ↓3,1 kg SBP : ↓ - 100 mg : ↓4,4 mmHg - 300 mg : ↓5,1 mmHg **Statin Users** HbA1c : - 100 mg : ↓0,84% - 300 mg : ↓ 1,06% Weight : - 100 mg : ↓2,9 kg - 300 mg : ↓3,3 kg SBP : - 100 mg : ↓ 4,9 mmHg - 300 mg : ↓ 4,9 mmHg **Not taking statins** HbA1c : - 100 mg : ↓0,88% - 300 mg : ↓ 1,04% Weight : - 100 mg : ↓2,2 kg - 300 mg : ↓3,0 kg SBP : - 100 mg : ↓4,2 mmHg - 300 mg : ↓5,4 mmHg **0-1 factor risk CVD** HbA1c : - 100 mg : ↓0,85% - 300 mg : ↓1,01% Weight : - 100 mg : ↓2,5 kg - 300 mg : ↓3,0 kg SBP : - 100 mg : ↓3,8 mmHg - 300 mg : ↓4,3 mmHg **≥ 2 factor risk CVD** HbA1c : - 100 mg : ↓0,84%	

			- 300 mg : ↓1,12% Weight : - 100 mg : ↓2,6 kg - 300 mg : ↓3,5 kg SBP : - 100 mg : ↓ 5,7 mmHg - 300 mg : ↓7,0 mmHg	
2016	106 DMT2 patients	USA, Germany, Canaaeen	HbA1c : 0,91% ↓ FPG : 1,7 mmol/L (29,8 mg/dL) ↓ ↓ Weight : 3,4% (3,1kg) ↓ ↓ SBP : 5,88 mm ↓	[20]
2019	10142 patients, average age 63.3 years, 35.8% of women who had a history of DM 13.5 years and 65.6% had a cardiovascular history	North America, Central America, Europe	HbA1c : 0.42% (0.02, <0,001%) ↓ SBP : 4.86 mmHg (0.19, p<0,001) ↓ DBP: 3.21 mmHg (0.11,0<001%) ↓ Weight : 3.21 kg (0.08, <0,001%) ↓ eGFR : 1,82 (0,19) mL/min per 1,73 m^2 ↓	[27]

Keterangan : HbA1c (haemoglobin terglikasi); FPG (*Fasting Plasma Glucose*); SBP (*Systolik Blood Pressure*); eGFR (*estimated Glomerular Filtration Rate*); UACR (*Urine Albumin-to-creatinine ratio*); L-FABP (*liver-type free acid binding protein*); NAG (*N-acetyl-β-d-glucosaminidase*); γ-GTP (*γ-glutamyl transpeptidase*);

Tabel 5. Effectiveness of Ertugliflozin on various Clinical Parameters related to DM, Weight¸ and cardiovascular disease.

Year	Research Subjects	Country	Changes in Clinical Parameters	Reference
2018	1,232 DMT2 patients	Amerika Utara, Amerika Selatan, Eropa, Asia, Australia, Selandia Baru.	Hb : - E5: 0% - E15 : ↓1,1%E5/S100 : ↓1,5% - 15/S100 : ↓1,5% FPG : - E5 : ↓35,7 mg/dL - E15 : ↓36,9 mg/dL - E5/S100 : ↓44,0 mg/dL - E15/S100 : ↓48,7 mg/dL Wei : - E5 : ↓2, ka g - E15 : ↓3,7 kgE5/S100 : ↓2,5 kg	[21]

			- E15/S100 : ↓2,9 k BP - E5 : ↓3, nine mmHg - E15 : ↓3, seven mmHgE5/S100 : ↓3, four mmHg - 15/S100 : ↓3, seven mmHg	

Keterangan : HbA1c (haemoglobin terglikasi); FPG (*Fasting Plasma Glucose*); SBP (*Systolik Blood Pressure*); E5 (Ertugliflozin 5mg); E15 (ertugliflozin 15 mg); S100 (Sitagliptin 100mg).

Table 6. Effectiveness of Remogliflozin on various Clinical Parameters related to DM and cholesterol levels in the blood

Year	Research Subjects	Country	Changes in Clinical Parameters	Reference
2020	611 DMT2 patients grouped into three groups	India	HbA1: - R100 : ↓0,77% - R200: ↓0,58% Total Cholesterol: - R100 : ↓2,2 mg/Dl Trigliserid: - R100 : ↓11,3 mg - R200 : ↓11,3 mg/Dl Total kolesterol/HDL-C :R100 mg : 0,36R200 mg : 0,31 ↓ ↓	[13]

Keterangan : HbA1c (haemoglobin terglikasi); HDL-C (*high-density lipoprotein cholesterol*); R100 (Remogliflozin 100 mg); R200 (Remogliflozin 200 mg)

Table 7. Effectiveness of Luseogliflozin on various Clinical Parameters related to DM, Weight, kidney disease, and cardiovascular disease.

Year	Research Subjects	Country	Changes in Clinical Parameters	Reference
2019	37 patients with type 2 diabetes mellitus	Japan	HbA1c : - Week ke-24 : ↓0,514% ± 0,658 - Week ke-52 : ↓0,549% ± 0,570 FPG : - Wek ke-24 : ↓1,54 mmol/L ± 1,58 - Wek ke-52 : ↓1,86 mmol/L ± 1,70 F-I : - Wek ke-24 : ↓35,8 pmol/L - Wek ke-52 : ↓36,1 pmol/L F-CPR : - Week ke-24 : ↓0,124 nmol/L ± 0,361 - Week ke-52 : ↓0,159 nmol/L ± 0,346 TG : - Wek ke-24 : ↓0,314 mmol/L ± 2,37 - Wek ke-52 : ↓0,597 mmol/L ± 2,01 SBP :	[24]

			- Wek ke-24 : ↓2,19 mmHg ± 11,3 - Wek ke52 : ↓2,16 mmHg ± 13,2 DBP : - Wek ke-24 : ↓2,59 ± 10,0 - Wek ke-52 : ↓3,49 mmHg ± 9,70 Weight - Wek ke-24 : ↓2,6 kg - Wek ke-52 : ↓3,1 kg Kreatinin : - Wek ke-24 : ↓0,239 µmol/L ± 5,64 eGFR : - Week ke-24 : ↓ 0,462 mL/min/1,73 m^2 ± 9,10 - Week ke-52 : ↓ 0,481 mL/min/1,73 m^2 ± 8,92 AST : - Wek ke-24 : ↓4,14 U/L ± 7,88 - Wek ke-52 : ↓3,73 U/L ± 8,61 ALT : - Wek ke-24 : ↓9,14 U/L ± 13,3 - Wek ke-52 : ↓7,65 U/L ± 15,8 Urine Albumin kreatinin : - Wek ke-24 : ↓25,4 mg/g Cr ± 111 - Wek ke-52 : ↓13,0 mg/g Cr ± 67,9 Albumin excretion : - Wek ke-24 : ↓0,0396 g/24 h ± 0,105	

Keterangan : HbA1c (haemoglobin terglikasi); FPG (*Fasting Plasma Glucose*); F-IRI ; F-CPR ; TG (*Trigliserida*); SBP (*Systolic Blood Pressure*); DBP (*Dyastolic Blood Pressure*); eGFR (*estimated glomerular filtration rate*) ; AST (*aspartate aminotransferase*) ; ALT (*alanine aminotransferase*)

CONCLUSION

SGLT2 inhibitors are the latest antidiabetics that have proven their efficacy. SGLT2 inhibitors, in addition to being shown in improving blood glucose control, have also been linked to decreased weight, blood pressure, and serum uric acid. SGLT2 inhibitors can also lower the risk of cardiovascular disease and protect the kidneys.

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