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# A review article of $SGLT_2$ inhibitors for the treatment of diabetes and obesity

**P. Soni Dixitha, Dr.M. Vijaya Bhargavi, Prof.Dr.M. Sumakanth**

*Department of Pharmaceutical Chemistry,*
*RBVRR women's college of pharmacy, Barkatpura, Hyderabad.*

**Abstract**

SGLT-2 inhibitors are a novel class of anti-diabetic agents and glucose lowering drugs that reduce plasma glucose levels by inhibiting glucose reabsorption in proximal convoluted tubules of kidney and thus resulting glucosuria. Their effects consequently include reductions in HbA1c, blood glucose levels, and blood pressure, but also reductions in body weight and adiposity. The ability to reduce body weight is consistently observed in individuals taking SGLT2 inhibitors, but this weight loss is moderate due to counter-regulatory mechanisms striving to maintain body weight. Apart from maintaining glucose homeostasis they exert a number of positive effects on the cardiovascular system like weight loss, decreasing blood pressure, preserving renal function, reducing triglycerides, natriuresis and improving endothelial dysfunction. In large clinical trials, all the three prototype agents – empagliflozin, canagliflozin and dapagliflozin have shown reductions in major adverse cardiovascular events.

**Keywords:** Sodium glucose co-transporters2, obesity, diabetes mellitus

## INTRODUCTION

### *Diabetes*

Diabetes is a group of metabolic diseases characterized by hyperglycemia and microvascular and macrovascular complications caused by insulin secretion defect and/or its biological function disorder [1–3].Type 1 diabetes mellitus ($T_1DM$) presents many challenges for patients and prescribers when trying to control blood glucose levels. The lack of novel treatment options, coupled with the challenges of long-term insulin therapy, makes it difficult for patients with $T_1DM$ to reach and maintain hemoglobin $A_1c$ goals, which increases the risk of complications [4-5]. Among the drugs currently being tested as adjuncts to insulin therapy in randomized clinical trials (RCTs), sodium glucose co-transport-2 (SGLT2) inhibitors appear promising because they are unique and independent of the mechanism of action of insulin[6].

Type 2 diabetes mellitus ($T_2DM$) patients with incident stroke have a higher risk of mortality than those with diabetes alone [7]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral hypoglycemic agents for the treatment of T2DM that have a unique antidiabetic mechanism that inhibits the proximal renal tubule's reabsorption of glucose and sodium, thus reducing the level of blood glucose [8].Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which block glucose reabsorption in the kidneys, represent a novel class of non-insulin glucose-lowering medication used in the pharmacological therapy of type 2 diabetes mellitus (T2DM). They became available after the introduction of incretin-based therapies with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or dipeptidyl peptidase-4 (DPP4) inhibitors [9].

### *Obesity*

Overweight and obesity are major risk factors for several diseases, such as hypertension, dyslipidaemia, type 2 diabetes, cardiovascular disease, osteoarthritis, obstructive sleep apnoea, fatty liver disease cancers and other diseases[10-11]. In addition, various musculoskeletal, respiratory, renal, gastrointestinal, and psychiatric complications are linked to obesity[12-13]. Moderate weight loss (5% of body weight) can improve glycaemic control and insulin homeostasis and mitigate cardiovascular risk factors associated with overweight and obesity[14]. Sodium-glucose transporter 2 (SGLT2) inhibitors are a novel class of oral therapeutic medications that have been approved for the treatment of type 2 diabetes mellitus by the Food and Drug Administration (FDA) [15]. SGLT2 inhibitors have been shown to be successful in improving glycaemic control and lowering body weight [16].

## Role of $SGLT_2$ inhibitors

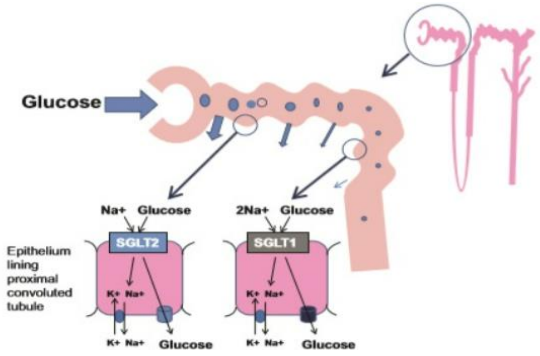
### *Diabetes:*

The progressive nature of T2DM usually requires combinations of differently acting agents to maintain glycaemic control when monotherapy is inadequate[17-20].

SGLT2 inhibitors act independently of insulin to eliminate excess glucose in the urine (i.e. increase glycosuria). They do this by inhibiting the SGLT2 transporter in the kidney, which normally reabsorbs most of the glucose from the renal filtrate.

SGLT2 inhibitors act to potentiate this effect, thereby enhancing elimination of excess glucose. The caloric loss associated with this glycosuria assists weight loss, and a modest osmotic diuresis can facilitate a small decrease in blood pressure. The term "glucuretic" may therefore usefully describe the effects of SGLT2 inhibitors (by analogy with diuretic for fluid elimination). Since SGLT2 inhibitors do not stimulate insulin secretion or action, and their effect diminishes as blood glucose levels fall, they do not cause hypoglycaemia[20-22].

SGLT1 is responsible for dietary glucose and galactose absorption but has a much lower capacity than SGLT2 for glucose absorption. SGLT1 is found predominantly in the gut, but is also located in S2-3 of the convoluted tubule, whereas SGLT2 is expressed solely in the S1 segment of the proximal convoluted tubule [23-24].




***lucose transport across cell membranes:***

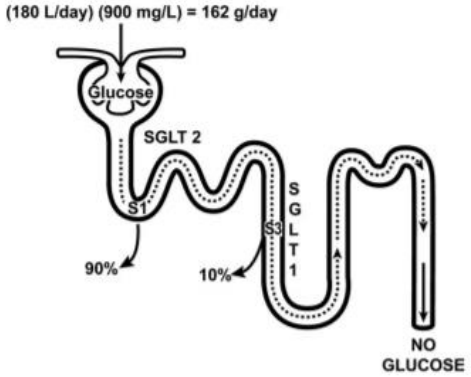
Glucose is an essential fuel source for cellular metabolism. The glucose molecule is highly polar and does not cross the lipid bilayer that comprises the plasma membrane of all living cells. Because of this, membrane proteins that facilitate glucose transport from the extracellular to the intracellular space are pivotal for glucose movement across cell membranes. Two distinct classes of glucose transporters exist in the human body [25,26].

1) Facilitative glucose transporters (GLUT), a family of proteins that passively facilitate glucose movement from the extracellular to the intracellular space along its chemical gradient and, thus, do not consume energy[25,26].
2) sodium-glucose cotransporters (SGLT), a family of proteins that actively transport glucose across cell membranes against its concentration gradient, thereby requiring an energy source for their action.

SGLT couple glucose with sodium transport into the cell[25-26]. Because sodium is transported along its electrochemical gradient, it provides the energy required for SGLT to transport glucose against its concentration gradient into the cell. SGLT mediate glucose transport across the intestinal lumen and across the epithelial cell in the proximal renal tubule[27].

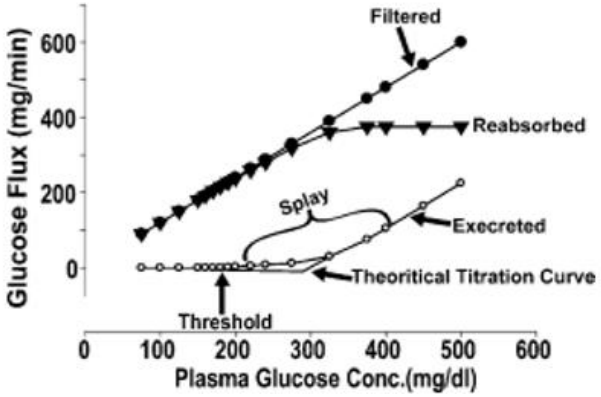
***Filtration of glucose by the kidney:***

The kidney plays a pivotal role in the regulation of the plasma glucose concentration. Approximately 180 litres of plasma with a glucose concentration of approximately 90 mg/dl are filtered by the glomeruli every day. The filtered plasma, in addition to water, salts, and amino acids, contains approximately 162 g of glucose each day. In normal glucose-tolerant subjects virtually all of this glucose is completely reabsorbed in the proximal tubule. The net result is that no glucose is excreted in the urine. Glucose transport from the lumen across the apical membrane of the epithelial cell occurs against a concentration gradient and, therefore, requires an active transport process. The early convoluted segment (S1) of the proximal tubule reabsorbs approximately 90% of the filtered renal glucose. This is accomplished by the high-capacity, low-affinity SGLT2 transporter. The remaining 10% of the filtered glucose is reabsorbed by the high-affinity, low-capacity SGLT1 transporter in the distal straight segment (S3) of the proximal tubule[28-29]. Both SGLT1 and SGLT2 couple glucose transport to the sodium gradient, and the sodium electrochemical gradient generated by active sodium transport provides the energy required for glucose transport. After glucose has been transported into the renal proximal tubular cell by the SGLT2 transporter, the sugar exits the basolateral cell border via the GLUT2 transporter. The maximum glucose transport capacity (Tm) of the proximal tubule varies between individuals and, on average, has a value of approximately 375 mg/min[28].Because the filtered glucose load is less than 375 mg/min in nondiabetic subjects, all of the filtered glucose is reabsorbed and returned to the circulation (Fig. 1).




**( Fig. 1) Renal tubular regulation of glucose reabsorption**

The amount of filtered glucose is directly related to the plasma glucose concentration. If the filtered glucose load exceeds 375 mg/min, as may occur in T2DM subjects, the Tm is exceeded, and all glucose in excess of the Tm is excreted in the urine (Fig. 2).The plasma glucose concentration at which the filtered glucose load reaches 375 mg/min is called the threshold. When the threshold is exceeded, the glucose excretion rate increases linearly and parallels the filtered load. The reabsorption and excretion curves display a nonlinear transition as the Tm for glucose is approached (Fig. 2).




**(Fig.2) Glucose reabsorption and excretion by the kidney**

***Sodium-Glucose co-transporters***:

Only the SGLT1 and SGLT2 have been well characterized in man, and their role in gut and kidney glucose transport, respectively[27]. The SGLT1 gene was first cloned from an

intestinal rabbit cDNA library[28]. The human SGLT1 gene is located at chromosome 22 q13.1 and spans 72 kb of genomic DNA[30]. It is highly conserved throughout evolution, and more than 55 members of SGLT1 have been described in bacteria, yeast, invertebrates, and vertebrates.The human SGLT1 gene encodes a 670-amino acid protein, the SGLT1 transporter, which is found in the intestinal mucosa where it transports glucose and galactose from the intestinal lumen across the intestinal mucosa. SGLT1 is also expressed in the S3 segment of the renal proximal tubule[31]. SGLT1 transports both glucose and galactose with similar affinity for both molecules. It has a glucose/galactose to sodium stoichiometry of 2:1 (Table 1) and possesses a high affinity for both glucose and galactose (Km = 0.2 mM) but a low transport capacity (Tmax = 2 nmol/mg protein . min)[32].

**Table1: Anatomical location and biochemical characteristics of the $SGL_1$ and $SGL_2$ transporters**

| | $SGL_1$ | $SGL_2$ |
|---|---|---|
| Renal location | $S_3$ segment of proximal tubule | $S_1$ segment of proximal tubule |
| Extrarenal location sugar selectivity | Gut, heart, RBC Glucose = Galactose | Brain, Liver Glucose>>Galactose |
| Na/glucose stoichiometry Glucose affinity Glucose transport capacity | 1:2 High (0.4mM) Low (2nmol/mg . min) | 1:1 Low (2mM) High (10nmol/mg . min) |
| Clinical syndrome resulting from mutation | Diarrhoea | Glucosuria |

The SGLT2 gene is located at chromosome 13[33], and it is expressed primarily in kidney cortex[27]. The SGLT2 transporter also is expressed at low levels in the brain and liver[28]. It is the principal glucose transporter in the renal proximal tubule, and it is highly selective for glucose over galactose. It has a low affinity for glucose (Km =2 mM) with high transport capacity (Tmax =10 nmol/mg protein . min), and it transports one glucose molecule for every sodium ion.

***Obesity:***

***Clinical effect of $SGLT_2$ inhibitors***:

In addition to glucose control, SGLT2 inhibitors have been shown to have beneficial effects on body weight, systolic blood pressure, and on the risks for major cardiovascular and renal events.

***Glycemic control***:

SGLT2 inhibitors have shown consistent reductions in HbA1c levels from baseline in patients with T2D.clinical trials examining the effects of SGLT2 inhibitors in HbA1c in overweight or obese subjects without T2D are limited (Table.2).

BMI body mass index, SBP systolic blood pressure, UGE urinary glucose excretion, LDL-C low density lipoprotein-cholesterol, HDL-C highdensity lipoprotein-cholesterol, IWQOL Impact of Weight on Quality of Life, TG triglycerides, FPG fasting plasma glucose, VAT visceral adipose tissue, SAT subcutaneous adipose tissue, TAT total adipose tissue, 2-h PG 2-h post-OGTT plasma glucose, IFG impaired fasting glucose, ↓ reduction, ↑ increase, =no change.

The glucose-lowering capacity of SGLT2 inhibitors is blood glucose-dependent [41] which minimizes hypoglycemic events. The plasma glucose concentration is mainly determined by hormonal and neural factors (like insulin, glucagon, and catecholamines), which regulate endogenous production of glucose [42].

SGLT2 inhibitors stimulate hepatic glucose production and also increase glucagon secretion, which promotes endogenous glucose production and restricts their glucose-lowering capacity[43].

**Table 2 Effects of SGLT2 inhibitors on body weight in obese individuals without type 2 diabetes**

| Reference, year | Duration ( week) | Treatment arms | Bodyweight change from baseline (kg) | Other effects |
|---|---|---|---|---|
| SGLT2 inhibitors Bays et al. 2014[35] | 12 | Placebo<br>Canaglifozin 50 mg Canaglifozin 100 mg Canaglifozin 300 mg | − 1.1<br>− 1.9<br>− 2.8<br>− 2.4 | ↓ BMI, SBP<br>↑UGE/creatinine ratio, LDL-C/HDL-C, IWQOL-Litetotal scores = TG, HDL-C, FPG, HbA1c, pulse rate |
| Napolitano et al. 2014[36] | 8 | Placebo+diet (− 500 cal)<br>Remoglifozin etaborate 250 mg+diet (− 500 cal) Serglifozin etaborate 1,000 mg+diet (− 500 cal) | − 5.1<br>− 7.6<br>− 6.1 | ↓ Fat mass,<br>fat free mass,leptin/ adiponectin<br>↑ UGE |
| Ramirez-Rodriguez et al. 2018 [37] | 12 | Placebo<br>Dapaglifozin 10 mg | − 1.0<br>− 3.0 | ↓ FPG, uric acid |
| SGLT2 inhibitors +GLP1-RA Lundkvist et al. 2016[38] | 24 | Placebo<br>Dapaglifozin 10 mg+Exenatide 2 mg | − 0.4<br>− 4.5 | ↓ VAT, SAT, TAT, HbA1c, 2-h PG, IFG, SBP ↑ UGE = total lean tissue, liver fat, serum lipids |
| Lundkvist et al. 2017 [39] | 52 | Dapaglifozin 10 mg+Exenatide 2 mg | − 5.7 | |
| SGLT2inhibitors+phentermine Hollander et al. 2017[40] | 26 | Placebo<br>Canaglifozin 300 mg Phentermine 15 mg Canaglifozin+Phentermine 15 mg | − 0.6<br>− 1.9<br>− 4.1<br>− 7.3 | ↓ SBP ↑ Pulse rate (Phentermine, Canaglifozin+Phentermine) = plasma lipids |

***Effects on body weight and adiposity:***

SGLT2 inhibitors directly cause body weight loss via glucose excretion (calorie loss) in the kidneys. Inhibition of SGLT2 acts in a glucose-dependent manner and can result in the elimination of about 60–100 g of glucose per day in the urine. SGLT2 inhibitors cause substantially less weight loss than expected from the energy excreted via glycosuria, because it elicits an adaptive increase in energy intake, including compensatory increases in appetite/caloric intake[44]. Therefore, combining SGLT2 inhibitors with drugs acting via different mechanisms might be the most effective approach for major weight loss and address counter-regulatory mechanisms that maintain body weight [45].

In patients with T2D or with obesity without diabetes, SGLT2 inhibitor-induced glycosuria lowers plasma glucose and insulin levels and raises fasting and post-meal glucagon concentrations. The reduction in the circulatory glucose concentration, together with the hormonal changes, results in mobilization of lipid storage [46]. This leads to changes in energy substrate use, favoring the utilization of lipids for energy production [47]. Under conditions of reduced portal insulin-to-glucagon ratio, lipolysis increases in adipose tissue and releases non-esterified fatty acids which are converted to ketone bodies in the liver through mitochondrial beta oxidation and ketogenesis[48], resulting in a metabolic condition resembling a prolonged fast [49].

Reduction of inflammation in adipose tissue would be especially important in obesity, as low-grade chronic inflammation in adipose tissue is an important mediator in the development of obesity-related complications, such as insulin resistance and T2D[50].

**Sodium Glucose co-transporters2 inhibitors ($SGLT_2$i ) :**

Reabsorption of glucose in proximal convoluted tubule (PCT) is achieved by passive transporter, facilitative glucose transporter (GLUT) and active co-transporter, sodium glucose co-transporter (SGLT)[51]. SGLT2 inhibitors inhibit the SGLT2 present in PCT which prevents reabsorption of glucose and enhances the excretion of glucose in urine (Fig.3).As glucose is excreted in urine, the glucose level in the blood is maintained and other glycaemic parameters are maintained [52]. All new antidiabetic agents have to present effective results on glycemic control to apply for marketing authorization. The SGLT2i have completed a series of phase III, double blind, placebo-controlled trials that examine the glycemic effect when added on either treatment-naive patients, or patients treated with ***metformin, SU, TZD, DPP4i, GLP1-RA*** or basal insulin as monotherapy.

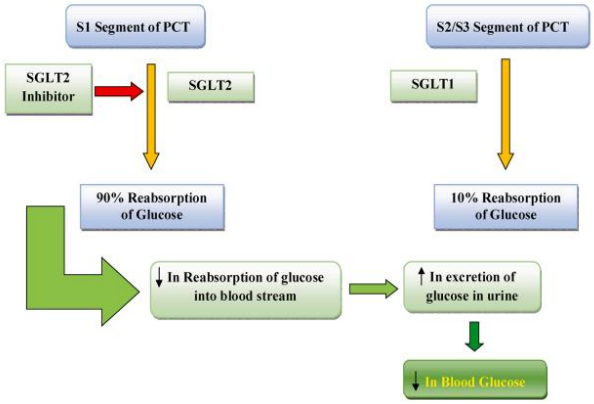



**Fig.3. Schematic representation of mechanism of action of $SGLT_2$ inhibitors.**

The available molecules in this category are Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin and Tofogliflozin [53], Phlorizin[54]. SGLT2 inhibitors are used in monotherapy or in combination with metformin, sulfonylurea or thiazolidinediones or as add on with insulin[55] .

**Phlorizin**

The first molecule identified as interfering with SGLT2 was phlorizin, isolated from the bark of apple trees in 1835 and initially studied as an antipyretic agent.The finding of major glycosuria in these experiments lead to improved insights on glucose reabsorption. Phlorizin blocks the action of both SGLT1 and SGLT2 by binding to the aglucone binding site and the glucose-binding/translocation site of the SGLT2 molecule[54].Subsequent studies in the 1950s focused on the cellular mechanism of phlorizin action and demonstrated that lower concentrations of phlorizin blocked facilitated glucose transport in erythrocytes, kidney, and small intestine[55]. The glucosuric action of phlorizin resulted from inhibition of active glucose transport in the apical membrane of the renal proximal tubule [54, 57, 58]. Phlorizin competitively inhibits both SGLT1 and SGLT2 in the proximal tubule with a higher affinity (10-fold) for the SGLT2 vs. SGLT1 transporter and, when given to normal subjects, produces glucosuria that resembles familial renal glucosuria [59].

**Table 3: Advantages and disadvantages of $SGLT_2$-inhibitors**

| Advantages | Disadvantages |
|---|---|
| • Improved glucose control, independent of insulin secretion or action | • Less effective in advanced renal failure (eGFR<60ml/min 1.73m$^3$). |
| • Significant weight loss, reduction of fat mass, beneficial effect on adipose tissue distribution | • Increased urinary tract infections |
| • Blood pressure reduction | • Increased genital infections |
| • Low risk of hypoglycemia | • Risk of dehydration |

Firstly, after oral administration, the majority of phlorizin is converted to phloretin in the gut by the enzyme disaccharidase [60]; therefore, the bioavailability of oral phlorizin is very low (15%). Secondly, phloretin, a metabolite of phlorizin, is a potent inhibitor of both GLUT2- and GLUT1- mediated glucose absorption across the brush-border membrane of the gut. At high plasma concentrations, it can inhibit insulin secretion and insulin-stimulated glucose transport. Lastly, phlorizin has low selectivity for SGLT2 compared with SGLT1 . Thus, gastrointestinal side effects are frequent after phlorizin administration. Because of these limitations of phlorizin, other compounds with greater bioavailability after oral administration and higher selectivity for SGLT2 compared with SGLT1 have been developed.

**T-1095**

T-1095 is a phlorizin derivative with higher bioavailability after oral administration [61]. It was developed by Tanabe Seiyaku Co. by the addition of a methyl-carbonate group to phlorizin to prevent its degradation in the gut by glucosidase.T-1095 is a prodrug and, after its oral administration, is metabolized in the liver to T-1095A, the active form of the compound.T-1095A acts on the proximal tubule to inhibit SGLT2 and produce glucosuria [61]. The prodrug, T-1095, also inhibits SGLT1 and, after its oral administration, has the potential to inhibit the intestinal SGLT1 transporter. Therefore, the major hypoglycemic action of T-1095 results from inhibition of SGLT2 by its active metabolite. Kinetic analysis of the inhibition of SGLT2 with T-1095 demonstrated that T-1095 causes glucosuria by decreasing the Tm for glucose reabsorption in the proximal tubule [62].

However, because of the nonselective nature of the drug and concerns over its safety, T-1095 was discontinued after phase II clinical trials.

**Dapagliflozin**

Preclinical trials have shown that dapagliflozin is a highly selective SLGT2-inhibitor, leading to a dose-dependent glycosuria and significant reduction in blood glucose levels compared to controls[63]. It has greater efficacy in inhibiting renal glucose reabsorption and possesses greater selectivity for SGLT2 vs. SGLT1 compared with both T-1095 and Serglifozin. The favourable pharmacokinetic profile and the similar beneficial results in infusion-induced hyperglycemia in healthy subjects lead to further clinical development[64].

***Glycemic control***

Dapagliflozin improves glycemic control in patients with T2DM when used as monotherapy, or when added to metformin, glimepiride or insulin . Beneficial effects are shown both on fasting plasma glucose, postprandial glycemia as HbA1. An active-controlled, non-inferiority trial randomized patients with T2DM in monotherapy with metformin, to add-on dapagliflozin or the sulfonylureum glipizide and showed similar 52-week glycaemic efficacy (HbA1c reduction of 0.52%, 95% CI 0.44% to 0.60%) [65].

***Weight loss and body composition***

In addition to improvements in glycaemic control, dapagliflozin therapy is also associated with beneficial reductions in total body weight. Glycosuria of 70-80 g a day, induced by dapagliflozin represents a net calorie loss of approximately 200-300 kilocalories per day [66]. Using dual energy x-ray absorptiometry (DEXA), it has been shown that the observed weight loss mainly appears to be reduction of fat mass (FM).

***Renal impairment***

No detrimental effects on kidney function are to be expected on theoretical bases, but it is logical that the glucose-lowering potency of dapagliflozin will be dependent on filtration rate. In patients with moderate renal impairment, the degree of inhibition of glucose reabsorption caused by dapagliflozin remained unaltered. However, the overall renal glucose clearance was declined due to the decreased eGFR, leading to a smaller intraluminal glucose concentration for a given plasma glucose concentration.

Therefore, the additional effect of SGLT2-inhibtion appears to be limited in patients with renal impairment and interventions with dapagliflozin should be reserved for patients with a GFR greater than 60mL/min [67, 68].

**Serglifozin**

It is a more potent inhibitor for renal glucose reabsorption than T-1095 [69]. Importantly,sergliflozin also has a higher selectivity for human SGLT2 [70]. Similar to T-1095, sergliflozin is converted in vivo to an active metabolite, sergliflozin A [69] . However, unlike phloretin (a phlorizin metabolite), neither sergliflozin A nor T-1095A exerts any significantinhibitoryeffect on GLUT2.In a single-dose pharmacodynamic/pharmacokinetic study in man, sergliflozin caused a dose-related (5, 15, 50, 100, 200, and 500 mg) glucosuria under fasting conditions and after glucose loading [71] . However, it is possible that further dose escalations would have caused a greater increase in 24-h glucose excretion because it is clear that the maximally effective dose of sergliflozin was not achieved. Like T-1095, sergliflozin has been discontinued after phase II clinical trials.

**Canagliflozin and empagliflozin**

Canagliflozin and empagliflozin are also high selective, well absorbed SGLT2-inhibitors. Empagliflozin has the highest selectivity for SGLT2 over SGLT1 (>2500-fold), followed by dapagliflozin (>1200-fold) and canagliflozin(>250-fold)[72]. In preclinical studies, a single oral administration of canagliflozin 3 to 30 mg/kg lead to areduced threshold for glycosuria, decreased postprandial glucose levels and a significant decline of HbA1c compared to placebo [72, 73]. Also in healthy subjects, canagliflozin reduced the renal threshold for glucose reabsorption, increased the urinary glucose excretion, reduced plasma glucose and caused weight loss [74]. In a double blind, randomized control Phase $I_b$ trial, canagliflozin was studied in patients with inadequate glycaemic control on insulin.High dose canagliflozin significantly induced body weight reduction of 2.0 to 2.9 kg versus 0.8 kg in placebo ($p<0.001$) [75, 76].

When used as add on to metformin, empagliflozin showed similar reductions in HbA1c compared to the DPP4-inhibitor sitagliptin (0.34 to 0.63% in empagliflozin groups, 0.40% in sitagliptin), but a significant difference in body weight reduction (3.14 to 4.03 kg in empagliflozin

groups, 0.41 kg in sitagliptin) [77]. The number of adverse events of canagliflozin and empagliflozin seem to be similar to the adverse events seen with dapagliflozin.

**Combination therapy with $SGLT_2$ inhibitors:**

The anticipated weight loss with SGLT2i is less than expected, possibly explained bycompensatory increase in food intake. It therefore seems logical to combine SGLT2i with anorexigenic drugs.

**With phentermine**

Phase-II trial of the combination of phentermine 15 mg (an appetite suppressant) with canagliflozin 300 mg in individuals without diabetes showed greater weight loss with combination therapy than with use of either agent alone [78].

SGLT2 inhibitor in combination with a drug that reduces food intake is appealing as a mean to mitigate the physiologic mechanisms that counteract weight loss (Fig.4)[79].

Such combination pharmacotherapy may achieve greater reduction of body weight in two ways. First, the increased food intake evoked by energy loss during SGLT2 inhibition could partly be prevented by an appetite-reducing therapy. Second, the reduced cellular energy expenditure occurring after weight loss achieved by an appetite-reducing drug may be balanced by the urinary caloric loss secondary to glucosuria[80].

Further support for the combination of an SGLT2 inhibitor with agents that reduce appetite (and/or increase satiety) is provided by a clinical trial of canagliflozin and phentermine, given either in combination or each drug alone. It would be of interest to further explore combination therapies involving an SGLT2 inhibitor together with an agent that reduces food intake.

SGLT2 inhibitors increase glucagon secretion according to some reports, and this might reduce the glucose lowering effect[81].

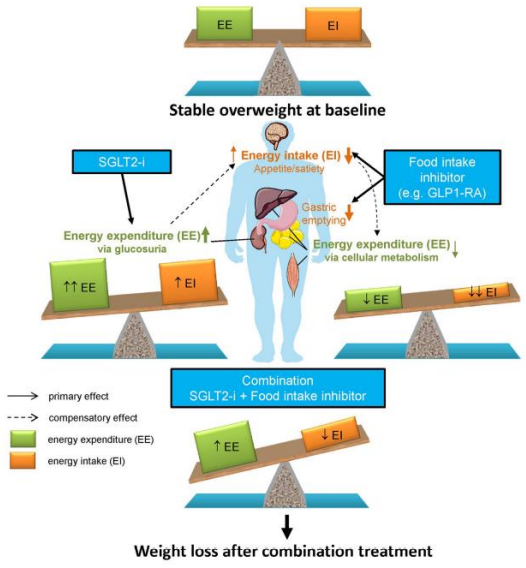



**Fig.4: Effect of $SGLT_2$ inhibitors in combination with a drug that reduces food intake on energy intake and energy expenditure and compensatory effects**

**Introduction of $SLT_2$ inhibitors for clinical practice**:

***Diabetes:***

In April 2012, the ***Committee for Medicinal Products for Human Use (CHMP)*** of EMA approved dapagliflozin 5 mg and 10 mg for the treatment of T2DM in monotherapy or as addon in case of insufficient glycemic control with oral antidiabetics or insulin. Dapagliflozin will be distributed under the brand name Forxiga. Because increased glycosuria results in caloric loss, the glycosuric agents can be expected to yield weight loss along with a reduction in plasma glucose levels. With these properties, the SGLT2 inhibitors have the potential for use throughout the continuum of diabetes treatment. Although dapagliflozin has proven its effect in different stages of the disease, we expect that dapagliflozin will mainly be used as add-on to oral antidiabetics or insulin.When dapagliflozin is used in combination with sulfonylureas or insulin, a timely reduction of the dose of sulfonylureas or insulin is warranted due to the hypoglycemic risk. Subsequent use of pioglitazone causes an increased risk of bladder cancer, subsequent use of loop diuretics causes dehydration [81].

***Obesity:***

Over the last decade, five anti-obesity medications have received approval by the US Food & Drug Administration (FDA), providing promising anti-obesity therapeutic optionsorlistat, phentermine/topiramate, bupropion/naltrexone, liraglutide, and more recently, semaglutide [82-86]. In February 2020, Lorcaserin was withdrawn from the US market, as clinical trials showed an increased occurrence of malignancies [87]. Most of the FDA-approved anti-obesity medications are administered orally, except for liraglutide and semaglutide, which require daily injectable subcutaneous administration[88-89]. The existing anti-obesity drugs act either in the central nervous system (CNS) or in the peripheral tissues, controlling appetite and metabolism.

## CONCLUSION:

SGLT2-inhibitors are a promising new class of oral anti-diabetic agents which reduce hyperglycemia by increasing urinary glucose excretion independently of insulin secretion or action.Dapagliflozin is the first highly selective SGLT2-inhibitor approved by EMA. Several studies support the concept that SGLT2 inhibitors can be effective as adjuvant weight loss therapy when given together with agents that reduce food intake and such combination treatments appear attractive. $SGLT_2$ inhibitors are most promising tools for the treatment of diabetes, obesity and we will expect more drugs near future.

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## REFERENCES


[1] American Diabetes Association, "2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019," Diabetes Care, vol. 42, Supplement 1, pp. S13–s28, 2019.

[2] M. Gong, S. Wen, T. Nguyen, C. Wang, J. Jin, and L. Zhou, "Converging relationships of obesity and hyperuricemia with special reference to metabolic disorders and plausible therapeutic implications," Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, vol. 13, pp. 943–962, 2020.

[3] S. Wen, C. Wang, M. Gong, and L. Zhou, "An overview of energy and metabolic regulation," Science China Life Sciences, vol. 62, no. 6, pp. 771–790, 2019.

[4] Fattah H, Vallon V. The potential role of SGLT2 inhibitors in the treatment of Type 1 diabetes mellitus. Drugs 2018;78:717–26.

[5] Zhong T, Tang R, Gong S, et al. The remission phase in type 1 diabetes: changing epidemiology, definitions, and emerging immuno-metabolic mechanisms. Diabetes Metab Res Rev 2020;36:e3207.

[6] Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129:587–97.

[7] Hu, G., Jousilahti, P., Sarti, C., Antikainen, R. &Tuomilehto, J. The effect of diabetes and stroke at baseline and during follow-up on stroke mortality. *Diabetologia* **49**, 2309–2316. https://doi.org/10.1007/s00125-006-0378-1 (2006).

[8] Chao, E. C. & Henry, R. R. SGLT2 inhibition-a novel strategy for diabetes treatment. *Nat. Rev. Drug Discov.* **9**, 551–559. https://doi.org/10.1038/nrd3180 (2010).

[9] Wilding JPH, Rajeev SP, DeFronzo RA. Positioning SGLT2 Inhibitors/Incretin-Based Therapies in the Treatment Algorithm. *Diabetes Care* (2016) 39:S154–64. doi: 10.2337/dcS15-3005.

[10] Li S, Nemeth I, Donnelly L, Hapca S, Zhou K, Pearson ER. Visit-To-Visit HbA1c Variability Is Associated With Cardiovascular Disease and Microvascular Complications in Patients With Newly Diagnosed Type 2 Diabetes. *Diabetes Care* (2020) 43:426–32. doi: 10.2337/dc19-0823.

[11] Zhou YL, Zhang YG, Zhang R, Zhou YL, Li N, Wang MY, et al. Population Diversity of Cardiovascular Outcome Trials and Real-World Patients With Diabetes in a Chinese Tertiary Hospital. *Chin Med J* (2021) 134:1317–23. doi: 10.1097/CM9.0000000000001407.

[12]. Simon GE, Von Korf M, Saunders K, Miglioretti DL, Crane PK, van Belle G, et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry. 2006;63(7):824–30.

[13] Malnick SD, Knobler H. The medical complications of obesity. QJM. 2006;99(9):565–79.

[14] Klein S, Sheard NF, Pi-K, et al. Weight Management Through Lifestyle Modification for the Prevention and Management of Type 2 Diabetes: Rationale and Strategies: A Statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Diabetes Care* (2004) 27:2067–73. doi: 10.1093/ajcn/80.2.257.

[15] U.S. FOOD & DRUG ADMINISTRATION. *Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors* (2021). Available at: https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm446852.htm (Accessed Feb 27, 2021).

[16] Heerspink HJL, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a Glucose-Regulating Drug With Diuretic Properties in Subjects With Type 2 Diabetes. *Diabetes ObesMetab* (2013) 15:853–62. doi: 10.1111/dom.12127.

[17] Inzucchi S, Bergenstal R, Buse J, et al. *Diabetologia* 2012;55:1577-96 and Diabetes Care 2012;35:1364-79

[18] Day C. *Br J Fam Med* 2013;1:21-24

[19] Bailey C, Feher MD 2009. *Diabetes Therapies: treating hyperglycaemia.* MedEd UK. Birmingham.

[20] UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65.

[21] Bailey C, Day C. Br J *Diabetes Vasc* Dis 2010:10,193-99.

[22] Day C, Bailey AV. Br J *Diabetes Vasc* Dis 2013:13,2-6.

[23] Oku A, Ueta, K, Arakawa K, et al. Diabetes 1999; 48: 1794–1800.

[24] Wright E. *American Journal of Physiology: Renal Physiology* 2001; 280: F10-18.

[25] Brown GK2000 Glucose transporters: structure, function and consequences of deficiency. J Inherit Metab Dis 23: 237–246

[26] . Wood IS, Trayhurn P 2003 Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins. Br J Nutr 89:3–9

[27] Wright EM, Hirayama BA, Loo DF 2007 Active sugar transport in health and disease. J Intern Med 261:32– 43.

[28] Turk E, Martín MG, Wright EM 1994 Structure of the human Na/glucose cotransporter gene SGLT1. J Biol Chem 269:15204 –15209

[29] Valtin H 1983 Renal function: mechanisms preserving fluid and solute balance in health. Boston: Little, Brown and Company.

[30] Turk E, Klisak I, Bacallao R, Sparkes RS, Wright EM 1993 Assignment of the human Na/glucose cotransporter gene SGLT1 to chromosome 22q13.1. Genomics 17:752–754.

[31] Wright EM, Turk E 2004 The sodium/glucose cotransport family SLC5. Pflugers Arch 447:510 –518.

[32] Hirayama BA, Lostao MP, Panayotova-Heiermann M, Loo DD, Turk E, Wright EM 1996 Kinetic and specificity differences between rat, human, and rabbit Na-glucose cotransporters (SGLT-1). Am J Physiol 270:G919 –G926.

[33] Wells RG, Pajor AM, Kanai Y, Turk E, Wright EM, Hediger MA 1992 Cloning of a human kidney cDNA with similarity to the sodium-glucose cotransporter. Am J Physiol 263:F459 –F465.

[34] Kanai Y, LeeWS, You G, Brown D, Hediger MA 1994 The human kidney low affinity Na/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. J Clin Invest 93:397.

[35] Bays HE, Weinstein R, Law G, Canovatchel W. Canaglifozin: effects in overweight and obese subjects without diabetes mellitus. Obesity (Silver Spring). 2014;22(4):1042–9.

[36] Napolitano A, Miller S, Murgatroyd PR, Hussey E, Dobbins RL, Bullmore ET et al. Exploring glycosuria as a mechanism for weight and fat mass reduction. A pilot study with remoglifozin etabonate and serglifozin etabonate in healthy obese subjects. J Clin Transl Endocrinol. 2014;1(1):e3-e8.

[37] Ramirez-Rodriguez AM, Gonzalez-Ortiz M, Martinez-Abundis E. Efect of Dapaglifozin on Insulin Secretion and Insulin Sensitivity in Patients with Prediabetes. Exp Clin Endocrinol Diabetes. 2018.

[38] Lundkvist P, Sjostrom CD, Amini S, Pereira MJ, Johnsson E, Eriksson JW. Dapagliflozin once-daily and exenatide onceweekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. Diabetes ObesMetab. 2016.

[39] Lundkvist P, Pereira MJ, Katsogiannos P, Sjostrom CD, Johnsson E, Eriksson JW. Dapaglifozin once daily plus exenatide once weekly in obese adults without diabetes: sustained reductions in bodyweight, glycaemia, and blood pressure over 1 year. Diabetes ObesMetab. 2017.

[40] Hollander P, Bays HE, Rosenstock J, Frustaci ME, Fung A, Vercruysse F, et al. Coadministration of Canaglifozin and Phentermine for Weight Management in Overweight and Obese Individuals Without Diabetes: a Randomized Clinical Trial. Diabetes Care. 2017;40(5):632–9.

[41] Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes ObesMetab. 2014;16(5):457–66.

[42] Gerich JE. Physiology of glucose homeostasis. Diabetes ObesMetab. 2000;2(6):345–50.

[43] Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, et al. Dapaglifozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest. 2014;124(2):509–14

[44] Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD, Ferrannini E. Energy Balance After Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015;38(9):1730–5.

[45] Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332(10):621–8.

[46] Busch RS, Kane MP. Combination SGLT2 inhibitor and GLP-1 receptor agonist therapy: a complementary approach to the treatment of type 2 diabetes. Postgrad Med. 2017;129(7):686–9.

[47] Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, et al. Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes. Diabetes. 2016;65(5):1190–5.
[48] Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159(4):262–74.
[49] Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes ObesMetab. 2016;18(8):783–94.
[50] Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr. 2006;83(2):461S–5S.
[51] D. Hsia, O. Grove, W. Cefalu, An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus, Curr. Opin. Endocrinol. Diabetes. Obes. 24 (2017) 73–79, https://doi.org/10.1097/med.0000000000000311.
[52] A. Scheen, Pharmacodynamics, Efficacy and Safety of Sodium–Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus, Drugs 75 (2015) 33–59, https://doi.org/10.1007/s40265-014-0337-y.
[53] A. Tentolouris, P. Vlachakis, E. Tzeravini, I. Eleftheriadou, N. Tentolouris, SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects, Int. J. Environ. Res. Public. Health 16 (2019) 2965–2991, https://doi.org/10.3390/ ijerph16162965.
[54] Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest 1987; 79(5): 1510-1515.
[55] S. Kalra, J. Kesavadev, M. Chadha, G. Kumar, Sodium-glucose cotransporter-2 inhibitors in combination with other glucose-lowering agents for the treatment of type 2 diabetes mellitus, Indian J. Endocr. Metab. 22 (2018) 827, https://doi.org/ 10.4103/ijem.ijem_162_17.
[56] Alvarado F, Crane RK 1962 Phlorizin as a competitive inhibitor of the active transport of sugars by hamster small intestine, in vitro. BiochimBiophys Acta 56:170 –172.
[57] Castaneda-Sceppa C, Castaneda F. Sodium-dependent glucose transporter protein as a potential therapeutic target for improving glycemic control in diabetes. Nutr Rev.
[58] Ehrenkranz JR, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes Metab Res Rev 2005; 21: 31-38.
[59] Chasis H, Jolliffe N, Smith HW 1933 The action of phlorizin on the excretion of glucose, xylose, sucrose, creatinine and urea by man. J Clin Invest 12:1083–1090.
[60] Wuthrich M, Sterchi EE 1997 Human lactase-phlorizin hydrolase expressed in COS-1 cells is proteolytically processed by the lysosomal pathway.
[61] Oku A, Ueta K, Arakawa K, Ishihara T, Nawano M, Kuronuma Y, Matsumoto M, Saito A, Tsujihara K, Anai M, Asano T, Kanai Y, Endou H 1999 T-1095, an inhibitor of renal Na+-glucose cotransporters, may provide a novel approach to treating diabetes. Diabetes 48:1794 –1800.
[62] Ueta K, Yoneda H, Oku A, Nishiyama S, Saito A, Arakawa K 2006 Reduction of renal transport maximum for glucose by inhibition of Na(+)-glucose cotransporter suppresses blood glucose elevation in dogs. Biol Pharm Bull 29:114 – 118.
[63] .Meng W. et al. Discovery of dapagliflozin: a potent, selective renal sodiumdependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. J Med Chem 2008; 51: 1145-1149.
[64] Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, Pfister M. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin PharmacolTher 2009; 85: 520-52.
[65]. Nauck MA, Del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M, Parikh SJ. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011; 34: 2015-2022.
[66]. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 20.
[67]. FDA briefing document NDA 202293, Advisory Committee meeting July 19, 2011. Retrieved Oct 5 2012 from the FDA website: http://www.fda.gov/downloads/Advisory Committees/ CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolic DrugsAdvisoryCommittee/UCM262996.pdf
[68]. Kasichayanula S et al. The influence of kidney function on dapagliflozin exposure, metabolism, and efficacy in healthy subjects and in patients with type 2 diabetes mellitus. Br J Clin Pharmacol 2012; Epub. Retrieved Dec 5th 2012 from http://dx.doi.org/10.1111 /bcp.12056.
[69]. Katsuno K, Fujimori Y, Takemura Y, Hiratochi M, Itoh F, Komatsu Y, Fujikura H, Isaji M 2007 Sergliflozin, a novel selective inhibitor of low-affinity sodium glucose cotransporter (SGLT2), validates the critical role of SGLT2 in renal glucose reabsorption and modulates plasma glucose level. J Pharmacol Exp Ther 320:323–330.
[70]. Pajor AM, Randolph KM, Kerner SA, Smith CD 2008 Inhibitor binding in the human renal low- and high-affinity Na+/glucose cotransporters. J Pharmacol Exp Ther 324: 985–991.
[71]. Hussey EK, Clark RV, Amin DM, Kipnes MS, O'ConnorSemmes RL, O'Driscoll EC, Leong J, Murray SC, Dobbins RL, Layko D, Nunez DJ 2010 Single-dose pharmacokinetics and pharmacodynamics of sergliflozin etabonate, a novel inhibitor of glucose reabsorption, in healthy volunteers and patients with type 2 diabetes mellitus. J Clin Pharmacol 50:623– 635.
[72]. Grempler R et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes ObesMetab 2012; 14: 83-90.
[73]. Nomura S et al. Discovery of canagliflozin, a novel C-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus. J Med Chem 2010; 53: 6355-6360.
[74]. Liang et al. Effect of canagliflozin on renal threshold for glucose, glycemia, and body weight in normal and diabetic animal models. PLoS One 2012; 7: e30555.
[75]. Devineni et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes ObesMetab 2012; 14: 539-545.
[76]. Rosenstock J et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012; 35: 123.
[77]. Woerle HJ et al. Safety and Efficacy of Empagliflozin as Monotherapy or Add-On to Metformin in a 78-Week Open-Label Extension Study in Patients With Type 2 Diabetes. Abstract #49-LB. Presented at the American Diabetes Association's (ADA's) 72nd Scientific Sessions®. June 8-12 2012, Philadelphia, PA.
[78]. Hollander P, Bays HE, Rosenstock J, 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(5):632-639.
[79]. Ravussin Y, Leibel RL, Ferrante AW Jr. A missing link in body weight homeostasis: the catabolic signal of the overfed state. Cell Metab. 2014;20(4):565–72.
[80]. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332(10):621–8.
[81]. Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, et al. Dapaglifozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest. 2014;124(2):509–14.
[82]. Dapagliflozin (Forxiga): EU summary of product characteristics. Retrieved Dec 1 2012 from URL: http://www.medicines.org.uk/emc/medicine/27188/SPC/ Forxiga.
[83]. Halpern, B.; Mancini, M.C. Safety Assessment of Combination Therapies in the Treatment of Obesity: Focus on Naltrexone/Bupropion Extended Release and Phentermine-Topiramate Extended Release. Expert Opin. Drug Saf. 2017, 16, 27
[84]. Halpern, B.; Halpern, A. Safety Assessment of FDA-Approved (Orlistat and Lorcaserin) Anti-Obesity Medications. Expert Opin. Drug Saf. 2015, 14, 305–315.
[85]. Nuffer, W.A.; Trujillo, J.M. Liraglutide: A New Option for the Treatment of Obesity. Pharmacotherapy 2015, 35, 926–934.

[86]. Lewis, A.L.; McEntee, N.; Holland, J.; Patel, A. Development and Approval of Rybelsus (Oral Semaglutide): Ushering in a New Era in Peptide Delivery. Drug Deliv. Transl. Res. 2021.
[87]. Sharretts, J.; Galescu, O.; Gomatam, S.; Andraca-Carrera, E.; Hampp, C.; Yanoff, L. Cancer Risk Associated with Lorcaserin—The FDA's Review of the CAMELLIA-TIMI 61 Trial. N. Engl. J. Med. 2020, 383, 1000–1002.
[88]. Anderson, S.L.; Beutel, T.R.; Trujillo, J.M. Oral Semaglutide in Type 2 Diabetes. J. Diabetes Complicat. 2020, 34, 107520.
[89]. Srivastava, G.; Apovian, C. Future Pharmacotherapy for Obesity: New Anti-Obesity Drugs on the Horizon. Curr. Obes. Rep. 2018, 7, 147–161.