# Current strategies used for better management of Type-2 diabetes mellitus

**Kawalpreet Kaur and S. Verma**

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India-144411

## Abstract

Type-2 diabetes is a chronic metabolic disorder affecting primarily the metabolism of carbohydrates. The main clinical features associated with type 2 diabetes are hyperglycemia, polyuria, and polydipsia. Several other types of complications have also been linked to type-2 diabetes. These include cardiomyopathy, neuropathy, nephropathy, retinopathy, and various microvascular and macrovascular complications. The causes of type-2 diabetes are multi-factorial and involve certain environmental or lifestyle factors and genetic factors which affect the sensitivity of body tissues towards insulin and pancreatic β-cell function. The treatment strategy for type-2 diabetes mainly focus on alleviating the symptoms associated with it such as hyperglycemia. Thus, the medication used for its management such as SGLT-2 inhibitors, sulfonylureas, and biguanides target the high blood sugar levels in the body. Other main drug classes such as thiazolidinediones, and DPP-4 inhibitors exert their anti-diabetic action through different mechanisms such as improving the tissue sensitivity towards insulin or stimulating the release of insulin from the pancreas. Diet and exercise have a very important role to play in the management of type-2 diabetes. The consumption of nuts, legumes, sea food, low-fat diet, low-carbohydrate diet and the incorporation of physical activity in the daily routine can significantly improve the life quality of the diabetic patients.

**Keywords:** Type-2 diabetes, hyperglycemia, insulin, diet

## Introduction

Type-2 diabetes (or non-insulin dependent diabetes), formerly named as adult-onset diabetes, is a chronic disorder of metabolism characterized mainly by hyperglycemia, lack of insulin in the body and insulin resistance. It accounts for around 90% of the total diabetic cases occurring worldwide. The symptoms of type-2 diabetes mellitus include weight loss, frequent urination (polyuria), increased thirst (polydipsia), and hunger (polyphagia). Chronic (long-term) complications associated with hyperglycemia include cardiovascular diseases, peripheral neuropathy, retinopathy, nephropathy and hampered flow of blood in the limbs (1). Around two-thirds of patients suffering from type 2 diabetes (T2D) experience arterial hypertension (2). The pathophysiology associating cardiovascular disease (CVD) and diabetes is multifactorial and complex. The particular form of cardiomyopathy linked with diabetes (called as diabetic cardiomyopathy) is observed as asymptomatic development of functional and structural remodelling in the heart of T2D patients in the absence of hypertension and coronary atherosclerosis (3). With the development of diabetic nephropathy, renal cells get stimulated due to hyperglycemia, resulting in the release of cytokines, humoral mediators, and growth factors. Consequently, certain structural abnormalities such as enhanced permeability of the basement membrane of the glomerulus, increased deposition of collagen on the extracellular matrix and hyaline arteriolosclerosis (mainly of the efferent arteriole) are observed in the glomeruli of the T2D patients. Such structural variations cause an enhancement in the filtration pressure and also cause microalbuminemia (4). Consequently, a compensatory stimulation of the renin-angiotensin system (RAAS) takes place. This chronic activation of the RAAS often leads to the hypertension, putting additional stress on the glomerulus and causing more damage to the nephrons (diabetic nephropathy). Mainly, certain genetic and lifestyle factors are found to be responsible for the development of type-2 diabetes mellitus. Lack of sleep and the presence of intestinal bacteria *Bacteroides vulgatus* and *Prevotella copri* has also been considered as an etiological factor

accounting for the development of this particular ailment. Lifestyle factors responsible for T2D include stress, lack of physical activity, smoking, poor diet, and obesity. Several studies have proven that lack of physical activity, obesity, diet rich in saturated fatty acids, and high-fat diet elevate the T2D risk. Moreover, on the basis of epidemiological data, less intake of cereals derived from whole grain, dietary fiber, and low-glycemic carbohydrates have been shown to increase the risk of type 2 diabetes mellitus (5). The fully illustrative genetic architecture associated with T2D has not yet been accurately established. However, few studies have revealed that there might be the involvement of multiple gene interactions in the pathogenesis of T2D. Gene-diet interactions have also been taken into consideration as a factor responsible for T2D (6). Some studies have reported the interaction of whole-grain and dietary fiber intake with *TCF7L2* variants on T2D incidence. The effect of interaction between *PPARγ* variants and fat intake, alcohol and *ADH1C *1/*2* variant on T2D incidence have also been demonstrated (7), (8). It has been shown that medium-level of alcohol intake reduced the T2D risk (9). Consuming 15 grams or more in a day weakened the positive association between T2D incidence and glycemic load by modifying the insulin sensitivity (8). Thus, the effective management of T2D is quite cumbersome and requires the complete understanding of the actual underlying cause (genetic factors or environmental factors) of the disease.

**Genetics of Type 2 Diabetes**

To a certain extent, mutations in specific set of genes increase the susceptibility to T2D. Linkage analysis revealed the involvement of two genes, namely *CAPN10* (calpain 10) and *TCF7L2* (transcription factor 7-like 2), in the pathogenesis of T2D. So far, TCF7L2 locus has been intensively analysed for type 2 diabetes risk. The T2D risk conferring alleles of the gene TCF7L2 have been found to be linked with the increased expression of this specific gene in the human islets (10). These results were verified by Dennis and colleagues and their study revealed that the TCF7L2 variant rs7903146 conferred risk of T2D by varying the incretins' effect on the secretion of insulin (11). The gene TCF7L2 has also been found to cause certain alterations in the morphology of pancreatic islets (12). Another evidence to establish the role of TCF7L2 gene in T2D comes from the observation of its impact on the Wnt signaling pathway (due to the impact of TCF4 transcription factor encoded by TCF7L2), which has a major role to play in the pathogenesis of T2D (13). Further, from the genome-wide association studies in various ethnic groups, a strong confirmation was obtained pertaining to the association between T2D and certain single-nucleotide polymorphisms affecting the gene *TCF7L2*. A variant near MTNR1B gene has also been found to be linked to an elevated fasting plasma glucose levels and higher risk of T2D. Dupuis and colleagues, in the year 2010, carried out the meta-analysis involving 21 genome-wide association studies. They observed GCK, DGKB/TMEM195, ADCY5, GCKR, and PROX1 as new genetic loci responsible for T2D susceptibility. Out of them, ADCY5, DGKB/TMEM195, PROX1, and GCK primarily affects the functioning of β-cells, whereas the locus identified in GCKR exhibits an effect on the action of insulin (14). Further, from the candidate gene studies, the involvement of various other genes in T2D has been clearly demonstrated. These genes involve wolfram syndrome 1 (*WFS1*), insulin receptor substrate 1 (*IRS1*) & *IRS-2*, peroxisome proliferator-activated receptor gamma (*PPARG*), HNF1 homeobox A (*HNF1A*), *HNF4A*, and *HNF1B* (15). *KCNQ1* (codes for the pore-forming α-subunit of the voltage-gated potassium channel, that is found primarily in the pancreas and heart) has been concomitantly reported as a T2D risk allele in two studies involving the East Asian populations. Genetic variants of CDKN2BAS, WFS1, HHEX, TCF7L2, CDKAL1, KCNQ1, and TCF2 have been found to be linked to the risk of type-2 diabetes with metabolic syndrome. The T2D risk alleles of rs972283 near KLF14 enhanced the risk of increased blood pressure and the T2D risk alleles of rs11634397 near ZFAND6 and rs972283 near KLF14 were linked to a greater risk for increased levels of triglycerides (16). Yasuda *et al.* (2008) conducted a genome-wide association study pertaining to type 2 diabetes and they observed an association between a single nucleotide polymorphism (SNP rs2237892 in intron 15) in *KCNQ1* and T2D risk (17). In the same year (2008), Unoki *et al.* carried out a genome-wide association study employing 207,097 SNP markers in Japanese individuals and they detected a strong link between a SNP rs2283228 in the gene *KCNQ1* and T2D risk (18). Though several T2D risk variants have been identified through the genome-wide association studies but still only a small proportion of the observed heritability has been explained by these variants.

**Lifestyle factors: Exercise, Diet, and Obesity**

Certain lifestyle factors have been found to be important for the progression of T2D. These include lack of physical activity, cigarette smoking, sedentary lifestyle and alcohol consumption **(Fig. 1).** Obesity has been found to result in around 55% of the cases of T2D. Most of the people with early onset T2D are obese (around 80–92%) as compared with 56% of older adults exhibiting a linear inverse relationship between the age during T2D diagnosis and body mass index (BMI) (19). Certain environmental toxins may also be responsible for the recent increases in the rate of T2D. A positive correlation has been noticed recently between the incidence of T2D and the concentration of bisphenol A in the urine, independent of the confounding factors such as body mass index (BMI), gender, ethnicity, and levels of serum cholesterol (20). Diet is also considered to be a factor affecting the T2D susceptibility. Srinivasan *et al.* (2005) analysed the effects of high-fat diet on low-dose streptozotocin-treated rats (a type 2 diabetes model). They observed hyperinsulinemia and a noticeable reduction in the *K*-value (glucose disappearance rate), indicating the development of insulin resistance in rats after they were fed with high-fat diet (21). In another study done by H. Sone & Y. Kagawa (2005), high-fat diet-induced diabetic mice showed pancreatic β-cell senescence and impaired insulin secretion (22). Smoking results in the impairment of glucose homeostasis, causes chronic diabetic complications and increases the diabetic incidence. The onset and development of diabetic nephropathy (microvascular complications) is strongly linked with smoking. It is also found to be linked with greater incidence of CHD and mortality (macrovascular complications) (23). On the other hand, research done pertaining to the association between the risk for T2D and alcohol consumption has presented some heterogeneous findings. Moderate and light alcohol consumption has been linked with the reduced risk for T2D, whereas extensive alcohol consumption has not been linked to the T2D risk (24,25).

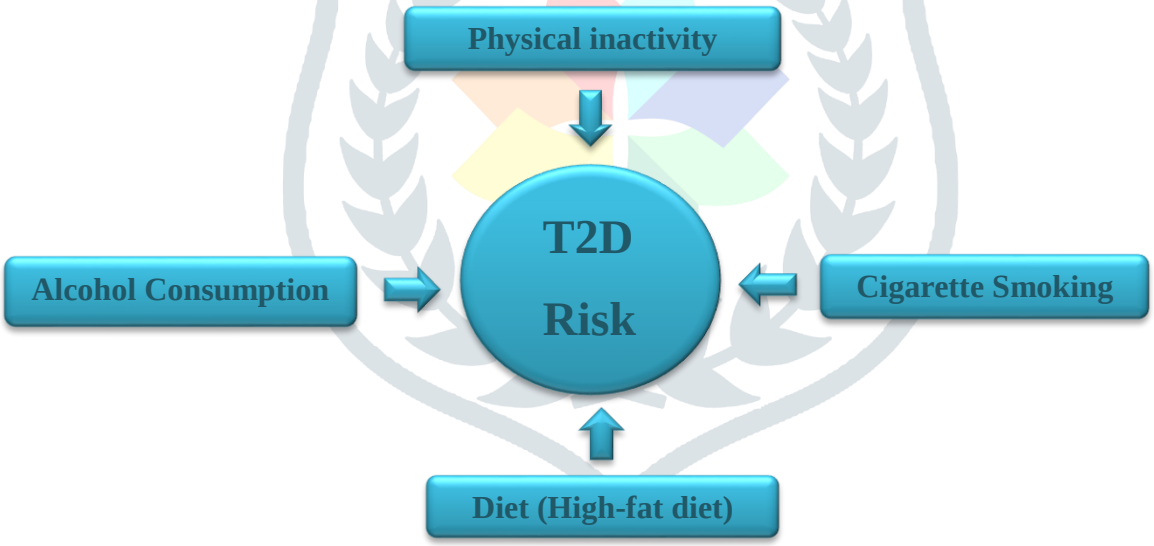


**Fig 1:** Lifestyle factors affecting T2D risk

**Management of Type-2 diabetes**

**Pharmacotherapy**

Management of T2D using drugs is merely based upon the regulation of hyperglycemia associated with the disease. Thus, several therapeutic classes of hypoglycemic drugs have been developed to manage hyperglycemia in T2D **(Table 1)**. These include biguanides (metformin), sulfonylureas (glyburide, glimepiride, glipizide), thiazolidinediones (rosiglitazone, pioglitazone), alpha-glucosidase inhibitors (acarbose, miglitol), incretins (exenatide, liraglutide), SGLT-2 inhibitors (Gliflozins) and DPP-4 inhibitors (saxagliptin, sitagliptin, linagliptin).

**Table 1:** Drug classes employed for the treatment of type 2 diabetes mellitus

| Drug class | Expected reduction in HbA1c after employing monotherapy (%) | Benefits | Side-effects |
|---|---|---|---|
| Sulfonylureas | 1.0-2.0 | Rapid effect | Hypoglycemia, weight gain |
| Biguanides | 1.0-2.0 | Lesser side-effects, weight neutral | Megaloblastic anemia, gastro-intestinal side effects |
| Meglitinides | 0.5-1.5 | Suitable in case of postprandial hyperglycemia | Three-times dosing/day, weight gain |
| Thiazolidinediones | 0.5-1.4 | Positive effect on lipid parameters | Weight gain, fluid retention, bone fractures |
| Dipeptidyl peptidase-4 inhibitors | 0.5-0.8 | Does not result in weight gain | Pancreatitis |
| Alpha-glucosidase inhibitors | 0.5-0.8 | Minimal risk of hypoglycemia | Inflammatory bowel disease, liver cirrhosis, colon ulcer |
| Glucagon-like peptide-1 agonists | 0.5-1.0 | Weight loss | Gastro-intestinal adverse effects, pancreatitis |
| Bile acid sequestrants | 0.5-0.9 | Weight-neutral | Constipation |

**Sulfonylureas**

Sulfonylureas (First-generation sulfonylureas & second-generation sulfonylureas) work by closing the ATP-sensitive potassium channels present on the plasma membrane of β-cells and ultimately resulting in the enhanced secretion of insulin **(Fig. 2)**. The ATP-sensitive potassium channel of β-cells is a complex consisting mainly of two proteins: a drug-binding subunit (SUR1) that acts as the receptor for sulfonylureas and a pore-forming subunit (known as Kir6.2) (27). Sulfonylureas enhance the late postprandial and fasting insulin, resulting in the reduced glucose levels in the blood and $HbA_{1c}$ values. Sulfonylureas get primarily metabolized or transformed in the liver. The adjustments in the dosage should be done with the drugs which generate active metabolites or which are excreted via the renal route in the patients whose renal system does not function normally. Commonly observed adverse effects with the use of sulfonylureas includes water retention, weight gain, and hypoglycaemia. First-generation sulfonylureas exhibit lower potency and this particular class include tolazamide, acetohexamide, tolbutamide, and chlorpropamide. The second-generation drugs penetrate into the cell membranes more easily as compared to the first-generation sulfonylureas and this class includes glyburide, glipizide, and glimepiride. The first-generation sulfonylureas exhibit higher possibility for the occurrence of adverse events because they attach ionically to the plasma proteins, and result in greater drug-drug interactions. The University Group Diabetes Program (UGDP) clinical trial noticed an increment in the number of deaths occurring because of heart disease in patients treated with tolbutamide as compared to the patients treated with placebo or insulin. The main mechanism involved is the inhibition of

ischemic preconditioning because of the blockage of potassium ATP channels present on the cells of myocardium (SUR2A). The second-generation sulfonylureas do not inhibit the ischemic preconditioning because they are considered to be more selective for the pancreatic β-cell receptors. The U.K. Prospective Diabetes Study (UKPDS 33) involved 3,867 patients who were newly diagnosed with T2D (persisting for more than 10 years). The rates of diabetes-related deaths or myocardial infarction (MI) were found to be same between the insulin groups and sulfonylurea groups. The patients in the insulin, glyburide, and chlorpropamide groups exhibited similar sudden death rates (28). The CAROLINA (cardiovascular outcome study of linagliptin versus glimepiride in T2D patients) study was a randomised, multicentre, double blind study which was conducted (November 11, 2010- August 21, 2018) in order to analyse the cardiovascular safety of linagliptin versus glimepiride in patients suffering from T2D at higher risk of cardiovascular disease. The study demonstrated that glimepiride (sulfonylurea) and DPP-4 inhibitor linagliptin exhibits fairly similar cardiovascular safety in the type 2 diabetes patients. This was a very crucial finding because some studies done previously have suggested that sulfonylureas might not be safe for the heart. Currently, the USFDA has a product-label warning for adverse cardiovascular event for all of the sulfonylureas (29).

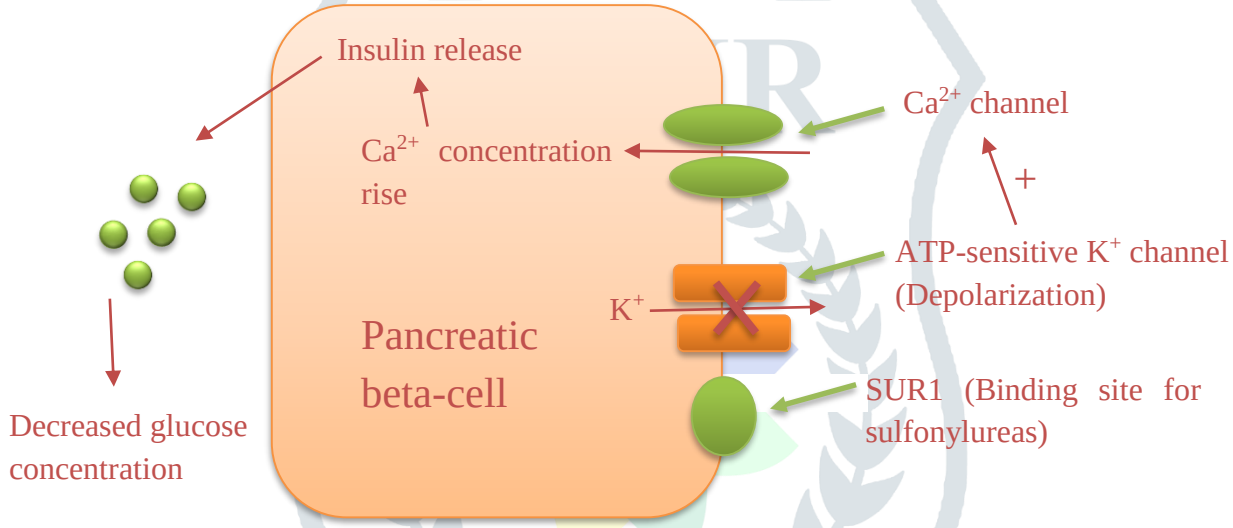


**Fig 2:** Mechanism of action of sulfonylureas

**Biguanides**

Biguanides represent the class of drugs which possess multiple clinical uses. Metformin, a commonly used anti-hyperglycemic agent belongs to this class and it works by inhibiting the mitochondrial respiration by suppressing the respiratory complex I (30). Initially, metformin is administered as 500 mg oral dose every 12 hours or 850 mg once daily. The oral tablet of metformin is normally supplied in two different forms: extended-release tablet and immediate-release tablet. The immediate-release tablet is marketed under the brand name Glucophage whereas the extended-release tablet is marketed under the brand names Glumetza**,** Fortamet, and Glucophage XR. However, the drug metformin is also available in the market as extended-release suspension **(**5 mL once a day administered along with the evening meal) and solution **(**initially, 5 mL twice daily, or 8.5 mL once a day with the meals). It causes 1% to 2% reductions in $HbA_{1c}$ levels and may also lead to lesser macrovascular complications (31). In the initial United Kingdom Prospective Diabetes Study (UKPDS) study, the newly diagnosed overweight T2D patients who were given metformin observed around 39% decrease in the myocardial infarction risk and around 36% decrease in the total mortality after a follow-up period of around 10 years. No such reduction was observed in the patients who were assigned randomly to receive insulin or sulfonylureas. The side-effects observed with the use of metformin include

lactic acidosis (biguanides elevate the risk of lactic acidosis), metallic taste, vitamin $B_{12}$ deficiency, and GIT symptoms. Up to 25% of patients suffer metformin-associated gastrointestinal (GI) side-effects. Metformin must be avoided in patients suffering from renal impairment, severe liver disease, heart failure, shock, and tissue hypoperfusion. The glycaemic response to metformin is considered to vary from patient to patient and it gets influenced to a certain extent by the genetic factors (rs8192675 variant plays a major role in this regard). A very strong association between the metformin-induced HbA1c reduction and rs8192675 variant has been established. The C allele of rs8192675 in the intron of *SLC2A2* gene (codes for GLUT2), has been linked to a 0.17% ($p=6.6\times10^{-14}$) higher metformin-induced decrease in the levels of HbA1c (32). Some of the patients respond very well to the metformin treatment, whereas others exhibit non-responsiveness towards it. One of the reasons behind this is the presence of some level of interindividual variability in metformin pharmacokinetics. Normally, the drug (metformin) does not get metabolized in the body and thus gets excreted in the urine in an unchanged form. It has a half-life of approximately 5 hours. The drug gets immensely distributed into various tissues of the body including the kidney, liver, and intestine. The hepatic uptake, renal excretion, and oral absorption of metformin are performed mainly via the organic cation transporters (OCTs) (33). An intron variant of OCT1 (SNP rs622342) have been linked to a reduced impact on blood glucose in the case of heterozygotes and an absence of metformin effect on the plasma glucose levels in the case of homozygotes (34). The plasma membrane monoamine transporter (gene *SLC29A4*) and OCT3 (gene *SLC22A3*) are considered to mediate the intestinal absorption of metformin. In addition, OCT1 (encoded by the gene *SLC22A1*) may promote the uptake of metformin into the interstitial fluid. The hepatic uptake of metformin is performed mainly by OCT1 (*SLC22A1*) and to a certain extent by OCT3 (*SLC22A3*). In one study, in the OCT1-deficient mice, the concentration of metformin in the liver was found to be significantly lower as compared to that found in control mice, indicating that OCT1 is crucial for the metformin uptake in the liver (35).

**Thiazolidinediones**

The thiazolidinediones are a newer class of drugs prescribed for the management of type-2 diabetes. They primarily show their action by improving the sensitivity of body tissues towards insulin by engaging with the PPAR-γ (peroxisome proliferator-activated receptor gamma). Upon binding with the ligand, PPAR-γ receptor stimulates a set of genes which essentially play a critical role in the metabolism of glucose and fatty acids, ultimately resulting in an increase in the insulin effect. The thiazolidinediones cause a reduction in the levels of blood glucose in T2D patients and also work additively with certain other antidiabetic drugs. The first drug under this class which was granted approval for its use as an antidiabetic medication in the US was troglitazone (in the year 1997). However, reports of serious hepatic injury and deaths occurring from acute liver failure started to appear, within a year of its approval. Certain recommendations and cautionary statements were made for the monitoring of ALT levels, but after the reporting of around two dozen cases of liver failure and the launch of two new thiazolidinediones in the year 1999, troglitazone was finally withdrawn from the market in the year 2000. The newer drugs in this class, pioglitazone and rosiglitazone, have been linked to only rare chances of acute hepatic injury. Both pioglitazone and rosiglitazone are associated with heart failure, increased weight gain, and fracture risk. They are regarded as second-line agents for T2D and prescribed only after the failure of lifestyle modifications and metformin (36). The most significant advantage of TZDs is that they do not result in hypoglycaemia when employed as monotherapy and are also not contraindicated in patients suffering from renal disease. Effectiveness of sulfonylureas, thiazolidinediones, and DPP-4 inhibitors given after metformin to reduce HbA1c level up to 7% or less of the total hemoglobin was found to be fairly similar in patients with type 2 diabetes (37).

**SGLT-2 inhibitors**

Hyperglycemia is an important pathogenic factor involved in the development of various microvascular and macrovascular problems in type-2 diabetes. The inhibition of reabsorption of glucose from the renal tubules

responsible for the generation of glycosuria have been recommended as a new mechanism to achieve normal glucose levels in the body and thus alleviate such complications. The sodium glucose cotransporter 2 (SGLT2) has a major role to play in the glucose reabsorption in kidney. SGLT-2 inhibitors prevent the reabsorption of glucose from renal tubules, thus enhancing the urinary excretion of glucose and lowering the levels of plasma glucose. These drugs possess a very unique mode of action that is not dependent on the functioning of $\beta$- cells or modulation of tissue sensitivity towards insulin. Thus, these drugs possess the potential to be employed in combination with insulin as well as certain other oral antidiabetic agents. The first SGLT2 inhibitor that received market approval in the U.S. was canagliflozin (Invokana™, manufactured by Johnson & Johnson). Canagliflozin resulted in the reduction of fat mass, white adipose tissue weight, and body weight. It also inhibited adipocyte hypertrophy and resulted in an improvement in the lipid and glucose metabolic disorders caused by the consumption of high-fat diet (38). Singh *et al.* (2020) prepared solid SMEDDS through spray drying utilizing neusilin US2 as an adsorbent. The pharmacological assessment of solid SMEDDS showed increased anti-diabetic effect of canagliflozin predominantly through the inhibition of SGLT II in rats (39). The CANVAS program consisted of two randomised, double-blind trials which evaluated placebo against canagliflozin in the participants (suffering from type-2 diabetes) who were at increased risk of the occurrence of cardiovascular events. Canagliflozin treatment was found to be linked with a decreased risk of kidney functions deterioration, attenuated eGFR decline, and a decline in albuminuria, that explains the possible reno-protective action of the drug in T2D patients (40). In the year 2014, the US FDA approved INVOKAMET™, a fixed-dose therapy combining metformin hydrochloride and canagliflozin in a single tablet, for the management of T2D in adults. In the same year, the US FDA approved empagliflozin (Jardiance®) tablets as an adjunct to exercise and diet to effectively manage the levels of blood glucose, in adults with T2D. It is not recommended for people with type 1 diabetes or for people with diabetic ketoacidosis (41). Ipragliflozin (a selective SGLT2 inhibitor), developed jointly by Kotobuki Pharmaceutical and Astellas Pharma, received approval in Japan in the year 2014, and in Russia in the year 2019. In Japan, the safety and efficacy of ipragliflozin in monotherapy was assessed in a Phase III study and the same in combination with other hypoglycemic agents were evaluated in clinical studies. The most common adverse events noticed were infections of the upper respiratory tract and urinary tract (42). As compared to the antidiabetic drugs used currently, SGLT2 inhibitors do not pose the risk of hypoglycemia since they do not stimulate the secretion of insulin. Moreover, they do not pose any risk of the occurrence of gastrointestinal side effects.

**Table 2:** Current status of various SGLT2 inhibitors (43,44,45)

| Drug Candidate | Manufacturing company | Indication | Side-effects | Status |
|---|---|---|---|---|
| Canagliflozin | Johnson & Johnson | Type 2 diabetes mellitus, myocardial infarction, stroke | UTI, low blood sugar, vaginal yeast infection, hives | Approved by US FDA |
| Ertugliflozin | Pfizer | Type 2 diabetes mellitus | adrenal medullary pheochromocytoma | Approved by US FDA |
| Tofogliflozin | Chugai Pharmaceuticals | Type 2 diabetes mellitus | Nasopharyngitis, upper respiratory tract infections, pollakiuria, hypoglycaemia and increased blood | Approved in Japan |

| | | | | |
|---|---|---|---|---|
| | | | ketone bodies | |
| Luseogliflozin Hydrate | Taisho Pharmaceuticals Co. Ltd & Novartis | Type 2 diabetes mellitus | Hypoglycaemia (only observed in luseogliflozin-SU combination therapy) | Approved by Pharmaceuticals and Medical Devices Agency of Japan (PMDA) |
| Ipragliflozin | Astella Pharma. Inc. | Type 2 diabetes mellitus | UTI, upper respiratory tract infections | Approved in Japan and Russia |
| Empagliflozin | Boehringer Ingelheim | Type 2 diabetes mellitus | Diabetic ketoacidosis, UTI, fungal infections | Approved by US FDA |
| ISIS 388626 | Isis Pharmaceuticals | Type 2 diabetes mellitus | Serum creatinine increase, renal dysfunction | Completed phase I trial in Netherlands in 2012 (Clinical trial: NCT00836225) |
| Sotagliflozin (LX 4211) | Lexicon Pharmaceuticals | Type 2 diabetes mellitus | | Under clinical development |

**DPP-4 inhibitors**

DPP-4 inhibitors enhance the secretion of insulin and decrease the secretion of glucagon by elevating the concentrations of endogenous glucagon-like peptide-1 (GLP-1). This class include the drugs saxagliptin, sitagliptin, alogliptin, and linagliptin). They do not pose any risk of hypoglycaemia and are considered to be body weight neutral. The side-effects observed with their use are upper respiratory tract infections, headache and sore throat. Majority of drugs in this class can be used to treat patients with hampered renal function. In the recent years, DPP-4 inhibitors highly substituted sulfonylureas as the second line mode of treatment after the metformin failure and nowadays several DPP-4 inhibitor/metformin fixed dose combinations are currently available in the market. The treatment employing DPP-4 inhibitors must be terminated if GLP-1 receptor agonists are employed. DPP-4 inhibitors may also be employed as monotherapy in case metformin is not tolerated or contraindicated (46). The cardiovascular safety of these drugs has been questioned after the conduct of clinical trials (EXAMINE and SAVOR-TIMI 53). The SAVOR-TIMI 53 clinical trial findings revealed around 27% rise in hospitalization for heart failure in the diabetic patients (who received saxagliptin). VERIFY was a double-blind, randomised, parallel-group study involving the patients who were newly diagnosed with T2D. The findings of the study suggested that the combination therapy of metformin with vildagliptin imparts more long-term benefits (revealed by the findings of VERIFY) as compared to the metformin monotherapy (47).

**Other medications**

Some other classes of drugs such as incretin (GLP1) mimetics (albiglutide, dulaglutide exenatide, liraglutide, and lixisenatide), meglitinides (nateglinide), amylin mimetics (pramlintide), bile acid sequestrants (colesevelam), basal insulin, and alpha-glucosidase inhibitors (acarbose, miglitol) are also employed for the management of type 2 diabetes. De Ciuceis *et al.* (2018) investigated the effect of incretin mimetics (exenatide, liraglutide) on the circulating endothelial progenitor cells and capillary density in the patients of T2D. Their findings revealed that the body mass index and blood pressure got decreased after treatment with liraglutide, while the patients treated with exenatide did not show any such change. The circulating endothelial progenitor cells increased significantly post treatment with exenatide, but no such enhancement was observed after the treatment with liraglutide. The microvascular density slightly increased after treatment (4 weeks

duration) with exenatide (48). When compared insulin glargine with exenatide in patients with type-2 diabetes, similar decrease was witnessed in the levels of HbA1c in both the insulin and exenatide groups (49). Moreover, exenatide caused weight loss and reduced postprandial glycaemia contrary to any other treatment strategy utilizing insulin. It also showed smaller instances of nocturnal hypoglycaemia as compared to the insulin glargine. The anti-diabetic potential of lixisenatide have been assessed as monotherapy and in combination with other orally-active anti-diabetic agents (sulfonylureas, pioglitazone, metformin). In a 24-week double-blind clinical trial of placebo vs 20 mcg lixisenatide once daily in 680 type-2 diabetes patients not adequately controlled with metformin (with mean 8.1% HbA1c value), the mean decrease in HbA1c was higher with lixisenatide (-0.9%) (50). Lixisenatide have also been used in conjunction with basal insulin. In a 24-week double-blind clinical trial involving 495 diabetic patients not effectively managed with metformin and insulin glargine, the reduction in HbA1c was found to be higher in the lixisenatide group (-0.6%) contrary to the placebo group (-0.3%) (51). The combination of basal insulin with incretin mimetics have also been linked to the improvements in the postprandial and basal glucose control, reduction in the risk of hypoglycaemia and weight gain (52). At present, the incretin (GLP-1) mimetics are only available as injectables (administered either as once daily or once weekly). The once-weekly injection of semaglutide, which is a long-acting incretin mimetic or GLP-1 agonist, has recently been granted approval by the U.S. FDA for use as an adjunct to exercise and diet (53). The oral semaglutide is the first GLP-1 agonist that received approval from the U.S. FDA (in September 2019) for the treatment of type-2 diabetes (54). All GLP-1 agonists must not be used in patients having any history of pancreatitis and are not approved for the treatment of type-1 diabetes. Colesevelam has also been proven to be very effective in the management of T2D. The phase III clinical data have revealed that colesevelam is capable of reducing HbA1c levels by ~5 mmol/mol. It has also been found to reduce low-density lipoprotein (LDL) levels and total cholesterol (55). In addition, colesevelam has also been used as an add-on treatment for the control of hyperglycaemia and dyslipidemia in the patients type 2 diabetes mellitus (56). GPR119 (G protein-coupled receptor 119, mainly expressed in the gastrointestinal tract and pancreas) agonists have been proposed as novel treatment method for diabetes (because GPR119 has been shown to regulate insulin secretion and incretin) and obesity (57). Technosphere insulin (which is a new inhaled insulin) can be employed in conjunction with the basal insulin injections. It exerts lesser hypoglycaemic effect as compared to the rapidly acting insulin, but is associated with lesser extent of hypoglycaemia. Main side-effects noticed with its use are reduction in the forced expiratory volume and cough and it is not recommended for use in patients suffering from chronic lung disorder (58). Novel chitosan derived formulations (CS-6 & CS-7) containing derivatives of xanthine have been developed as antioxidant and antidiabetic treatment strategy. The formulation containing xanthine-6 (CS-6) has been proven to decrease the levels of glucose in the blood by 59.3% (and HbA1c level of 4.53%) (59). A novel smart patch of insulin has also been developed, which is a square-shaped thin patch containing around 100 small needles packed with enzymes sensitive to glucose and insulin in microscopic storage compartments. When the blood glucose levels increase, this patch releases the stored enzymes. The patch administration depicted decreased glucose levels for up to 9 hours in a mouse model (60).

**Diet and exercise**

Low-carbohydrate and low-fat based diet are normally prescribed for the effective management of type-2 diabetes. Both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend a low-carbohydrate based diet and support the short-term use of low carbohydrate diet for the purpose of weight loss. High egg intake has also been found to elevate the risk of type 2 diabetes and certain cardiovascular diseases. The consumption of up to 7 eggs/week is considered to be safe in healthy individuals, but the consumption of eggs in T2D patients should be strictly regulated (61). Lee *et al.* (2016) assessed the effect of a conventional diet recommended to the diabetic patients and the vegan diet on the control of glucose levels in the body among Koreans. Both the diets caused reductions in the levels of HbA1c. However, the glycaemic control was found to be much better with the use of vegan diet as compared to the conventional diet. Therefore, the dietary guidelines for the T2D patients must incorporate a vegan diet for the effective management of type 2 diabetes (62). It has also been observed that the individuals who had higher intakes of nuts, legumes, sea food, and monounsaturated fatty acids were at a lower risk of developing T2D (63). On the basis of recent epidemiological data and research data, it has been found that long-term

consumption of coffee lowers the risk of developing T2D in healthy people (64). Exercise also forms a crucial component of obesity and diabetes prevention. Exercise, whether resistance training or aerobic or a combination of both, has been linked to improved glucose regulation (65).

## Conclusion

While metformin and lifestyle improvements form the most important component in the initial management of type-2 diabetes, certain second-line and third-line pharmacological agents have already been developed for the management of this disease. Different classes of injectable and oral drugs are currently available in the market. These include meglitinides, sulfonylureas, thiazolidinediones, SGLT-2 inhibitors, DPP-4 inhibitors, incretin mimetics, amylin mimetics, bile-acid sequestrants, and alpha-glucosidase inhibitors. Moreover, certain insulin analogues have also which stimulate the secretion of endogenous insulin have also been introduced. Metformin is commonly employed for the management of type-2 diabetes and thus represents the first treatment choice for majority of the diabetic patients. However, the second-choice of treatment must be personalized by considering various patient characteristics such as the presence of other health problems and extent of hyperglycaemia. Although it is not clear that the ultimate cure of type-2 diabetes will be found in the near future, novel effective anti-diabetic drugs that may improve the quality of life of the patients suffering from diabetes, are being developed.

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