IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 7 Issue 7, July 2020
ISSN (Online) 2348 – 7968 | Impact Factor (2020) – 6.72
www.ijiset.com

Diabetes Mellitus and Treatment of T2DM with SGLT-2 Inhibitor and DPP-4 Inhibitor in a Combined Tablet Dosage Form

Tayal Deepak[1], Bajaj Sakshi[*2],

[1] Department of quality assurance, Delhi Institute of Pharmaceutical Sciences and Research pushp vihar, sector-III, M. B road, New Delhi - 110017, India.

[2] Department of Pharmacognosy and phytochemistry, Delhi Institute of Pharmaceutical Sciences and Research pushp vihar sector-III, M. B road, New Delhi - 110017, India.

Abstract

Diabetes mellitus (DM) is a metabolic disorder resulting from a imperfection in insulin secretion, insulin action, or both. Insulin deficiency results into chronic hyperglycemia with troubles of carbohydrate, fat and protein metabolism. Diabetes mellitus may be characterized into numerous types but the two main types are type 1 and type 2. Drugs are used mainly to save life and improve symptoms. Insulin replacement therapy is the support for patients with T1DM while diet and lifestyle changes are well-thought-out the keystone for the treatment and management of T2DM. Insulin is also important in DMT2 when blood glucose levels cannot be maintained by diet, weight loss, exercise and oral medicines. Oral hypoglycemic agents are also valuable in the treatment of T2DM. Oral hypoglycemic agents include sulfonylureas, biguanides, alpha glucosidase inhibitors, meglitinide analogues, thiazolidinediones, DPP-4 inhibitors and SGLT-2 protein inhibitor. The aim of these drugs is to correct the basic metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an suitable diet and lifestyle fluctuations. Diet and lifestyle plans are to decrease weight, improve glycemic control and decrease the risk of cardiovascular problems, which account for 70% to 80% of deaths among those with diabetes. Together, DPP-4i and SGLT2i fulfil a requirement for pharmacological agents with complementary mechanisms of action that can be used in combination to recover glucose control in a wide range of patients with T2DM, with a low risk of adverse events, such as hypoglycaemia or weight gain and the potential of cardiovascular protection. Qtern is a new fixed- dose combination of the DPP-4 inhibitor saxagliptin with the SGLT2 inhibitor dapagliflozin for the control of type 2 diabetes launched by AstraZeneca**.**

keywords

Diabetes mellitus, T2DM, treatment of T2DM, combination therapy of DPP-4i and SGLT-2i, dapagliflozin plus saxagliptin and Qtern (AstraZeneca).

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic illness in which blood glucose level rises beyond the prescribed limit and it results from a fault in insulin secretion, insulin action, or both.[1-5] Insulin deficiency

results into chronic hyperglycemia with troubles of carbohydrate, fat and protein metabolism which results into hyperglycaemia, glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonaemia.[1-6] It is the most common endocrine illness.[1,7-9]

As the disease grows tissue or vascular damage ensues resulting into severe diabetic problems such as neuropathy, retinopathy, nephropathy, cardiovascular problems, ulceration and UTIs etc. Thus, diabetes covers a wide range of heterogeneous diseases.[1,10-17]

It is projected that by the year 2010, more than 200 million people worldwide will have DM and 300 million will afterward have the disease by 2025. [1,7-9]

Diabetes mellitus can be categorised into several types but the two main types are type 1 and type 2. Out of which type 2 is the most common.[18,19]

Drugs being used mainly to save life and decrease the symptoms. Secondary objectives are to avoid long-term diabetic problems and, by removing various risk factors, to increase durability.[20]

Insulin replacement therapy is the crucial treatment for patients with T1DM while diet and lifestyle changes like daily routine physical exercise are well-thought-out best for the treatment and management of T2DM. Also, T2DM can be treated with exogenous insulin and few hypoglycemic agents like sulfonylureas, biguanides, DPP-4i, thiazolidinedione, alpha-glucosidase inhibitors, GLP-1 and SGLT-2 inhibitors.[21]

Table 1. Classification of diabetes mellitus on the basis of etiology:[19,22-25]

S.NO	Type of DM	Further classification	Etiology
1.	Type 1 DM (IDDM)		due to immunological destruction of pancreatic ß cells resulting in insulin deficiency.
1a.		Type 1a	Type 1a is characterized by the presence of islet cell antibody (ICA), anti-glutamic acid decarboxylate (anti-GAD), IA-2 or insulin antibodies that identify the autoimmune process with ß -cell destruction. Autoimmune diseases such as Grave's disease, Hashimoto's thyroiditis and Addison's disease may be associated with type 1 diabetes mellitus.
1b.		Type1b	there is no evidence of autoimmunity. There is no known etiological basis for type 1b diabetes mellitus. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity.

2.	Type 2 DM (NIDDM) Maturity onset DM:		There is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal or even high, no anti-β-cell antibody is demonstrable; has a high degree of genetic predisposition; generally, has a late onset (past middle age). Over 90% cases of diabetes are type 2 DM.

2. Pathophysiology of type 2 DM:

Also called as noninsulin-dependent diabetes mellitus (NIDDM)/maturity onset diabetes mellitus as there is no harm or judicious reduction in β cell mass; insulin in blood circulation is low, normal or even high, no anti-β-cell antibody is noticeable; also has a very large degree of genetic tendency; generally has a late onset (past middle age). Over 90% cases of diabetes are T2DM.[6,26,27]

2.a. Etiology

T2DM is triggered by a combination of genetic factors linked to reduced insulin secretion and insulin resistance and environmental factors such as obesity, overeating, lack of exercise, and stress, as well as aging. A fact well-thought-out significant in pathogenesis is that Japanese show lesser insulin secretory capacity after sugar stacking, telling smaller potential for pancreatic cell function than Western people. It has also been indicated out that Japanese persons may have many diabetes-sensitive genes with thrifty genes. The number of diabetic patients is increasing quickly reflecting the variations in lifestyle.[26-27]

2.a.1. Genetic factors involved in the pathogenesis of diabetes:

The pathogenesis has been expected to involve genetic anomaly in the molecules linked to the regulatory system of glucose metabolism.[26] The analysis of candidate genes targeted at glucose-stimulated insulin secretion of pancreatic cells and the molecules containing the molecular mechanism for insulin action have identified genetic anomalies that can be self-determining causes of pathogenesis, together with those in glucokinase genes, mitochondrial genes, and insulin receptor genes. Recently, a genome wide association study (GWAS) has identified the mutation in the KCNQ1 gene related to insulin secretion anomaly as an significant disease-susceptible gene related to the pathogenesis of diabetes in Asian ethnic groups including the Japanese.[28] The genetic anomalies described so far, all combined, explain about 30% of the genetic factors for diabetes.[27,28]

2.a.2. Roles of environmental factors:

Aging, obesity, insufficient energy consumption, alcohol drinking, smoking, etc. are self-regulating risk factors of pathogenesis. Obesity (specifically visceral fat obesity) due to absence of exercise is accompanied by a reduction in muscle mass, encourages insulin resistance, and is closely related with the quick increase in the number of middle- and high-aged patients. The alerations in dietary energy sources,

specifically the increase in fat intake, the reduction in starch intake, the increase in the intake of simple sugars, and the reduction in dietary fiber consumption, contribute to obesity and cause worsening of glucose tolerance. Even mild obesity (BMI 25) causes a 4- to 5-fold increase in the risk of emerging diabetes, if accompanied by the increase in visceral fat mass. (Table 1).[29,30]

Table 2. Factors causing increase in visceral fat.[26]

1. Stress-related factors
• Overeating, especially extreme intake of simple sugars
• Smoking
• Increase in alcohol intake
• Ailments of nervous and endocrine systems: increase in cortisol, anomaly in sex hormone secretion
2. Lowered energy consumption due to a lack of exercise
3. Genetic factors
4. Aging

2.b. Pathogenesis of type-2 DM [26,31]

persons with NIDDM have quantifiable levels of circulating insulin, unlike patients with IDDM and the pathophysiology of type 2 diabetes is labelled in Figure 2. On the basis of oral glucose tolerance testing the crucial elements of NIDDM can be divided into four distinct groups:

i) Those with normal glucose tolerance.

ii) Chemical diabetes (called impaired glucose tolerance).

iii) Diabetes with minimal fasting hyperglycaemia (fasting plasma glucose less than 140 mg/dl).

iv) Diabetes mellitus related to overt fasting hyperglycaemia (fasting plasma glucose greater than 140 mg/dl).[31]

2.b.1. Impaired insulin secretion [26]

Diminished insulin secretion is a reduction in glucose sensitivity, which is detected before the clinical onset of disease. More specifically, impaired glucose tolerance (IGT) is made by a reduction in glucose-responsive early-phase insulin secretion, and a reduction in extra insulin secretion after meals causes postprandial hyperglycemia.[26] An oral glucose tolerance test (OGTT) in IGT cases usually specifies an over-response in Western and Hispanic persons, who have obviously high insulin resistance. On the other hand, Japanese patients often respond to this test with reduced insulin secretion.[29] Even when an over-response is seen in individuals with obesity or other factors, they show a reduction in early-phase secretory response. The reduction in early-phase secretion is an important part of this disease, and is very important as a basic pathophysiological alteration during the onset of disease in all ethnic groups. diminished insulin secretion is generally progressive, and its progression involves glucose toxicity and lipo-toxicity. When untouched, these are known to cause a reduction in pancreatic cell mass in animal experiments. The progression of the diminishing of pancreatic cell function significantly affects the long-

term control of blood glucose. While patients in early stages after disease onset mainly show an increase in postprandial blood glucose as a result of increased insulin resistance and reduced early-phase secretion, the progression of the worsening of pancreatic cell function afterward causes permanent raise of blood glucose.[29]

2.b.2. Insulin resistance:[26,30]

Insulin resistance is a ailment in which insulin in the body is not to apply sufficient action comparative to its blood concentration. The diminishing of insulin action in main target organs such as liver and muscles is a common pathophysiological feature of T2DM. Insulin resistance progresses and increases before the onset of disease. The analysis into the molecular mechanism for insulin action has given the idea about how insulin resistance is linked to genetic factors and environmental factors (hyperglycemia, free fatty acids, inflammatory mechanism, etc.). Known genetic factors, include not only insulin receptor and insulin receptor substrate (IRS)-1 gene polymorphisms that directly affect insulin signals but also polymorphisms of thrifty genes such as the 3 adrenergic receptor gene and the uncoupling protein (UCP) gene, linked with visceral obesity and encourages insulin resistance. Recent attention has focused on the involvement of adipocyte-derived bioactive substances (adipokines) in insulin resistance. While TNF, leptin, resistin, and free fatty acids act to increase resistance, adiponectin improves resistance. Clinical tests to assess the extent of insulin resistance include homeostasis model assessment for insulin resistance (HOMA-IR), insulin sensitivity test (loading test), steady-state plasma glucose (SSPG), minimal model analysis, and insulin clamp technique.[26,30]

2.c. Symptoms:[1]

Symptoms are same in both types of diabetes but they vary in their concentration. Symptoms develop more quickly in T1DM and more typical. The symptoms include polyurea, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision, and candidiasis.[1,2] Long-lasting T1DM patients are more prone to microvascular diseases and macrovascular complications (coronary artery, heart, and peripheral vascular diseases).[10-17]

Symptoms in T2DM are same but insidious in onset. Most cases are diagnosed because of complications or incidentally. Type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidaemia and obesity.[14-17,32-33] Most patients with T2DM die from cardiovascular problems and end stage renal disease.[14-17]

2.d. Prevention:[1]

Insulin replacement therapy is the main support of treatment in patient with T1DM, while T2DM is observed as a potentially preventable disease. A study done in Australia Aborigines proved marked improvement in carbohydrate and lipid metabolism in patients with T2DM who returned to a traditional lifestyle.[1,35] An important large-scale potential study in China, studied the effects of diet and exercise upon the rate of development of IGT to diabetes; both the measures, alone or together reduced the development of the disease by 40% after 6 years.[1,35] Similar studies done in Sweden also reveal the efficiency of life-style modifications in preventing diabetes.[1,36] More recently, the Finnish Diabetes Prevention Study showed that lifestyle interferences reduced by 58% the risk of subjects with IGT developing to T2DM.[1,37]

3. Therapy for type 2 diabetes mellitus Diet [38]

3.a. Diet therapy [38]

Although vital for the prevention as well as the treatment of all stages of T2DM, continues to remain poorly understood and highly controversial.[39,40] When obesity also exists with hyperglycemia, as seen in most of people with T2DM, weight loss is the major goal of dietary therapy.[41-44] Traditional recommendations underline decrease of both the total and saturated fat content and replacement with complex carbohydrates to 50–55% of the dietary calories. In type 2 diabetic patients, such diets may cause noticeable postprandial hyperglycemia. As there is significant patient variability in the rate of glucose absorption, arduous attention to postprandial glucose monitoring and the adding of high fiber contents to the diet become critically significant. Additionally, as the glycemic response of the diet is also dependent upon the texture and content of other food stuffs in the diet as well as the rate of intestinal motility, the diet as well as the stage and duration of T2DM have to be measured on an individual basis. [40,45,46]

3.b. Exercise [38]

exercise has been shown to be valuable in the prevention of the onset of T2DM as well as in the improvement of glucose control as a result of improved insulin sensitivity.[47-50] reduced intra-abdominal fat, an increase in insulin-sensitive glucose transporters (GLUT-4) in muscle, improved blood flow to insulin-sensitive tissues, and decreased free fatty acid levels seem to be the best mechanisms by which exercise reestablishes insulin sensitivity.[51] In addition, exercise delivers the added profits of lowering blood pressure, improving myocardial presentation, and lowering serum triglycerides while rising high density lipoprotein cholesterol levels.[38]

3.c. Pharmacotherapy therapy for type 2 diabetes mellitus [38]

Current therapeutic drugs existing for T2DM include sulfonylureas and related compounds, biguanides, thiazolidinediones, alpha -glucosidase inhibitors and insulin (Table 1). In addition, several other classes of therapeutic drugs are also available like DPP-4i, GLP-1 peptides and SGLT-2i etc. A rational approach would be to begin with the agents mainly suited to the stage and nature of the disease, progressing, if necessary, to combination therapy.[38]

3.c.1. SULFONYLUREAS [38]

They have been used to treat type 2 diabetes since 1942 and need functional pancreatic b-cells for their hypoglycemic outcome.[52,53] All currently available sulfonylureas bind to specific receptors on b-cells, resulting in closure of potassium ATP channels, which leads to the opening of calcium channels, leading to an increase in cytoplastic calcium that stimulates insulin release.[54] A newer sulfonylurea, glimepiride, given in doses of 1, 2, or 4mg pre-prandial, seems to have a more quick onset than previous sulfonylureas (both glyburide and glipizide) and thus less risk of hypoglycemia.[55] To a lesser degree than insulin administration, sulfonylureas, through endogenous hyperinsulinemia, cause a tendency for hypoglycemia and weight gain.[56] Still controversial effect of sulfonylureas is the influence on cardiovascular mortality, an observation first described by the University Group Diabetes Program.[57] due to the variability of baseline data and succeeding studies that failed to validate the observation, sulfonylureas have not been

considered to potentiate cardiovascular risk in diabetic patients.[58] However, newer data has revealed that sulfonylureas, with the exception of glimepiride, block the vasodilator effect to ischemia in animals, thereby potentially increasing cardiovascular risk. currently, the question about sulfonylurea use in cardiac mortality in humans remains questionable.[59,60] Placed in the context of our increasing understanding of the pathogenesis of type 2 diabetes, sulfonylureas would be most suitable in those patients in whom hypoinsulinemia is the main cause of hyperglycemia. These patients would characteristically be lean, with lower basal and postprandial insulin levels. In addition, based upon the recent United Kingdom study, these patients tend to be younger (,46yr of age) and are more likely to require insulin therapy.[61]

3.c.2. Biguanides: (metformin and phenformin)[62]

They are basically the AMP_k activator[6]

3.c.2.a. Phenformin was previously approved for use in the United States but was removed from the market because it caused lactic acidosis.[6]

3.c.2.b. Metformin (Glucophage, Bristol-Myers Squibb, Princeton, NJ), a biguanide that has been in clinical use since 17 August 1999, was announced in the United States in 1995.[63] Metformin, which differs structurally from phenformin, has low lipid solubility and, when used in diabetic patients with normal renal function, rarely causes lactic acidosis.[6] metformin increases the sensitivity of both hepatic and peripheral tissues (primarily muscle) to insulin.[64-66] Metformin prevents hepatic gluconeogenesis both in vitro and in vivo.[65,67] The decrease in basal hepatic glucose production is closely associated with the decrease in fasting plasma glucose level.[68] Metformin also increases muscle insulin sensitivity through direct and indirect effects.[69,70] At the cellular level, improved insulin action in muscle is described by multiple actions, including enhanced insulin receptor tyrosine kinase activity,[71] increased GLUT4 transporter number and activity,[72] and increased glycogen synthesis.[73] Metformin has no direct effect on b-cell function. In diabetic patients treated with metformin, fasting and postprandial insulin levels constantly, reflecting the normal compensatory response of the pancreas to increased insulin sensitivity. Around 25% of patients with type 2 diabetes treated with metformin monotherapy attained a fasting plasma glucose level less than 7.8 mmol/L (,140 mg/dL) and a HbA1c value less than 7%. Thus, metformin and sulfonylureas are equal in their effects in decreasing fasting plasma glucose and HbA1c values in patients with type 2 diabetes, and both are shown as primary therapy.[62] The initial metformin dosage is 500 mg twice daily, given with the two main meals to lessen gastrointestinal side effects. The fasting plasma glucose level begins to decline within 3 to 5 days after therapy is started and reaches a nadir within 1 to 2 weeks.[62] side effects include are abdominal discomfort, diarrhoea, interference with vitamin B12 absorption, hypoglycemia is rare in diabetic patients treated with metformin alone.[62] Although uncommon, lactic acidosis has been reported with a frequency of 3 cases per 100 000 patient-years. No cases of lactic acidosis with metformin therapy were observed in the UKPDS.[62]

3.c.3. Dipeptidyl peptidase-4 inhibitor (DPP-4i) [74]

DPP-4 breaks the active peptide (GLP-1 and GIP) at the position 2 alanine (N-terminal) which results into the inactivation of peptide. DPP-4 is widely present in human tissues including the brain, lungs, kidneys, adrenals, pancreas, intestine, and lymphocytes.[74] DPP-4 has effects beyond its proteolytic action, including T-cell proliferation. In addition, many neuropeptides, growth factors, cytokines, and chemokines have been recognized as potential DPP-4 substrates.[74] DPP-4 is found in the endothelial cells of the blood vessels that releases out intestinal mucosa where the L-cells are present. This suggests that

most GLP-1 is inactivated almost immediately after secretion. This quick inactivation of GLP-1 and GIP leads to a half-life (t½) of less than 2 minutes and 5-7 minutes, respectively. Thus, the short half-life of incretins limits their therapeutic potential. DPP-4 belongs to a entire enzyme family of endopeptidases; therefore, to inhibit DPP-4 exclusively, DPP-4 inhibitors need to be very specific.[74] Inhibition of DPP-4 results into the raised levels of endogenous uncleaved, biologically-active incretins and prolongs their action. However, endogenous GLP-1 levels attained with DPP-4 inhibitors are lower than those attained by pharmacological administration of injectable GLP-1 analogs.[74]

Preclinical studies for DPP-4 inhibitors presented improvement of the biological actions of GLP-1 receptor agonists, including an enhancement in insulin secretion, and increase of β-cell proliferation, β-cell regeneration, neogenesis, islet-cell function and survival, and insulin biosynthesis. DPP-4 inhibitors, unlike GLP-1 analogs, do not cause significant weight loss and are generally considered as weight neutral. Saxagliptin when given as monotherapy or in combination with other hypoglycemic drugs (including metformin, SUs, and pioglitazone), lowered HbA1c, fasting glucose levels, and postprandial glucose levels.[74]

3.c.3.a. SAXAGLIPTIN[74]

Development

Saxagliptin is a novel DPP-4 inhibitor developed by Bristol-Myers Squibb and AstraZeneca for the treatment of T2DM.[74]

Pharmacokinetics and Pharmacodynamics

Saxagliptin is a selective, durable, but reversible inhibitor of DPP-4. Saxagliptin shows greater specificity for DPP-4 than for either the DPP-8 or DPP-9 enzymes (400- and 75-fold, respectively). The active metabolite of saxagliptin (BMS-510849) is two-fold less potent than the parent. Both saxagliptin and its metabolite are highly selective (>4000-fold) for the inhibition of DPP-4 compared with a range of other proteases (selectivity of sitagliptin and vildagliptin for DPP-4 is >2600 and 32-250-fold, respectively, compared with DPP-8/9). Separation of Saxagliptin and its metabolite from DPP-4 is slow, with a t½ of 50 and 23 minutes, respectively. Slow separation of Saxagliptin from DPP-4 has not been detected with any other enzymes tested, including DPP-8 and DPP-9. Preclinical studies suggest that Saxagliptin demonstrates a high specificity for DPP-4 (the half maximal inhibitory concentration [IC50] =3.5, 18, and 26 nM for vildagliptin, sitagliptin, and saxagliptin, respectively).[74]

Mechanism of action:

It is a competitive and selective DPP-4 inhibitor which potentiates the action of GLP-1 and GIP, enhances post prandial insulin release, reduces glucagon secretion and lowers meal-time as well as fasting blood glucose level in type 2 diabetics.[6] No effect on gastric emptying and appetite have been noticed. It is body weight neutral and have low risk of hypoglycaemia unless combined with SUs or insulin. The HbA1c lowering caused by saxagliptin is corresponding to that with metformin. Further when it is added to pioglitazone/SUs/insulin with or without metformin lowering of HbA1c occurs. However, saxagliptin monotherapy is suggested only when metformin cannot be used.[6] Most professional guidelines acclaim DPP-4 inhibitors primarily as adjuvant drugs in type 2 diabetics not well controlled by metformin/SUs/pioglitazone or insulin.[6]

The efficacy of DPP-4i (saxagliptin) as monotherapy in T2DM

The efficacy and safety of saxagliptin monotherapy was studied in a randomized, double-blind, placebo-controlled, phase 2 study in drug-naïve patients with inadequately-controlled T2DM (HbA1c, 6.8%9.7%).[74] Drug-naïve patients received either a low (2.5-40 mg; n=338) or high (100 mg; n=85) dose of saxagliptin once daily for 12 or 6 weeks, respectively. At week 12 in the low-dose cohort (mean baseline HbA1c, 7.9%), all saxagliptin doses provided significant (P<0.007) decrease in adjusted-mean HbA1c change from baseline (range –0.72% to –0.90%) compared with the placebo (–0.27%;). A higher proportion of patients attained glycemic control (HbA1c, <7%) with saxagliptin treatment (41%-53%) compared with the placebo (20%). Saxagliptin also provided greater decline in fasting plasma glucose (FPG; 11-22 mg/dL) and postprandial glucose (PPG; 24-41 mg/dL) compared with the placebo (an increase of 3 mg/dL and a reduction of 1 mg/dL, respectively). At week 6 in the high-dose cohort (mean baseline HbA1c, 7.7%), saxagliptin 100 mg treatment showed similar results to the low-dose cohort with an adjusted-mean HbA1c change from baseline of –1.09%, compared with the placebo (–0.36%). In both cohorts, enhancement in β-cell function (measured by homeostatic model assessment; HOMA-β) were observed in all saxagliptin-treatment arms.[74]

At week 24, saxagliptin at all doses provided significant (P<0.0001) declines in HbA1c from baseline (–0.62% to –0.73%) compared with the placebo, with declines observed comparative to the placebo as early as week 4. Significant (P<0.0075) declines in FPG compared with the placebo were observed in all saxagliptin treatment arms (15-23 mg/dL), with declines observed as early as week 2. Saxagliptin decreased PPG area under the curve (AUC; placebo- subtracted differences, –6221 to –7437 mg·min/ dL), and patients attaining target HbA1c levels (<7%) was higher with saxagliptin (35%-41%) than with the placebo (24%). The efficacy and safety of saxagliptin as add-on therapy was studied in three trials in patients with T2DM inadequately controlled by treatment with metformin, a TZD, or an SU alone. The efficacy of saxagliptin as addon therapy was studied in 743 patients with T2DM inadequately controlled (HbA1c, 7%-10%) with metformin (1500-2550 mg/day) alone. At week 24, once-daily saxagliptin (2.5-10 mg) add-on treatment to stable metformin provided significant (P<0.0001) reductions in HbA1c (0.71%-0.83%) over the placebo. Saxagliptin treatment significantly (P<0.0001) reducions in FPG (adjusted-mean differences of 16-24 mg/dL) and PPG compared with the placebo, following a standard oral glucose tolerance test (OGTT).[74]

The HbA1c-lowering efficacy of DPP-4 inhibitors as monotherapy in placebo-controlled trials is reported to be 0.6%–0.7% (mean baseline HbA1C, 7.8%–8.0%; study duration, 24 or 26 weeks). In addition, greater decline in HbA1c (1.0%–1.5%) have been detected in patients with baseline HbA1c ≥9% who were given sitagliptin or linagliptin compared with placebo. Although GLP-1 levels are raised with DPP-4 inhibitor use, the effect is not large enough to translate to weight loss. This class of drugs has either a neutral effect or causes small reductions in blood pressure; the potential mechanism for this finding is unknown, although vasodilation and stimulation of natriuresis have been measured.[74]

Safety and Tolerability[74,76]

The DPP-4 inhibitors (linagliptin, alogliptin, sitagliptin, saxagliptin, and vildagliptin [not available in the United States]) are generally well tolerated. Because incretin-enhanced insulin secretion occurs when food is taken (i.e., in a glucose-dependent manner), the DPP-4 inhibitor class is not related with an augmented risk of hypoglycemia, except when used concurrently with insulin or an insulin secretagogue (e.g., a sulfonylurea).[76] In post-marketing cases, severe and disabling arthralgia has been reported, and withdrawal of appropriate should be considered if severe joint pain continues. Hypersensitivity-associated

events including anaphylaxis, angioedema, and severe skin conditions have also been known in post-marketing reports of DPP-4 therapy, and in these cases, treatment should be promptly withdrawn and commencement of an alternative diabetes treatment is recommended.[76] Data on the risk of bone fracture with the use of DPP-4 inhibitors have been contradictory; however, a recent meta-analysis of randomized clinical trials presented that the overall risk of bone fracture with DPP-4 inhibitors was similar to that of controls. Similarly, an analysis of data from TECOS (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin) presented that compared with placebo, sitagliptin was not linked with a higher fracture risk. Acute pancreatitis has been detected in patients treated with DPP-4 inhibitors, and prompt withdrawal of therapy is suggested if pancreatitis is suspected.[76]

Side effects:

The most commonly informed adverse events with Saxagliptin monotherapy include headache, upper respiratory tract infections, and urinary tract infections,[74] nausea, loose stools, rashes, allergic reactions and edema. Nasopharyngitis and cough occurs in some patients, which has been recognized to prevention of substance P degradation. Pancreatitis is rare.[6]

Drug Interactions[81]

S. No	Drug	Drug interaction
1.	2,4-thiazolidinedione	The risk or severity of hypoglycemia can be increased when Saxagliptin is combined with 2,4-thiazolidinedione.
2.	5-(2-methylpiperazine-1-sulfonyl) isoquinoline	The therapeutic efficacy of Saxagliptin can be enhanced when used in combination with 5-(2-methylpiperazine-1-sulfonyl) isoquinoline.
3.	7,8-Dichloro-1,2,3,4-tetrahydroisoquinoline	7,8-Dichloro-1,2,3,4-tetrahydroisoquinoline may enhances the hypoglycaemic response of Saxagliptin.
4.	Abacavir	Abacavir may reduce the excretion rate of Saxagliptin which could result in a higher serum level.
5.	Aceclofenac	Aceclofenac may reduce the excretion rate of Saxagliptin which could result in a higher serum level.

Therapeutic Applications

All available data recommend that Saxagliptin can be used as monotherapy or in combination with other antidiabetic drugs. Once-daily administration might also enhance patient compliance. The lack of an enhanced risk of hypoglycemia and the possible neutral effect on weight makes Saxagliptin an emerging therapy option for the treatment of T2DM.[74]

3.c.4. Sodium glucose co-transporter protein inhibitor[75]

Inhibitors of sodium–glucose co-transporter type 2 (SGLT2) are new glucose-lowering agents with an original non-insulin dependent mode of action. They mainly act on the kidney by inhibiting the reabsorption of filtered glucose, thus resulting into enhanced urinary glucose excretion (UGE), especially when hyperglycaemia occurs.[75] This mode of action holds promise for patients with T2DM not only in terms of enhancements in glycaemic control, with minimum risk of hypoglycaemia, but also considering

the potential benefits of weight loss which occurs because of increased glucosuria and arterial blood pressure decline linked with the osmotic effect.[75] SGLT2 inhibitors may be used as monotherapy in diet maintained patients or in combination with any other glucose reducing agent. The pharmacokinetic characteristics of SGLT2 inhibitors demonstrate an outstanding oral bioavailability, a rather long elimination half-life (t) allowing once-daily administration, a low accumulation index, no active metabolites and a limited renal excretion.[75]

At present, three SGLT-2 inhibitors are available in the market of Europe and the USA (dapagliflozin, canagliflozin and empagliflozin). A few others are commercialised or approved by the regulatory agency in Japan (ipragliflozin, luseogliflozin and tofogliflozin) and some others are in the late phase of development (ertugliflozin, remogliflozin, etc.).[75]

3.c.4.a. Dapagliflozin[75]

Pharmacokinetic/Pharmacodynamic Analysis[75]

Normal Kidney/Liver Function[75]

when dapagliflozin is Orally given they are quickly absorbed, generally reaching maximum (peak) plasma concentrations (Cmax) within 1–2 h. Dose-related systemic exposure to dapagliflozin has been detected over a wide dose range (0.1–500 mg) with an oral bioavailability of 78 %.[75] Dapagliflozin has wide-ranging extravascular distribution, as revealed by a mean average volume of distribution which is 118 L. Dapagliflozin metabolism take place mainly in the liver and kidneys by uridine diphosphate-glucuronosyltransferase-1A9 (UGT1A9) to the major inactive metabolite dapagliflozin 3-O-glucuronide (D3OG). Dapagliflozin is not noticeably cleared by renal excretion (\2 % of dose is recovered in urine as parent), in contrast to its major metabolite which is predominantly eliminated via renal excretion.[75]

Impaired Kidney Function

after a single 50 mg dose of dapagliflozin, plasma concentrations of dapagliflozin and D3OG were incrementally raised with diminishing kidney function. Steady-state Cmax values for dapagliflozin were 4, 6 and 9 % higher and for D3OG were 20, 37 and 52 % higher in patients with mild, moderate and severe renal impairment (RI), respectively, than in persons with normal function. Total exposure [area under the concentration–time curve (AUC)] was likewise higher in patients with Renal Impairment. These observations show that the kidney, besides the liver, meaningfully contributes to dapagliflozin metabolism, leading to higher systemic exposure with diminishing kidney function. Compared with patients with normal renal function, steady-state renal glucose clearance was decreased by 42, 83 and 84 % in patients with mild, moderate or severe renal impairment, respectively, resulting into a progressive reduction of the glucose-lowering effect.[75]

Impaired Liver Function

Compared with healthy individuals, systemic exposure to dapagliflozin in subjects with chronic liver disease was corelated with the degree of hepatic impairment. Due to the higher dapagliflozin exposures in cases of severe hepatic failure, a decreased starting dose of dapagliflozin 5 mg instead of 10 mg is recommended in patients with severe hepatic impairment.[75]

Drug interaction

Highly rare drug–drug interactions (without obvious clinical significance) were detected between dapagliflozin and other oral antidiabetic drugs, cardiovascular (CV) drugs or various other drugs of potential interest because of a low therapeutic index. Maximal increases in UGE were seen at doses C20

mg/ day in patients with T2DM. Pharmacodynamic alterations are based upon the plasma glucose and renal function, and decreases in UGE were reported due to the lower filtered load [plasma glucose 9 glomerular filtration rate (GFR)] in healthy volunteers than in subjects with T2DM. following multiple doses of dapagliflozin, UGE was linked with dose-related reduction in plasma glucose parameters in subjects with T2DM. Besides rising UGE, dapagliflozin exerts indirect metabolic effects. It enhanced muscle insulin sensitivity due to a decreased glucotoxicity. However, unexpectedly, after dapagliflozin treatment, endogenous glucose production enhanced significantly and was accompanied by a rise in fasting plasma glucagon concentration. Thus, glucosuria induction after SGLT2 inhibition is related with a paradoxical rise in blood glucose level.[75]

Efficacy of the SGLT-2i (Dapagliflozin) as monotherapy in T2DM[75,76]

Blood Glucose Control

The efficiency of dapagliflozin has been examined in placebo-controlled randomised clinical trials (RCTs) in T2DM patients treated with diet and exercise (monotherapy), in combination with metformin, a sulfonylurea (glimepiride), a thiazolidinedione (pioglitazone) or a dipeptidyl peptidase-4 (DPP-4) inhibitor (saxagliptin), in triple therapy with metformin plus sitagliptin, as add-on therapy to usual care in patients with cardiovascular complications or in patients with moderate chronic kidney disease (CKD), and in combination with insulin (with or without metformin). The results are remarkably reliable about the decrease in HbA1c and fasting plasma glucose across the trials, independently of the background glucose-lowering therapy. In all conditions, dapagliflozin enhanced the proportion of T2DM patients attaining an HbA1c level below 7 %. Overall, dapagliflozin 10 mg once daily leads to some extent great fall in fasting plasma glucose and HbA1c than dapagliflozin 5 mg once daily, whatever the background therapy. The most important trials have already been defined in earlier reviews and pooled in a few recent meta-analyses. 12 RCTs were eligible for quantitative synthesis and meta-analysis of dapagliflozin combined with conventional antidiabetic drugs. The overall effect size of HbA1c calculated from mean difference was -0.52 % with a 95 % confidence interval (CI) -0.60 to -0.45 (p\0.001). The effect size of fasting plasma glucose was -1.13 mmol/L (95 % CI -1.33 to -0.93; p\0.001) [51].[76]

Overall, dapagliflozin monotherapy did not result into hypoglycaemia [relative risk (RR) 1.44; 95 % CI 0.86–2.41; p = 0.17], although hypoglycaemic risk to some extent enhanced (RR 1.16; 95 % CI 1.05–1.29; p = 0.005) when dapagliflozin was combined with other hypoglycaemic drugs.[75]

Weight Loss

Due to the caloric loss linked with raised UGE, treatment with SGLT2 inhibitors provide the benefit of weight loss to overweight/obese patients with T2DM. In a meta-analysis of 12 RCTs, the effect size of dapagliflozin on body weight was -2.10 kg with a 95 % CI -2.32 to -1.88 (p\0.001), while in another meta-analysis of 10 RCTs, dapagliflozin treatment was also related with a significant decrease in body weight (WMD: -1.63 kg; 95 % CI -1.83 to -1.43; p\0.00001). Overall, dapagliflozin 10 mg offered a greater weight loss than dapagliflozin 5 mg, although this difference was rather small and not present in all studies.[75]

Blood Pressure Reduction

Dapagliflozin-induced SGLT2 inhibition for 12 weeks was linked with the decrease in 24-h blood pressure, body weight, GFR and possibly plasma volume. Cumulatively, these effects recommend that dapagliflozin may have a diuretic like tendency to lower blood pressure in addition to beneficial effects on glycaemic control. In a pre-specified continued Study Treatment (mg) (once daily) Duration (weeks)

Patients (n) Mean HbA1c (%) Mean body weight (kg) Baseline Change from baseline EMPA Rosenstock et al.[75]

Safety

Urinary/Genital Infections Safety data from 12 placebo-controlled RCTs with dapagliflozin were extracted to assess the connection between glucosuria and urinary tract infections (UTIs) in patients with inadequately controlled diabetes. Patients were treated with dapagliflozin (2.5, 5 or 10 mg, all once daily) or placebo once daily, either as monotherapy or as combined therapy for 12–24 weeks. Treatment of T2DM with dapagliflozin 5 or 10 mg was associated with a slightly increased risk of UTI (5.7 and 4.3 %, respectively, vs. 3.7 % with placebo). Infections were generally mild to moderate and clinically controllable. There was no absolute dose relationship between glucosuria and UTI. Treatment with dapagliflozin results into the induction of glucosuria which was accompanied by an increased risk of vulvovaginitis or balanitis. Because of osmotic diuresis linked with SGLT2 inhibitor therapy, the susceptible patients (e.g., elderly, low SBP, diuretic use, renal impairment, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use) may be at high risk of events linked with volume depletion such as hypotension.[76]

As the glycemic efficiency of SGLT2 inhibitors declines with the decreased renal function, this class of drugs is contraindicated in patients with severe renal impairment, end-stage renal disease, or on dialysis. Diabetic ketoacidosis (DKA), a rare adverse event (AE) related to the SGLT2 inhibitor use, was described in post-marketing reports. Cases identified in patients with T2DM and T1DM (i.e., off-label use) included reports of euglycemic DKA (i.e., blood glucose levels close to normal).[76]

Other Concerns

Dapagliflozin had no effect on markers of bone formation and resorption or bone mass densitometry after 50 weeks of treatment in both male and post-menopausal female patients whose T2DM was inadequately controlled on metformin. Over 102 weeks, dapagliflozin did not affect markers of bone formation or bone mass density in patients with T2DM inadequately controlled on metformin.[75]

4. Rationale of DPP-4 inhibitor plus SGLT2 inhibitor combination[77]

Together, DPP-4i and SGLT2i fulfil the demand for pharmacological drugs with complementary mechanisms of action that can be used in combination to enhance glucose control in a wide range of patients with T2DM, with a low risk of adverse events, such as hypoglycaemia or weight gain and the potential of cardiovascular protection. DPP-4i enhance postprandial insulin secretion and decreases glucagon secretion by inhibiting the inactivation of endogenously released incretin hormones [glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP)], two intestinal peptides whose systemic concentrations increase after food intake. Of major interest, DPP-4 inhibitors enhance insulin secretion and prevent glucagon secretion in a glucose-dependent manner, thus decreasing glycemic level while minimizing hypoglycemia. [10] Furthermore, they do not induce weight gain and have confirmed their cardiovascular safety in several large potential cardiovascular outcome studies.[77]

SGLT2i, by specifically acting on the kidney, prevent glucose reabsorption at the proximal tubule and thereby enhance glucosuria, an effect which is non-insulin dependent. Because of the progressive destruction of beta-cell function that characterizes T2DM, a pharmacological mechanism of action that is independent of pancreatic beta-cell function makes SGLT2i a best suitable option for patients with advanced T2DM, especially if their glycaemic control is insufficient with other oral glucose-lowering drugs. By enhancing glucosuria and decreasing hyperglycaemia, SGLT2i reduce glucotoxicity, which

indirectly leads to the enhancement in beta-cell function and peripheral insulin sensitivity. However, treatment with SGLT2i leads to a rise in plasma glucagon concentrations, which was associated by a considerable increase in endogenous (hepatic) glucose production. The later has been estimated to offset around half of the glucose excreted in the urine as a result of SGLT2i. Thus, the addition of a DPP-4 inhibitor which prevents glucagon secretion and enhances insulin secretion may have the capacity to prevent the increase in endogenous glucose production and potentiates the glucose-lowering ability of SGLT2i.[77]

5. Saxagliptin plus dapagliflozin

The potential therapeutic value of a combination therapy with saxagliptin and dapagliflozin for the treatment of T2DM has been recently reviewed.[77]

5.a. Pharmacokinetics

The absolute oral bioavailability of saxagliptin and dapagliflozin was examined using concurrent intravenous 14C-microdose/therapeutic oral dosing in healthy volunteers. The geometric mean point estimates (90% confidence interval – CI –) values for saxagliptin and dapagliflozin were 50% (48, 53%) and 78% (73, 83%), respectively. The arithmetic mean half-life values for the intravenous and oral doses were similar (for saxagliptin: 7.5±0.6 and 5.7±0.4 h, respectively; for dapagliflozin: 12.2±5.3 and 13.7±3.4 h, respectively) and the plasma concentration-time terminal elimination phases for each route were parallel. Overall, the intravenous micro-dosing had similar pharmacokinetics to the therapeutic oral dosing.[77]

The bioequivalence of saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets compared with coadministration of the individual tablets was evaluated in an open-label, randomised, single-dose crossover study in 72 healthy subjects. Saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets were bioequivalent to coadministration of the individual tablets in healthy subjects under fasting conditions. Furthermore, this study examined the potential effect of food and concluded that food had no clinically meaningful influence on the bioavailability of saxagliptin/dapagliflozin FDC.[77]

5.b. Pharmacodynamics

The combination of saxagliptin plus dapagliflozin provided additional decrease in glucose area under the curve from 0 to 180 minutes (AUC0-180 min) and HbA1c without the rise in plasma insulin level seen with saxagliptin and without the rise in plasma glucagon seen with dapagliflozin. Changes in plasma insulin and glucose but not glucagon AUC0-180 min correlated with change in HbA1c.[77]

5.c. Efficacy of Dapagliflozin and Saxagliptin combination therapy: Add-on to metformin

A double-blind trial randomised adults with poorly controlled T2DM on background metformin to saxagliptin 5 mg/day plus dapagliflozin 10 mg/day, or saxagliptin 5 mg/day and placebo, or dapagliflozin 10 mg/day and placebo. As a primary goal, modifications from baseline in HbA1c were compared with the triple therapy versus each dual therapy at week 24. Greater progression in glycaemic control were obtained with the triple therapy by the dual addition of saxagliptin and dapagliflozin than dual therapy with the addition of saxagliptin or dapagliflozin alone to background metformin monotherapy. The positive impact concerned with the decrease in HbA1c, the proportion of patients attaining an HbA1c target < 7%, and the decrease in both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). The decrease in body weight was greater with the triple therapy than with metformin plus saxagliptin but not than the decrease seen with metformin plus dapagliflozin. Even if the objective was

not to compare metformin plus saxagliptin versus metformin plus dapagliflozin, it appears that the difference in blood glucose control was better when the triple therapy was compared with the dual therapy metformin + saxagliptin than when compared with the dual therapy metformin plus dapagliflozin.[77]

Two other randomised, double-blind, phase 3 trials in T2DM patients evaluated the efficiency of a triple therapy combining metformin plus saxagliptin plus dapagliflozin but using a different protocol. One study tested the efficiency of adding dapagliflozin 10 mg versus placebo to a saxagliptin plus metformin background therapy whereas the other examined the efficiency of adding saxagliptin 5 mg versus placebo to a dapagliflozin plus metformin background therapy. Treatment with dapagliflozin add-on to saxagliptin plus metformin leads to a better mean HbA1c fall than placebo (-0.82 vs. -0.10%, $P < 0.0001$) whereas treatment with saxagliptin add-on to dapagliflozin plus metformin leads to a less marked fall in HbA1c (-0.51% versus -0.16% with placebo), but still highly significant ($P < 0.0001$). These differences translate into higher proportions of T2DM patients attaining a target HbA1c < 7 % among those treated with the triple therapy compared to those receiving pacebo added to the background dual therapy.[77]

5.d. Safety of Dapagliflozin and Saxagliptin combination therapy: Add-on to Metformin

In a study comparing triple therapy by the dual addition of saxagliptin and dapagliflozin to dual therapies with the addition of saxagliptin or dapagliflozin alone in patients not well maintained by metformin, the percentage of patients with adverse events was similar across treatment groups. Despite large reduction in HbA1c, hypoglycaemic event rates were low (around 1%) and similar across treatment groups, with no incidents of major hypoglycaemia. Similar encouraging discoveries concerning the risk of hypoglyacemia were reported in two other studies having evaluated the safety of the triple therapy metformin saxagliptin-dapagliflozin. Urinary and genital infections occurred less frequently in patients receiving the triple therapy than in those receiving any of the dual therapies. This unexpected outcome was also detected in another study reporting a lower rate of genital infections when a saxagliptin was added to dapagliflozin compared with the SGLT2 inhibitor alone.[78]

6. Why use a combination of SGLT2 and DPP-4 inhibition?[77]

The combination of an SGLT2 inhibitor and a DPP-4 inhibitor targets different pathophysiologic defects related to T2DM through different mechanisms of action that are both complementary to that of metformin. Metabolic studies with SGLT2 inhibitors have proved that decrease in plasma glucose level using a drug that acts via the kidney enhances peripheral insulin sensitivity and β-cell function, despite a rise in endogenous glucose production. These effects are likely due to reversal of glucotoxicity, and may include beneficial effects on α- and β-cell function, as shown in two studies using a combination of saxagliptin and dapagliflozin and linagliptin and empagliflozin in patients with T2DM, which proved additive effects on postprandial glucose levels.[77] In addition, both drug categories have good tolerability profiles, including no increased risk of hypoglycemia when used in combination with other drugs except that of insulin or an insulin secretagogue (e.g., sulfonylurea).[77] Weight loss is another potential benefit of combination therapy given that SGLT2 inhibitors are linked with weight loss and DPP-4 inhibitors are weight neutral.[77] As earlier described, the SGLT2 inhibitor empagliflozin has proved cardiovascular benefit, and DPP-4 inhibitors have proved cardiovascular safety, although the effects of DPP-4 inhibitors on heart failure need additional assessment. No cases of heart failure were detected in clinical trials with empagliflozin/linagliptin as initial combination or add-on to metformin therapy and rates were low in trials of dapagliflozin/saxagliptin.[77] A single-pill combination could potentially enhance long-term adherence and may decrease the treatment costs (i.e., single co-payment). As combinations, these

drugs are not re-tested in similar clinical trial programs to the individual drugs because the drugs are bioequivalent.[77]

7. QTERN (DPP-4 and SGLT2 inhibitor combination for type 2 diabetes)[78]

Qtern is a new fixed- dose combination of the DPP-4 inhibitor saxagliptin with the SGLT2 inhibitor dapagliflozin for the maintenance of T2DM launched by AstraZeneca.[78] Qtern is licensed to enhance glycaemic control in adults with T2DM when double or triple therapy (with metformin and/or a sulfonylurea and one of the component drugs of Qtern) does not provide significant glycaemic control, and for patients already taking dapagliflozin and saxagliptin as a free combination. The recommended dose is one 5mg saxagliptin/ 10mg dapagliflozin tablet once daily. Qtern shares the prescribing cautions and contraindications of its component drugs. No dose adjustment according to age is suggested, though renal function and risk of volume depletion should be taken into account in people over 65 years. Experience is very limited in people of age 75 years and older and so Qtern is not suggested in this individuals. Qtern is contraindicated in patients with moderate to severe renal impairment or severe hepatic impairment.[78]

8. Discussion[77]

In the clinical trials discussed, combinations of empagliflozin/linagliptin and dapagliflozin and saxagliptin were well tolerated, with safety profiles one would typically expect based on the individual drug categories. Reported AEs included UTI and genital infection, reliable with the labeled profile of SGLT2 inhibitors. Low rates of hypoglycemia were detected and incidents of severe hypoglycemia was rare with the combination therapy of an SGLT2 inhibitor and DPP-4 inhibitor. Low rates of bone fracture were detected among the 3 studies of dapagliflozin and saxagliptin. Pancreatitis was detected in 3 patients among the 4 studies of empagliflozin/linagliptin. There were no reports of DKA in any of the empagliflozin/linagliptin or dapagliflozin and saxagliptin studies discussed here.[77] These findings reveal the beneficial effects of a DPP-4 inhibitor and/or an SGLT2 inhibitor on glycemia when used in dual or triple combination therapy. For some treatment-naïve patients, monotherapy may not be enough to attain glycemic goals, and initial combination therapy with metformin and a DPP-4 inhibitor or an SGLT2 inhibitor, drugs with complementary mechanisms of action, may be helpful.[80]

Although additional long-term studies are needed, current data demonstrate that both categories of medication maintain efficiency and tolerability with prolonged exposure. In choosing which medicines to combine, attention should be given to each agent's individual adverse event profile. For example, although DPP-4 inhibitors have a neutral effect on weight and SGLT2 inhibitors are linked with weight loss, sulfonylureas and TZDs are linked with weight gain. Additionally, although DPP-4 inhibitors and SGLT2 inhibitors are individually related to a low risk of hypoglycemia, an enhanced risk of hypoglycemia was detected when treatment was combined with a sulfonylurea. Importantly, the addition of a DPP-4 inhibitor or an SGLT2 inhibitor to insulin therapy was generally shown to enhance glycemic control without significantly enhancing the risk of hypoglycemia or weight gain. Furthermore, compared with placebo, fewer patients in the DPP-4 inhibitor or SGLT2 inhibitor groups required insulin up titration.[80]

9. Conclusion

Patients receiving one glucose-lowering agent will often require additional agents to maintain glycemic control over time. The combination of empagliflozin/linagliptin or dapagliflozin/ saxagliptin in addition to background metformin therapy effectively enhances glucose control compared with dual therapy (metformin plus either an SGLT2 inhibitor or a DPP-4 inhibitor). Additional effects of empagliflozin/linagliptin or dapagliflozin/saxagliptin in addition to background metformin include decreased body weight and modest decrease in blood pressure. Combining these two classes of glucose-lowering drugs is well tolerated with few serious adverse events.[77] In summary, dapagliflozin exerts better effects in enhancing peripheral insulin sensitivity than saxagliptin. However, dapagliflozin and saxagliptin share a similar e fficiency in de dysfunction, brain apoptosis, and brain inflammation, and preventing cognitive decrease. However, only dapagliflozin treatment led to a decrease in body weight and decreased visceral fat mass. The combined agents therapy in the HFD-induced obese condition exerted greater anti-oxidative e ffects and enha brain insulin sensitivity to a greater degree than the single therapy.[78] Clinical trials proved that the combination of an SGLT2i and DPP-4i is effective and safe in patients with T2DM treated with diet alone or metformin. FDC formulations combining saxagliptin plus dapagliflozin and linagliptin plus empagliflozin are already commercialized and other combinations are currently examined for the management of T2DM. Although the precise positioning of a DPP-4i–SGLT2i combination should be better described by further studies, this approach appears to be a new option for the management of patients with T2D, with a good efficacy/safety ratio. However, because of the higher cost of this combination, careful pharmacoeconomic evaluation would be of major interest.

References

1. https://pdfs.semanticscholar.org/fdbe/614aa032e34dc5be736708c000714d41a10f.pdf.

2. Kumar PJ, Clark M. Textbook of Clinical Medicine. Pub: Saunders (London), pp 1099-1121, 2002. 3. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of Diabetes Mellitus. Diabetes Care 1997; 20: 1183-1197.

4. Beverley B, Eschwège E. The diagnosis and classification of diabetes and impaired glucose tolerance. In: Textbook of Diabetes 1 Ed: John C Pickup and Gareth Williams Third edition; Chapter 2, pp 2.1-2.11, 2003.

5. Lindberg G, Lindblad U, Melander A. Sulfonylureas for treating type 2 diabetes mellitus. Cochrane Database Systemic Reviews volume 3, 2004.

6. KD Tripathi, Essentials of Medical Pharmacology Seventh Edition, Jaypee brothers' medical publishers (p) ltd.

7. Amos A, McCarty D, Zimmet P. The rising global burden of diabetes and its complications, estimates and projections to the year 2010. Diabetic Med 1997; 14: S1-S85.

8. King H, Aubert R, Herman W. Global burden of diabetes, 1995-2025. Prevalence, numerical estimates and projections. Diabetes Care 1998; 21: 1414-1431.

9. Zimmet P. Globalization, coca-colonization and the chronic disease epidemic: can the Doomsday scenario be averted? J Med 2000; 247: 301-310.

10. Bearse MA Jr, Han T, Schneck ME, et al. Local multifocal oscillatory potential abnormalities in diabetes and early diabetic retinopathy. Invest Ophthal Vis Sci 2004; 45 : 3259-3265.

11. Hove MN, Kristensen JK, Lauritzen T, Bek T. The prevalence of retinopathy in an unselected population of type 2 diabetes patients from Arhus County, Denmark. Acta Ophthalmol Scand 2004; 82: 443-448.

12. Seki M, Tanaka T, Nawa H, et al. Involvement of brain-derived neurotrophic factor in early retinal neuropathy of streptozotocin-induced diabetes in rats: therapeutic potential of brain-derived neurotrophic factors for dopaminergic amacrine cells. Diabetes 2004; 53: 2412-2419.

13. Moran A, Palmas W, Field L, et al. Cardiovascular autonomic neuropathy is associated with microalbuminuria in older patients with type 2 diabetes. Diabetes care 2004; 27: 972-977.

14. Huang C, Kim Y, Caramori ML, et al. Cellular basis of diabetic nephropathy: II. The transforming growth factor-beta system and diabetic nephropathy lesions in type 1 diabetes. Diabetes 2002; 51: 3577-3581.

15. Shukla N, Angelini GD, Jeremy JY, et al. Homocysteine as a risk factor for nephropathy and retinopathy in type 2 diabetes. Diabetologia 2003; 46; 766-772.

16. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. Diabetes Care 2004; 27: 955-962.

17. Saely CH, Aczel S, Marte T, et al. Cardiovascular complications in type 2 diabetes mellitus depend on the coronary angiographic state rather than on the diabetes state. Diabetologia 2004; 47: 145-146.

18. World Health Organization Study Group. Diabetes Mellitus: WHO Technical Report, Series 727. Geneva: World Health Organization, 1985.

19. Zimmet P, Cowie C, Ekoe JM, Shaw JE. Classification of diabetes mellitus and other categories of glucose intolerance. In: International Textbook of Diabetes Mellitus chapter 1, 3rd Ed., pg 3-14, 2004.

20. Watkins PJ, Drury PL, Taylor KW. An Overview of management. In: diabetes and its Management. ED Blackwell Scientific Publication; fourth edition, 1990, pp 63-66.

21. Kumar PJ, Clark M. Textbook of Clinical Medicine. Pub: Saunders (London), pp 1099-1121, 2002.

22. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med 1994; 331: 1428-1436.

23. Betterle C, Zannette F, Pedini B, et al. Clinical and subclinical organ-specific autoimmune manifestations in type 1 (insulin-dependent) diabetic patients and their first-degree relatives. Diabetologia 1983; 26: 431-436.

24. McLarty DG, Athaide I, Bottazzo GF, et al. Islet cell antibodies are not specifically associated with insulindependent diabetes in rural Tanzanian Africans. Diabetes Res Clin Pract 1990; 9: 219-224.

25. Ahrén B, Corrigan CB. Intermittent need for insulin in a subgroup of diabetic patients in Tanzania. Diabet Med 1984; 2: 262-264.

26. https://www.med.or.jp/english/journal/pdf/2010_01/041_046.pdf

27. Pyke DA. Diabetes: the genetic connections. Diabetologia. 1979;17:333–343.

28. Unoki H, Takahashi A, Kawaguchi T, et al. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat Genet. 2008;40:1098–1102.

29. Abdul-Ghani MA, Matsuda M, Jani R, et al. The relationship between fasting hyperglycemia and insulin secretion in subjects with normal or impaired glucose tolerance. Am J Physiol Endocrinol Metab. 2008;295:E401–E406.

30. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999;22:1462–1470.

31. Ozougwu, O. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. Journal of Physiology and Pathophysiology, 4(4), 46–57. doi:10.5897/jpap2013.0001.

32. Zimmet P, Dowse G, Finch C, Serjeantson S, King H. The epidemiology and natural history of NIDDMlessons from the South Pacific. Diabetes Metab Rev 1990; 6: 91-124.

33. Eriksson J, Saloranta C, Widen E, et al. Non-esterified fatty acids do not contribute to insulin resistance in persons at increased risk of developing type 2 (noninsulin-dependent) diabetes mellitus. [Journal Article] Diabetologia. 1991; 34:192-197.

34. O'Dea K. Marked improvement in carbohydrate and lipid metabolism in diabetic Australian Aborigines after temporary reversion to traditional lifestyle. Diabetes 1984; 33: 596-603.

35. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetic Care 1997; 20: 537-544. 36. Eriksson KF, Lindgarde F. Prevention of type 2 (Noninsulin-dependent) diabetes mellitus by diet and physical exercise: 6 -year Malmo feasibility study. Diabetologia 1991; 34: 891-898.

37. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incident of type 2 diabetes with lifestyle intervention or metformin. N Eng J Med 2002; 346: 393-403.

38. Mahler, R. J., & Adler, M. L. (1999). Type 2 Diabetes Mellitus: Update on Diagnosis, Pathophysiology, and Treatment. The Journal of Clinical Endocrinology & Metabolism, 84(4), 1165–1171. doi:10.1210/jcem.84.4.5612.

39. Henry RR, Griver K. 1998 Diet therapy of type 2 diabetes mellitus. In: DeFronzo R, ed. Current therapy of diabetes mellitus. Chicago: Mosby-Yearbook; 79.

40. GrundySM.1991Diettherapyindiabetesmellitus:isthereasinglebestdiet? Diabetes Care. 14:796–821. 41. WingRR.1995Useofverylow-caloriedietinthetreatmentofobesepersons with non-insulin dependent diabetes mellitus. J Am Diet Assoc. 95:569–572.

42. HenryRR,GumbinerB.1991Benefitsandlimitationsofverylowcaloriediet therapy in obese NIDDM. Diabetes Care. 14:802–823.

43. Hanson RL, Narayaan KM, McConce DR, et al. 1995 Rate of weight gain, weight fluctuation, and incidence of NIDDM. Diabetes. 44:261–266.

44. Albu J, Konnarides C, Pi-Sunyer FX. 1995 Weight control: metabolic and cardiovascular effects. Diabetes Rev. 3:335–347.

45. Franz MJ, Horton ES, Bantle JP, et al. 1994 Nutrition principles in the management of diabetes and related complications. Diabetes Care. 17:490–518.

46. Riccardi G, Rivellese AA. 1991 Effects of dietary fiber and carbohydrate on glucose and lipoprotein metabolism in diabetic patients. Diabetic Care. 14:1115–1125.

47. HelmrichSP,RaglandDR,PaffenbergerRS.1994Preventionofnon-insulin diabetes mellitus with physical activity. Med Sci Sports Exerc. 26:824–850.

48. Manson JE, Rimm EB, Stampfer MJ, et al. 1991 Physical activity and incidence of non-insulin dependent diabetes mellitus in women. Lancet. 338:774–778.

49. Martin IK, Wahren J. 1993 Glucose metabolism during physical exercise in patients with non-insulin dependent (type 2) diabetes. Adv Exp Med Biol. 334:221–233.

50. EriksonnKF,LindgardeF.1991Preventionoftype2(non-insulindependent) diabetes mellitus by diet and physical exercise. Diabetologia. 34:891–898.

51. Erisonn J, Taimola S, Eriksson K, Parviainen S, Peltonen J, Kujula U. 1997 Resistance training in the treatment of non-insulin dependent diabetes mellitus. Int J Sports Med. 18:242–246.

52. Groop LC, Ratheiser K, Luzi L, et al. 1991 Effect of sulphonylureas on glucose-stimulated insulin secretion in healthy and non-insulin-dependent diabetes subjects: a dose response study. Acta Diabetol. 28:162–168.

53. Loubatieres A. 1957 The mechanism of action of the hypoglycemic sulfonamides:aconceptbasedoninvestigationsinanimalsandhumanbeings.Ann NY Acad Sci. 71:192–206.

54. Pilipson LH, Steiner DF. 1995 Pas de deux or more: the sulphonylurea receptor and K1 channels. Science. 268:372–373.

55. GeisenK.1988Specialpharmacologyofthenewsulphonylureaglimepiride. Drug Res. 38:1120–1130. 56. Harrower AD. 1994 Comparison of efficacy, secondary failure rate, and complications of sulphonylureas. J Diabetic Complications. 8:201–203. 77. Meinert CL, Knatterud GL, Prout TE, Klmt CR. 1970 A study of the effects of hypoglycemic agents on vascular complications in patients with adultonset diabetes. Diabetes. 19:787–791.

58. Feinstein AR. 1971 Clinical biostatistics. VIII. An analytical appraisal of the University Group Diabetes Program (UGDP) study. Clin Pharmacol Therapeut. 12:167–170.

59. Leibowitz G, Cerasi E. 1996 Sulphonylurea treatment of NIDDM patients with cardiovascular disease: a mixed blessing? Diabetologia. 39:503–514.

60. Smits P, Thien T. 1995 Cardiovascular effects of sulphonylurea derivatives. Implications for the treatment of NIDDM? Diabetologia. 38:116–121.

61. U.K.ProspectiveDiabetesStudyGroup.1995UKprospectivediabetesstudy 16. Overview of 6 years therapy of type 2 diabetes: a progressive disease. Diabetes. 44:1249–1258.

62. DeFronzo, R. A. (1999). Pharmacologic Therapy for Type 2 Diabetes Mellitus. Annals of Internal Medicine, 131(4), 281. doi:10.7326/0003-4819-131-4-199908170-00008.

63. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with noninsulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995;333:541-9.

64. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. J Clin Endocrinol Metab. 1991;73:1294-301.

65. Stumvoll N, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med. 1995;333:550-4.

66. Johnson AB, Webster JM, Sum CF, Heseltine L, Argyraki M, Cooper BG, et al. The impact of metformin therapy on hepatic glucose production and skeletal muscle glycogen synthase activity in overweight type II diabetic patients. Metabolism. 1993;42:1217-22.

67. Wollen N, Bailey CJ. Inhibition of hepatic gluconeogenesis by metformin. Synergism with insulin. Biochem Pharmacol. 1988;37:4353-8.

68. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1996;81:4059-67. 69. Widen EI, Eriksson JG, Groop LC. Metformin normalizes nonoxidative glucose metabolism in insulin-resistant normoglycemic first-degree relatives of patients with NIDDM. Diabetes. 1992;41:354-8.

70. Stith BJ, Goalstone ML, Espinoza R, Mossel C, Roberts D, Wiernsperger N. The antidiabetic drug metformin elevates receptor tyrosine kinase activity and inositol 1,4,5-triphosphate mass in Xenopus oocytes. Endocrinology. 1996;137:2990-9.

71. Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. Diabetes Rev. 1998;6:89-131.

72. Rossetti L, DeFronzo RA, Gherzi R, Stein P, Andraghetti G, Falzetti G, et al. Effect of metformin treatment on insulin action in diabetic rats: in vivo and in vitro correlations. Metabolism. 1990;39:425-35.

73. Klip A, Leiter LA. Cellular mechanism of action of metformin. Diabetes Care. 1990;13:696-704.

74. Tahrani, A. A., Piya, M. K., & Barnett, A. H. (2009). Saxagliptin: a new DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. Advances in Therapy, 26(3), 249–262. doi:10.1007/s12325-009-0014-9.

75. Scheen, A. J. (2014). Pharmacodynamics, Efficacy and Safety of Sodium–Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus. Drugs, 75(1), 33–59. doi:10.1007/s40265-014-0337-y.

76. Dey, J. (2017). SGLT2 inhibitor/DPP-4 inhibitor combination therapy – complementary mechanisms of action for management of type 2 diabetes mellitus. Postgraduate Medicine, 129(4), 409–420. doi:10.1080/00325481.2017.1307081.

77. Scheen, A. J. (2016). DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert Opinion on Drug Metabolism & Toxicology, 12(12), 1407–1417. doi:10.1080/17425255.2016.1215427.

78. Chaplin, S. (2017). Qtern: DPP-4 and SGLT2 inhibitor combination for type 2 diabetes. Prescriber, 28(4), 47–49. doi:10.1002/psb.1564.

79. Scheen, A. J. (2016). Pharmacokinetic Characteristics and Clinical Efficacy of an SGLT2 Inhibitor Plus DPP-4 Inhibitor Combination Therapy in Type 2 Diabetes. Clinical Pharmacokinetics, 56(7), 703–718. doi:10.1007/s40262-016-0498-9.

80. Guthrie, R. M. (2015). Clinical use of dipeptidyl peptidase-4 and sodium-glucose cotransporter 2 inhibitors in combination therapy for type 2 diabetes mellitus. Postgraduate Medicine, 127(5), 463–479. doi:10.1080/00325481.2015.1044756.

81. https://www.drugbank.ca/drugs/DB06335.