DIPEPTIDYL PEPTIDASE - 4 INHIBITORS - AN OVERVIEW OF THE COMBINATION OF THESE MOLECULES AND HYPOGLICEMIC ORAL DRUGS

Mini-review Article

Abstract: The purpose of the current review is to bring up to date some studies and data about the effects of hypoglycemic oral drugs in combination with DPP-4 inhibitors. As the medicine and pharmaceutical industry are revolutionary in type 2 diabetes protocols, scientists made a close research on patients that have combined metformin plus sulfonyurea and metformin plus DPP-4 inhibitors. Statistics showed that sulfonylurea compared to DPP-4 inhibitors, in combination with metformin, increased the risk of severe hypoglycemia, fatal and nonfatal cardiovascular diseases, and mortality. Another important discovery showed that the insulin associated with metformin increased the risk of all-caused mortality, compared with the DPP-4 inhibitors plus metformin.

Keywords: dipeptidyl peptidase-4 inhibitor, type 2 diabetes, oral drugs.

Introduction

Currently, diabetes is a major illness all around the world that implicates dysfunction in glucose metabolism and the blood level of glucose is very high. Either the glucose cannot be used by the cells in order to normalise the blood level, if there is not enough insulin, or the receptors for insulin does not recognise it. Type 2 diabetes (T2DM) spread world - wide, therefore, medicine and pharmacology play an important role in managing T2DM, mostly in controlling glucose levels, cholesterol levels, blood pressure, and body weight and it is often observed that T2D patients who receive identical antidiabetic regimens have significant variability in glycated hemoglobin (HbA1c) level, glycemic control, drug efficacy and tolerability and incidence of side effects (1). T2D affects more than 400 million people throughout the world and it is projected to reach 552 million cases by the year 2030 (2). T2D may lead to blindness, kidney failure, heart attacks, stroke and lower-limb amputation and can result in lower life expectancy by 5–10 years. Interindividual variation may be caused by numerous factors, such as genetic factors, physical inactivity, hypertension, age, gender and others (3-6).

The manifestations of insulin-resistant glucose metabolism include reduced glucose transport and phosphorylation and reduced rates of glycogen synthesis whereas abnormal fatty acid metabolism entails increased accumulation of triglyceride and other lipids as well as dysregulation of lipid oxidation during fasting and insulin-stimulated conditions. A reduction in the activity of marker enzymes of oxidative pathways has been observed in skeletal muscle obtained from individuals with obesity and type 2 diabetes and it is correlated with the severity of insulin resistant glucose metabolism. Skeletal muscle is one of the major insulin-target tissues responsible for the maintenance of whole-body glucose homeostasis and accounts for the bulk of insulin-stimulated glucose disposal (70-80%) after a meal (7). Chronic hyperglycaemia, the predominant metabolic state of diabetes, can exacerbate defective glucose disposal by interfering with insulin action in

insulin-target tissues, including skeletal muscle (8,9). Recently, substantial progress in understanding the insulin induced GLUT4 translocation process has been made by using cultured adipocyte models (10).

One of the most popular and recently target for T2DM therapy is finding molecules that increase the effects of incretin hormones, the glucagon-like peptide-1 hormone (GLP-1) and the gastric inhibitory peptide hormone (GIP). The incretin hormones are released by the L intestinal cells (GLP-1) and K intestinal cells (GIP) as a consequence of food ingestion. The protein structure of these two hormones includes in the second position of the amino-acids chain a unit of alanine, therefore the dipeptidyl peptidase-4 (DPP-4) enzyme has a high affinity for the hormones and the enzyme activity is at the maximum level when peptides have this amino acid on this position. The GLP-1 stimulates cyclic adenosine monophosphate synthesis in cardiomyocytes and potentiates the effects of stromal cell-derived factor-1 that can aggravate cardiac fibrosis, this would be less notable if the drugs were to promote sodium excretion, but the natriuretic effect of DPP-4 inhibitors is low.

The enzyme recognizes another bioactive peptide like Y neuropeptide, gastrin releasing peptide (GRP), insulin like growth factor, therefore DPP-4 is part of many homeostatic mechanisms that influence blood pressure (11). Many of the non-hypoglycemic actions of DPP-4 inhibitors are mediated by their effect to potentiate endogenous stromal cell-derived factor (SDF-1). SDF-1 is a stem cell chemokine that activate the mesenchymal cells to sites of tissue injury, promoting inflammation, regeneration and repair (12). Low levels of DPP-4 have been noticed in lupus erythematous, polyarthritis rheumatoid, Crohn's disease, and high levels in multiple sclerosis.

DPP-4 inhibitors are a new class of Oral Hypoglycemic Drugs (OHD) that can control T2DM (10).

DPP-4 inhitors are molecules that block the enzyme activity so the incretins remain active and this leads to low blood glucose. This mechanism provided molecules that inhibit the enzyme activity and increased the effect of the GLP-1 and the GIP hormones to maintain glucose homeostasis.

DPP-4 is produced by the liver, lungs, kidneys, placenta, intestine, biliary duct, epithelial cells of thyroid, tymocytes, and leucocytes (13,14). DPP-4 is part of an enzyme family, along with DPP-7, DPP-8 and DPP-9, included in a subfamily of dipeptidil-pepdidase. It has two forms, one attached to the membrane cell and another one plasmatic. The plasmatic one is obtained by cleavage the hydrophobic part of the DPP-4 from the endothelial cells and released in the blood, which can not only bind to the incretin hormones, but also to plasminogen and streptokinase (15).

DPP-4 inhibitors have been reported to have neutral effect on thromboembolic events in large scale trials, they potentiate several endogenous peptides that can express cardiovascular side effects. Unlike other antidiabetic drugs, the use of DPP-4 inhibitors is not accompanied by weight gain and carries a low risk of hypoglycemia. While the sodium-glucose transporter-2 (SGLT2) inhibitors can cause genitourinary infections, the DPP-4 inhibitors did not register such effects and also did not have adverse effects on lipid metabolism. Heart failure is the most important and preventable macrovascular complication of diabetes, and the clinical courses of these two disorders often progress in parallel (16). DPP-4 inhibitors have positive inotropic effects that are mediated because of their ability to enhance the actions of GLP-1 to stimulate cyclic adenosine monophosphate synthesis (cAMP) in cardiomyocytes. These molecules can also promote sodium excretion by the kidney, but this side effect appears to be modest when compared with other antidiabetic drugs (17). The modest nature of natriuretic effects of DPP-4 inhibitors can be explained by their unique site of action. They act primarily on the proximal renal tubule, where the majority of sodium reabsorption takes place (18).

There are different approaches around the world that combines molecules in order to control the glucose blood level and also many studies that showed pros and cons in these associations. As searching in the literature, we found an impressive number of articles that aimed the efficacy and safety of new DPP-4 inhibitor – alogliptin, compared to existing DPP-4 inhibitors – sitagliptin, saxagliptin, linagliptin, vidagliptin, in combination with metformin or sulfonylurea (19).

Metformin is an oral hypoglycemic agent and the only member of the biguanide class of drugs used in clinical practice. Metformin is commonly used as the first-line medication for the T2D treatment according to the recommendations of clinical guidelines (20). Despite the popularity of metformin in diabetes treatment, the exact mechanism underlying the glucose level-lowering effects of this medication still remains poorly understood (21). However, some metformin effects are undeniable (suppression of enhanced basal endogenous glucose production in patients with T2D through a 25–40% decrease in the hepatic gluconeogenesis rate that is hypothesized to be caused via activation of AMPkinase (AMPK) and direct inhibitory effects on mitochondrial function) (22). Metformin is able to improve insulin sensitivity and insulin-stimulated glucose uptake in skeletal muscle. Metformin is not metabolized in the body and is excreted unchanged in the urine through active tubular secretion in the kidney (23,24). Moreover, metformin therapy is associated with more gastrointestinal symptoms (range 2–63% in different clinical trials) than most other oral antidiabetic agents.

Sulfonylureas are the oral drugs used in T2D treatment, whose mechanism of action is stimulation of insulin secretion as well as of basal insulin via binding to sulfonylurea receptor 1 (SUR1). SUR1 is a part of the ATP-sensitive K^+ (KATP) channel. The interaction between sulfonylurea and SUR1 causes inhibition of the KATP channel, decreasing the K^+ efflux and depolarization of the β-cells. This leads to opening of voltage dependent Ca^{2+} channels, eliciting Ca^{2+} influx and increasing in intracellular Ca^{2+}. The spike of intracellular Ca^{2+} levels triggers insulin zymogen fusion with the plasma membrane and insulin secretion (25).

The purpose of the current review is to bring up to date some studies and data about the effects of hypoglycemic oral drugs in combination with DPP-4 inhibitors.

MATERIAL AND METHODS

This study is a retrospective analysis of the influence of DPP-4 inhibitors on the incretin hormones and also an overview on the combination of these molecules with classic oral hypoglycemic drugs. We focused our attention mainly on newest articles and used criteria and filters were the year of publication 2002 - 2021. We searched on electronic databases such as *Web of Science*, *ScienceDirect*, *PubMed*, *Google scholar*. We used keywords such as DPP-4 inhibitor (3788 results), type 2 diabetes (217639 results), hypoglycemia (36826 results), cardiovascular effects (183290 results), sulfonylurea (10092 results), metformin (34024), insulin (498936 results), GLP-1 (16216 results) and GIP (4575 results), on Web of Science database.

RESULTS AND DISCUSSION

Some researchers made a study in Sweden during 2006 until 2013 on patients with prescription of an incident combination treatment of either a sulphonylurea or a DPP-4 inhibitor together with metformin. First the patients had a monotherapy with one non-insulin antidiabetic drug (NIAD), prior to the start of combination treatment. The study included those with interrupted or changed treatment and all the patients had type 2 diabetes moving from treatment with one NIAD to dual NIAD. During the study there were some endpoints such as severe hypoglycemia or diabetes with coma, fatal or non-fatal myocardial infarction, ischemic stroke, unstable angina pectoris, or cardiovascular death, also death at any cause.

The trial included 52760 patients with type 2 diabetes second-line treatment with metformin plus sulphonylurea (77.2%) or metformin plus DPP-4 inhibitor (22.8%). The results obtained by the group study regarding the association metformin plus sulphonylurea (Group 1 - G 1) and metformin plus DPP-4 inhibitor (Group 2 - G 2) indicate the following results of side effects of the used drugs: cardiovascular diseases G1 - 32.3%, G2 – 27.8%, myocardial infarction G1 – 8.5%, G2 - 7.4%, angina pectoris G1 – 17.5%, G2 – 15.9%, heart failure G1 – 6.1%, G2 – 4.7%, stoke G1 – 7.9%, G2 – 5.5%, kidney disease G1 – 1.1%, G2 – 1.1%, severe hypoglycemia G1 – 0.9%, G2 – 0.6%, cancer G1 – 13.6%, G2 – 11.1%.

The main results were an increased incidence of severe side effects and a crude number of death, mostly in the metformin plus sulphonylurea group. Also, for the patients with type 2 diabetes, regardless of treatment group, with severe hypoglycemia episode compared to those who did not, the risk of fatal cardiovascular disease was increased (26).

Another study made in Sweden during 2007 and 2014 compared the risk of cardiovascular diseases, severe hypoglycemia and mortality in patients with type 2 diabetes on metformin monotherapy that started the second-line treatment with insulin or DPP-4 inhibitors. The study included 27767 patients, 55.7% started insulin (Group 1 – G1) and 44.3% started a DPP-4 inhibitor (Group 2 – G2). All patients had the monotherapy with metformin for 6 months at least before starting the second-line treatment with insulin or DPP-4 inhibitor. The results regarding the side effects were as follow: myocardial infarction G1 – 12%, G2 – 8%, angina pectoris G1 – 15%, G2 – 11%, heart failure G1 – 12%, G2 – 5%, and stroke G1 – 12%, G2 – 6%.

The insulin and the DPP-4 inhibitors group were very similar in all baseline parameters. Low prevalence of severe hypoglycemia was found in both groups, although the fatal and non-fatal cardiovascular diseases were less than 50% in the DPP-4 inhibitors group compared to the insulin group and the increased incidence in the insulin group of all types of events could be observed in the first 6 month of treatment (27).

One of the explanations of these results can be the high risk of severe hypoglycemia associated with insulin and sulphonylurea compared with DPP-4 inhibitors and a risk for cardiovascular diseases (28). Hypoglycemic responses have been suspected to trigger cardiovascular events and could be a connection between insulin treatment and the severe risks including serious cardiac arrhythmias. Other mechanisms could be the modification of the coagulation status and endothelial function, the inflammatory processes that will explain associations between insulin and cardiovascular diseases (29, 30). The treatment with DPP-4 inhibitors is not associated with weight gain in contrast to the association with insulin.

Muskiet and collaborators compared effects of a DPP-4 inhibitor – linagliptin with a sulfonylurea on renal physiology in metformin treated patients with T2DM and the work was published in 2020 in Diabetes Care. This was a double-blind randomized trial, with 46 T2DM patients without renal defacement; they received once - daily linagliptin or sulfonylurea for 8 weeks, as a second line treatment over metformin. At the end, fasting glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by inulin and para-aminohippuric acid clearances (31). Eligible T2DM patients were caucasian, men/postmenopausal women, aged 35–75 years, who received metformin alone and had HbA_{1c} (glycated haemoglobin) 6.5–9.0%, BMI (body mass index) ≥25 kg/m^2, and estimated glomerular filtration rate (GFR) >60 mL/min/1.73 m^2. After a 6-week run-in, patients were randomly assigned to receive once-daily linagliptin 5 mg or sulfonylurea 1 mg added to ongoing metformin; study drugs were overencapsulated.

Eight-week linagliptin did not change GFR, ERPF, filtration fraction, or renal vascular resistance compared with sulfonylurea relative to baseline. Linagliptin did not affect FE_{Na}, (fractional excretion of sodium) FE_U (fractional excretion of urea), or urinary pH, whereas sulfonylurea

increased urinary pH. Sulfonylurea versus linagliptin increased body weight (increase of 0.8 kg). No treatment differences were observed in BP/heart rate. Metabolic variables generally did not reveal relevant differences between groups. DPP-4 activity was reduced with linagliptin versus sulfonylurea. Linagliptin increased intact GLP-1 compared with sulfonylurea. Fewer patients experienced a probable symptomatic hypoglycemic event with linagliptin versus sulfonylurea (4% vs. 25%). Reported adverse events were all moderate in intensity. As 8-week treatment with linagliptin and sulfonylurea reduced HbA_{1c} and fasting glucose to a similar extent, nonglycemic advantages and disadvantages of the two drugs could be explored in this trial.

DPP-4i–mediated natriuresis may involve inhibition of the Na-H exchanger (NHE)3—located at the brush border of the proximal tubule, bound to a complex that also contains DPP-4—either through direct membrane-bound pathways or mediated by active GLP-1 levels (31-33). Indeed, acute GLP-1 receptor agonist (GLP-1RA) administration confers natriuresis, perhaps by NHE3 inhibition (34).

CONCLUSIONS

According to the studies that we read the metformin plus sulphonyl urea and metformin plus DPP-4 inhibitors are the most common non-insulin second line treatment protocols in patients with type 2 diabetes. That statistics showed that sulfonylurea compared to DPP-4 inhibitors, in combination with metformin, elevated the risk of sever hypoglycemia, fatal and non-fatal cardiovascular events, and mortality.

Another important discovery was showed by the clinical study that compared the effects of insulin versus DPP-4 inhibitors associated with metformin. The results of this study were that the insulin associated with metformin increased the risk of all-cause mortality, fatal and non-fatal cardiovascular diseases and severe hypoglycemia compared with the DPP-4 inhibitors + metformin.

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