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DIPEPTIDYL PEPTIDASE-4 INHIBITORS, A NEW OPTION FOR THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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Abstract

Objective: *Despite the diversity of antidiabetic medication currently available, less than half of the patients with type 2 diabetes meet the therapeutic targets recommended by the guidelines: HbA1c <7%, or even <6.5%. This study aimed to investigate the efficacy and safety of sitagliptin in patients with type 2 diabetes mellitus, with inadequate glycemic control, as well as the effects on cardiovascular risk factors.* ***Material and method:*** *The study included 348 patients, 161 men (46.3%) and 187 women (53.7%), with mean age of 56.1 ± 6.2 years, who started treatment with sitagliptin, combined with either metformin, sulphonylurea or both.* ***Results and discussions:*** *Sitagliptin improved glycemic control reducing average HbA1c with 1.1%; the average weight decreased with 1.7 kg after 24 weeks of treatment, and the lipid profile improved significantly.* ***Conclusions:*** *Sitagliptin offers a new therapeutic option in patients with type 2 diabetes mellitus, with the advantage of a single dose oral administration.*

key words: *dipeptidyl peptidase-4 inhibitors, sitagliptin, type 2 diabetes mellitus.*

Introduction

Type 2 diabetes mellitus (T2DM) is nowadays the most common metabolic disorder worldwide. In the pathogenesis of the disease are involved the decrease of insulin secretion by the pancreatic β-cells and insulin resis

tance (IR), which causes metabolic disturbances (glycemic, lipid, protein, hydro-electrolytic), finally leading to severe acute and chronic complications, which decrease survival and alter the quality of life [1,2].

Hyperglycemia and hyperlipidemia are the key promoters which, by distinct mechanisms (formation of advanced glycation end products-AGEs, reactive oxygen species-ROS), cause cellular destruction and IR. The main quantitative changes of dyslipidemia associated with T2DM are hyper-triglyceridemia, reduced HDL-cholesterol, increased small and dense particles of LDL-

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cholesterol, number of LDL-cholesterol particles, postprandial hyperlipidemia and changes in the plasma concentration of apolipoproteins [3].

The growing prevalence of diabetes mellitus and the difficulty to achieve an optimal glycemic control, even when using double or triple combinations, justify the investigation of new therapeutic agents to improve glycemic control, without notable side effects (weight gain, hypoglycemia, increased cardiovascular risk) [4].

There is no doubt that an optimal glycemic control slows down the onset and reduces the progression rate of T2DM complications. The UKPDS study (United Kingdom Prospective Diabetic Study) demonstrated that each decrease of HbA1c with 1%, reduces micro-vascular complications with 37% and all investigated endpoints with 21% [5,6]. Given that patients with DM are included in the high cardiovascular risk category, such results are extremely encouraging.

T2DM treatment results are far below expectations and targets, not only due to the medication, but also due to the patient's compliance and the experience of the physician.

Despite the diversity of antidiabetic medication currently available, less than half of T2DM patients meet the therapeutic targets recommended by the guidelines (HbA1c < 7%, or even < 6.5%) [7].

Several studies show that the combination of substances with complementary mechanisms of action determines better long-term glycemic control, as the combined treatment has a higher efficacy and reduces the risk of adverse effects [8,9].

In the last half of the century, the physiological and pathophysiological relationship between the intestinal hormones known as incretins (acronym for „*In*testinal Se*cre*tion of Insul*in*") and the secretion of insulin was established, demonstrating their key role in the glycemic homeostasis [10,11].

Incretins are hormones that are released by the gastrointestinal tract in response to nutrient ingestion. There are two main incretin hormones: glucagon-like peptide-1 (GLP-1) that is released as an inactive 37-amino acid peptide from the L-cells located mostly in the distal gastrointestinal tract (ileum and colon), and glucose-dependent insulinotropic peptide (GIP), a 42-amino acid peptide released from the endocrine K-cells located in the proximal gastrointestinal tract (duodenum and proximal jejunum). After secretion, these two incretins are rapidly metabolized by the dipeptidyl peptidase-4 (DPP-4) enzyme (an enzyme responsible for inactivating endogenous incretins), with GIP having a plasma half-life of 5 minutes and GLP-1 of 2 minutes [12].

The oral intake of glucose by people without diabetes produces a significantly higher insulin secretion compared to matched intravenous glucose administration. This apparent paradox has been called the „*incretin effect*" and is significantly lower in people with type 2 DM. Therefore, the main action of GLP-l is to stimulate glucose-dependent insulin secretion, thus restoring the postprandial glycemic control (about 70% of the insulin secretion following glucose ingestion is due to the incretin effect). This effect results from the binding of GLP-l to specific receptors on the membrane of the pancreatic beta-cells, thus determining the activation of adenylate cyclase, the

consecutive accumulation of intracellular AMPc, the activation of protein kinase A, an increased intracellular Ca^{++} and, finally the stimulation of insulin secretion. This physiological cascade is strictly dependent on glucose and is not triggered at low glucose levels [12].

In addition, due to the presence of specific GLP-1 receptors in other organs and tissues (kidney, heart, lungs, stomach, intestine, central and peripheral nervous system), GLP-l exerts several other benefic effects: it inhibits the glucose-dependent glucagon secretion; it slows down the gastric emptying; it increases satiety, lowers appetite and subsequently, increases weight loss; cardioprotective effect, including the increase of the ventricular ejection fraction after a myocardial infarction. Several studies proved that GLP-l has also trophic effects, stimulating proliferation and neogenesis of β cells [12].

Sitagliptin (S), a DPP-4 inhibitor, has been approved by FDA (Food and Drug Administration) in October 2006, to be used in single or combined therapy in patients with type 2 DM. By inhibiting DPP-4, S increases GLP-1 levels.

Objective

The main objective of this study was to assess the efficacy and safety of the treatment with S in association with metformin (M), a sulphonylurea (SU), or both in patients with type 2 DM, with inadequate glycemic control. We also investigated the effects of the treatment with S on some cardiovascular risk factors (body weight, lipid fractions, etc).

Material and method

The study included 348 T2DM patients, 161 men (46.3%) and 187 women (53.7%), with an average age of 56.1 ± 6.2 years, treated with M, a SU or both. Sitagliptin 100 mg daily was added to their current diabetes medication and patients were followed for 24 weeks.

The following parameters have been recorded at baseline and at the end of the study: age, sex, weight (W), body mass index (BMI), waist circumference (WC) in men and women, duration of DM. As biological parameters, we measured HbA1c, total cholesterol (TC), serum triglycerides (TG), HDLc, and LDLc was calculated using the Friedwald formula.

The patients were instructed to check their blood sugar level in case hypoglycemia symptoms occur. Hypoglycemia was defined as a blood glucose level < 70 mg% or presence of suggestive symptoms for hypoglycemia regardless of the plasma glucose level.

Our group was organized in a database created in Microsoft Excel, and data analysis was performed with specialized software EPI 3.2.2 and Open Epi. This analysis consisted of:

1. calculation of frequencies and percentages for qualitative variables;

2. calculation of the arithmetic mean and standard deviation for quantitative variables;

3. statistical comparison of tested samples: t-student unpaired test (unpaired t-test) and t-student pair test (paired t-test) were used for the comparison of two samples; ANOVA (ANalysis Of VAriance - "variance analysis") was used for more samples

4. statistical comparison of percentages with chi square ($\chi 2$ test).

Statistical estimates of data was performed using statistical test: $p > 0.05$ =

difference not significant, p <0.05 = significant difference, p <0.01 = highly significant difference and p <0.001 = extremely significant difference.

Results

The main baseline characteristics of the patients included in the study are presented in Table 1.

Table 1. Main characteristics of the patients included in the study.

Characteristic	Study group
Total number (%)	348
Men (%)	161 (46.3)
Women (%)	187 (53.7)
Average age (years)	56.1 ± 6.2
Average duration of DM (years)	8.4 ± 4.1
Average BMI (kg/m^2)	30.7 ± 4.3
Average WC (cm) **- men** **- women**	 114 ± 12 91 ± 9.8
W_0 (kg)	92.8 ± 15.6
$HbA1c_0$ (%)	8.8 ± 1.1
CT (mg/dL)	217 ± 37.4
TC (mg/dL)	208 ± 94.3
HDLc (mg/dL)	44.6 ± 6.8
LDLc (mg/dL)	131 ± 44.5

$HbA1c_0$ = average HbA1c at baseline, W_0 = average W at baseline.

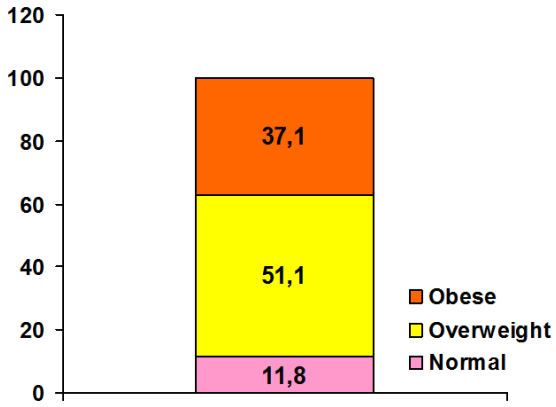

Figure 1. Distribution of study group according to weight status at baseline.

Within the study group, only 41 patients (11.8%) had a BMI < 25 kg/m^2; 178 patients (51.1%) were overweight (BMI between 25-29.9 kg/m^2), and 129 patients (37.1%) were obese (BMI > 30 kg/m^2) (Figure 1).

Of the entire study group, 203 patients (58.3%) followed combined treatment with M and SU, 98 patients (28.2%) with M alone, and 47 patients (13.5%) with SU alone (Figure 2).

Depending on the HbA1c value at the initiation of the treatment with S, the distribution of the study group was as follows: 83 patients (23.9%) had HbA1c between 7 and 8%, 179 patients (51.4%) between 8 and 9 %, and 86 patients (24.7%) over 9% (Table 2).

The average HbA1c decreased with 1.1%, from 8.8 ± 1.1% to 7.7 ± 0.8 % after 24 weeks of observation (p<0.0001) (Figure 3). Average W decreased with 1.7 kg: from 92.8 ± 15.6 kg, to 91.1 ± 14.3 kg (p (p=0.13) (Figure 4).

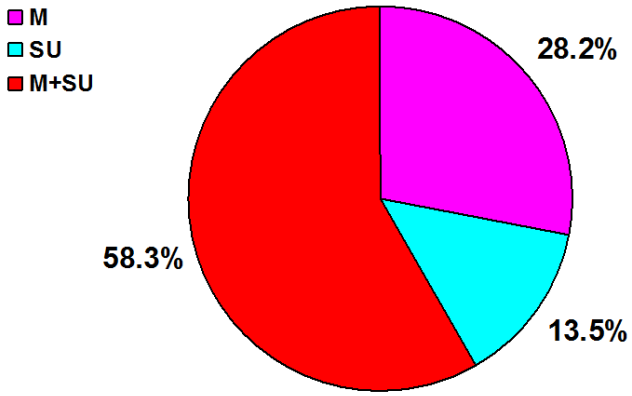

Figure 2. The study group, according to the antidiabetic therapy at baseline.

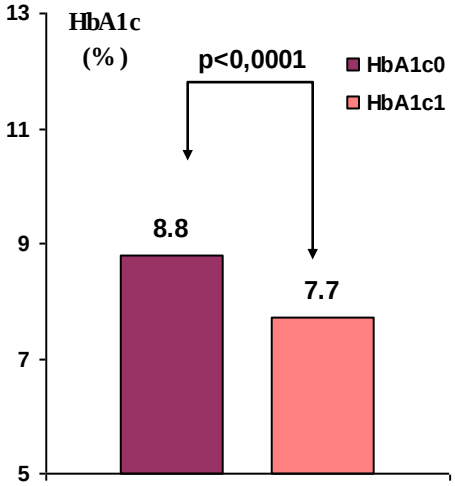

Figure 3. Average HbA1c, before and after the observation period.

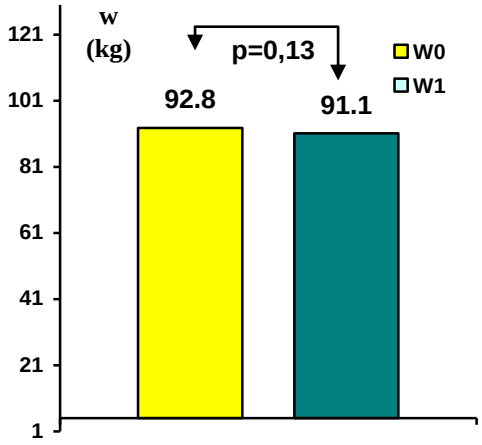

Figure 4. Average W, before and after the observation period.

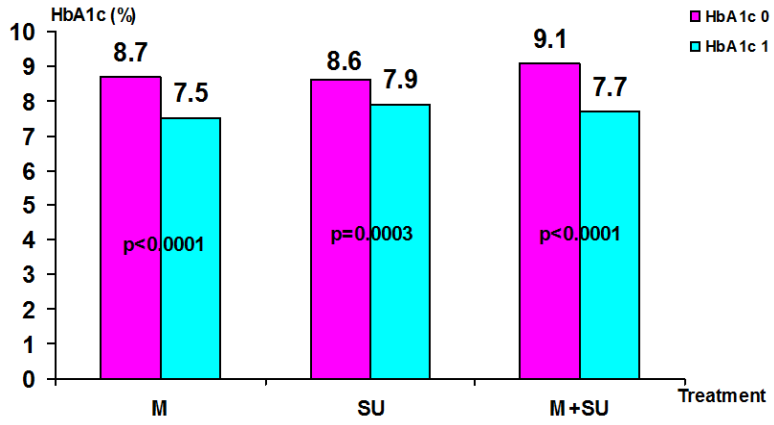

Figure 5. Decrease of HbA1c according to the previous antidiabetic treatment.

Depending on the previous antidiabetic therapy, average HbA1c decreased statistically significant in all three subgroups studied, but the highest decrease was observed in the subgroup of patients previously treated with M and SU combined: 1.4% (p<0.0001) (Figure 5).

After 24 weeks of S treatment, we found out that nearly 25% of the patients included in the study reached the recommended target for HbA1c (< 7%); furthermore, in 37 patients (10.6%), the HbA1c level was less than 6.5%. In addition, the number of patients with HbA1c ≥ 9% decreased to 3.4%. If at the initiation of the treatment with S, 265 patients (76.1%) had HbA1c ≥ 8%, after the observation period their number was reduced to 104 patients (29.8%) (Table 2).

Table 2. Distribution of patients according to HbA1c values at baseline and after 24 weeks of treatment with S.

HbA1c	< 7%	7-8 %	8-9%	≥ 9%
$HbA1c_0$: No. of patients (%)	0	83 (23.9)	179 (51.4)	86 (24.7)
$HbA1c_1$: No. of patients (%)	83 (23.9)	161 (46.3)	92 (26.4)	12 (3.4)

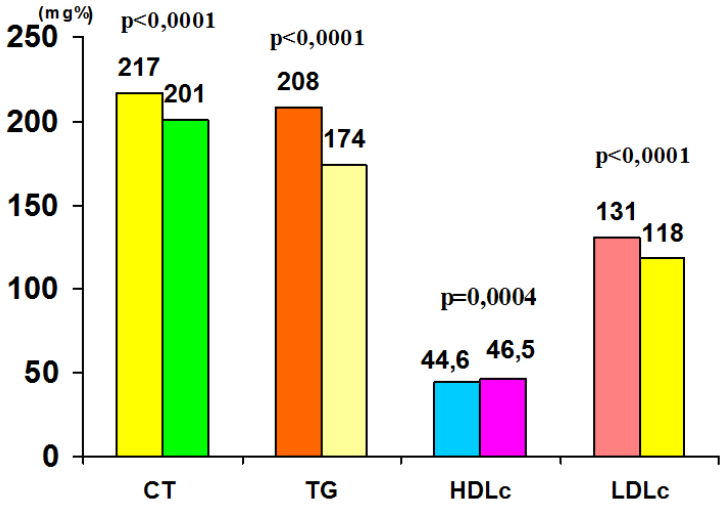

Figure 6. Mean values of lipid fractions, at baseline and after 24 weeks of S treatment.

We observed that the highest HbA1c decrease was recorded in subjects with the highest HbA1c at baseline. Thus, HbA1c decreased by an average of 1.3% in patients with HbA1c> 9%, 0.9% in those with HbA1c between 8 and 9% and 0.7% in those with HbA1c between 7 and 8%.

The therapy with S improved the lipid profile; the average levels of TC, TG, LDLc decreased statistically significant, and the HDLc levels increased. (Figure 6).

The incidence of hypoglycemic episodes was very low (1.7%): these were recorded in 3 of the patients previously treated with M and SU in combination, and in 3 of those treated with SU alone; the administration of SU was interrupted in 4 of these patients. No hypoglycemic episodes were reported in patients treated with M + S.

Discussions

Several studies revealed the beneficial effect of S on glycemic control. Thus, a study aiming to investigate the efficiency of the therapy with S alone compared with placebo treatment in patients with an inadequate DM

control (HbA1c ≥8.1%), found that after 18 weeks of treatment, HbA1c decreased by 0.6% in subjects treated with S, as compared to 0.4% in placebo treated cases [13].

Aschner et al. showed that HbA1c decreased by 0.79% in a group of T2DM patients treated for 24 weeks with S alone in a dose of 100 mg/day [14].

A study performed on 701 T2DM patients showed that HbA1c decreased by 0.65%, (from an initial A1c value of 8%) after combining S with M. In 47% of patients A1c decreased below 7% and in 17% cases HbA1c decreased below 6.5% [15].

Some studies have shown that the treatment with S in association with M increases the secretion of GLP-1 and reduces its degradation [16].

In another study, Nauck et al. compared the efficacy and safety of the treatment with S versus glipizide in T2DM patients inadequately controlled on metformin alone. The 1172 patients enrolled, received either S 100 mg/day or glipizide 5-20 mg/day. The HbA1c value decreased similarly in both groups, but several hypoglycemic episodes occurred in patients treated with glipizide [17].

Another study showed the beneficial effects of the treatment with S 100 mg/day on the postprandial TG and on the free fatty acids (FFA), compared with placebo, after only 6 weeks of therapy. The values of postprandial glycemia and glucagon decreased statistically significant after the treatment with S, and no important changes in the postprandial insulinemia and C-peptide levels have been observed. The therapy with S also improved IR (HOMA) and the β-cell function [18]. These data are in line with the previous reports of Zander et al., proving that the continuous administration of GLP-1 in patients with T2DM is associated with an improvement of insulin sensitivity and β-cell function, as well as with a lower concentration of FFA [19].

It seems that the DPP-4 inhibition by sitagliptin reduces plasma glucagon levels, glycemia and postprandial hyperlipidemia (serum TG), thereby improving the insulin sensitivity and the β–cell function. Such beneficial effects on serum TG have important clinical implications, knowing that postprandial hypertriglyceridemia is associated with a higher risk of cardiovascular events.

By all such effects (the significant improvement of glycemic control, of the lipid fractions, neutral on the body weight), the treatment with S offers real therapeutic benefits in the management of both DM and macrovascular complications, reducing significantly the cardiometabolic risk.

Our study confirmed that the therapy with S for an average period of 24 weeks significantly improved the glycemic control in patients with T2DM. After initiation of the treatment with S, HbA1c decreased significantly ($p<0.0001$), with 1.1% for the whole study group. The HbAlc-lowering effect of S is more important when the initial glycemic imbalance is more pronounced (HbAlc >9%).

The limitation of this study is that it is an open interventional study, not a randomized, placebo controlled study.

The treatment with S is an extremely efficient therapeutic option in patients with T2DM as it enhances the compliance and adherence to treatment, being readily accepted by the patient, mainly due to its easy

administration (single oral dose). In addition, the physiological mechanism of action of S makes it to be generally well tolerated by patients, with minimum risk of adverse effects (hypoglycemia in particular).

Conclusions

Our study has shown that S significantly improves the glycemic control (expressed by HbA1c) in T2DM patients not controlled on treatment with M and/or SU, having a neutral effect on body weight.

Due to its proven efficacy in achieving glycemic control and the safety of its administration, S has found out its place in the list of antihyperglycemic agents recommended in the pharmacotherapy of T2DM.

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