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SITAGLIPTIN AND VILDAGLIPTIN EFFICACY ON CARBOHYDRATE AND LIPID METABOLISM IN ELDERLY PATIENTS WITH TYPE 2 DIABETES

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Abstract

Background and Aims: *For many patients with type 2 diabetes (T2DM) classic oral anti-diabetic treatment is not effective and patients don't meet the currently recommended therapeutic goals. The aim of our study was to evaluate the efficacy of dipeptydil peptidase 4 (DPP-4) inhibitors as add-on therapy to oral antidiabetics in reducing HbA1c in elderly patients with poorly controlled T2DM.* ***Material and methods:*** *The study included 75 elderly patients with poorly controlled T2DM, treated with known oral antihyperglycemic agents. DPP-4 inhibitors were added to current oral treatment and patients were followed for 12 months, evaluating clinical and biological parameters at baseline and after 3 months, 6 months and 12 months of therapy.* ***Results:*** *After the first 3 months of treatment with DPP-4 inhibitors, fasting glucose (mg/dl) decreased from 148.27 ± 44.68 to 128.94 ± 22.71, and HbA1c (%) from 7.40 ± 1.39 to 6.93 ± 0.78. Values of these two parameters continued to decline until month 12 of follow-up, but to a lesser extent, up to mean fasting glucose (mg/dl) of 127.58 ± 20.91 and HbA1c (%) of 6.72 ± 0.52.* ***Conclusion:*** *Glycemic profile was significantly improved after 12 months of DPP-4 treatment, with a significant decrease of HbA1c.*

key words: *type 2 diabetes, DPP-4 inhibitors, sitagliptin, vildagliptin.*

Background and Aims

Type 2 diabetes mellitus - the need for new therapeutic options

The incidence and prevalence of type 2 diabetes mellitus (T2DM) greatly increases worldwide, especially in countries where lifestyle is sedentary and diet is high in cheap, calorie dense foods. Growth in T2DM prevalence is expected to double over the next 20 years. Thus, it is estimated that 440 million people will be diagnosed with T2DM by 2030 (International Diabetes Federation 2009) [1]. The prevalence of diabetes varies significantly

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depending on the studied population, age, sex, socio-economic status and lifestyle. However, T2DM increasingly affects the young groups of the population, with a high and increasing incidence in children and adolescents [2].

In many T2DM patients, currently available treatment is not effective and patients don't reach the recommended therapeutic goals. In addition, important objectives such as weight loss and prevention of hypoglycemia are not met. Insufficient metabolic control in T2DM is associated with the development of micro and macrovascular complications, increasing the risk of cardiovascular mortality (75% of T2DM patients die due to cardiovascular events). It was consistently shown that the risk of micro and macrovascular complications can be decreased by improving metabolic control [3,4]. Thus, follow-up for 10 years of the UKPDS study cohort showed that early treatment of diabetes decreases significantly not only microvascular, but also the macrovascular complications. This is why newly diagnosed T2DM patients should receive a treatment that achieves normoglycemia in a safe manner, without the risk of hypoglycemia or weight gain.

Incretin therapy

Chronic hyperglycemia that characterizes T2DM results from the combination of two pathogenic mechanisms that influence each other: decreased insulin secretion and insulin resistance. In addition, there is a high concentration of glucagon, which paradoxically increases after administration of glucose or after ingestion of carbohydrates. Unfortunately, none of the currently available classes of anti-hyperglycemic agents acts on all these pathogenic components. Moreover, many of these classes have several limitations such as moderate effectiveness, inadequate control of postprandial hyperglycemia, side effects such as weight gain, increased risk of hypoglycemia and digestive symptoms.

Incretin-based therapies address multiple aspects of T2DM patho-physiological mechanism and include Glucagon-like peptide 1 (GLP-1) receptor agonists (that mimic the effects of endogenous GLP-1) and Dipeptydil Peptidase 4 (DPP-4) inhibitors (that prevent the rapid degradation of the endogenously secreted GLP-1 hormone).

Both GLP-1 receptor agonists and DPP-4 inhibitors minimize the risk of hypoglycemia seen with insulin and some oral anti-diabetic drugs. In addition, it is hypothesized that incretin treatment could produce an improvement of β-cell function in humans. This would be highly relevant since both the β-cell mass and β-cell function are already significantly decreased at T2DM diagnosis.

Indications of incretin-based therapies in the treatment guidelines for T2DM

DPP-4 inhibitors (sitagliptin, vildagliptin and saxagliptin) are already approved in many countries for use in combined oral therapy when treatment goals are not achieved only through lifestyle changes and treatment with metformin. In this regard, DPP-4 inhibitors have been already placed in the German guidelines [5]. In addition, a recommendation by the British "National Institute for Health and Clinical Excellence" (NICE) suggested patients should not be treated with sulphonylureas in order to avoid hypoglycemia and weight gain [6] since a recent retrospective study showed that the

incidence of hypoglycemia may promote the development of dementia [7].

Incretin-based treatments proved to be effective both in the initial and advanced stages of T2DM. Preliminary data showed that adding a DPP-4 inhibitor to existing insulin therapy lowers HbA1c and may have positive effects on hypoglycemic events [8,9]. However, data on these new therapeutic agents are still scarce in the elderly population.

The main objective of our study was to evaluate the efficacy of DPP-4 inhibitors (sitagliptin and vildagliptin) as add-on therapy to oral antidiabetics (OADs) in reducing glycosylated hemoglobin (HbA1c) in elderly patients with insufficiently controlled T2DM.

Secondary study objectives were to evaluate the effect of DPP-4 inhibitors (sitagliptin and vildagliptin) on lipid parameters (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides).

Material and Methods

The study was conducted between January 2010 - January 2012, in Greece, Messinia region, Center for Health Messinia, Koroni town. Patients included in the study were recruited from the outpatient clinic after signing the informed consent. The study protocol was approved by the Ethics Committee of the University of Medicine and Pharmacy Craiova. The study included 75 patients with poorly controlled T2DM (HbA1c $\geq$ 7%), treated with known OADs. DPP-4 inhibitors were added to current OADs and patients were followed for 12 months with clinical and biological evaluation at baseline and after 3 months, 6 months and 12 months of treatment.

OADs therapy in the study group at baseline was the following: 25 patients were treated exclusively with metformin (M), 15 patients were treated with metformin + sulfonylurea (SU) (gliclazide 10 patients, glibenclamide 3 patients and glimepiride 2 patients), 15 patients were treated with metformin + thiazolidindiones (TZDs) (12 patients received rosiglitazone 4 mg/day and 3 patients received pioglitazone 30 mg/day) and 20 patients were treated with M + SU + TZDs. All patients treated with rosiglitazone were included in study in the first 4 months (January 2010 – April 2010) and no patients did receive rosiglitazone after July 2010.

In the first month of treatment with DPP-4 inhibitors, 5 patients (2 patients treated with sitagliptin and 3 patients treated with vildagliptin) dropped out the study due to gastrointestinal side effects (diarrhea). Of the 70 patients remaining in the study, 40 patients received sitagliptin 100 mg once-daily and 30 patients received vildagliptin 50 mg twice a day. The average age of patients included in the study was 74.43 ± 7.63 years. The most prevalent age group was 71-80 years (55%). Of the 70 patients remaining in the study, there were 35 women (50%) and 35 men (50%).

Laboratory investigations included fasting plasma glucose (FPG), HbA1c and serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides).

Statistical analysis

Statistical analysis was performed in order to accept or reject the null hypothesis: - TREATMENT HAS NO EFFECT - within a risk of 5% (0.05), a widely accepted threshold in such studies. Because the data did not meet the conditions for using the Student test (t) in order to compare the means, we used the

Wilcoxon Signed Ranks test, an alternative to the Student-t test used when the population distribution is not normal. Spearman correlation coefficient was used to analyze the relationship between data sets in our study.

Results

Effect of DPP-4 on carbohydrate metabolism parameters

After the first 3 months of treatment with DPP-4 inhibitors, FPG (mg/dl) decreased from 148.27 ± 44.68 to 128.94 ± 22.71, and HbA1c (%) from 7.40 ± 1.39 to 6.93 ± 0.78. Following improvement of HbA1c in the first three months of treatment with DPP-4 inhibitors, M therapy was discontinued for 15 patients, SU therapy was discontinued for 13 patients and TZDs therapy for 29 patients. Values of the two parameters continued to decline until month 12 of follow-up, but to a lesser extent, so that at the end of the study the mean FPG (mg/dl) was 127.58 ± 20.91, and HbA1c (%) was 6.72 ± 0.52.

As shown in Table 1 and Table 2, significant decreases for both FPG and HbA1c were recorded at Month 3 but these parameters did not decreased significantly at subsequently evaluations.

Table 1. Wilcoxon Signed Ranks Test- Difference of mean in FPG.

	FPG mg/dl M3-M0	**FPG mg/dl M6-M0**	**FPG mg/dl M12-M0**	**FPG mg/dl M6-M3**	**FPG mg/dl M12-M3**	**FPG mg/dl M12-M6**
Z	-3.697[a]	-2.796[a]	-3.346[a]	-.547[b]	-.791[a]	-1.360[a]
Asymp. Sig. (2-tailed)	**.000**	**.005**	**.001**	.584	.429	.174

M = months of evaluation; a = based on negative ranks; b = based on positive ranks.

Table 2. Wilcoxon Signed Ranks Test- Difference of mean in HbA1c (%).

	HbA1c% M3-M0	**HbA1c% M6-M0**	**HbA1c% M12-M0**	**HbA1c% M6-M3**	**HbA1c% M12-M3**	**HbA1c% M12-M6**
Z	-3.817[a]	-4.181[a]	-5.055[a]	-1.437[a]	-2.527[a]	-1.874[a]
Asymp. Sig. (2-tailed)	**.000**	**.000**	**.000**	.151	**.011**	.061

M = months of evaluation; a = based on negative ranks.

Table 3. Wilcoxon Signed Ranks Test- Difference of mean in total cholesterol.

	Total cholesterol mg/dl M3-M0	**Total cholesterol mg/dl M6-M0**	**Total cholesterol mg/dl M12-M0**	**Total cholesterol mg/dl M6-M3**	**Total cholesterol mg/dl M12-M3**	**Total cholesterol mg/dl M12-M6**
Z	-1.761[a]	-2.262[a]	-2.347[a]	-.050[b]	-.668[a]	-.219[a]
Asymp. Sig. (2-tailed)	.078	**.024**	**.019**	.960	.504	.827

M = months of evaluation; a = based on negative ranks; b = based on positive ranks.

Effect of DPP-4 on lipid metabolism parameters

Regarding lipid metabolism, there was a slight decrease of total cholesterol (mg/dl), from 199.58 ± 42.06 at baseline to 185.58 ± 28.60 at month 12 (Table 3). LDL-cholesterol (mg/dl) decreased slightly from 116.42 ± 31.51, at baseline to 104.30 ± 26.74 after 12 months of therapy with DPP-4 inhibitors.

Regarding HDL-cholesterol, there were no significant changes during the 12 months of DPP-4 inhibitor treatment (Table 4).

Table 4. Wilcoxon Signed Ranks Test- Difference of mean in HDL cholesterol.

	HDL col. mg/dl M3-M0	HDL col. mg/dl M6-M0	HDL col. mg/dl M12-M0	HDL col. mg/dl M6-M3	HDL col. mg/dl L12-M3	HDL col. mg/dl M12-M6
Z	-.542[a]	-.175[a]	-.377[b]	-.102[b]	-.313[b]	-.738[a]
Asymp. Sig. (2-tailed)	.588	.861	.706	.919	.754	.460

M = months of evaluation; a = based on negative ranks; b = based on positive ranks.

Table 5. Wilcoxon Signed Ranks Test- Difference of mean in triglycerides.

	TGL mg/dl M3-M0	TGL mg/dl M6-M0	TGL mg/dl M12-M0	TGL mg/dl M6-M3	TGL mg/dl M12-M3	TGL mg/dl M12-M6
Z	-2.133[a]	-2.747[a]	-2.373[a]	-.246[a]	-.196[b]	-.309[b]
Asymp. Sig. (2-tailed)	.033	.006	.018	.806	.845	.757

M = months of evaluation; a = based on negative ranks; b = based on positive ranks.

Finally, triglyceride levels decreased significantly after the first three months of the study compared with baseline (Table 5), but not anymore at subsequent visits.

The incidence of hypoglycaemia was similar before and after treatment with sitagliptin or vildagliptin, proving that DPP-4 inhibitors don't increase the risk of hypoglycemia.

Discussions

As metformin is considered the first-line drug for T2DM treatment, most studies have examined the efficacy and safety of adding a DPP-4 inhibitor to metformin and found that adding any DPP-4 inhibitor is superior to placebo, with a mean reduction HbA1c of 0.6 to 0.8% [10].

Gliptins were also compared with SUs (glimepiride [11], glipizide [12,13] and gliclazide [14]), TZDs (pioglitazone 30 mg or rosiglitazone 8 mg) [15] and GLP-1 receptor agonists (exenatide or liraglutide) [16-18]. All the studies compared the above mentioned medications as add-on to baseline metformin treatment. Compared to SUs, DPP-4 inhibitors led to a similar reduction in the HbA1c levels and a similar increase in the rate of patients achieving HbA1c < 7%, but with a lower incidence of hypoglycaemic events. Compared with TZDs, DPP-4 inhibitors were not inferior in terms of improving glycemic control. Moreover, initial observations suggested that DPP-4 inhibitors may be more potent than TZD.

The data of our own study showed that DPP-4 inhibitors have a good efficacy in lowering FPG and HbA1c as add-on therapy to metformin, SU or TZD in elderly patients with poorly controlled T2DM. Moreover, the therapeutic effect installs quickly in the first three months, after which maintenance of FPG and HbA1c levels is observed during the following months of therapy rather than their decrease (Figure 1).

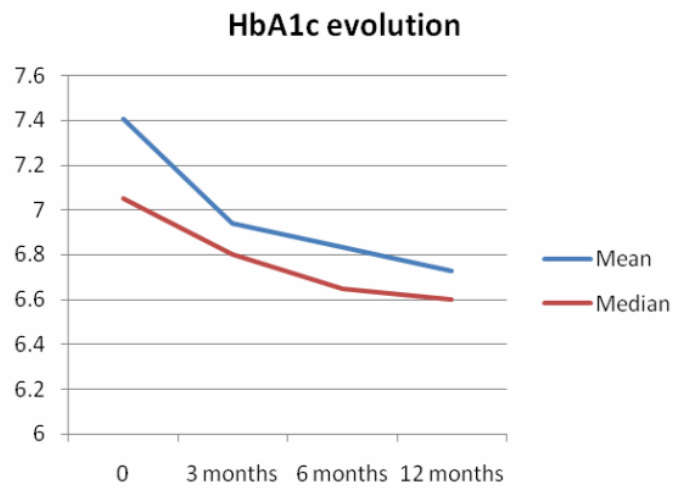

Figure 1. Evolution of HbA1c levels.

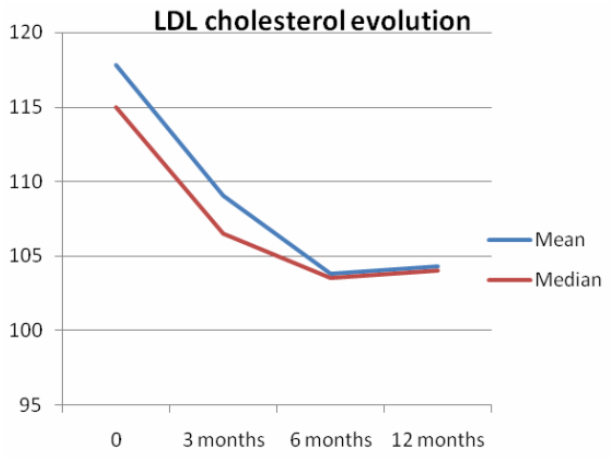

Figure 2. Evolution of LDL- cholesterol levels.

LDL cholesterol is one of the most important predictors of cardiovascular disease whether the patient has T2DM or not. In our study, LDL-cholesterol value of 104.3 ± 26.74 mg/dl at the end of the study was close to the recommended therapeutic target in T2DM.

It should be noted that the baseline mean of the LDL-cholesterol was only moderately increased (117.8 ± 31.022 mg/dl), thus reduction of LDL-cholesterol was modest but still significant. The difference in LDL-cholesterol values (Figure 2) led us to conclude that sitagliptin and vildagliptin may have a beneficial effect on LDL-cholesterol and could possibly decrease cardiovascular risk in patients with T2DM.

In our study, triglyceride levels decreased significantly after 3 months of treatment. Previously Matikainen et al. showed that vildagliptin administered for 4 weeks improves postprandial plasma triglyceride levels and metabolism of triglyceride-rich lipoprotein particles containing apolipoprotein B-48, in previously untreated patients [19].

Insulin therapy in patients with T2DM is often initiated after OADs failure and often OADs are maintained after insulin initiation. Therefore, it may be also possible to speculate

on the clinical efficacy of the combination of a DPP-4 inhibitor with insulin. In this respect, several studies reported consistent results, with a mean reduction in HbA1c levels of 0.5 to 0.6% when insulin dosage remained unchanged [20-22].

In our study, all 20 patients who received oral triple therapy at baseline (without adequate control of diabetes) had the alternative of insulin therapy initiation. However, after administration of DPP-4 inhibitors (sitagliptin, vildagliptin), glucose metabolism improved in most of these patients. Finally only 8 patients required insulin during the 12-month study, demonstrating that incretin therapy may delay the time of insulin introduction. It should be noted that the average age of patients who received insulin was 80 ± 5.50 years, compared with the average age of the entire study group (74.42 ± 7.63 years), while diabetes duration in these patients was 147.5 ± 30.11 months, compared with 78.82 ± 46.31 months in the whole study group. Thus, both age of the patients and diabetes duration were significantly higher in the 8 patients who received insulin during the study compared with the entire study group, which could explain the DPP-4 inhibitors therapy worse outcome in achieving optimal diabetes control in this subgroup of patients.

Conclusions

In our study, sitagliptin and vildagliptin treatment in combination with other oral antidiabetic therapy on a group of elderly patients with T2DM significantly improved the glycemic profile after 12 months of treatment, with a significant decrease of HbA1c. DPP-4 inhibitor treatment did not increase the risk of hypoglycemia. The study also showed that the mean levels of total cholesterol, LDL-cholesterol and triglycerides decreased significantly during the study, suggesting that sitagliptin and vildagliptin could decrease cardiovascular risk in these patients.

This new class of anti-diabetic drugs is another step in the progress towards personalized medicine. Potential disadvantages of DPP-4 inhibitors include cost and relative lack of information on the efficacy and long-term safety.

REFERENCES

1. International Diabetes Federation (IDF) Diabetes atlas. http://www.diabetesatlas.org, 2009.

2. Zeitler P. Update on nonautoimmune diabetes in children. *J Clin Endocrinol Metab* 94: 2215–2220, 2009.

3. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348: 383–393, 2003.

4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359: 1577–1589, 2008.

5. German Diabetes Association, Matthaei S, Bierwirth R et al. Medical antihyperglycemic therapy of type 2 diabetes mellitus: update of the evidence-based guideline of the German Diabetes Association. *Exp Clin Endocrinol Diabetes* 117: 522–557, 2009.

6. National Institute for Health and Clinical Excellence http://www.guidance.nice.org.uk/ CG87, 2009.

7. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 301: 1565–1572, 2009.

8. Vilsboll T, Rosenstock J, Yki-Jarvinen H et al. Sitagliptin, a selective DPP-4 inhibitor, improves glycemic control when added to insulin, with or without metformin, in patients with type 2. *Diabetes* 58[Suppl 1]: 588, 2009.

9. Fonseca V, Baron M, Shao Q, Dejager S. Sustained efficacy and reduced hypoglycemia during one year of treatment with vildagliptin added to insulin in patients with type 2 diabetes mellitus. *Horm Metab Res* 40: 427–430, 2008.

10. Scheen AJ, Radermecker RP. Addition of incretin therapy to metformin in type 2 diabetes. *Lancet* 375: 1410–1412, 2010.

11. Arechavaleta R, Seck T, Chen Y et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 13: 160–168, 2011.

12. Seck T, Nauck M, Sheng D et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. *Int J Clin Pract* 64: 562–576, 2010.

13. Goke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I; D1680C00001 Investigators. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int J Clin Pract* 64: 1619–1631, 2010.

14. Filozof C, Gautier JF. A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. *Diabet Med* 27: 318–326, 2010.

15. Blonde L, Dagogo-Jack S, Banerji MA et al. Comparison of vildagliptin and thiazolidinedione as add-on therapy in patients inadequately controlled with metformin: results of the GALIANT trial – a primary care, type 2 diabetes study. *Diabetes Obes Metab* 11: 978–986, 2009.

16. Bergenstal RM, Wysham C, Macconell L et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 376: 431–439, 2010.

17. Pratley RE, Nauck M, Bailey T et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 375: 1447–1456, 2010.

18. Pratley R, Nauck M, Bailey T et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. *Int J Clin Pract* 65: 397–407, 2011.

19. Matikainen N, Mänttäri S, Schweizer A et al. Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. *Diabetologia* 49: 2049–2057, 2006.

20. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S. Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia* 50: 1148–1155, 2007.

21. Vilsboll T, Rosenstock J, Yki-Jarvinen H et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 12: 167–177, 2010.

22. Barnett AH, Charbonnel B, Li J, Donovan M, Fleming D. Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy. *Diabetologia* 54[Suppl. 1]: S108–S109, 2011.