# LIRAGLUTIDE AND DPP-4 INHIBITORS – SIDE EFFECTS COMPARATIVE CLINICAL STUDY

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**Abstract**

*The objective of this study was to monitor the side effects of the GLP-1 receptor agonist liraglutide in comparison to those of DPP-4 inhibitors (sitagliptin and vildagliptin), in order to determine their safety, tolerability and therapeutic efficiency. The study was carried out in the "Heart and Diabetes Center NRW" and included overweight patients with type 2 diabetes whose therapeutic regimen was switched to liraglutide or DPP-4 inhibitors. A validated questionnaire method was used to monitor the side effects during the hospitalization period, then again at 3, and 6 months after the beginning of the therapy.*

*The therapy with liraglutide was associated with more side effects than the one with DPP-4 inhibitors. In general, side effects were declining with time, thus only few patients stopped therapy. The incretin therapy turned out to be a safe and effective therapeutic option for patients with type 2 diabetes mellitus.*

**Keywords:** liraglutide, DPP-4 inhibitors, side effects.

## Introduction

Research in recent years has placed a particular focus on the study of the Glucagon-like peptide 1 (GLP-1) intestinal hormone, which is synthesized in response to food stimulus and is involved in glycemic control [1]. Dipeptidylpeptidase-4 (DPP-4) was identified as being responsible for the rapid inactivation of GLP-1 [2]. Based on the study of this hormone, further research led to the development of new therapeutic options for the treatment of type 2 diabetes mellitus (T2DM).

Liraglutide is an acylated GLP-1 receptor agonist, with a 97% amino acid sequence identity to endogenous human GLP-1 (7-37), but is resistant to the hydrolysis of DPP-4 [3,4]. Used in T2DM therapy, liraglutide is administered by subcutaneous injection once daily [5]. Similar to the GLP-1 hormone, liraglutide has multiple roles: restriction of appetite and delay of gastric emptying [6], weight loss, lowering of blood pressure [7], inhibition of glucagon secretion [8], growth of pancreatic β-cell function through β-cell proliferation, decrease of β-cell apoptosis and increase of glucose stimulated insulin secretion [9,10]. Liraglutide also exerts anti-inflammatory effects on the vascular endothelium [11].

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DPP-4 inhibitors (e.g. sitagliptine, vildagliptine) prolong the action of the natural GLP-1 hormone through the inactivation of DPP-4 enzyme [12]. Through the oral administration of DPP-4 inhibitors, and through the lower frequency of side effects [13,14,15], this therapeutic option recommends itself as a progress of diabetology.

## Patients and Methods

The patients submitted to the evaluation with liraglutide and DPP-4 inhibitors were selected consecutively over an 11 months' period from the Heart and Diabetes Center NRW in Bad Oeynhausen, Germany. The ethics committee of the Ruhr University of Bochum located at the Heart and Diabetes Center NRW approved this data acquisition. None of the patients have been treated with these substances before; therapy change was performed during hospital stay following clinical affordance. An informed consent was obtained from the patients who were asked to take part in this data collection and were followed up for 6 months. The new therapy for the treatment of T2DM consisted of: liraglutide, or sitagliptin, or vildagliptin, respectively – which were administered as a therapy associated to other antidiabetic drugs (metformin, glimepiride, pioglitazone, etc.).

As these patients were selected consecutively and not based on predetermined criteria this cohort presents a

real life patient cohort. The clinical parameters concerning side effects were: nausea, vomiting, heartburns (pyrosis), hiccups (eructation), diarrhea, constipation, headaches, and dizziness.

The overall profile of these side effects was based on the questionnaire method which followed three chronological points of reference in time: "point 0" – the hospitalization period (the beginning of the therapy), "point 1" – three months after the therapy started, "point 2" – six months after the therapy started. At "point 0" the records had in view the side effects incidence within every single day of the approximately 7-10 days of the hospitalization. The questionnaires used at point 1 and 2 focused solely on recording the incidence of these adverse reactions within three consecutive days.

Before monitoring the side effects, records had been made with data regarding the incidence of these reactions in the patients before the hospitalization period. In order to record all data as precisely as possible, the factors taken into consideration were extended to: the history of previous medication, the medication associated to the study therapy, and other factors like environment, temperature, diet etc. which could have influenced the patient's condition.

## Results and Discussion

The study initially included 192 patients with available data sets. Of those, 98 patients (mean age 57.9±11.8 years) were treated with liraglutide and 94 patients (mean age 62.3±11.5 years) received DPP-4 inhibitors (sitagliptin or vildagliptin).

For the side effects monitoring, each occurrence of a side effect during the hospitalizing period was counted as 'negative event'. Each improvement in relation to the patient's condition before the therapy started was counted as 'positive event'. In the results tables, the incidence of side effects occurrence is presented as follows: each side effect during hospitalization period was counted only once, regardless of its duration.

During the hospitalizing period, fewer side effects occurred under the therapy with DPP-4 inhibitors, except for vomiting, pyrosis and headaches (table I). Three months after the start of monitoring, the incidence of all side effects was lower as compared to the hospitalizing period, except for pyrosis under liraglutide therapy and nausea, eructation, headaches and dizziness under the use of DPP-4 inhibitors (table II). Six months after the therapy, side effects incidence recorded the lowest rates throughout the monitoring period, both under therapy with liraglutide and DPP-4 inhibitors (table III). At each of the three chronological points of reference in time, the frequency of headaches was increased under therapy with DPP-4 inhibitors.

**Table I.** Incidence of side effects throughout the hospitalization period.

| | **Liraglutide** N=98 patients | | **DPP-4 inhibitors** N=94 patients | |
|---|---|---|---|---|
| | – | + | – | + |
| Nausea | 25 (25.5%) | 9 (9.2%) | 9 (9.6%) | 4 (4.3%) |
| Vomiting | 3 (3.1%) | 4 (4.1%) | 5 (5.3%) | 1 (1.1%) |
| Pyrosis | 7 (7.1%) | 10 (10.2%) | 8 (8.5%) | 2 (2.1%) |
| Eructation | 26 (26.5%) | 8 (8.2%) | 10 (10.6%) | 3 (3.2%) |
| Diarrhea | 20 (20.4%) | 16 (16.3%) | 14 (14.9%) | 9 (9.6%) |
| Constipation | 18 (18.4%) | 15 (15.3%) | 15 (16.0%) | 4 (4.3%) |
| Headaches | 13 (13.3%) | 9 (9.2%) | 14 (14.9%) | 4 (4.3%) |
| Dizziness | 14 (14.3%) | 9 (9.2%) | 12 (12.8%) | 6 (6.4%) |

**Table II.** Incidence of side effects three months after the therapy start.

| | **Liraglutide** N=83 patients | | **DPP-4 inhibitors** N=75 patients | |
|---|---|---|---|---|
| | – | + | – | + |
| Nausea | 20 (24.1%) | 4 (4.8%) | 8 (10.7) | 1 (1.3%) |
| Vomiting | 2 (2.4%) | 3 (3.6%) | 2 (2.7%) | - |
| Pyrosis | 11 (13.3%) | 8 (9.6%) | 5 (6.7%) | 1 (1.3%) |
| Eructation | 14 (16.9%) | 6 (7.2%) | 16 (21.3%) | 2 (2.7%) |
| Diarrhea | 14 (16.9%) | 12 (14.5%) | 9 (12.0%) | 8 (10.7%) |
| Constipation | 11 (13.3%) | 13 (15.7%) | 9 (12.0%) | 4 (5.3%) |
| Headaches | 5 (6.0%) | 6 (7.2%) | 15 (20.0%) | 4 (5.3%) |
| Dizziness | 8 (9.6%) | 5 (6.0%) | 10 (13.3%) | 4 (5.3%) |

**Table III.** Incidence of side effects six months after the therapy start.

| | **Liraglutide** N=76 patients | | **DPP-4 inhibitors** N=67 patients | |
|---|---|---|---|---|
| | – | + | – | + |
| Nausea | 5 (6.6%) | 4 (5.3%) | 2 (3.0%) | 1 (1.5%) |
| Vomiting | 1 (1.3%) | 2 (2.6%) | - | - |
| Pyrosis | 4 (5.3%) | 7 (9.2%) | 5 (7.5%) | 1 (1.5%) |
| Eructation | 5 (6.6%) | 5 (6.6%) | 7 (10.4%) | 2 (3.0%) |
| Diarrhea | 8 (10.5%) | 12 (15.8%) | 7 (10.4%) | 7 (10.4%) |
| Constipation | 8 (10.5%) | 12 (15.8%) | 6 (9.0%) | 4 (6.0%) |
| Headaches | - | 5 (6.6%) | 7 (10.4%) | 4 (6.0%) |
| Dizziness | 4 (5.3%) | 4 (5.3%) | 2 (3.0%) | 3 (4.5%) |

Outstanding positive events were recorded for each study group with patients reporting regular bowel disorders before therapy switch to incretins. That observation was especially obvious in patients treated with liraglutide, who had diarrhea (16.3%), and constipation (15.3%) (table I).

Throughout the monitoring period of six months, the side effects led to treatment interruption in 4 out of 98 patients treated with liraglutide, and in 6 out of 94 patients under DPP-4 inhibitors. Under the therapy with DPP-4 inhibitors, one patient reported the occurrence of edema, and another reported chest pain. Transient states of bloating or fullness were recorded in a small number of patients under both therapies.

## Conclusions

The incidence of the side effects found are in correlation with the data in the literature, i.e. GLP-1 receptor agonists cause more side effects than DPP-4 inhibitors [14,15]. Nevertheless, headache incidence was higher under DPP-4 inhibitors. Side effects were generally quickly reversible; their incidence was declining during the monitoring period. Under these therapies, the data recorded an improvement in some of the patients with bowel transit problems. The new therapeutic concept of GLP-1 receptor agonists is easily and successfully applied in overweight patients with T2DM.

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