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A prospective study of concomitant GLP-1 analogue and insulin use in type 2 diabetes in clinical practice

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ABSTRACT

Background: A small number of studies have shown a significant reduction in HbA1c, weight and total daily insulin dose when a glucagon-like-peptide-1 (GLP-1) analogue was added in type 2 diabetes patients already on insulin treatment. Therefore, in a clinical setting, we investigated the effect of adding GLP-1 analogues in patients with type 2 diabetes already using insulin with respect to glycaemic control, body weight and insulin dose.
Methods: In this prospective hospital-based study, we included 125 patients suffering from type 2 diabetes, treated with insulin and with a body mass index ≥ 35 kg/m^2, who had started on GLP-1 analogues (liraglutide/exenatide). HbA1c, body weight, daily insulin dose, and side effects were registered at baseline, and after three, six and 12 months.
Results: HbA1c and weight decreased significantly at all the timepoints ($p \leq 0.001$ compared with baseline; HbA1c: -5.5 mmol/mol (-0.5%) and weight: -14.3 kg after 12 months), with the largest decrease in the first three months. No significant correlation was found between weight loss and HbA1c reduction, and between duration of diabetes and both weight loss and HbA1c reduction. After six and 12 months, the total daily insulin dose decreased significantly ($p < 0.001$, -75.4 IU after 12 months). Moreover, 34% of the patients were able to stop using insulin therapy after 12 months.
Conclusion: By adding a GLP-1 analogue in obese patients with type 2 diabetes already on insulin therapy, a significant reduction of HbA1c levels and body weight, and a significant reduction in insulin dose or complete discontinuation of insulin can be achieved.

KEYWORDS

Diabetes mellitus (type 2), glucagon-like peptide 1, insulin, obesity

INTRODUCTION

Glucagon-like-peptide-1 (GLP-1) analogues are a relatively new category of glucose-lowering drugs for the treatment of type 2 diabetes. These drugs have broad glucoregulatory actions, including stimulation of endogenous insulin production and secretion, and suppression of glucagon secretion, both depending on blood glucose level. Additionally, they have an effect on the brain, enhancing satiety, and on the gastrointestinal tract, delaying gastric emptying.[1]
Clinical studies showed that GLP-1 analogues are effective in improving glycaemic control in patients with suboptimal control on one or two types of oral glucose-lowering drugs.[2] Furthermore, reduction of body weight was confirmed in recent meta-analyses.[3,4]
Several randomised clinical trials showed a significantly greater reduction of HbA1c using exenatide compared with placebo when added to a regime of oral glucose-lowering drugs and long-acting insulin.[5,6] Additionally, a few reviews showed that GLP-1 analogues establish glycaemic improvement and weight loss benefit, also in patients already using insulin.[7-10] Several studies showed a significant reduction in total daily insulin dose when a GLP-1 analogue was added in patients already on insulin treatment.[11-15] Furthermore, Morrow *et al.* examined the pharmacokinetic and pharmacodynamic effects of combining liraglutide with insulin detemir, and showed that the pharmacokinetic profile of detemir was not altered by co-administration of liraglutide, and that there was an indication of an additive glucose-lowering effect when combining them.[16] Recently, the combination of a GLP-1 analogue with long-acting insulin has been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) based on the aforementioned studies.

Since 2009, GLP-1 analogues have only been approved in the Netherlands for the treatment of type 2 diabetes in patients with a body mass index (BMI) > 35 kg/m² and inadequate glycaemic control while on maximal oral glucose-lowering medication.[17] The combination of insulin and GLP-1 analogues is not reimbursed in the Netherlands, which implies that GLP-1 analogues are not available for patients with type 2 diabetes using insulin. However, in several cases in clinical practice, we observed that starting GLP-1 analogues in patients already on insulin therapy led to improvement of glycaemic control, and a reduction of total daily insulin dose. Therefore, the current Dutch guidelines might lead to unavailability of an effective therapy for patients with type 2 diabetes already using insulin.
In a clinical setting, we investigated the effect of adding GLP-1 analogues in patients with type 2 diabetes and obesity already using insulin with respect to glycaemic control, body weight and total daily insulin dose.

METHODS

Study population

From April 2010 until May 2012 we included all patients starting treatment with GLP-1 analogues (liraglutide once daily or exenatide once weekly) at the Department of Internal Medicine of our hospital. All patients suffered from type 2 diabetes, were at least 18 years of age, had suboptimal glycaemic control (HbA1c > 53 mmol/mol or with frequent complications of insulin use) despite lifestyle modifications and maximum allowed or tolerated doses of oral glucose-lowering drugs, were using insulin (one, two or four times daily), and had a BMI ≥ 35 kg/m².

Procedures

When starting liraglutide or exenatide, the insulin dosage was adjusted based on the insulin frequency, i.e. 1) in patients using once- or twice-daily insulin, the doses were reduced by 50%, and 2) in patients using insulin four times daily, the short-acting insulin was stopped and the long-acting dose was reduced by 50%. Thereafter, the total insulin dose was tapered by the doctor using the observed glucose values with the intention to reduce the insulin dose towards zero. Liraglutide was uptitrated from 0.6 mg per day to 1.2 mg, and, if indicated, to 1.8 mg per day. Each titration had to be completed for at least one week.
At baseline, and after three, six and 12 months, HbA1c and body weight were registered.
HbA1c was measured in mmol/mol, and the values were afterwards converted towards National Glycohaemoglobin Standardisation Program (NGSP)-derived units (%). Weight was measured in kilograms, and BMI was calculated by dividing weight (kg) by the square of the height (m²). Furthermore, at baseline and after six and 12 months medication (oral medication, daily insulin dose in IU) was recorded.

Statistical analysis

For analyses, we used longitudinal analysis using repeated measures analysis with an unstructured covariance matrix to model the covariance structure. Analyses were performed for HbA1c and weight comparing baseline with three, six and 12 months, and for insulin dose at six and 12 months. These analyses were adjusted for age and sex. Furthermore, the correlation between HbA1c and weight change, between duration of diabetes and HbA1c and weight change, and between weight change and insulin dosage change was calculated at three, six and 12 months. In addition, adverse events and complications during the study period were registered. All analyses were performed using SPSS for Windows.

Results

During the study period we included 125 patients. *Table 1* lists the characteristics of the study population. The mean age was 59.3 years, and 61 (49%) patients were women. At baseline, mean HbA1c was 68.3 mmol/mol (8.4%),

Table 1. *Characteristics of the study population*

	Total (n = 125)
Age (years)	59.3 ± 10.0
Gender	
- Men (%)	64 (51)
- Women (%)	61 (49)
Weight (kg)	121.4 ± 19.1
BMI (kg/m²)	41.5 ± 5.1
HbA1c (%)	8.4 ± 1.2
HbA1c (mmol/mol)	68.3 ± 12.6
Insulin dose (IU)	114 ± 68
- Long acting (IU)	63 ± 33
- Short acting (IU)	49 ± 49
Duration of diabetes (years)	12.6 ± 7.5
Insulin daily frequency	
- Once (%)	27 (22%)
- Twice (%)	21 (17%)
- Four times (%)	74 (59%)
- Insulin pump (%)	3 (2%)
GLP-1 analogue	
- Liraglutide (%)	121 (96.8)
- Exenatide (%)	4 (3.2)

Values are means (± standard deviation) or numbers (percentages).

while mean BMI and mean body weight were 41.5 kg/m² and 121.4 kg, respectively. Furthermore, the average daily insulin therapy dose was 114 IU. A total of 121 patients (97%) started liraglutide, the others used exenatide.

Table 2, figure 1 and *figure 2* show HbA1c and weight over time. HbA1c decreased significantly at all three timepoints (-4.1 mmol/mol (-0.4%), -5.4 mmol/mol (-0.5%), and -5.5 mmol/mol (-0.5%) at three, six and 12 months respectively, $p \leq 0.001$ compared with baseline), with the largest decrease in the first three months. Similarly, a significant weight reduction was seen at all timepoints (-9.7 kg, -12.5 kg, and -14.3 kg at three, six and 12 months respectively, $p < 0.001$ compared with baseline), with the largest decrease in the first three months as well.

After both six and 12 months, the total daily insulin dose decreased significantly (-75.0 IU and -75.4 IU respectively, $p < 0.001$). Moreover, 36 patients (29%) were able to discontinue any form of insulin therapy at six months, while at 12 months 42 patients (34%) were able to do this.

There was no significant correlation between HbA1c and weight change at three, six and 12 months. Additionally, no significant correlation between duration of diabetes and HbA1c or weight change, respectively, was found. A significant correlation between weight change and insulin dosage change ($p < 0.001$) at six and 12 months was found.

Table 2. *Change from baseline for HbA1c, weight and insulin dosage*

	3 months	6 months	12 months
Weight (kg)	-9.7 ± 6.6 *	-12.5 ± 8.4 *	-14.3 ± 9.5 *
HbA1c (%)	-0.4 ± 1.2 *	-0.5 ± 1.4 *	-0.5 ± 1.3 *
HbA1c (mmol/mol)	-4.1 ± 12.9 *	-5.4 ± 15.8 *	-5.5 ± 14.2 *
Insulin dosage (IU)		-75.0 ± 55.8 *	-75.4 ± 60.3 *
- Long acting (IU)		-25.6 ± 29.0 *	-26.6 ± 31.6 *
- Short acting (IU)		-43.5 ± 45.8 *	-37.5 ± 40.2 *
Correlation between change of weight and change of HbA1c (r)	-0.11	-0.11	-0.04
Correlation between change of weight and duration of diabetes (r)	-0.08	-0.20	-0.16
Correlation between change of HbA1c and duration of diabetes (r)	0.05	0.07	0.10
Correlation between change of weight and change of insulin dosage (r)		0.38	0.44

Values are means (± standard deviation) or correlation coefficient.
*** p-value ≤ 0.001 compared with baseline adjusted for age and sex.**

Figure 1. *Bar graphs showing HbA1c change over time*

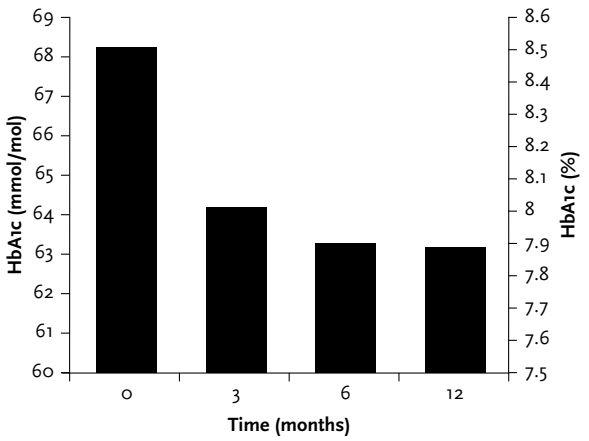
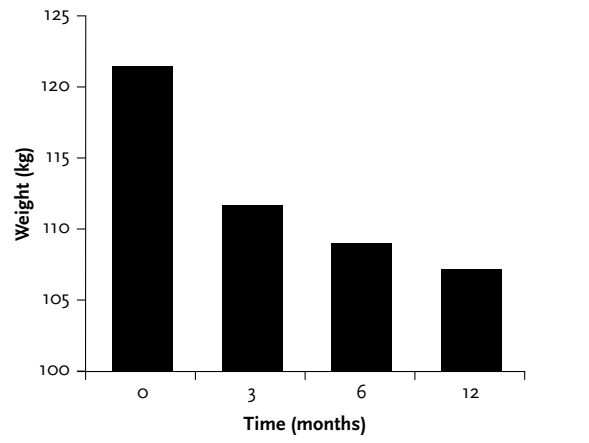


Figure 2. *Bar graphs showing weight change over time*



During the study, 19 patients (15%) discontinued the GLP-1 analogues due to lack of effect on glycaemic control, while five patients (4%) stopped due to intolerable side effects. No pancreatitis or diabetic ketoacidosis was observed during the study period.

DISCUSSION

We have shown that patients with type 2 diabetes already on insulin therapy benefit from adding GLP-1 analogues, as both HbA1c levels and body weight decreased despite a significant reduction or discontinuation of the insulin dose. Remarkably, no significant correlation between weight loss and HbA1c reduction could be observed.

During the study period no diabetic ketoacidosis was observed. This is probably due to the method that insulin therapy was not discontinued at the start, but tapered based on the glucose values.

We found that HbA1c decreased significantly at three, six and 12 months, with the decrease in the first three months being the largest. Previous clinical studies, also including patients on insulin therapy, showed a decrease in HbA1c of 0.9% after 13 weeks,[18] 0.55% after 12 months and 0.54% after 27 months,[12] and 0.32% after 12 months.[11] Our result of 5.5 mmol/mol (0.5%) after 12 months is therefore comparable with other clinical studies.

We observed a significant weight reduction at all timepoints, with the largest decrease in the first three months leading to a total reduction of 14 kg (12%) after 12 months. In clinical studies evaluating patients on insulin therapy, Mulligan *et al.* retrospectively showed a mean weight reduction of 2.4 kg (2%) after 13 weeks.[18] Yoon *et al.* showed a decrease of 4.3 kg (4%) and Thong *et al.* of 7.6 kg (7%) after 12 months in patients also using insulin.[11,12] In a prospective study, Nayak *et al.* showed a weight decrease of 12.8 kg (11%) after 12 months.[13] Our observations are in line with the observations of this last-mentioned prospective clinical study. However, the total weight loss observed in our study population was considerably higher than reported by Thong *et al.*, Yoon *et al.*, and Mulligan *et al.*[11,12,18] This difference might be explained by our inclusion criterion of a BMI ≥ 35 kg/m^2 which is considerably higher than other studies. Therefore, our patients had more excessive weight and therefore one might argue that there is potentially more weight that can be lost.

Insulin dose was decreased significantly during the study, both at six and 12 months (64% after 12 months) with almost all the decrease seen in the first six months. In a retrospective study with 27 months of follow-up, Yoon *et al.* also showed a significant decrease in total daily insulin dose in the first 12 months with respect to baseline.[12] The largest reduction was seen in the first six months, however; thereafter insulin doses increased again but stayed below the baseline dose, even after 27 months. Moreover, several other studies showed a significant reduction in daily insulin dose when a GLP-1 analogue was added to insulin treatment.[11,13-15]

Of our patients, 34% were able to discontinue any form of insulin. After adding a GLP-1 analogue to insulin, Thong *et al.* found that 16.6% of their patients were able to stop using insulin and for Lind *et al.* this was 8%.[11,15] This is lower than the percentage observed in our study, which might be caused by the fact that our study was designed to decrease or discontinue insulin, while their studies were retrospective.

Four percent of our study patients discontinued GLP-1 analogues due to intolerable side effects. Gastrointestinal side effects are common in GLP-1 analogues; Buse *et al.* reported nausea in 21% of patients using liraglutide and in 9% of patients using exenatide. Furthermore, diarrhoea was seen by them in 13% and 6%, respectively.[19]

Due to lack of glycaemic control, 15% of our study population discontinued GLP-1 analogues. Davis *et al.* showed that 18% of their patients treated with exenatide lost glycaemic control before week 16, and that pre-treatment C-peptide levels and baseline body weight were the best estimators of successful glycaemic control.[20]

We observed no significant correlation between HbA1c reduction and weight loss after three, six and 12 months. Yoon *et al.* did not observe a significant correlation between HbA1c and weight change after six and 12 months either.[12] This absence of correlation is an interesting observation as it was thought that these two go together.[21,22] Furthermore, we found no correlation between HbA1c reduction and duration of diabetes, and between weight change and duration of diabetes. It could be hypothesised that differences in endogenous GLP-1 production or insulin rest capacity play a crucial role in these inter-individual differences. Further studies are needed to confirm our findings.

A significant correlation between weight change and insulin dosage change was found. This might be explained by the fact that reducing weight leads to decreasing insulin resistance and therefore less insulin is needed, but it might also be the other way around.

The prospective character of our study is one of its main strengths since most clinical studies have a retrospective design. Additionally, its clinical setting gives a direction for daily practice. Limitations include its single-arm design, so no conclusions can be drawn about the benefits of combination therapy over insulin therapy alone, and factors other than GLP-analogue treatment affecting weight and HbA1c reduction cannot be ruled out, e.g. positive impulse by initial weight loss resulting in lifestyle change. Further research might include a prospective double-arm design, comparing combination treatment with GLP-1 analogues and insulin with insulin treatment only to overcome these difficulties. Moreover, starting a GLP-1 analogue, and then inclusion in the study, was a decision made by the patient's clinician, resulting in the fact that he/she only included a patient when benefit was expected; this might lead to confounding by indication. However, it might also be that we omitted patients who would have benefited from GLP-1 analogues, and this type of inclusion is how clinical practice works.

In conclusion, our study shows that obese patients with type 2 diabetes already on insulin therapy benefit from GLP-1 analogues: despite significant reduction or discontinuation of insulin dose, HbA1c levels and body weight decreased. Therefore, we suggest that the present indication for the use of GLP-1 analogues in

the Netherlands should be reconsidered. Further studies are needed to find an explanation why reduction in body weight and change in HbA1c are not correlated.

DISCLOSURES

The authors declare no conflicts of interest.

Statement of Human Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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