Are Insulin Analogues Detemir or Glulisine Used Preferentially in Overweight/Obese Subjects? A German Multicentre Analysis of 38 560 Type 2 Diabetic Patients from the DPV Registry

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Are Insulin Analogues Detemir or Glulisine Used Preferentially in Overweight/Obese Subjects? A German Multicentre Analysis of 38 560 Type 2 Diabetic Patients from the DPV Registry

Authors

B. Bohn1, N. Scheuing1, P. M. Jehle1, K. Laubner3, B. Born1, S. Merger1, M. Hummel1, D. Krakow1, A. Voll1, A. Zimmermann1, S. Zimny10, R. W. Höl1; for the DPV and APV initiatives and the German BMBF

Affiliation

Correspondence

B. Bohn, M.Sc. Public Health Nutrition
Institute of Epidemiology and Medical Biometry, ZIBMT
University of Ulm
Albert-Einstein-Allee 41
D-89081 Ulm
Germany
Tel.: +49/731/5025 483
Fax: +49/731/5025 309
barbara.bohn@uni-ulm.de

Abstract

Objective: Several studies suggest benefits of insulin analogues detemir or glulisine in overweight and obese patients with type 2 diabetes. The present multicentre study therefore examines, whether these insulin analogues are used more frequently in patients with increased body mass index.

Methods: Data of 38 560 adult type 2 diabetic patients using insulin analogues, from 150 centres in Germany, registered in a standardized, prospective, computer-based documentation program (DPV), were included. Patients were classified into body mass index categories according to World Health Organization. Analysis was stratified by 3 time periods. To adjust for confounding effects, multivariable logistic regression models were created.

Results: Detemir was preferentially used in overweight (OR 1.36, 95%-CI 1.20–1.53) and obese patients (OR 2.06, 95%-CI 1.84–2.31) compared to normal-weight patients. These effects remained significant after adjusting for sex, age, new/old federal state of Germany, size of centre, treatment in university clinic and clinic/specialized private practice. Models were additionally adjusted for time period and interaction of BMI category with age or sex. For glulisine, a minor effect was present when comparing obese to normal-weight patients (OR 1.26, 95%-CI 1.06–1.50). After adjustment, this finding was no longer significant. Stratified by obesity grade, class III obese patients more frequently used detemir or glulisine compared to class I obese patients. Comparing time periods, odds ratios did not differ, neither for detemir nor for glulisine.

Conclusion: Detemir is used more often in overweight and obese patients compared to normal-weight patients. For glulisine, the relationship is less pronounced.

Introduction

Weight gain is a detrimental effect of insulin therapy in patients with diabetes [1,2]. As many patients with type 2 diabetes are already overweight or obese [3], an additional insulin-induced weight gain is relevant. Increased body weight (in particular visceral adipose tissue) worsens the insulin resistance and therefore leads to a higher requirement of insulin to achieve glycemic control [1,4]. Additionally, it may also raise the risk for hypertension or cardiovascular disease [5,6]. Furthermore, with regard to the vast number of overweight and obese patients with type 2 diabetes, it is important that insulin analogues maintain their pharmacokinetic (PK) and pharmacodynamic (PD) profiles regardless of body mass index (BMI) or skin thickness. However, studies indicate that obesity may lead to lower insulin absorption and a delayed onset of activity [7]. Insulin analogues detemir (long-acting) and glulisine (rapid-acting) were approved by the European Medicines Agency in 2004. Detemir: Studies indicate that long-acting analogue detemir may lead to less nocturnal hypoglycemia and reduced weight gain in patients with type 1 and type 2 diabetes compared to long-acting analogue glargine or NPH [8–12]. It was further reported that pharmacodynamics appear to be independent of BMI and that patients with the highest BMI (>35 kg/m²) treated with detemir even lost weight [3,13,14]. Glulisine: In contrast to other rapid-acting analogues glulisine seems to have a faster onset and a shorter duration of action in patients with type 1 and type 2 diabetes. This appears to be independent of skin thickness or BMI [15–19]. Hence, it is hypothesized...
that glulisine maintains its PK and PD profiles in overweight and obese patients with type 2 diabetes [15,18]. The potential advantages of detemir or glulisine promoted by the manufacturers might lead to a more frequent use of these insulin analogues in overweight and obese patients with type 2 diabetes compared to normal-weight patients. Therefore, this study aims to investigate whether there is a BMI-dependent use of detemir or glulisine compared to respective alternative insulin analogues in type 2 diabetic patients from Germany.

Materials and Methods

Patients and data documentation

Patients were selected from the DPV database, a computer-based documentation program for diabetes diagnosis and patient care currently used by 392 specialized centres from Germany and Austria. Anonymized, prospectively documented data are transmitted twice a year from participating health care facilities to Ulm, Germany, for central analysis and quality assurance [20–22]. Implausible and inconsistent data are reported back to the centres for verification or correction. The DPV initiative is approved by the Ethics Committee of the University of Ulm, Germany and data collection by the local review boards.

For the present analysis, data of 173455 adult type 2 diabetic patients (≥ 18 years) documented between the years 2004–2012 were available (Fig. 1). Datasets were aggregated over the last 2 years. Austrian patients and patients not treated with insulin were excluded, leaving 95691 patients. Further exclusion criteria were use of insulin pump, missing BMI value and use of 2 rapid-acting analogues or 2 long-acting analogues simultaneously. The final study population comprised 21066 patients using long-acting analogues and 17494 patients using rapid-acting analogues from 150 specialized diabetes care centres in Germany (Fig. 1).

Statistical analysis

Descriptive statistics were implemented for all German adult patients with type 2 diabetes in the database as well as for all patients treated with insulin and separately for patients using either long- or rapid-acting analogues. Baseline characteristics are presented as median with lower (Q1) and upper quartile (Q3) or as percentage. To analyze the relationship between BMI and the use of analogues, patients were classified into BMI categories according to WHO recommendation (BMI <25 kg/m²; BMI ≥25–<30 kg/m²; BMI ≥30 kg/m²). For further analysis, obesity was additionally stratified by 3 classes (obesity class I: BMI ≥30–<35 kg/m², obesity class II: BMI ≥35–<40 kg/m², obesity class III: BMI ≥40 kg/m²). To account for other factors that may contribute to prescription preferences, multivariable regression modelling was applied. Sex, age, new/old federal states of Germany, size of centre, treatment in university centre, clinic/specialized private practice or time effects were considered as possible confounders. Age was categorized as <65/≥65 years, time period as 2004–2006, 2007–2009 and 2010–2012. To define a large center, the median number of patients treated in 2012 by specialized diabetes care centres included in this study was used as cut-off (≥830). Multivariable logistic regression models were created for each confounder separately. Every model included the confounders time period, age, sex and interaction terms for BMI category with the respective confounder, age or sex. A final model included all confounding variables and the interaction terms between BMI and age/sex simultaneously. Receiver operating characteristics with area under the curve (ROC-AUC) were applied to proof goodness of fit. Results are presented as odds ratio (point estimate and 95% confidence interval). A two-sided p-value <0.05 was considered significant. All statistical analyses were implemented with SAS 9.3 (Statistical Analysis Software, SAS Institute, Cary, NC, USA).

Results

Study population

Baseline characteristics of all German adult type 2 diabetic patients from the DPV database, of insulin-treated patients and of patients using long- or patients using rapid-acting analogues are presented in Table 1. Final study population comprised 38560 patients using insulin analogues. 30.5% of patients with long-acting analogues used detemir, 13.2% of patients with rapid-acting analogues used glulisine. Between patients using analogues and patients in the other groups, there were no major differences for age, sex, residence in new/old federal states of Germany or treatment in university centre. However, differences were observed for BMI. The percentage of obese patients was higher in the final study population. Compared to the other groups, the study population was treated more often in large centres and less often in clinics.
Use of analogues detemir or glulisine in 3 BMI categories

**Fig. 2** illustrates the use of detemir or glulisine according to BMI category. Detemir was used more frequently in overweight (OR 1.36, 95%-CI 1.20–1.53) and obese (OR 2.06, 95%-CI 1.84–2.31) patients compared to normal-weight patients. Moreover, the use of detemir was higher in subjects with class II obesity (BMI ≥ 35–< 40 kg/m²) (OR 1.14, 95%-CI 1.01–1.29) or class III obesity (BMI ≥ 40 kg/m²) (OR 1.49, 95%-CI 1.29–1.72) compared to subjects with class I obesity (BMI ≥ 30–< 35 kg/m²). The use of glulisine was similar in overweight and in normal-weight patients (OR 0.91, 95%-CI 0.75–1.11). However, glulisine was used slightly more often in obese compared to normal-weight patients (OR 1.26, 95%-CI 1.06–1.50). Stratified by obesity class, patients with class II (OR 1.28, 95%-CI 1.07–1.53) or class III obesity (OR 1.38, 95%-CI 1.14–1.68) used glulisine more frequently than patients with class I obesity.

**Fig. 3** demonstrates that the use of detemir increased during the last 9 years. In each of the 3 time periods, detemir was used by a higher percentage of obese or overweight patients compared to normal-weight patients. The odds ratios (obese vs. normal-weight) did not differ between the time periods 2004–2006 (OR 2.12, 95%-CI 1.34–3.43), 2007–2009 (OR 1.84, 95%-CI 1.39–2.43) and 2010–2012 (OR 1.75, 95%-CI 1.41–2.18).

As depicted in **Fig. 3b**, the use of glulisine increased also during the respective time periods. However, in none of the 3 periods, a significant BMI-dependent use (obese vs. normal-weight) of glulisine was present (2004–2006: OR 0.99, 95%-CI 0.51–1.95, 2007–2009: OR 1.17, 95%-CI 0.76–1.80 and 2010–2012: OR 1.34, 95%-CI 0.96–1.89).
Table 2 Change in ORs and ROC-AUCs for the use of detemir or glulisine between overweight or obese patients and normal-weight patients after stepwise adjustment for confounders.

<table>
<thead>
<tr>
<th>Detemir</th>
<th>Glulisine</th>
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<tr>
<td>overweight vs. normal-weight</td>
<td>overweight vs. normal-weight</td>
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<tr>
<td>OR [95%-CI]</td>
<td>OR [95%-CI]</td>
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<tr>
<td>1.36 [1.20–1.53]</td>
<td>2.06 [1.84–2.31]</td>
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<tr>
<td>OR [95%-CI]</td>
<td>OR [95%-CI]</td>
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<td>0.57 [0.56–0.58]</td>
<td>0.91 [0.75–1.11]</td>
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<tr>
<td>AUC-ROC [95%-CI]</td>
<td>AUC-ROC [95%-CI]</td>
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<td>1.26 [1.06–1.15]</td>
<td>0.54 [0.53–0.55]</td>
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<td>adjusted for demographic variables: sex, age, interaction BMI category/sex, interaction BMI category/age</td>
<td>adjusted for demographic variables: sex, age, interaction BMI category/sex, interaction BMI category/age</td>
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<td>OR [95%-CI]</td>
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<td>1.15 [1.13–1.49]</td>
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<td>OR [95%-CI]</td>
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<td>0.58 [0.58–0.59]</td>
<td>0.97 [0.78–1.20]</td>
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<td>AUC-ROC [95%-CI]</td>
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<td>1.28 [1.05–1.56]</td>
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<td>+ time effects</td>
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<td>OR [95%-CI]</td>
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<td>OR [95%-CI]</td>
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<tr>
<td>0.64 [0.63–0.65]</td>
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<td>AUC-ROC [95%-CI]</td>
<td>AUC-ROC [95%-CI]</td>
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<td>1.24 [1.02–1.52]</td>
<td>0.62 [0.61–0.63]</td>
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<td>+ centre characteristics: size of centre, new/old federal states of Germany, treatment in university clinic, clinic/specialized private practice</td>
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<td>OR [95%-CI]</td>
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<td>1.23 [1.07–1.42]</td>
<td>1.74 [1.53–1.99]</td>
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<td>OR [95%-CI]</td>
<td>OR [95%-CI]</td>
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<tr>
<td>0.65 [0.64–0.66]</td>
<td>0.92 [0.76–1.18]</td>
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<td>AUC-ROC [95%-CI]</td>
<td>AUC-ROC [95%-CI]</td>
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<td>1.21 [0.99–1.48]</td>
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<td>+ socioeconomic status: sociocultural background, school education/vocational education, school success</td>
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<td>1.21 [1.02–1.44]</td>
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Multivariable logistic regression analysis
The BMI-dependent use of detemir remained significant after adjusting for each confounder separately. Sex, age, new/old federal states of Germany, size of centre, treatment in university clinic, clinic/specialized private practice or time effects were considered as confounders. Additionally, every model included time period, sex, age, the interaction for BMI category and the respective confounder as well as the interactions of BMI category with age or sex. Even after adjusting for all confounders and the interactions between BMI category and age or sex simultaneously, the results remained significant (overweight: OR 1.23, 95%-CI 1.07–1.42/obesity: OR 1.74, 95%-CI 1.53–1.99; reference: normal-weight). Stratified by obesity class, result for detemir use was still significant for the comparison of class III with class I obesity (OR 1.40, 95%-CI 1.20–1.63) after adjustment in the full model. For the comparison between class II and class I obesity (OR 1.12, 95%-CI 0.98–1.27), significance lacked. For the use of glulisine, associations in obesity classes remained significant (class II vs. class I: OR 1.25, 95%-CI 1.04–1.50/class III vs. class I: OR 1.40, 95%-CI 1.15–1.71) if adjusted for all confounders. However, no significant relationship between obese and normal-weight patients and the use of glulisine was present (OR 1.21, 95%-CI 0.99–1.48).

Even the additional adjustment for socioeconomic status (sociocultural background, school education/vocational education, school success) in the full model did not alter our results (Table 2).

Table 2 presents the change in ORs and ROC-AUCs for the use of detemir or glulisine between overweight or obese patients and normal-weight patients after stepwise adjustment for confounders, separately.

Discussion

This study does not address advantages or disadvantages of the insulin analogues detemir or glulisine in overweight or obese type 2 diabetic patients [13,14]. Hence, we do not make a statement, whether the prescription of detemir or glulisine should be preferred in overweight and obese patients. Rather, the aim of our study was to analyze whether the promotion for detemir or glulisine leads to a more frequent use in higher BMI categories. The present survey confirmed that insulin analogue detemir was used preferentially in overweight or obese subjects. Even after adjustment, the findings remained significant. For glulisine, the relation to BMI category was weak and with the exception of the associations within the 3 obesity classes no longer present after adjustment. For use of detemir, there was a significant association with BMI category in each of the 3 time periods. In contrast, for glulisine, in none of the periods, significance was attained.

There are several possible explanations for the preferential use of detemir, but not of glulisine in obese patients: One reason might be, that the evidence for the advantages of detemir is more convincing compared to glulisine. Studies focusing on the PK and PD profiles of glulisine in obese type 2 diabetic patients are very scarce and have just a small sample size [18,19]. It is also controversial whether the use of glulisine leads to clinically relevant improvement of metabolic control or treatment satisfaction compared to other rapid-acting analogues [23,24]. Another reason could be that the propagated benefits of detemir (reduced weight gain or even weight loss [13,14]) in the treatment of overweight or obese patients are more relevant for physicians and patients than potential advantages of glulisine (faster subcutaneous absorption and an earlier onset of activity, independent of skin thickness or BMI [18,19]). Maybe potential advantages of detemir in obese subjects were more successfully communicated to the medical community by the manufacturers. It is also possible, that the personal experience of physicians and patients with detemir was more convincing than the experience with glulisine. Another reason might be a handier insulin pen for detemir preferred by overweight or obese patients. In general, familiarity with a specific pen might also contribute to the prescription of detemir or glulisine. For example, if patients already use the respective rapid-acting insulin analogue or the glucagon-like-peptid-1 (GLP-1) analogue of the company...
producing detemir, physicians might prescribe detemir because patients are familiar with the pen. A possible association between the use of aspart and the use of detemir can be supported by our data. 59.01% of patients with detemir use also aspart, both from the same company and compatible with the same pen. For glulisine, a similar association was present. Moreover, there is a possibility that analogues detemir or glulisine are possibly not prescribed due to a higher BMI, but rather due to patient’s comorbidities, for example a low glomerular filtration rate (GFR), excluding the use of other pharmaceuticals. Furthermore, it has to be considered that discount agreements between pharmaceutical companies and health insurance providers were not identical for all available analogues. As socioeconomic status (SES) of insured patients differs among providers, and BMI is closely related to SES, this may contribute to BMI-dependent prescribing preferences.

For glulisine, it has been assumed that the faster subcutaneous absorption, which is supposed to be independent of skin thickness or BMI, is based on the zinc-free formulation of glulisine [17, 23]. For detemir several theories exist. In response to hypoglycemic events, patients increase their carbohydrate intake and consequently their total calorie intake. This in turn may result in weight gain. Accordingly, one theory for the weight-sparing effect of detemir assumes that the reduced risk of nocturnal hypoglycemia leads to less additional carbohydrate intake [3, 14, 16]. Another potential explanation is that detemir might suppress hepatic glucose output more effectively without enhancing peripheral lipogenesis. This is ascribed to the prolonged action via albumin binding [25, 26]. Based on the assumption of an increased permeability of the blood-brain-barrier for detemir, a third hypothesis is that detemir improves insulin signaling in the hypothalamus which is involved in the modulation of hunger and satiety. As a result, detemir may contribute to a greater suppression of appetite than NPH insulin [14, 25, 27]. A comparison of our results with current literature is limited, because, to our knowledge, this is the first study investigating whether the prescription of insulin analogues detemir or glulisine depends on BMI in routine diabetes care.

A strength of our study is its large multicentre cohort of patients. Furthermore, the DPV database provides detailed information on patient characteristics that allow careful adjustment for potential confounders. However, due to the multicentre nature of data collection, variability in the measurements of body height and weight (and therefore BMI) may occur despite standardized procedures. The large number of patients excluded due to missing BMI values (n = 6887) can be explained by immobility, curved spine or being bedridden in older patients. A further limitation might be the exclusion of patients who used more than one long-acting or more than one rapid-acting insulin analogue simultaneously (long-acting: n = 323; rapid-acting: n = 466).

Conclusion ▼

In conclusion, the results of our multicentre analysis of current DPV data show a statistically significant relation between overweight or obesity and the use of insulin analogue detemir. With the exception of the associations within the 3 obesity classes, the use of glulisine did not depend on BMI.

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**Conflict of interest:** The authors report no conflicts of interest.

**Affiliations**
1 Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany
2 Department of Internal Medicine, Academic Hospital Paul Gerhardt Stift, Lutherstadt Wittenberg, Martin-Luther-University Halle-Wittenberg, Germany
3 Division of Endocrinology and Diabetology, Department of Internal Medicine II, University Hospital of Freiburg, Freiburg, Germany
4 Department of Diabetology and Infectiology, Medical Clinic I, Reutlingen, Germany
5 Division of Endocrinology, Diabetes and Metabolism, Graduate School of Molecular Diabetology and Endocrinology, Ulm University, Ulm, Germany
6 Specialized Diabetes Practice, Rosenheim, Germany
7 Diabetes Centre Forchheim, Germany
8 Specialized Diabetes Practice, Traunstein, Germany
9 Specialized Diabetes Practice, Bad Aibling, Germany
10 Department for General Internal Medicine, Endocrinology and Diabetes, HELIOS Kliniken Schwerin, Schwerin, Germany

**References**
9 Peterson GE. Analog insulin detemir for patients with type 1 and type 2 diabetes: a review. Diabetes Metab Syndr Obes 2008; 2: 31–36
10 Marre M, Pinget M, Gin H et al. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain: 52-week data from the PREDICTIVE study in a cohort of French patients with type 1 or type 2 diabetes. Diabetes Metab 2009; 35: 469–475
13 Ruslowa K, Tamer SSC, Clauson P et al. Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. Clin Drug Invest 2007; 27: 279–285
24 Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. Diabetes Obes Metab 2012; 14: 780–788
26 Hcombina SC, Wright JE, Umpleby AM et al. Comparison of the effects on glucose and lipid metabolism of equipotent doses of insulin detemir and NPH insulin with a 16-h euglycaemic clamp. Diabetologia 2005; 48: 420–426