Received: 23 November 2023 | Revised: 19 January 2024 | Accepted: 28 January 2024

DOI: 10.1111/dom.15496

WILEY

RESEARCH LETTER

Insulin glargine 300 U/ml versus insulin degludec 100 U/ml improves nocturnal glycaemic control and variability in type 1 diabetes under routine clinical practice: A glucodensities-based post hoc analysis of the *OneCare* study

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Funding information
Sanofi España

KEYWORDS: basal insulins, continuous glucose monitoring, diabetes mellitus, glucodensity

1 | BACKGROUND

Long-term micro- and macrovascular complications are the main cause of disability and mortality in people with type 1 diabetes (T1D). In the Diabetes Control and Complications Trial (DCCT), intensive insulin treatment improving glycaemic control was associated with a 50%-76% reduction in the onset and progression of microvascular complications.[1] International guidelines recommend close monitoring to achieve and maintain controlled glycaemic levels in people with T1D, that is, reach 70% of the time in the recommended range of 70-180 mg/dl [3.9-10.0 mmol/L; time in range (TIR)].[2,3] Despite the continuous development of insulin preparations over the past 100 years, a great proportion of people with T1D remain uncontrolled.[4,5]

Second-generation basal insulin (BI) analogues, with a longer and flatter profile and less variability, have been developed to help people with T1D face their daily challenges.[6] The latest second-generation BI, insulin glargine 300 U/ml (Gla-300), and insulin degludec (IDeg-100) are currently available for use in the T1D population.[7,8]

The generalized use of continuous glucose monitoring (CGM) is also improving glycaemic control.[9] This technique is said to become

the gold standard for clinical research in T1D,[10] particularly for comparison between new insulins.[11] However, from a mathematical point of view, the analysis of CGM data is challenging in any setting, and therefore, several new CGM-derived metrics were proposed recently in the literature. In this study, we explore, for the first time in diabetes clinical research, one of the most recent glucometric analyses called glucodensity. The glucodensity is a functional representation of biosensor data that characterizes the distribution of glucose levels across a specified time frame. Roughly speaking, the analysis integrates the proportion of time each individual spends at each glucose concentration.[12] Therefore, it comprises the information of every glucose value frequency across the whole glycaemic range, rather than a coarsely defined range. Unlike the currently used glucometrics, which measure the time spent within a glucose range (as broad as 70-180 for the main proposed TIR) or over/under a threshold [for time above range (TAR) and time below range (TBR)]. As a result, the glucodensity automatically and simultaneously captures all parameters arising from the individual glucose distributions. In addition, the glucodensity allows for a more comprehensive analysis of the glycaemic variability through the comparison of all the glycaemic range values included in each glucodensity profile. This procedure offers a marked improvement concerning state-of-the-art analysis methods.[13] The glucodensity approach has previously shown a higher sensitivity than the standard TIR metric to predict sound biomarkers in diabetes, such as HbA1c or HOMA-IR, and accepted glycaemic variability metrics such as MODD, MAGE and CONGA. It is promising to use this approach in clinical practice and in epidemiological studies. In summary, potential advantages can be cited as the following: (a) provides a comprehensive representation of the glucose across the whole glycaemic range concentration in a single variable; (b) it informs about every glucose value frequency rather than a sum of variables informing of times in several predefined ranges; (c) the glucodensity allows for a more comprehensive analysis of the glycaemic variability; (d) it has a higher sensitivity than the standard TIR metric to predict diabetes biomarkers and glycaemic metrics.

The *OneCare* study was an observational, retrospective, multicentre study describing the effectiveness and safety of Gla-300 versus IDeg-100 using CGM in adults with T1D switching from a first-generation BI in routine clinical practice.[14] This post hoc analysis of the original *OneCare* study data is aimed at comparing the performance of Gla-300 versus IDeg-100 in real-world T1D therapy using the glucodensity procedure and testing its new functional representation of CGM data.

2 | METHODS

2.1 | Design

The *OneCare* study has been previously described in detail.[14] In the present study, we present a post-hoc analysis of the original *OneCare* data using the glucodensity CGM data representation for each patient's time series.

2.2 | Population

The study included 199 participants with T1D, whose baseline characteristics are presented in Table S1. The mean age of the participants was 42.6 ± 13.4 (mean ± SD) years, with an average duration of diabetes of 18.4 ± 10.4 years. Of the total participants, 104 received Gla-300 and 95 received IDeg-100. Importantly, the patients' characteristics were well-balanced between the two groups examined, as shown in Table S1.

2.3 | Outcomes and statistical analysis

Substitute by: The glucodensity function of the CGM raw data of 14 consecutive days within the last month before inclusion was assessed for each patient. The full-day, night (24:00-05:59 h) or day (06:00-23:59 h) periods were separately evaluated.

The corresponding CGM-derived glucometrics were quantified: TIR 70-180 mg/dl (3.9-10.0 mmol/L), time in tight range 70-140 mg/dl (3.9-7.8 mmol/L), TBR 70 mg/dl (3.9 mmol/L) and TAR 180 mg/dl (10.0 mmol/L) (TAR180) and 250 mg/dl (13.9 mmol/L) (TAR250). The analysis compared the mean and quantile of variability of the individual glucodensities in the Gla-300 and IDeg-100 insulin groups to test and quantify any potential differences. The percentage of cases reaching the considered clinically relevant difference in TIR of at least 5% was calculated to quantify the possible clinical meaning of the differences in the overall glycaemic control.[10] Glycaemic variability was determined by the quantile function values of variability related to each glucodensity profile as a reference. The means of both treatment populations values were compared with the test and quantify the differences between groups.

To determine if there are statistically significant differences among glucodensities presented in the form of curves, we employ a specialized method designed for this data structure based on the energy distance. This technique belongs to a family of statistical tests specifically tailored for this purpose. A similar methodology can be found in our previous work, Matabuena et al.[15] This approach is consistent with the methodology used and explained in the original glucodensity paper for testing statistical differences between two populations.[10]

3 | RESULTS

There were no statistically significant differences in the complete day or the diurnal period outcomes (Table 1, Figures S1 and S2). In the nocturnal period, Gla-300 users showed different overall glucodensity values versus IDeg-100 ($p = 0.001$). Higher TIR (50.6% vs. 44.1%; $p = 0.009$) and time in tight range (30.8% vs. 25.4%; $p = 0.005$) and lower TAR250 (15.8% vs. 20.8%; $p = 0.038$) were observed in the Gla-300 group (Figure 1A). The results on the rest of the outcomes, including TBR70 mg/dl, did not reach statistically significant differences.

TABLE 1 Numerical results of the main glucodensity analysis.

	Total			Day			Night		
	Gla-300	IDeg-100	*p*-Value	Gla-300	IDeg-100	*p*-Value	Gla-300	IDeg-100	*p*-Value
TBR <70 (%)	7.7	6.5	0.090	7.6	6.5	0.11	8.6	7.2	0.12
TIR 70-180 (%)	51.1	47.4	0.056	51.1	48.3	0.152	50.6	44.1	0.009
TTR 70-140 (%)	31	28	0.05	31	29	0.14	30.8	25.4	0.001
TAR >180 (%)	25.3	26.8	0.12	25.3	26.3	0.27	25	27.9	0.05
TAR >250 (%)	15.9	19.3	0.06	16	18.9	0.11	15.8	20.8	0.038
Global			0.09			0.1			0.001
Variance quantile function values			0.077			0.081			0.003

Abbreviations: Gla-300, insulin glargine 300 U/ml; IDeg-100, insulin degludec 100 U/ml; TAR, time above range; TBR, time below range; TIR, time in range; TTR, time in tight range.

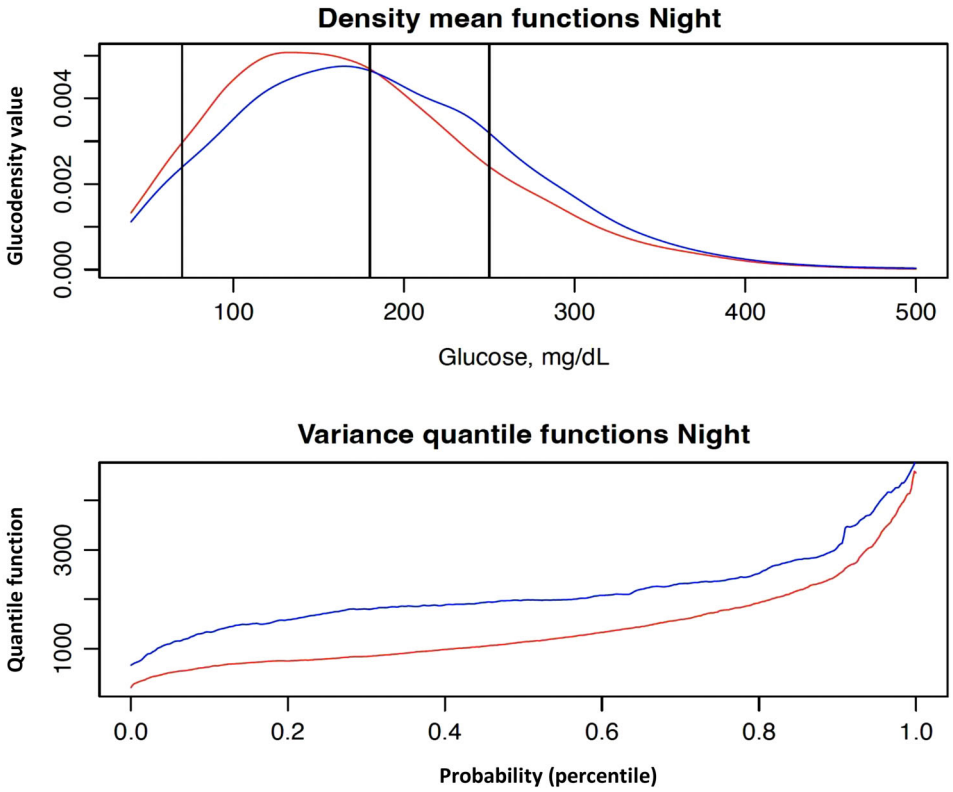

FIGURE 1 (A) Glucose density for the mean values of Gla-300 insulin (in red) and IDeg-100 insulin (in blue) during the night-time period. In the TIR (70-180 mg/dl), it is clearly observed that Gla-300 insulin users spend a significantly larger percentage of time within the TIR, while IDeg-100 insulin users show higher concentrations in hyperglycaemia (glucose >180 mg/dl). (B) Variability curve for Gla-300 insulin (in red) and IDeg-100 insulin (in blue). For different percentiles, *p*, it is evident that the glucose variability of Gla-300 users is much lower compared to IDeg-100 users. These differences are noticeable for small percentiles ($p < 0.1$, the lower glucose decile, associated with hypoglycaemia), $0.1 < p < 0.9$ (intermediate deciles, associated with TIR) and $p > 0.9$ (upper glucose decile, associated with the hyperglycaemia range). Gla-300, insulin glargine 300 U/ml; IDeg-100, insulin degludec 100 U/ml; TIR, time in range.

Overall TIR was numerically higher in the Gla-300 group (51.1% vs. 47.4%, difference +3,7%; $p = 0.056$), with the TIR difference with Gla-300 versus IDeg-100 greater than the clinically relevant 5% in 53% of cases. Moreover, during the nocturnal period, the Gla-300 users reached a +6.5% difference in TIR (50.6 vs. 44.1; $p = 0.009$).

A clearly lower glucose variability was observed during the nocturnal period in the Gla-300 versus IDeg-100 users in all ranges of variance quantile function values ($p = 0.004$) (Figure 1B).

4 | DISCUSSION

Using a glucodensity approach, Gla-300 seems to improve nocturnal glucometrics and produce more stable and predictable glucose profiles in comparison with IDeg-100 in patients with T1D in a real-world setting.

Epidemiological studies consistently show that individuals with T1D struggle to reach international glycaemic targets.[5] Recent therapeutic advances include second-generation BI and CGM technology. These insulins have been associated with improved glucose metrics and less variability, which can help people with T1D achieve better management of their condition.[7,8] However, these insulins were developed using different approaches, resulting in distinct pharmacokinetics/pharmacodynamics profiles.[6] While clinicians and patients notice differences in daily use, randomized clinical trials have not been able to detect consistently the significant differences between the two insulins using CGM methodology.[11] Real-world studies are also limited by selection bias and other confounding factors.

One critical issue is that a multiple daily injection regimen in people with T1D is based on, at least, one BI dose and several (ideally before every food ingestion) rapid insulin injections every day, making it difficult to quantify the isolated profile of the basal insulin. It can be challenging to separate the rapid insulin injections and meal influence on glucose dynamics from those of basal insulin, particularly during the diurnal period. Moreover, the use of a different BI can change the doses of rapid insulin, further complicating the analysis. Traditional approaches may not be sensitive enough to describe the differences between the two BI. Therefore, there is a need for clinical research to analyse CGM data properly and capture the benefits and differences between new insulins. The glucodensity analysis of CGM data offers a more sensitive approach to capturing various glycaemic control ranges, and it is a natural generalization of the time-in-range metrics, which is the gold standard in handling CGM data. A recent study by Cui et al. confirmed the reproducibility of the glucodensity method.[16]

In the present *OneCare* study post hoc analysis, the results confirmed that the main differences between both BI are seen in the nocturnal period, probably the target period to focus on during the 24-h cycle from a clinical perspective.

The present glucodensity measurement of retrospective data showed that Gla-300 had lower glucose variability versus IDeg-100, which can increase trust in insulin therapy and support more intensive management. A more predictable glucodynamic profile during the night is an important base for the patient's confidence.

An increase of ≥5% points in TIR is accepted as clinically relevant and valid as an endpoint for clinical research, as the recently published International Consensus Statement on Continuous Glucose Monitoring and Metrics for Clinical Trials stated.[10] Our data showed that total TIR was numerically higher in the Gla-300 group (51.1% vs. 47.4%, difference 3.7%; $p = 0.056$). The TIR difference was greater than this clinically relevant 5% in 53% of cases with Gla-300 versus IDeg. I Moreover, during the nocturnal period, the Gla-300 users reached a mean 6.5% difference in TIR (50.6% vs. 44.1%; $p = 0.009$). These results pointed to the possible associated long-term clinical benefits.

The pharmacokinetic/pharmacodynamic studies of IDeg-100 and Gla-300 have shown conflicting results on their stability and variability, probably depending on the methodology used, including the compared doses.[17] A few randomized controlled trials have compared both basal insulins in T1D.[18,19] Using canonical CGM metrics, they were unable to detect differences between the second-generation basal insulins.

The study findings support the use of Gla-300 as a potentially more effective insulin for managing glucose levels in patients with T1D, and further investigations could shed more light on this treatment option. However, the retrospective nature of the study and the limited sample size and follow-up are limitations, and larger, longer, prospective studies using glucodensity analysis are needed to confirm these results.

Overall, this study highlights the essential differences between Gla-300 and IDeg-100 captured by the glucodensity approach in real-world patient responses. Gla-300 seems to improve nocturnal glucometrics and produce a more stable and predictable glucose profile. This procedure offers a reliable and advantageous way to analyse CGM data in a clinical research setting.

ACKNOWLEDGMENTS

The authors acknowledge the editorial assistance of NicoleQuinn, Always English S.L.

FUNDING INFORMATION

This project was supported by Sanofi.

CONFLICT OF INTEREST STATEMENT

Fernando Gomez-Peralta has taken part in advisory panels for Sanofi, Insulcloud S.L., and Novo Nordisk; has received research support from Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals and Lilly; and has acted as a speaker for Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Co. and Lilly. Ana Chico Ballesteros has taken part in advisory panels and has acted as a speaker for Sanofi. Amparo Marco Martínez has taken part in advisory panels and has acted as a speaker for Sanofi. Begoña Pérez Corral has taken part in advisory panels and has acted as a speaker for Sanofi. Ignacio Conget Donlo received a fee from Sanofi Aventis for coordination of the OneCARE study, and received lecturing and consulting fees from Medtronic, Bayer, GlaxoSmithKline, Eli Lilly, Novo Nordisk, Sanofi Aventis, Novartis, AstraZeneca and MSD.Paulina Fuentealba Melo and Fernando Zaragozá Arnáez are Sanofi employees. Marcos Matabuena Rodríguez has no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15496.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gomez-Peralta F, Chico Ballesteros A, Marco Martínez A, et al. Insulin glargine 300 U/ml versus insulin degludec 100 U/ml improves nocturnal glycaemic control and variability in type 1 diabetes under routine clinical practice: A glucodensities-based post hoc analysis of the *OneCare* study. *Diabetes Obes Metab*. 2024;26(5):1993-1997. doi:10.1111/dom.15496