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Original article

The dawn phenomenon in type 2 diabetes: How to assess it in clinical practice?

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Abstract

Aim. – The study was aimed at determining whether the dawn phenomenon in type 2 diabetes (T2D) can be predicted and quantified using simple and easily accessible glucose determinations.

Methods. – A total of 210 non-insulin-treated persons with T2D underwent continuous glucose monitoring (CGM). The dawn phenomenon was quantified as the absolute increment from the nocturnal glucose nadir to the pre-breakfast value (Δ dawn, mg/dL). Pre-lunch (preL) and pre-dinner (preD) glucose, and their averaged values (preLD), were compared with the nocturnal nadir. These pre-meal values were subtracted from the pre-breakfast values. The differences obtained (Δ pre-meal L, Δ pre-meal D and Δ pre-meal LD) were correlated with Δ dawn values. The receiver operating characteristic (ROC) curve was used to select the optimal Δ pre-meal value that best predicted a dawn phenomenon, set at a threshold of 20 mg/dL.

Results. – All pre-meal glucose levels and differences from pre-breakfast values (Δ pre-meal) significantly correlated ($P < 0.0001$) with the nocturnal nadir and Δ dawn values, respectively. The strongest correlations were observed for the parameters averaged at preL and preD time points: $r = 0.83$ for preLD and $r = 0.58$ for Δ pre-meal LD. ROC curve analysis indicated that the dawn phenomenon at a threshold of 20 mg/dL can be significantly predicted by a Δ pre-meal LD cut off value of 10 mg/dL. The relationship between Δ dawn (Y, mg/dL) and Δ pre-meal LD (X, mg/dL) was $Y = 0.49 X + 15$.

Conclusion. – The self-monitoring of preprandial glucose values at the three main mealtimes can predict the presence/absence of the dawn phenomenon, and permits reliable assessment of its magnitude without requiring continuous overnight glucose monitoring.

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Keywords: Dawn phenomenon; Glucose monitoring; Type 2 diabetes

1. Introduction

The dawn phenomenon has been extensively investigated for more than 30 years [1,2]. By using continuous glucose monitoring (CGM), it has recently been demonstrated that, in non-insulin-treated persons with type 2 diabetes (T2D), the dawn phenomenon—defined as an excessive increment from the nocturnal glucose nadir to the pre-breakfast glucose value—is

a glycaemic disorder with a magnitude and frequency that are relatively stable across all groups of subjects, irrespective of treatment, HbA_{1c} or age [3]. Its frequency can be as high as 40% [3], and its impact on HbA_{1c} levels approximates 0.4% (4 mmol/mol) [4] and therefore cannot be ignored in the management of persons with T2D. Currently, healthcare providers fail to take the dawn phenomenon into consideration as one of the targets in the management of the disorder. This is very likely linked to the fact that its quantification requires CGM to accurately detect the nocturnal glucose nadir [4–7], and permit the calculation of the absolute differences between the nocturnal glucose nadir and pre-breakfast glucose values [3,4]. Access to CGM remains costly and is therefore only available to physicians working at clinics located in specialized diabetes units [8].

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Thus, any attempt to increase awareness of the dawn phenomenon and its management requires a simpler method for its quantification. Such a method would ideally be based on an appropriate cost-effective frequency of self-monitoring of blood glucose (SMBG) in people with T2D [9]. However, structured SMBG is inadequate for detecting glucose nadirs, especially those occurring during nocturnal periods [3,4]. Consequently, the question is whether SMBG at specific time points of the diurnal period can provide an alternative in clinical practice for detecting the presence of the dawn phenomenon and further quantifying its magnitude. Using CGM through an observational study, the present study set out to ascertain, first, whether one or several preprandial or interprandial glucose values could approximate the nocturnal glucose nadir and, second, whether it is possible to predict the presence or absence of the dawn phenomenon by calculating the decrement or increment between pre-breakfast glucose levels and those observed at other pre-meal time points.

2. Methods

A total of 210 persons with T2D (mean age = 60.1 years, mean body mass index [BMI] = 30.4 kg/m² and mean HbA_{1c} = 7.5% [58 mmol/mol]) were selected after screening for eligibility from a total population of 242 non-insulin-treated patients with T2D who underwent 3-day ambulatory CGM. The key criteria for exclusion from the initial screened list of potential participants included having abnormal eating habits or eating patterns characterized by unexpected food intakes during both diurnal and nocturnal periods. All participants who reported at least one clinical hypoglycaemic event over the test period were also excluded to avoid any misinterpretation due to either glucose rises in the early morning or excessive glucose rebound after correction of the hypoglycaemic episode. To avoid any interference of carbohydrate intake on pre-meal glucose values, all individuals for whom the time intervals between two consecutive meals were < 4 h were also excluded. Accordingly, all subjects who reported having a mid-afternoon snack were excluded from the final analysis. Additional criteria for exclusion were a recent illness or treatment with steroids during the preceding 3 months, and any disruption in glucose monitoring or an insufficient number of blood glucose tests for calibration during CGM (four tests a day are required for this purpose). Unacceptable calibration meant an accuracy criterion with a coefficient correlation < 0.79.

All study participants were investigated from 2003 to 2011 at the outpatients facilities of the University Hospital in Montpellier, France, and placed on a stable treatment regimen with either dietary measures alone or the addition of oral hypoglycaemic agents (OHAs) for at least 3 months prior to CGM. Modalities of treatment were classified into three categories: (i) dietary measures alone ($n = 6$); (ii) insulin sensitizers alone (metformin and/or pioglitazone, $n = 82$); and (iii) insulin secretagogues (sulphonylureas, glinides) or incretin enhancers (dipeptidyl peptidase [DPP]-4 inhibitors) taken alone or in combination with insulin sensitizers ($n = 122$). DPP-4 inhibitors were categorized along with sulphonylureas and glinides because these drugs are all insulinotropic agents, although

Table 1
Characteristics of study patients.

Patients tested (n)	210
Age (years)	60.1 (0.7)
Body mass index (kg/m ²)	30.4 (0.5)
Gender ratio (males/females)	134/76
Mean daily energy intake (kcal)	2193 (23)
Mean daily carbohydrate intake (g)	274 (3)
HbA _{1c} (mmol/mol)	58 (0.9)
HbA _{1c} (%)	7.5 (0.1)
Average 24 h mean glucose concentrations (mg/dL)	144.8 (2.4)
Mean glucose value (mg/dL) at the following time points	
Nocturnal nadir	113.0 (2.3)
Pre-breakfast	131.4 (2.5)
Pre-lunch	126.5 (2.7)
Pre-dinner	121.1 (2.9)
Mean preLD ^a (mg/dL)	123.8 (2.4)
Diabetes treatment (patients, n)	
Diet alone	6
Insulin sensitizers alone (metformin and/or glitazones)	82
Insulin secretagogues/insulin enhancers alone or in combination with insulin sensitizers	122
Δ Dawn ^b (mg/dL)	18.4 (1.3)
Time of nocturnal glucose nadir ^c (h)	0341 [0157]

Data are expressed as means (SEM) unless stated otherwise.

^a Averaged mean glucose values at pre-lunch and pre-dinner time points.

^b Difference between pre-breakfast and nocturnal nadir glucose values.

^c Calculated only for patients ($n = 80$) exhibiting an overt dawn phenomenon, expressed as mean [SD].

the mechanism of action of DPP-4 inhibitors is much broader than its effects on insulin secretion alone [10]. This categorization has previously been used [4] and justified in a letter [11] in response to a question raised by Carr et al. [12]. In addition, no differences were observed between glycaemic profiles in the two main groups selected by categories of treatment (insulin sensitizers alone, and either insulin secretagogues/insulin enhancers alone or in combination with insulin sensitizers). This lack of difference (data not shown) has reinforced our strategy to analyze our study population as a whole, and not as separate groups categorized by type of antidiabetic treatment.

Dietary measures were based on a weight-maintaining diet with three main meals per day and with carbohydrates providing 50% of the total daily energy intake. Energy intake was assumed to be equal to total energy expenditure. The latter was determined by calculating the basal metabolic rate using Schofield's equations [13] and then multiplying the result by 1.35, a coefficient that corresponds to a sedentary lifestyle with low physical activity, as seen in most of our patients. A daily ratio of 1:2:2 was recommended for calorie and carbohydrate distributions across breakfast, lunch and dinner, respectively. The expected mean daily energy and carbohydrate intakes estimated by this calculation are shown in Table 1. At the beginning and end of each 3-day study period, dietary recommendations were carefully re-emphasised and validated by trained dietitians, and instructions were given to all participants to help them maintain their current

routine low-level physical activity while avoiding any vigorous exercise.

All investigations were routinely performed at diabetes outpatients clinics and were in compliance with the Helsinki Declaration [14]. The study was conducted after each subject had given oral informed consent in accordance with European directives that require no approval from an ethics committee for the non-interventional protocol described below [15].

2.1. Clinical investigations and laboratory determinations

All participants underwent ambulatory CGM for 3 consecutive days, using the same technology, between 2003 and 2011 (a second-generation MiniMed system, Medtronic, Inc., Minneapolis, MN, USA). The glucose sensor was inserted on day 0 and removed mid-morning on day 3. Sensor insertion for CGM was made on Monday/Tuesday and removal on Thursday/Friday to avoid any overlap into the weekend. All calculations were derived from data obtained over a 48 h period during days 1 and 2 to avoid any bias due to either insertion or removal of the sensor. Status of chronic hyperglycaemia (ambient hyperglycaemia) was assessed on study day 0 by HbA_{1c} levels that were determined using a high-performance liquid chromatography (HPLC) assay [16–18]. The intra- and interassay coefficients of variation (CVs) were <2%, with a non-diabetic reference range of 16.7–32.1 mmol/mol (3.7–5.1%) for HbA_{1c}.

2.2. Analysis of data obtained by CGM

CGM was used to detect the nocturnal glucose nadir and to quantify glucose levels at pre-meal time points. The latter were determined in accordance with the data recorded by participants in their own SMBG log books. All CGM readings were concomitantly made by two investigators using the same methodology for data analysis and interpretation of the glycaemic profiles obtained from 2003 to 2011. All measurements provided by CGM were presented after averaging the data recorded on study days 1 and 2. This strategy was used to attenuate the day-to-day fluctuations seen in glucose profiles, including those of the dawn phenomenon.

The dawn phenomenon—defined as the spontaneous glucose rise during the early morning hours—was quantified by subtracting the glucose nadir from the glucose value observed just before breakfast. Although measurements of glucose in the interstitial fluid from CGM readings are known to be lower than venous plasma glucose concentrations [19], it should be noted that, in the present study, the dawn phenomenon was assessed only from differences between interstitial values. The upward glycaemic variation that occurs at night was only considered a dawn phenomenon if its magnitude exceeded the threshold of 20 mg/dL, chosen on the basis of two main observations/principles that reflect what we know of the spontaneous variability and fluctuations of glucose levels [4]. First, a value of 20 mg/dL approximates the 95% confidence interval (CI) of total intra- and interassay variability seen in relation to a true fasting glucose concentration of 126 mg/dL [20]. Second, this value of 20 mg/dL is above the spontaneous between-day

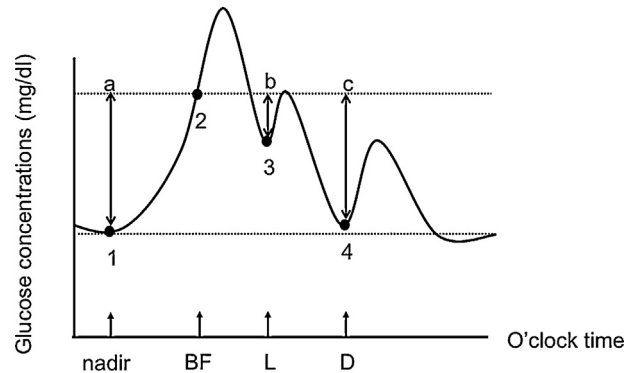


Fig. 1. Graphic representation of calculations of the differences between glucose values at pre-meal time points and the nocturnal nadir. Glucose values (GVs) at the nocturnal nadir and pre-breakfast (BF), pre-lunch (L) and pre-dinner (D) time points are indicated by numbers 1, 2, 3 and 4, respectively. GV for Δ dawn, Δ pre-meal L and Δ pre-meal D are indicated by a, b and c, respectively. preLD: average of pre-lunch (preL) and pre-dinner (preD) GV; Δ dawn: difference between pre-breakfast and nocturnal nadir GV; Δ pre-meal L: difference between pre-breakfast and preL GV; Δ pre-meal D: difference between pre-breakfast and preD GV; Δ pre-meal LD: difference between pre-breakfast and preLD (average of preL and preD) GV.

fluctuation in mean difference from nocturnal glucose nadir to pre-breakfast glucose values which, at an individual level, was 15 mg/dL (interquartile range [IQR]: 0–21.0 mg/dL) [4]. Pre-lunch (preL), pre-dinner (preD) and the averaged glucose values at preL and preD time points (preLD) were tested as surrogates of nocturnal glucose nadirs when tested against pre-breakfast glucose values to quantify the magnitude of dawn glucose rises during the early morning hours.

2.3. Calculations and statistical analyses

Mean glucose values were calculated at the nocturnal nadir and at pre-meal time points, and compared by analysis of variance (ANOVA) testing. The relationships between pre-meal glucose values and nocturnal nadirs were calculated using Pearson's test. Differences (Δ pre-meal) between the pre-breakfast and other pre-meal values, such as preL, preD and the averaged preLD, were calculated (mg/dL) and presented as Δ pre-meal L, Δ pre-meal D and Δ pre-meal LD, respectively. Details of the calculation are illustrated in Fig. 1. All Δ pre-meal values were further analyzed for statistical comparison and correlation with the magnitude of the dawn glucose rise (Δ dawn, mg/dL), determined according to the method mentioned above (by calculating the glucose increment from nocturnal nadir to pre-breakfast time point). It should be noted that, in all cases, the dawn glucose rise (Δ dawn) was quantified as ≥ 0 while the differences between pre-meal values (Δ pre-meal) could be affected by either a positive or negative sign, depending on whether the glucose values measured at preL and preD time points and calculated from the preLD were below or above the pre-breakfast glucose levels. Relationships between the Δ dawn and Δ pre-meal values were further tested using Pearson's correlation coefficient.

The performance for detecting the most appropriate Δ pre-meal that can be used as a cut off value for detecting the dawn phenomenon was tested. For that purpose the threshold for the

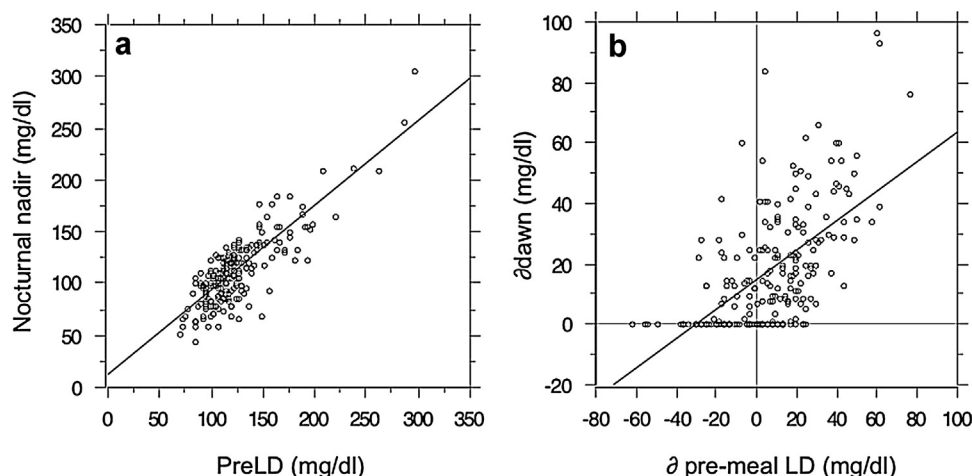


Fig. 2. a: Relationship between nocturnal nadir (Y, mg/dL) and the average of preL and preD glucose values (X, preLD, mg/dL): $r=0.83$, $P<0.0001$. The relationship is $Y=0.82 X + 11$; b: Relationship between the Δ dawn (Y, mg/dL) and the Δ pre-meal LD (X, mg/dL): $r=0.58$, $P<0.0001$. The relationship is $Y=0.49 X + 15$.

presence or absence of a dawn phenomenon was set at 20 mg/dL, a value selected on a previously described basis [4]. Sensitivity and specificity for predicting the presence or absence of a dawn phenomenon were calculated at different levels of Δ pre-meal (differences between the pre-breakfast and other measured or calculated pre-meal glucose values, using step-by-step increments from a negative [−30 mg/dL] to a positive [+30 mg/dL] value). Sensitivity (the true-positive fraction, TPF) was defined as the proportion of subjects to have a dawn phenomenon (> 20 mg/dL) in relation to those who indeed had one, while specificity was defined as the proportion of subjects predicted to not have a dawn phenomenon (≤ 20 mg/dL) in relation to those who actually did not. The optimal cut off differences between the pre-breakfast and other measured or calculated pre-meal values (Δ pre-meal) was selected by an ROC curve constructed by plotting sensitivity against the false-positive fraction (1−specificity, FPF) over ranges of the Δ pre-meal cut off points [21]. The optimal cut off point balancing sensitivity and specificity was selected at the shoulder of the ROC curve. The area under the curve (AUC) was calculated using ROCKIT software (available from the University of Chicago Department of Radiology website) [22].

3. Results

Clinical and laboratory data for the entire study population ($n=210$) are included in Table 1.

3.1. Glucose values at pre-meal time points vs. nocturnal nadirs

Mean pre-meal glucose values were seen to progressively decrease throughout the day from pre-breakfast to preD time points when the study population was considered as a whole (Table 1). All mean pre-meal glucose values were significantly greater ($P<0.0001$) than the nocturnal nadir of 113.0 ± 2.3 mg/dL (mean \pm SEM).

3.2. Relationships between nocturnal nadir and measured or averaged pre-meal glucose values

There was a strongly significant correlation ($P<0.0001$) between pre-meal glucose values, whether measured at preL ($r=0.78$) or preD time points ($r=0.77$), when tested against nocturnal glucose nadirs. When glucose values were averaged over preL and preD time points (preLD), an even better correlation was seen with the nocturnal nadir ($r=0.83$, $P<0.0001$). Multiple comparisons across the three correlation coefficients showed no significant differences. As illustrated in Fig. 2a, the relationship between the preLD and nocturnal glucose nadir, considered the “predictor” (X axis, mg/dL) and “response” (Y axis, mg/dL) variables, respectively, was close to the identity line: $Y=0.82 X + 11$. As a consequence, the Δ pre-meal LD was used to calculate the cut off value that was able to predict, with satisfactory and balanced sensitivity and specificity, the presence or absence of the dawn phenomenon when the increment to define this glycaemic disorder was set at 20 mg/dL.

3.3. Relationships between magnitude of dawn phenomenon (Δ dawn) and measured or averaged Δ pre-meal values

All measured and averaged Δ pre-meal values correlated with the Δ dawn value. However, the correlation with the greatest significance was observed when Δ dawn (Y axis, mg/dL) was correlated with the calculated Δ pre-meal LD (X axis, mg/dL): $r=0.58$, $P<0.0001$. Fig. 2b presents a graph of the relationship: $Y=0.49 X + 15$.

The ROC curve calculated from the stepwise increase in Δ pre-meal LD values with a 20 mg/dL threshold for the dawn phenomenon indicates that the best cut off point for a Δ pre-meal LD predicting the absence or presence of a dawn phenomenon was 10 mg/dL, with an FPF threshold of 0.32 (specificity = 68%) and a sensitivity of 71% (Fig. 3). In addition, significant and sufficient accuracy can be attributed to this predictive threshold as the area under the ROC curve was 0.76, a value recognized as

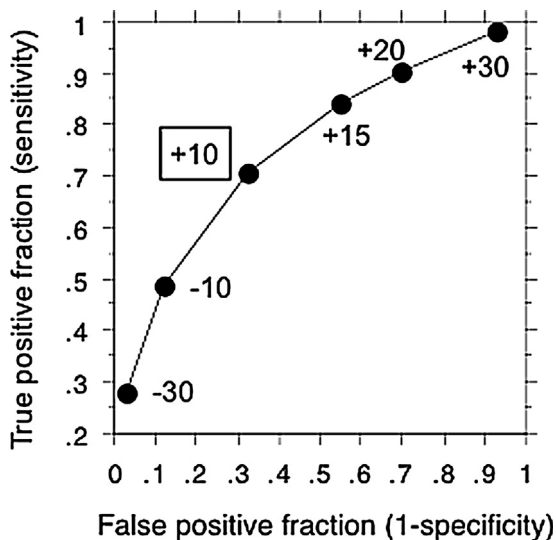


Fig. 3. Receiver operating characteristic (ROC) curve derived from the stepwise increase in Δ pre-meal LD. The threshold for defining the absence/presence of a dawn phenomenon (Δ dawn) was set at 20 mg/dL. The cut off value of Δ pre-meal LD for optimal prediction of the absence/presence of a dawn phenomenon (the optimal balance between highest sensitivity and specificity) is 10 mg/dL, indicated in the box at the shoulder of the ROC curve. The true-positive fraction ($Y =$ sensitivity) and the false-positive fraction ($X = 1 -$ specificity) indicate/reflect the specificity and sensitivity, respectively, of the Δ pre-meal LD for predicting a dawn phenomenon at a threshold of 20 mg/dL.

being in the fair range (0.70–0.80) according to the traditional academic point system [21].

4. Discussion

The present results indicate that the nocturnal glucose nadir occurred at an average clock time of 03 h 41 in the morning, which has previously been reported as corresponding to the nocturnal growth hormone peak and the beginning of the progressive increase in cortisol, epinephrine and norepinephrine in the early morning period/end of the night [23]. This nocturnal glucose nadir was well correlated with all daytime pre-meal values, although the correlation improved when the preL and preD values were averaged. Based on these results, we tested the accuracy of the relationship between the magnitude of the dawn glucose rise (Δ dawn; the difference between the nocturnal nadir and pre-breakfast value) vs. the other Δ pre-meal values, especially the Δ pre-meal LD (the difference between the pre-breakfast value and averaged glucose values at preL and preD time points). As mentioned above, the present study gave particular attention to the latter difference, as our results had shown that this parameter was better correlated with the magnitude of the dawn glucose rise during the early morning hours than with any of the other individual Δ pre-meal values. Furthermore, using stepwise analysis of the Δ pre-meal LD and calculating the ROC curves on the basis of the presence or absence of a dawn phenomenon at a threshold level of 20 mg/dL, it was found that the dawn phenomenon could be fairly predicted by a cut off value of 10 mg/dL for the averaged Δ pre-meal LD.

For obvious reasons, nocturnal glucose values cannot be easily measured in clinical practice by discontinuous SMBG. Therefore, it appears that defining a cut off point derived from the averaged Δ pre-meal LD as a predictor of the dawn phenomenon may be of importance, although many other barriers are yet to be overcome before the majority of healthcare providers can obtain easy access to such new technologies as CGM [8].

Consequently, as discontinuous self-monitoring of glucose concentrations at the three pre-meal time points is easily available in clinical practice, the difference between preLD and pre-breakfast glucose levels can be used as a substitute for detecting the presence or absence of the dawn phenomenon and as a reliable surrogate for its quantification. Measurements of preD, preL and pre-breakfast glucose values can easily be integrated into a patient-centred programme of structured SMBG, even in persons with T2D not treated with insulin. Such measurements would also be helpful for making both patients and their healthcare providers aware of the presence of a dawn phenomenon. Indeed, such a glycaemic disorder should not be ignored, given its global impact on HbA_{1c} of approximately 0.4% (4 mmol/mol) [4]. The dawn phenomenon is probably one of the earlier disorders in the natural history of T2D [23,24]. In addition, through one of its consequences—the extended dawn phenomenon, characterized by excessive post-breakfast glucose excursions during the morning period—the dawn phenomenon can contribute to overall glucose exposure in T2D [3–5,25]. Consequently, the dawn phenomenon should be taken into consideration in the management of T2D, and its presence should instigate the use of more aggressive therapy as early as possible in the time course of the disease. At present, little or no consideration is given to the dawn phenomenon by the various organizations that have published clinical guidelines or standards of medical care in diabetes [26,27], not even when these recommendations are made within a patient-centred approach [28].

The present study offers healthcare professionals a relatively simple method for assessing and quantifying the presence of the dawn phenomenon and, thus, its integration into the management process. Three measurements of blood glucose at the pre-breakfast, preL and preD time points, and the subsequent calculation of differences between the pre-breakfast glucose and the average of the preL and preD glucose values, will allow prediction of the absence/presence of a dawn phenomenon with a satisfactory balance between sensitivity (71%) and specificity (68%). In addition, this method provides a practical, realistic and reliable assessment of the magnitude of the dawn phenomenon that can be calculated by a formula generated from analysis of our results: $Y = 0.49X + 15$, where X is the difference between pre-breakfast glucose and the averaged preL and preD glucose values (Δ pre-meal LD). From a clinical point of view, this calculation would be of interest in determining whether the dawn phenomenon should be taken into account for the given individual. In addition, when treat-to-target strategies aimed at lowering the pre-breakfast glucose value to < 100 mg/dL are recommended, it is crucial to estimate the magnitude of the dawn phenomenon and reduce it to < 20 mg/dL to avoid the occurrence of overnight hypoglycaemia.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Louis Monnier (University Montpellier 1, Montpellier, France) contributed to the design of the study, participated to the clinical care of the patients, analyzed the data of the study, and wrote, reviewed and edited the manuscript.

Claude Colette (University Montpellier 1, Montpellier, France) contributed to the analysis of data and reviewed/edited the manuscript.

Sylvie Dejager, MD, PhD (Hospital Pitié-Salpêtrière, Paris, France) contributed to the design and reviewed the manuscript.

David Owens, MD, FRCP contributed to the design of the study and reviewed the manuscript.

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