Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com/en
Diabetes & Metabolism 41 (2015) 132–137

Original article

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

L. Monnier [a,*], C. Colette [a], S. Dejager [b], D. Owens [c]

[a] *Institute of Clinical Research, University Montpellier 1, France*
[b] *Department of Endocrinology, Hospital Pitié-Salpétrière, Paris, France*
[c] *Diabetes Research Group, Swansea University, United Kingdom*

Received 20 August 2014; received in revised form 2 October 2014; accepted 2 October 2014
Available online 6 November 2014

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 (Δdawn, 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 (Δpre-meal L, Δpre-meal D and Δpre-meal LD) were correlated with Δdawn values. The receiver operating characteristic (ROC) curve was used to select the optimal Δpre-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 (Δpre-meal) significantly correlated ($P < 0.0001$) with the nocturnal nadir and Δdawn 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 Δpre-meal LD. ROC curve analysis indicated that the dawn phenomenon at a threshold of 20 mg/dL can be significantly predicted by a Δpre-meal LD cut off value of 10 mg/dL. The relationship between Δdawn (Y, mg/dL) and Δpre-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.

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].

* Corresponding author. Institute of Clinical Research, 641, avenue du Doyen-Giraud, 34093 Montpellier cedex 5, France. Tel.: +33 4 11 75 98 91; fax: +33 4 11 75 98 98.
E-mail address: louis.monnier@inserm.fr (L. Monnier).

http://dx.doi.org/10.1016/j.diabet.2014.10.002
1262-3636/

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/m^2 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 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.

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)
HbA1c (mmol/mol)	58 (0.9)
HbA1c (%)	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].

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