The Dawn Phenomenon: An Unpredictable Cause for Fasting Hyperglycemia

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Abstract

Objective: The Dawn Phenomenon (an early morning rise in blood glucose) is a major cause of poor glucose control in diabetic patient's. Its variable occurrence precludes the automatic addition of extra insulin to counteract it. Being able to predict its occurrence from easily obtained demographic and glycemic parameters would be of great benefit to diabetic patients. Our study examined the predictability of the Dawn Phenomenon in type 1 diabetic individuals.

Research design and methods: We studied 39 Type 1 diabetes volunteers on multiple nights (376) in order to quantitate and characterize the Dawn Phenomenon using Continuous Glucose Monitoring for a maximum of five continuous days per individual. We correlated the occurrence of the Dawn Phenomenon with 10 different variables obtained from both demographic and continuous glucose monitoring data. Regression analysis was used for continuous variables whereas an analysis of variance was used for categorical variables. Significance was set at $p<0.05$.

Results: The Dawn Phenomenon occurred on 46% of the monitored nights. In contrast to a previous report, we were unable to identify any parameters that demonstrated a clinically significant predictability of the occurrence of the Dawn Phenomenon.

Conclusion: Our data suggests that the Dawn Phenomenon is not predictable from commonly measured variables

Key words: Hypoglycemia, Dawn Phenomenon, Hemoglobin A1c, Glucose control, Early Morning

Introduction

There have been over 150 publications describing the Dawn Phenomenon (1). By definition, it is the rise in blood glucose concentration in the early morning hours when not preceded by hypoglycemia or insulin deficiency. This terminology was first used by Schmidt et al. (2) and subsequently later defined by numerous other authors according to several parameters including: 1) the specific period of time in the morning, 2) the magnitude of the glucose elevation, and 3) whether it is the rise in glucose or the need for more insulin to maintain euglycemia (3, 4). All authors agree, however, that it is a principal cause of early morning hyperglycemia and poor glucose control, particularly in type 1 diabetes (5-7).

If the Dawn Phenomenon could be predicted, then additional insulin could be safely administered (by injection or programmed by continuous subcutaneous insulin infusion (CSII)) to counteract its hyperglycemic effect. To date, only one other study has attempted to correlate demographic and physiological parameters with the occurrence of the Dawn Phenomenon. Perriello and co-workers studied type 1 diabetic volunteers in an inpatient setting and concluded that the Dawn Phenomenon occurred on approximately 90% of the nights and positively correlated with A1C and negatively correlated with diabetes duration (3). This conclusion contrasted with our experience of an occurrence rate of approximately 50% in type 1 diabetes (8). Because of the importance of being able to predict the Dawn Phenomenon to prevent hyperglycemia, we reexamined our data and expanded the number of parameters that might predict the Dawn Phenomenon.

METHODS

Study cohort

Ninety-nine type 1 diabetes subjects between 18 and 70 years of age were screened for study criteria, availability, and willingness to follow the protocol. Forty subjects were eligible to participate in the 6 months' duration longitudinal study. The subjects utilized in this final analysis were obtained from a previous study (8), in which forty type 1 diabetic subjects were enrolled. Thirty-nine of this group completed the study and the data were obtained from this group of individuals. Because this was a sample of convenience, no formal power analysis was completed.

Eligible participants were insulin-dependent for at least one year prior to enrollment with a current hemoglobin A1C between 6.5% and 9% and a Sustacal® (Mead Johnson, Glenview, IL) stimulated C-peptide level of less than 0.5mg/dL. A random C-peptide was not checked. We excluded all volunteers with renal insufficiency, with significant mental or physical abnormalities, or who were pregnant. Of the 39 participants, 27 used continuous subcutaneous insulin infusion (CSII), 19 of them programed an early morning increase in insulin delivery and 12 used multiple daily injections (MDI) for insulin delivery. The insulin regimen for all subjects remained unchanged as determined by their own primary care physician. If the primary care physician felt that an adjustment in insulin dose was warranted, depending on daily glucose checks at home, then the change was made by the subjects. Demographics and baseline characteristics of subjects are shown in Table-1.

This study was approved by the University of New Mexico Health Science Center Institutional Review Board and all subjects provided written informed consent prior to entering the study.

Continuous Glucose Monitoring (CGM)

All participants were seen for monthly visits. All were instructed on the care of the CGM sensor (iPro™, Medtronic, Minneapolis, MN), which was placed on the abdomen of the volunteers by the research team on day 1 of visits 0, 2, 4 and 6. Each visit was separated by a 2-month interim period. After 5 days of monitoring, the CGM was removed and mailed to the investigator for data download. All CGM data were read independently by two investigators who were blinded to subjects' methods of insulin delivery in order to minimize bias in the analysis of the data.

Laboratory Analysis

Hemoglobin A1C was assayed utilizing a DCA 2000 (Bayer Healthcare LLC, Elkhart, IN) (9) at each monthly visit during the 6 month study period. 1,5-anhy-droglucitol was measured with a Glycomark test kit (GlycoMark®, Inc. New York, NY) (10).

Data Analysis

Both physiological and sensor obtained parameters were correlated to the occurrence of the Dawn Phenomenon. The Dawn Phenomenon was defined as an early morning increase in glucose (between the overnight nadir and the breakfast meal) of 10mg/dl or greater not preceded by hypoglycemia, as previously described (4). Subjects wore the CGM for a maximum of 5 days per study period, permitting analysis of a maximum of 4 overnight recordings. Thus, for any one individual, a maximum of 16 overnight observations (4 nights times 4 study periods) were possible from which to determine the occurrence of the Dawn Phenomenon during all the observed nights. The 24hr. mean glucose, the 24hr. mean glucose excursion, and the glucose variability for each patient were obtained from the CGM data. Patients' data including age, sex, type of insulin delivery (CSII or MDI), duration of diabetes, Body Mass Index (BMI), 1,5-anhydroglucitol and A1C were also analyzed.

Statistical analysis

The data were analyzed using statistical analysis software (NCSS 9, LLC. Kaysville. Utah, USA.) For nominal data, one-way analysis of the variance was used. Linear regression and correlation were used for numerical data. Statistical significance was taken as a 2-sided "p" value <0.05.

Results

Continuous Glucose Monitoring (CGM)

The data from a total of 384 overnight CGM observations were analyzed for determination of the frequency of the Dawn Phenomenon. Over 6 months of CGM, there was a wide range in Dawn Phenomenon frequency between the subjects, ranging from a minimum of 0% and a maximum of 100% of the nights tested. CSII programming for an early morning increase in insulin delivery was not associated with a reduction of the Dawn Phenomenon, which occurred with a mean rate of 42.3 % in CSII programmers versus 47.5 %in CSII nonprogrammers ($P = 0.6$).

Demographic variables

A statistical correlation was examined between the frequency of the Dawn Phenomenon and the following demographic variables: age, BMI, duration of diabetes, type of insulin delivery and gender. As shown in Figures 1 and 2, none of these correlations reached statistical significance.

Glycemic variables

The following physiological variables were also examined in an attempt to predict the Dawn Phenomenon: A1C, 1,5-anhydroglucitol, mean glucose, maximum glucose, and glucose variability as measured by the standard deviation of the change of

glucose from the overnight mean. As shown in Figure 3, none of these variables was significantly correlated with the frequency of the Dawn Phenomenon.

Discussion

Our study attempted to predict the occurrence of the Dawn Phenomenon from readily obtainable glycemic and demographic parameters. If possible, this would be a major advance in improving glucose control, because additional insulin could be given safely by injection or insulin pump to suppress the rise in early morning glucose. That this approach would be effective has been demonstrated by the use of automatic feedback delivery of overnight insulin delivery devices (11). Our results suggest that this benefit is not predictable from readily obtained physiological or CGM parameters.

Our data contrast with the report by Perriello and coworkers who demonstrated that the Dawn Phenomenon is predictable from Hemoglobin A1c and diabetes duration (3). However, the design of our study was significantly different (Table 2). Although both studies utilized a Type 1 diabetes population, their study defined the Dawn Phenomenon using the need for increased insulin delivery to maintain normoglycemia in contrast to our approach of using a 10mg/dl early morning rise in serum glucose level. In addition, their study was completed in an inpatient setting compared to our outpatient "real life" observations.

An alternative approach for controlling the magnitude of the Dawn Phenomenon is to program an automatic increase in insulin delivery each morning using CSII. This approach is often utilized clinically and suggested by various organizations (11,12) . However, data to support this approach is not available. In fact, this approach can be hazardous if the increase in programmed insulin delivery is given at the wrong time in the early morning hours or during a morning in which no Dawn Phenomenon occurs.

Our study has several limitations which should be considered. First, our study was performed in Type 1 diabetic individuals so that our results may not apply to individuals with other types of diabetes. Second, our sample size was limited so that a larger sample may demonstrate alternative findings. However, whether these results would be applicable to an individual patient is problematic because the variation in the occurrence of the Dawn Phenomenon in any given individual is so great. Third, our conclusion only applies to patients with A1C levels between 6.5% and 9.0%.

In contrast to these limitations, the strengths of our study include the large number of analyzable overnight glycemic data points, the blinded nature of data gathering and analysis, the "real world" outpatient setting, and the multiple parameters examined.

In summary, our study demonstrates that the occurrence of the Dawn Phenomenon is not predictable from readily obtainable demographic and glycemic parameters.

The authors have no conflict of interest to report

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Table 1 – Baseline Characteristics [a]				
	Total	**MDI**	**CSII**	**P value**
N	39	12	27	-
Age (years)	42	45	41	0.8
Male/Female(n)	18/21	6/6	12/15	-
HbA1c (%)	7.5	7.4	7.5	0.5
Diabetes Duration(years)	17	17	18	0.7

Abbreviations: CSII = continuous subcutaneous insulin infusion; HbA1c = glycated hemoglobin; MDI = multiple daily Injections.

[a] Data for continuous variables are presented as mean. Data for Categorical data are presents as total numbers (n).

Table 2 – Comparison of Protocols and Results in T1DM		
Parameter	**Ereifej et al.**	**Perriello et al.**
Definition of Dawn Phenomenon	Hyperglycemia > 10 mg/dl in early mornings	Insulin need > 20 Units in early mornings
Location	Outpatient	Inpatient
Method	CGMS	Frequent Blood draw
Observation Period	3:00 am to 8:00 am	5:00 am to 7:00 am
Number of observations per person	384	117
Diabetes treatment	MDI and CSII	IV Insulin Withdrawal
Frequency of Dawn Phenomenon	~50%	~90%
Correlation of Dawn Phenomenon vs A1c	No	Yes
Correlation of Dawn Phenomenon vs duration of diabetes	No	Yes
Correlation of Dawn Phenomenon vs age	No	No
Assessment of the correlation of Dawn Phenomenon with BMI, gender, type of Insulin , mean 24 h glucose excursion, mean 24 h glucose and 1, 5-anhydroglucitol	Yes	No

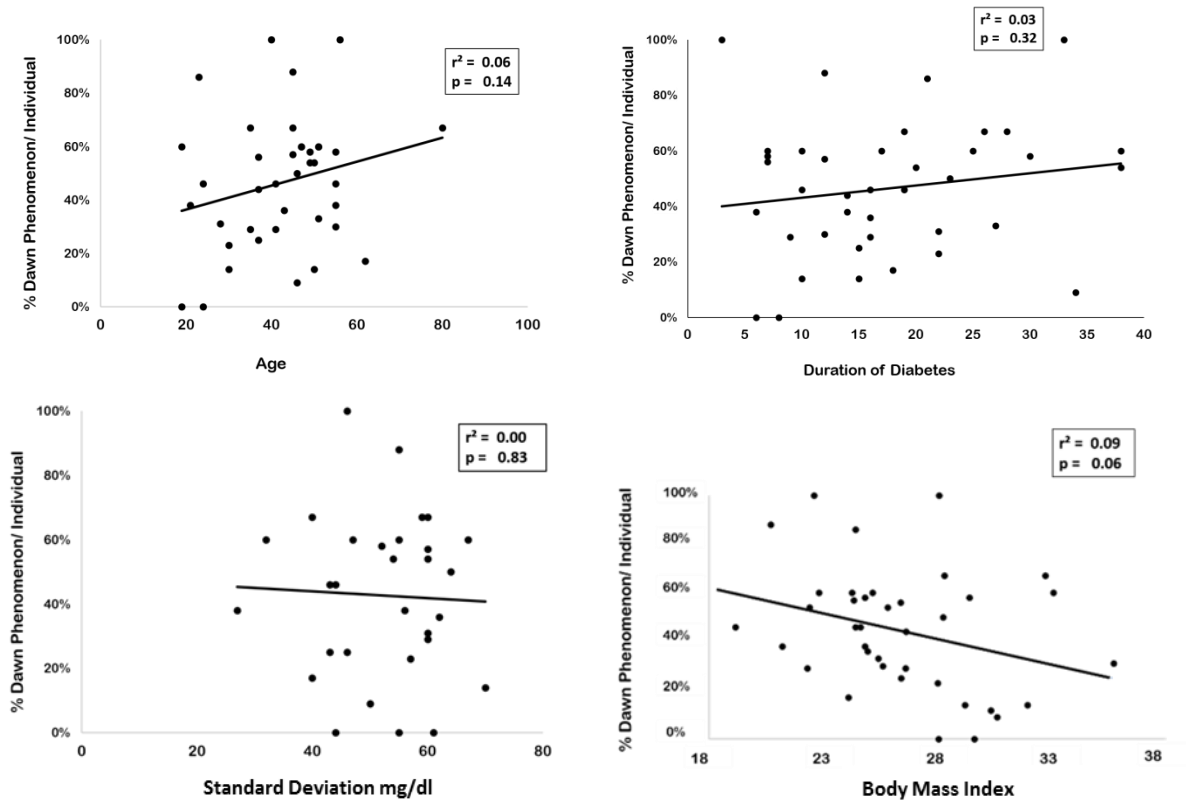


Figure 1: The Correlation of the Dawn Phenomenon with the patients' age, Body Mass Index, Standard deviations and diabetes duration.

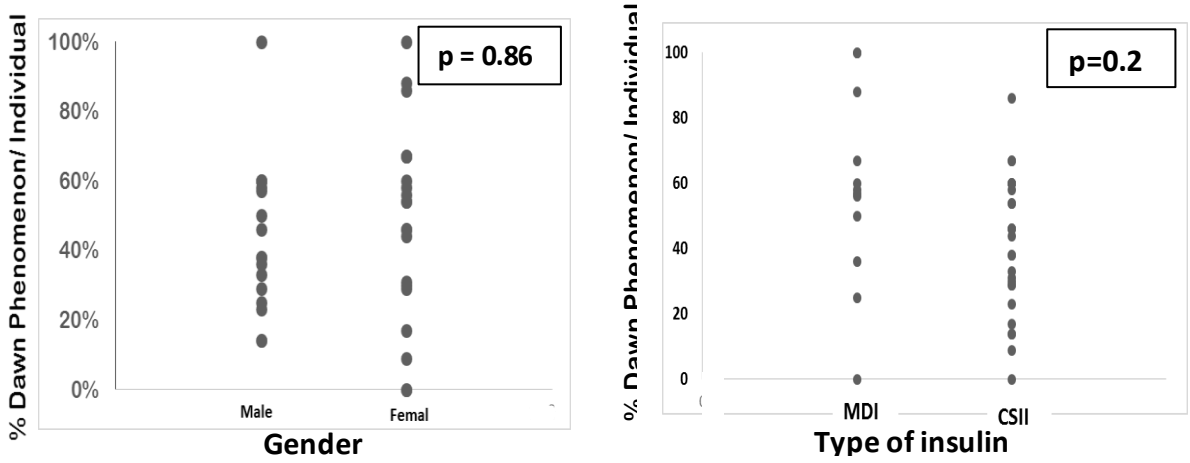
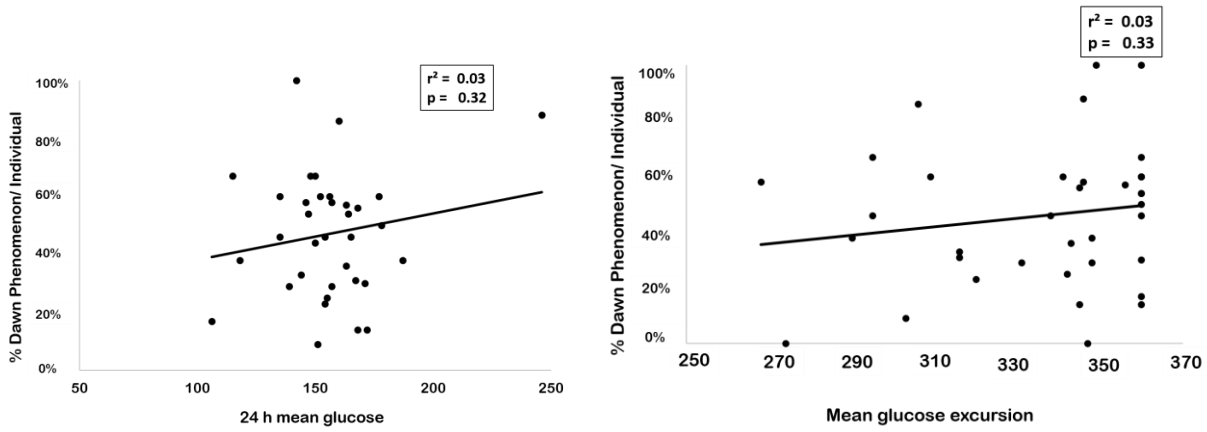


Figure 2: The Comparison of the Dawn Phenomenon with the patients' gender and type of insulin delivery.

A



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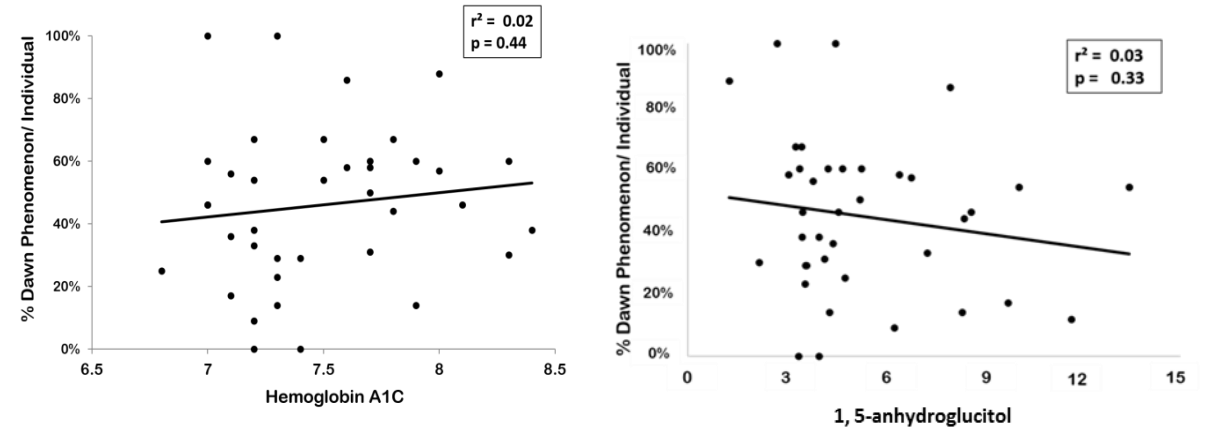

Figure 3: 3A: The Correlation of the Dawn Phenomenon with the 24 h mean glucose and the 24 h mean glucose excursion. **3B:** The Correlation of Dawn Phenomenon with Hemoglobin A1c and 1,5-anhydroglucitol.

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