



## Research Article

# The Effect of a Bedtime Meal on Fasting Hyperglycemia Assessed by Continuous Glucose Monitoring System in Type 2 Diabetes Mellitus Patients

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## Abstract

**Objective :** Fasting hyperglycemia is a significant abnormality in patients with diabetes mellitus and pre-diabetes. The dawn phenomenon is a major contributor to fasting hyperglycemia. We hypothesized that a meal just before bedtime might attenuate the dawn phenomenon and lower fasting hyperglycemia by increasing early morning insulin secretion in these patients.

**Design:** We investigated the effect of different compositions of bedtime meals on the dawn phenomenon and morning glucose level, using a continuous glucose monitoring system.

**Results:** We did not find any significant difference in morning glucose levels between eating any kind of food and not eating at bedtime, for the whole group of 11 patients. However, two patients showed a consistent lowering of fasting blood glucose in response to a bedtime snack, raising the possibility of individual response.

**Conclusions:** This work focuses on the bedtime meal as a simple tool for lowering fasting hyperglycemia in patients with Type 2 Diabetes. Our study implies that most patients would not show a favorable response. However, the study consisted of only 11 participants, and pointed to a possibility of individual response. Therefore, we encourage testing this simple tool of bedtime meal in patients with Type 2 Diabetes, and conducting a larger clinical study.

## Abbreviations

AUC	:	Area Under the Curve
CGMS	:	Continuous Glucose Monitoring System
DM	:	Diabetes Mellitus
DP	:	Dawn Phenomenon
FBG	:	Fasting Blood Glucose
FH	:	Fasting Hyperglycemia
IFG	:	Impaired Fasting Glucose

## Introduction

Fasting Hyperglycemia (FH) is an important component of glucose abnormalities in patients with Diabetes Mellitus (DM) and pre-diabetes. However, the blood glucose level rises towards waking-up time, even in people with normal glucose metabolism, as a result of the hormonal milieu prevalent in the early morning hours, a phenomenon known as the "Dawn Phenomenon" (DP) [1,2]. Morning blood insulin level is relatively low due to the overnight fast, while the levels of the counter-regulatory hormones, notably growth hormone and cortisol, are elevated due to the circadian rhythm in secretion of these hormones [3]. This

hormonal milieu increases hepatic glucose production. In patients with diabetes, the phenomenon is exaggerated probably due to the addition of hepatic insulin resistance [4,5]. In patient with Impaired Fasting Glucose (IFG) and in some of the patients with DM this may be the only glucose metabolism abnormality. Recently, the contribution of the DP to the average glucose level (or HbA1c) was demonstrated [6,7]. Most of the oral hypoglycemic agents and GLP-1 analogues have only a modest effect on FH [6,8]. The most effective way to lower FH significantly is by insulin treatment. Some patients have observed a lowering of morning glucose level following late night meals. We assumed that this might be explained by suppression of the DP by prolonged insulin secretion, in response to slowly digested food consumed late at night. To test this hypothesis, we examined the effect of different compositions of bedtime snacks on the DP and overnight and morning glucose levels, using a continuous glucose monitoring system.

## Study Design and Methods

The study was conducted at the Sheba Medical center, Tel-Hashomer, Israel. The study was approved by the local review board and was registered in the Clinical studies of the NIH (No. NCT00986700).

We included men and women ages 18-80 with Impaired Fasting Glucose (IFG) and diabetes, not treated with insulin and having a fasting blood glucose level higher than 110mg/dl. A detailed medical history was taken from each patient. Blood was drawn after overnight fasting, to test for: glucose, HbA1c, insulin, c-peptide, cortisol, growth hormone, lipid profile, and GOT. Patients were then equipped with retrospective continuous glucose monitoring system (Ipro, Medtronic, Northridge) for 6 consecutive days each time. During the 6 days of observation the patients consumed the following meal at bedtime, in a randomized manner: No meal for two nights, and on the other nights a meal containing mainly protein (200 grams of cheese), fat (30 grams of nuts) or carbohydrates (Extend bar energy snack, 40 grams). The patients were instructed not to eat after 21:00 except for the test meals. A diet diary was given to be filled by the patients.

DP was defined as the difference between the pre-breakfast time and the glucose nadir (between 00:00a.m and 06:00a.m). Pre-breakfast glucose level was defined as the average glucose level between 06:30a.m and 07:00a.m. The Area Under the Curve (AUC) for the whole night was calculated based on glucose levels between 00:00hrs and 07:00a.m. For patients who consumed a certain type of bedtime meal for more than one day, the average of the averages or the average of the AUCs were used. Insulin, C-peptide, GH and Cortisol were measured by solid-phase chemiluminescent immunoassays (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Insulin intra- and inter-assay coefficients of variation (CV) are <5.5%

and <7.3% respectively. C-peptide intra- and inter-assay CV are <2.3% and <4.8% respectively. GH intra- and inter-assay CV are <4.6% and <6.6% respectively. Cortisol intra- and inter-assay CV are <7.4% and <9.4% respectively. Hb-A1C was measured by ion-exchange high-performance liquid chromatography (HPLC) (Variant II Turbo (from 9/2015) or D-10 (until 8/2015), Bio-Rad Laboratories, Inc., Hercules, CA, USA). Intra- and inter-assay CV are <0.8% and <1.2%, respectively. Plasma glucose was measured using an auto-analyzer (AU5800 Chemistry Analyzer, Beckman Coulter). Plasma Total Cholesterol (TC), Triglycerides (TG), LDL-Cholesterol (LDL), and HDL-Cholesterol (HDL) were determined directly using an enzymatic color test (Olympus Diagnostic, GmBH, Lismeehan, Ireland).

## Statistical Analysis

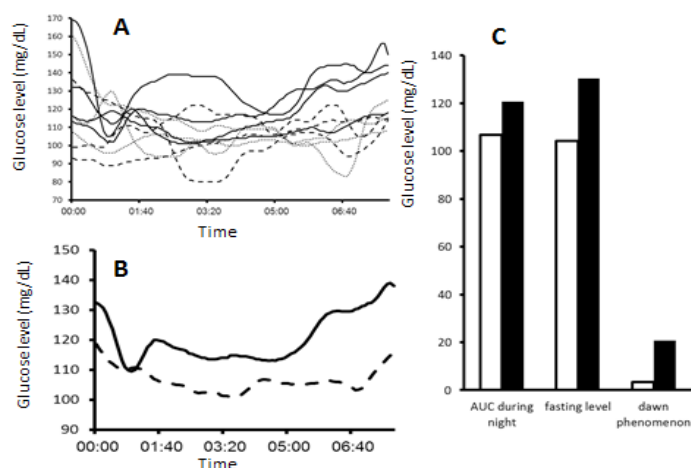
The effect of each type of bedtime meal compared with fasting was examined by the non-parametric Wilcoxon-rank-sum test for matched samples, using a two-sided p-value. Specifically, the DP was examined based on the differences between the pre-breakfast time and glucose nadir, by applying the Wilcoxon test for each bedtime meal type, i.e. cheese, nuts, and Extend bar energy snack, separately. In addition, the following two types of bedtime-meals were defined: "Sugar-free" was the average of nuts and cheese; and "Food" was the average of nuts, cheese and snack. Thus, in total, we tested five types of bedtime meals. Test results with p-value less than 0.05 were considered significant. A similar analysis was performed to compare the all-night glucose levels under fasting versus each of the five bedtime meals, using the AUCs.

## Results

The study included 11 patients, 4 males and 7 females, who underwent 21 weeks of glucose sensing (1 week for 2 patients, 2 weeks for 8, and 3 for 1 patient). All the patients had Type 2 DM excepting one, who had IFG. Mean age was 64 years (range 54-73) and mean weight 73Kg (59-92). Seven patients were treated by metformin. Mean HbA1c was 6.9% and mean FBG was 137mg/dl.

Eight patients had DP of more than 20mg/dl and three did not. No significant results were observed in comparing the all-night glucose levels and in comparing the DP under fasting versus each of the meal compositions.

Two patients out of 11 showed a consistent lowering of FBG associated with lower area under the curve at night with all bedtime snacks, in comparison to having no bedtime snack. For example, in patient no. 3, a 67-year-old woman with DM for 10 years, treated with diet only (Figure 1), eating a bedtime snack lowered the FBG by 26mg/dl on average, with meals containing fat as well as proteins. This happened concomitantly with reduced DP and smaller AUC for the glucose level during the night.



**Figure 1:** The effect of bedtime meal on glucose level in a “Responsive” patient.

- A.** Daily individual graphs of continuous glucose monitoring system showing glucose levels between midnight and morning. Each line represents a separate day. Solid line - nights without bedtime meal, dashed lines - nights after bedtime meal of nuts, and dotted line - after a meal including cheese.
- B.** Comparison of night glucose level with (dashed line) and without (solid line) a bedtime meal.
- C.** The effect of a bedtime meal on the overnight glucose level, fasting glucose level and the dawn phenomenon in this patient. Black bars - nights without a bedtime meal, white bars - nights with a bedtime meal.

## Discussion

Fasting hyperglycemia is an important component of glucose abnormalities in patients with DM and pre-diabetes. The diagnosis of DM can be made solely by elevated fasting glucose level and this is often the only glucose abnormality. Although less related to macrovascular complications of DM than post-prandial glucose level [9,10], fasting hyperglycemia significantly contributes to the average glucose and HbA1c levels [6,7]. Thus, improving fasting glucose level can help to improve DM control and might prevent diabetic microvascular complications. Unfortunately, this is not easily achievable as most anti-diabetic medications have only a modest effect in lowering fasting glucose levels and insulin treatment is often required [6,8].

The cause of early morning rising glucose levels despite overnight fasting is hepatic glucose production, a phenomenon known as the “Dawn Phenomenon”. The circadian rhythm of the insulin counter-regulatory hormones, particularly cortisol and growth hormone, that reach a peak in the early morning hours, together with the low insulin level during the night fast, are

considered to be the mechanism giving rise to this phenomenon [3-5]. The DP is a normal phenomenon even in healthy people [1,2]. However, it is exaggerated in patients with IFG and DM, causing an abnormal fasting glucose level.

This pilot study was devised following the testimonials of some patients with type 2 DM, reporting that their fasting glucose level was lower when they ate late the night before. We hypothesized that a late night meal can suppress the DP by increasing early morning insulin secretion due to slowly digested food that remains in the intestine at night. We examined the influence of bedtime meal on night and morning glucose levels by using the technic of CGMS. We tested for different kinds of food (consisting mainly of protein, fat or carbohydrates) taken at bedtime.

We did not find any significant difference in morning FBG or the average overnight glucose level, or with the DP itself, between not eating and eating different meal compositions for the whole group of patients. However, we found that two patients responded to a bedtime snack and showed consistently lower FBG the next morning. The reduction in FBG in these patients was comparable to the effect of oral anti-diabetic medications like DPP-4 inhibitors [11]. We were unable to identify any parameter that could predict which patient would respond to bedtime meal, but the number of patients in this study is too small to draw conclusions.

This is a small study, but we can probably conclude that the response to a bedtime meal by some patients is credible, though it is not a general phenomenon.

## Conclusion

We suggest that this “Natural” treatment can be offered to diabetic patients who experience fasting hyperglycemia with their regular treatment. However, a follow-up is required to verify responsiveness. If the response is not favorable, a bedtime meal should probably be avoided. Larger clinical studies are needed to characterize patients that are likely to respond favorably to a bedtime meal.

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