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Postprandial Glycaemia in Type-2 Diabetes: A Non-Random Trial According to Glucose Control

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Abstract

Introduction: Postprandial glycaemia contributes significantly to the overall glycaemic control and is a risk factor for cardiovascular complications in type-2 diabetes patients. As patients with good glycaemic control can show elevated postprandial hyperglycaemia, especially after breakfast, the study of glucose response after this meal can provide insight that will help nutrition intervention and treatment.

Methods: A group of 66 patients previously diagnosed with type 2 diabetes mellitus was recruited and categorized into patients with HbA1c below 7% (proper glycaemic control) and patients with HbA1c of 7% or above (poor glycaemic control). All subjects were interviewed and offered a nutritionally controlled breakfast. Glucose response was monitored for 120 minutes after the meal.

Results: There are no significant differences in postprandial glycaemia between patients with adequate glycaemic control and those with poor glycaemic control, up to 120 minutes after breakfast. The reported prevalence of self-monitoring of blood glucose is low. Mean differences between pre-prandial and postprandial glucose were not correlated with body mass index, age at diagnosis, diabetes duration, HbA1c, energy or carbohydrate intake.

Conclusions: Patients which are considered as having a proper glucose control may be unaware that they exceed the recommended rise in postprandial glycaemia. Meal plans should take into account the need to regulate postprandial glycaemia and patients should be empowered to overcome their low prevalence of glucose self-measure.

Keywords: Postprandial glucose; Type 2 diabetes; Nutrition

Introduction

Treatment and prevention approaches for type 2 diabetes mellitus (T2DM) focus on achieving glycaemic control, in order to manage the disease and to prevent or slow down its complications. General management of diabetes consists of patient education, medical nutrition therapy, physical activity, and pharmacological therapy combined with oral hypoglycaemic agents or insulin [1].

Recently, the role of postprandial glycaemia (PPG) in overall glycaemic control and as a risk factor for cardiovascular complications has been discussed, as patients with good glycaemic control can show elevated postprandial hyperglycaemia (PPHG), which contributes significantly to the overall glycaemic control. In fact, the postprandial state is the norm for individuals who consume at least three meals a day at relatively fixed times, and during the postprandial period insulin secretion does not fully compensate for insulin resistance in T2DM [2]. Evidence suggests that PPHG seems to be common in T2DM patients and that neither adequate fasting plasma glucose levels [3] nor good overall glycaemic control, indicated by glycated haemoglobin (HbA1c) levels below or around 7% [4], are necessarily correlated with proper glycaemic control throughout the day. Some research showthat T2DM patients with a standardized diet experience hyperglycaemia more than nine hours per day and that even those patients with apparent good glycaemic control, measured by HbA1c below 7.0%, experienced PPHG for nearly six hours per day [5].

According to long term prospective cohort studies and clinical trials [6-8], there is a strong correlation between glycaemic control and the incidence of microvascular and macrovascular complications. The DECODE study, which analysed 13 prospective European cohort studies [9], suggests that fasting-glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycaemia. This study reports that during the follow-up period the largest number of excess deaths was observed in subjects who had impaired glucose tolerance but normal fasting blood glucose levels and concludes that the glucose level two hours after the start of a meal is a better predictor of deaths from all causes and cardiovascular disease than is fasting blood glucose. PPHG also seems associated with an increased risk of retinopathy, impaired cognitive function, and with increased carotid intima-media thickness. PPHG is also identified as a causal factor in oxidative stress, inflammation, and endothelial dysfunction [10]. Further evidence [3] suggests that PPG values one hour after a meal are predictive of all-cause mortality and reports that PPHG is associated with increased cardiovascular risk, independent of fasting hyperglycaemia.

PPHG seems most common after breakfast, possibly due to an elevated hepatic glucose output in the early morning. Data from 200 non–insulin-treated patients with T2DM suggest that high plasma levels over morning periods after breakfast seem to occur independently of body mass index (BMI), HbA1c, therapy, and residual β-cell function [11, 12].

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It is proposed [13] that two-hour postprandial plasma glucose should not exceed 9.0 mmol/l (162 mg/dl) or, based on the correlation with HbA1c values and aiming at a conservative target, that in order to achieve an HbA1c of 7%, the peak postprandial capillary blood glucose that usually occurs one hour to two hours after the start of a meal, should be below 180 mg/dl (10.0 mmol/l) [4]. Other data suggests that the difference between pre-prandial and post-prandial glycaemia should normally be between 30 and 50 mg/dl [14].

PPHG is still considered a complex topic [4], with limited available data, and although target values exist for postprandial glycaemia, most practitioners and clinicians rely solely on HbA1c and fasting glucose concentrations to evaluate and adjust therapeutic strategies [10, 15, 16]. Fating glucose and HbA1c are easy to measure, and the latter is especially used in the clinical setting to monitor diabetes, and to establish the degree of metabolic control. Deviation from individualized HbA1C targets prompts physicians to modify treatment strategies [16]. Nevertheless, by focusing solely on HbA1C or FPG levels, clinicians may miss opportunities to help patients to meet glycaemic targets, and minimize glucose variations which can have negative effects on long-term outcomes [2, 5].

These findings can imply that additional assessments should be undertaken in patients with T2DM, so as to fully evaluate metabolic control. Additionally, as the main predictor of PPG is the nutritional content of the meal, especially in carbohydrates, it can be proposed that the best option for regulating PPHG can be nutritional therapy [17], as it can bring several added benefits to the management of diabetes and its complications (e.g., weight reduction, improvement in lipid profile), without the side effects and costs of pharmacotherapy.

Based on the available evidence, the goal of this study was to analyse glucose response to a nutritionally controlled meal, in T2DM patients with and without proper glucose control. The specific objectives where: a) describe the association between PPG levels and HbA1c; b) analyse glucose response according to dietary, anthropometric and clinical variables.

Methods

We conducted a non-random trial in T2DM patients receiving health care in a Diabetes Clinic in the municipality of Faro, in the Portuguese region of the Algarve. Patients were invited to be a part of this study during their consultations and a date was set up according to their availability to proceed with data collection. The inclusion criteria for this study were age below 85 years and medical diagnosis of T2DM for at least 12 complete weeks, obtained by previous assessment and identification of one or more of the following: HbA1c ≥ 6.5%, FPG ≥ 126 mg/dl (7.0 mmol/l), 2h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test, or presence of classic hyperglycaemia symptoms and a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l). Patients were excluded if they were undergoing a pharmacotherapy regimen with insulin or any antidiabetic oral agents other than metformin, had a diagnosis of degenerative disorder of the central nervous system, or if they were following a lactose-free or gluten-free diet. Patients were recruited and coded as group 1 (G1) if they had been recorded as having an HbA1c of 7.0% or above in the 60 days prior to data collection, or as group 2 (G2) if they had been recorded as having HbA1c below 7.0% in the 60 days prior to data collection. The final study sample was composed by 66 patients, 32 in G1 and 34 in G2. Regarding gender distribution, 56% of the sample (n=37) were men and 44% (n=29) were women. G1 was composed by 20 men (62.5%) and 12 women (37.5%) and G2 was composed by 17 men (50%) and 17 women (50%).

Patients were individually interviewed by a trained dietitian regarding their lifestyle and dietary habits and data were also collected from each patient's clinical records. Weight and height were collected by standardized methods in order to compute BMI. The assessment of usual dietary intake was achieved by a 24-hour recall, plus questions regarding usual eating habits, both aided by the use of images representing food items and different portions [18].

In order to assess glucose response, all patients were offered a controlled breakfast, constructed according to the dietetic recommendations for patients with T2DM [19, 20], and obeying to usual eating habits in the region. The experimental meal had the following composition (Table 1).

The experimental breakfast corresponded to 24.6% of a daily caloric intake of 2000 Kcal. It was decided that the breakfast should account for at least 400 kcal, based on prediction equations that estimate a daily energy requirement of 2000 Kcal for adults over 50 years old with a lifestyle that includes only the light physical activity associated with typical day-to-day life [21], and considering that a nutritionally balanced breakfast should account for 20% to 25% of the daily energy intake [22-24].

In the day scheduled for data collection, patients were asked to follow their usual pharmacologic therapy and were offered the experimental breakfast between 8:00h A.M. and 9:00h A.M., according to individual preferences and usual breakfast intake hour. Subjects were asked to completely eat the all food items it contained, while seated, and without significant interruptions.

Glucose response to the experimental breakfast was assessed by the measurement of capillary blood glucose while the patients were in fasting, and in 30-minute intervals after the start of breakfast, up to 120 minutes after the meal. Five glucose measurements were collected for all patients with a portable blood glucose monitoring system (Freestyle Lite, MK-23, Abbot, USA). This particular handheld device has showed good analytical performance and clinical accuracy [25]. The same device was used for all patients to minimize variability and test strips came from the same batch. Before the data collection with each patient, a test measurement with the Freestyle Control Solution was conducted, in order to guarantee compatibility and precision with the discardable test strips. The blood samples for testing were obtained by puncture in the fingers of the left hand. Following the strictest safety and hygiene procedures. Patients were asked to remain seated during the course of the measurements in order to minimize physical activity, which could influence glucose response during the postprandial period.

All stages of this study obeyed the ethical rules for health sciences research as stated in the sixth revision of the Declaration of Helsinki, including an informed consent form which was signed by every patient during the briefing and recruitment.

Data were analysed with IBM-SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Patient description and characterization were presented as mean values accompanied by standard deviations, and prevalence calculated as the percent of the total number of valid observations in each calculation.

The Kolmogorov-Smirnov test was used to assess adherence to the Normal distribution and Student's t-test was computed for comparisons

Table 1: Foods and nutritional values for the experimental breakfast

Food	Amount (g)	Energy (Kcal)	Protein (g)	Fat (g)	Carbohydrates (g)	Sugars (g)
Wheat bread	80	231.13	6.72	1.76	45.84	1.68
Ham	30	90.98	5.4	7.65	0.15	0.15
Milk	200	93.68	6.6	3.2	9.8	9.8
Apple	135	76.78	0.27	0.68	18.09	18.09
	Total	492.6	19	13.3	73.9	29.7

between two groups. Correlations were analysed with Pearson or Spearman's correlation coefficients and the chi-square test was used for group comparisons of qualitative variables.

Statistical significance in all procedures was determined by two-tailed analysis and set at 0.05.

Results

Table 2 presents data for clinical, dietary, anthropometric, and glucose response variables. Apart from the expected differences in HbA1c, there are also significant differences between G1 and G2 regarding age, age at diagnosis, BMI, total cholesterol, LDL cholesterol, and in the intake of sugars.

The analysis of the differences in glucose response to a mixed-meal containing 75 of carbohydrates shows that G1 and G2 do not significantly differ up to 120 minutes post-meal. According to the Student's t-test (df=64), statistical significance for group differences is achieved in fasting glycaemia. Mean values up to 120 minutes after the experimental breakfast were similar in G1 and G2.

All but 4 participants (2 in G1 and 2 in G2) showed a mean difference between pre-prandial and postprandial glucose above 40 mg/dl. The mean difference was 57.1 mg/dl in G1 (SD=13.29 mg/dl) and 63.0 mg/dl in G2 (SD=19.73 mg/dl), with the differences being statistically non-significant (t (64)=-1.4, P=0.159).

Mean differences between pre-prandial and postprandial glucose were not correlated with age at diagnosis (rSpearman=-0.006, P=0.963) or at data collection (rSpearman=0.024, P=0.827), diabetes duration (rSpearman=0.108, P=0.387), HbA1c (rSpearman=-0.215, P=0.084), energy (rSpearman=0.013, P=0.916) or carbohydrate intake (rSpearman=-0.129, P=0.302), BMI(rSpearman=0.017, P=0.892), or frequency of glycaemia self-measurement (rSpearman=0.282, P=0.068). We also did not find gender differences in PPG at any of the measurement times either considering the total sample or considering only participants in G1 or G2 (p>0.05).

All mean values throughout the glucose monitoring were below 200 mg/dl, even at 120 minutes, which corresponds to the diagnosis cut-off point for T2DM when using an oral glucose tolerance test [4].

No significant differences were found in the proportion of subjects above the 200 mg/dl threshold for glycaemia at 120 minutes after breakfast, and all subjects presented a PPG level above 140 mg/dl (Table 3).

Although we recorded a difference in mean BMI, the prevalence of overweight and obesity is statistically similar between groups (χ^2 (42)=9.34, P=0.063), as shown in figure 1.

Most participants self-measure their blood glucose weekly (39.4%) or at least once a day (34.8%). Nevertheless, we did not find statistically significant differences between G1 and G2 regarding self-measurement of blood glucose (Table 4).

Table 2: Mean differences between groups in clinical, anthropometric, and dietary variables

Variable	All participants (N=66)	Group 1 (N=32) Mean (SD)	Group 2 (N=34)	P-value of Student's t-test
HbA1c (%)	7.3 (1.62)	8.6 (1.40)	6.1 (0.51)	< 0.001*
Age (years)	60.9 (7.96)	57.8 (7.08)	63.7 (7.79)	0.002*
Age when diagnosed (years)	54.5 (7.62)	51.8 (6.45)	57.0 (7.87)	0.005*
Disease duration (years)	6.2 (4.47)	6.0 (3.65)	6.4 (5.18)	0.73
BMI (kg/m2)	30.0 (4.28)	31.3 (4.44)	28.9 (3.85)	0.024**
HDL cholesterol (mg/dl)	48.6 (15.22)	48 (16.84)	49.3 (13.76)	0.735
Total cholesterol (mg/dl)	172.8 (35.25)	182.9 (33.17)	163.4 (35.01)	0.026**
Energy (kcal)	2258.3 (686.98)	2449 (781)	2079 (536)	0.030*
Protein (g)	88.3 (27.74)	91.2 (29.81)	85.6 (25.78)	0.419
Total carbohydrates (g)	267.5 (104.16)	292.5 (124.12)	243.9 (75.62)	0.062
Sugars (g)	107.4 (68.29)	128.9 (77.92)	87.2 (51.14)	0.012*
Fibre (g)	18.0 (8.37)	18.3 (8.73)	17.7 (8.13)	0.783
Lipids (g)	89.5 (34.10)	94.4 (36.95)	84.9 (31.03)	0.263
Glycaemia (mg/dl)				
t_0 minutes	119.1 (8.21)	122.3 (7.25)	116.1 (8.00)	0.001*
t_{30} minutes	180.0 (27.16)	181.1 (25.70)	178.9 (28.80)	0.737
t_{60} minutes	172.1 (26.7)	173.1 (26.54)	171.1 (27.22)	0.77
t_{90} minutes	167.3 (24.72)	167.9 (23.21)	166.8 (26.41)	0.853
t_{120} minutes	179.3 (16.90)	179.4 (12.34)	179.1 (20.49)	0.939

SD – Standard deviation
*Significant differences between groups at the 0.01 probability level
**Significant differences between groups at the 0.05 probability level

Table 3: Proportion of participants above selected glycaemia thresholds

Glycaemia	Group 1 (N=32)	Group 2 (N=34)	X2 test P-value
Fasting levels ≥ 126 mg/dl	34.40%	11.80%	0.028*
≥ 140 mg/dl 120 minutes after breakfast	100%	100%	-
≥ 160 mg/dl 120 minutes after breakfast	100%	88.20%	0.065
≥ 200 mg/dl 120 minutes after breakfast	6.30%	11.80%	0.436

*Significant differences between groups at the 0.05 probability level

Table 4: Frequency of glucose measurement in cases and controls

Measurement frequency	All participants (N=66)	Group 1 (N=32) N (%)	Group 2 (N=34)	P-value for the X2 test
Daily	23 (34.8%)	8 (30.8%)	15 (50%)	0.454
Weekly	26 (39.4%)	15 (57.7%)	11 (36.75%)	
Monthly	4 (6%)	2 (7.7%)	2 (6.7%)	
Yearly	3 (4.5%)	1 (3.8%)	2 (6.7%)	

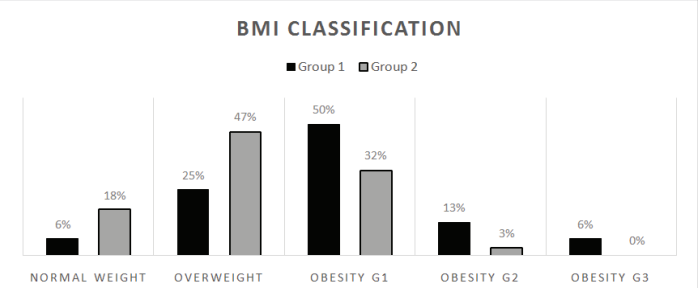

Figure 1: BMI classification, according to WHO (2000) Obesity: preventing and managing the global epidemic, World Health Organization. No underweight participants were present in the study. Differences between Group 1 and Group 2 are statistically non-significant ($\chi^2 = 9.34$, $P = 0.063$)

Discussion

Our data reflect the general overweight and obesity trends in T2DM patients. A systematic review of observational studies [26] reports that obesity rates exceeded 30% in 38 of the 44 studies analysed for this variable and 50% in 14 of the 44 studies. Additional data from 3637 UK patients in secondary care [27] showed that 86% of patients with T2DM were overweight or obese and, in Spain, a nationwide population-based cross-sectional survey with 12,077 individuals, reports that only 11.4% had BMI below 25 kg/m^2 or a recommended waist circumference [28].

In this study, participants did not significantly differ in glycaemia up to 120 minutes post-meal ($P>0.05$) and all the subjects presented a PPG level above 140 mg/dl, which, according to the literature [10, 29, 30], suggests a PPG level associated with diabetes complications. Furthermore, there are also recommendations that support that the difference between pre-prandial and postprandial glucose should not exceed 40 mg/dl [10]. All but 4 subjects (2 in G1 and 2 in G2) had differences above 40 mg/dl, which can be classified as glucose excursions (i.e. elevated differences between pre-prandial and postprandial glucose).

The results from the dietary assessment show that a high proportion of subjects have a diet that is inadequately high in energy, sugars, total carbohydrates, and lipids. Due to the high intake of total carbohydrates and sugars, subjects can experience postprandial hyperglycaemia, independently of their perceived glycaemic control, measured by HbA1c.

Our results allow us to suggest that there is no significant difference in PPG between patients with adequate glycaemic control and those with poor glycaemic control. Mean glycaemia values were similar in cases and controls up to 120 minutes after a meal.

Although the group of subjects in this study is a particular one (on metformin only as an oral antidiabetic agent), if we consider the high prevalence of excess energy and carbohydrates intake reported, diabetes patient's cardiovascular risk can be high in subjects who, based on HbA1c levels, believe themselves in a proper state of glycaemic control.

Similarities in PPG also extend to the mean difference between pre-prandial and postprandial glucose and further studies should be promoted in order to analyse the role of different oral antidiabetic agents in PPG in subjects with adequate HbA1c.

The similarities in PPG between the subjects also add to the evidence that HbA1c, despite being considered an adequate predictor of glycaemic control that can be used for establishing a diagnosis, does not account for daily fluctuations of glucose [31-33]. The mean values for glucose excursions in both G1 (M=57.1 mg/dl, SD=13.29 mg/dl) and G2 (M=63.0 mg/dl, SD=19.73 mg/dl) were significantly above the recommendations stating that this value should not exceed 40 mg/dl [10] and may imply an added risk for cardiovascular events [34]. Self-measure of blood glucose is the most appropriate way to identify PPHG and the results from this study show that patients should be empowered to overcome their low prevalence of glucose self-measure, as regular data of postprandial glycaemia can help to adjust diabetes care plans.

The major limitations of this study are related with the PPG assessment methods and with participant inclusion criteria. Due to financial and logistic restrictions, we were unable to use a continuous glucose monitor system or to assess insulin excursions. Although valid and a usual self-monitoring method, capillary blood glucose measurements are not the gold standard for assessing PPG and this can be addressed in further studies. Additionally, in order to prevent biases in PPG analysis, our inclusion criteria implied that subjects had a similar pharmacotherapy regimen, which resulted in a reduced sampling universe and restricts the applicability of this study's results to a specific subset of T2DM patients. The cross-sectional nature of our study did not allow us to assess variations in the diet, PPG patterns associated with other meals,or to confirm our results in other assays with the same participants.

Conclusions

Our data adds to the body of knowledge suggesting that patients which are considered as having a proper glucose control may be unaware that they exceed the recommended rise in PPG, and thus may be at a higher than expected risk for macro and microvascular events. This poses a challenge for dietetic and nutrition professionals, as meal plans for patients with diabetes should take into account the need to regulate PPG. Furthermore, our data also suggest that the prevalence of blood glucose self-monitoring is low and independent of glycaemic control. Thus, as self-monitoring is one of the most practical ways to detect PPG, providing immediate feedback on the effect of food and meals, efforts should be made to promote regular glucose self-monitoring among T2DM patients.

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Conflict of Interest Disclosure Statement

The authors confirm that the content of this article has no conflict of interest.

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