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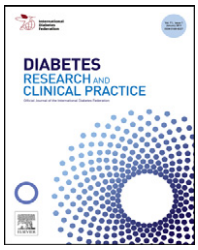

Postprandial hyperglycemia is highly prevalent throughout the day in type 2 diabetes patients

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ABSTRACT

Aim: Although postprandial hyperglycemia is recognized as an important target in type 2 diabetes treatment, information on the prevalence of postprandial hyperglycemia throughout the day is limited. Therefore, we assessed the prevalence of hyperglycemia throughout the day in type 2 diabetes patients and healthy controls under standardized dietary, but otherwise free-living conditions.

Methods: 60 male type 2 diabetes patients (HbA_{1c} 7.5 ± 0.1% [58 ± 1 mmol/mol]) and 24 age- and BMI-matched normal glucose tolerant controls were recruited to participate in a comparative study of daily glycemic control. During a 3-day experimental period, blood glucose concentrations throughout the day were assessed by continuous glucose monitoring.

Results: Type 2 diabetes patients experienced hyperglycemia (glucose concentrations >10 mmol/L) 38 ± 4% of the day. Even diabetes patients with an HbA_{1c} level below 7.0% (53 mmol/mol) experienced hyperglycemia for as much as 24 ± 5% throughout the day. Hyperglycemia was negligible in the control group (3 ± 1%).

Conclusion: Hyperglycemia is highly prevalent throughout the day in type 2 diabetes patients, even in those patients with a HbA_{1c} level well below 7.0% (53 mmol/mol). Standard medical care with prescription of oral blood glucose lowering medication does not provide ample protection against postprandial hyperglycemia.

1. Introduction

Over the last 15 years, epidemiological evidence has clearly shown a strong and independent relationship between post-challenge blood glucose increments and cardiovascular co-morbidities in type 2 diabetes patients [1–3]. Besides the fact that postprandial hyperglycemia significantly contributes to overall glycemic control in type 2 diabetes patients [4,5], several research groups attribute hyperglycemia and oscillating blood glucose concentrations directly to the development

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of cardiovascular disease [6–8]. Consequently, postprandial hyperglycemia is being considered a main target for type 2 diabetes treatment.

Although the European Association for the Study of Diabetes, the International Diabetes Federation and the American Diabetes Association have set stringent target values for postprandial blood glucose control [9–11], most practitioners and clinicians solely rely on blood HbA_{1c} and fasting plasma glucose concentrations to evaluate and adjust therapeutic strategies. This is not surprising as HbA_{1c} and fasting glucose levels are easy to measure and both have been extensively investigated. However, information on the prevalence of postprandial hyperglycemia is rather limited. Conventional or surrogate markers of postprandial hyperglycemia, such as self-monitored blood glucose or post-challenge plasma glucose concentrations do not provide true insight in the daily prevalence of hyperglycemia. In fact, with the introduction of the latest generation continuous glucose monitoring systems (CGMSs), previously undetected glycemic excursions appear common in type 2 diabetes patients [12,13]. However, inter- and intra-individual variation in diet composition, timing and frequency of food intake, and the level and distribution of habitual physical activity complicate the interpretation of the glucose profiles provided by these ambulatory glucose profiles. To accurately assess the prevalence of hyperglycemia within subjects, between subjects and/or between groups, appropriate standardization of dietary intake is warranted.

In the present study, we evaluated daily glycemic control in type 2 diabetes patients ($n = 60$) and healthy, normal glucose tolerant controls ($n = 24$) under strict dietary standardization, but otherwise free living conditions. This study provides more insight in the daily prevalence of hyperglycemia in type 2 diabetes patients under standard medical care.

2. Methods

2.1. Subjects

A total of 60 male type 2 diabetes patients and 24 age- and BMI-matched healthy, normal glucose tolerant controls were recruited by advertisements in the local newspaper. Both control subjects and type 2 diabetes patients in this study were recruited as part of a larger project investigating the impact of lifestyle intervention on glycemic control. Exclusion criteria were renal failure, liver disease, morbid obesity (BMI > 40 kg/m^2), history of severe cardiovascular problems (myocardial infarct in last year, stroke), hypertension (>160 mmHg systolic or >100 mmHg diastolic), and exogenous insulin therapy. All subjects were informed about the nature and the risks of the experimental procedures before their written informed consent was obtained. The Medical Ethical Committee of the Maastricht University Medical Centre approved all clinical experiments.

2.2. Medication

Type 2 diabetes patients were treated with either oral blood glucose lowering medication (metformin combined with sulfonylurea derivatives [SUD] and/or thiazolidinediones [TZD], $n = 30$; metformin, $n = 21$; SUDs, $n = 5$; or TZDs $n = 1$) or dietary modulation only ($n = 3$). All subjects had been on stable medication and/or dietary prescription for at least 3 months before being recruited. Blood glucose lowering medication was withheld 2 days prior to the screening but continued as usual throughout the entire experimental period. None of the control subjects were using any medication known to interfere with the glucose metabolism.

2.3. Screening

Before selection into the study, all subjects performed an oral glucose tolerance test (OGTT). After an overnight fast, subjects arrived at the laboratory at 08:00 by car or public transportation. A fasting blood sample was obtained, after which a bolus of 75 g glucose (dissolved in 250 mL water) was ingested ($t = 0$). Venous blood samples were collected every 30 min until $t = 120$. Plasma glucose concentrations were measured to determine normal glucose tolerance and/or type 2 diabetes according to ADA criteria [9]. Furthermore, HbA_{1c} content was determined in basal blood samples. Venous plasma glucose and insulin concentrations obtained during the OGTT were used to assess pancreatic β-cell function and insulin sensitivity. These parameters were assessed using the updated homeostasis model assessment HOMA [14], and the oral glucose insulin sensitivity (OGIS)-index [15], respectively.

2.4. Study design and protocol

The present study is a comparative study of daily glycemic control in normal glucose tolerant subjects and type 2 diabetes patients. During a 3-day experimental period, blood glucose concentrations throughout the day were assessed by ambulatory continuous glucose monitoring. Subjects were studied under standardized dietary, but otherwise free-living conditions. On the first day of the assessment period, subjects reported to the laboratory in the afternoon and were given instructions regarding the standardized diet and the proper use of the food intake and physical activity questionnaires. All subjects received a short training in the use of the capillary blood sampling method (Glucocard X Meter, Arkray Inc, Kyoto, Japan). Next, a microdialysis fiber (Medica, Medolla, Italy) was inserted in the peri-umbilical region. The micro-fiber was subsequently connected to a portable continuous glucose-measuring device (GlucoDay®S, A. Menarini Diagnostics, Firenze, Italy). The continuous glucose monitoring system is based on microdialysis principle and allows continuous glucose monitoring for up to 48 h [16]. The glucose sensor, consisting of immobilized glucose oxidase, measures the glucose concentration every min and stores an average value every 3 min for up to a 48 h period. The efficacy and the accuracy of the GlucoDay®S have been validated for both type 2 diabetic subjects [16,17] and healthy subjects [18]. After placement of the continuous glucose monitoring system, subjects were provided with their diet after which they went home and resumed their normal daily activities. Subjects consumed their designated meals, drinks and snacks at the predetermined time-points. Before consuming a meal, subjects obtained a capillary blood glucose sample. The third day, subjects reported back to the laboratory where the CGMS was removed.

2.5. Diet and physical activity

All subjects maintained habitual physical activity patterns throughout the entire experimental period, and refrained from exhaustive physical labor and exercise training for at least 3 days prior to and during the measurement period. During the experimental period, subjects were provided with a healthy, standardized diet, consisting of 3 meals and 3 snacks per day. The diet was entirely composed of commercially available food products. All meals and snacks were provided in pre-weighed packages and ingested at pre-determined time-points to ensure fully standardized diets during the 40 h test period. The prescribed standardized diet was composed according to the ADA dietary recommendations for type 2 diabetes [19] and provided on average 10.2 ± 0.1 MJ/day, consisting of 57 En% carbohydrate, 13 En% protein and 30 En% fat. The diet was designed to meet the energy requirements as calculated with the Harris and Bennedict equation multiplied with a physical activity index level of 1.4.

2.6. Glycemic profile analysis

The acquired data from the continuous glucose monitor were downloaded to a personal computer with GlucoDay® software (V3.0.5). Values reported by the CGMS were converted into glucose values using the self monitored blood glucose values. The glycemic profiles of the second day (from 07:00 to 07:00) were used to determine average glucose levels, the prevalence of hyperglycemia and the prevalence of hypoglycemia. Based on the ADA/EASD guidelines for glycemic control [9,11], the prevalence of hyperglycemia was defined as total time during which glucose concentrations exceeded 10 mmol/L, and the prevalence of hypoglycemia was defined as total time glucose concentrations were below 3.9 mmol/L. These parameters were determined over a 24 h time period, during daytime (from 06:00 to 00:00) and overnight (from 00:00 to 06:00). Additional analyses were performed specifically for the subpopulation type 2 diabetes patients that achieved target HbA_{1c} levels below 7% (53 mmol/mol), according to ADA/EASD targets for glycemic control [9,11].

2.7. Blood sample analysis

During the OGTT, blood samples (10 mL) were collected in EDTA containing tubes and centrifuged at 1000 *g* and 4 °C for 10 min. Aliquots of plasma were immediately frozen in liquid nitrogen and stored at −80 °C until analyses. Plasma glucose concentrations (Uni Kit III, Roche, Basel, Switzerland) were determined with the COBAS FARA semi-automatic analyzer (Roche). Plasma insulin concentrations were determined by radioimmunoassay (HI-14K, Linco research Inc, St. Charles, USA). To determine blood HbA_{1c} content, 3 mL blood samples were collected in EDTA containing tubes and analyzed by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany).

3. Statistics

Group comparisons were made by a two-tailed Student's *t*-test for unpaired observations. Time-dependent comparisons within subjects were performed using ANOVA for repeated measurements followed by pairwise comparisons with Bonferroni correction when applicable. Correlations between variables were determined by Pearson's correlation coefficient. Statistical comparisons were considered significant when *P* values were <0.05. All statistical calculations were performed using the SPSS 15.0.1.1 software package. HbA_{1c} values are reported in both NGSP (%) and IFCC (mmol/mol) units. Unless otherwise specified, shown results represent means ± SEM or frequencies.

4. Results

4.1. Subjects

Control subjects and type 2 diabetes patients were matched for age (58 ± 1 and 59 ± 1 year), body weight (86.7 ± 3.1 and 89.4 ± 1.5 kg) and BMI (27.3 ± 0.9 and 28.8 ± 0.4 kg/m^2, respectively; Table 1). HbA_{1c} values were significantly higher in the type 2 diabetes patients (7.5 ± 0.1% [58 ± 1 mmol/mol]) when compared with the control subjects (5.6 ± 0.1% [38 ± 1 mmol/mol]), respectively; $P < 0.001$). In addition, fasting plasma glucose concentrations were significantly higher in the type 2 diabetes patients when compared with the healthy controls

Table 1 – Subjects' characteristics.

Groups	Control	Type 2 diabetes	*P* value
n	24	60	NA
Age, year	58 ± 1	59 ± 1	0.22
Type 2 diabetes diagnosis, year	NA	7 ± 1	NA
Weight, kg	86.7 ± 3.1	89.4 ± 1.5	0.37
Height, m	1.78 ± 0.01	1.76 ± 0.01	0.12
BMI, kg/m^2	27.3 ± 0.9	28.8 ± 0.4	0.13
FPG[b], mmol/L	5.6 ± 0.1	10.0 ± 0.3	<0.001
Glucose OGTT 120 [b], mmol/L	4.8 ± 0.2[a]	17.4 ± 0.6[a]	<0.001
HbA_{1c}, %	5.6 ± 0.1	7.5 ± 0.1	<0.001
HbA_{1c}, mmol/mol	38 ± 1	58 ± 1	<0.001
FPI [b], mU/L	14.2 ± 1.6	17.0 ± 1.3	0.20
Insulin OGTT 120 [b], mU/L	45.2 ± 10.5[a]	43.8 ± 4.0[a]	0.87
HOMA-β% index[b]	115 ± 10	50 ± 3	<0.001
HOMA-S% index[b]	68 ± 6	49 ± 3	<0.001
OGIS index[b]	396 ± 10	264 ± 6	<0.001
Oral glucose lowering medication, No.	NA	57	NA
Metformin + SUD and/or TZD, No.	NA	30	NA
Metformin only, No.	NA	21	NA
SUD only, No.	NA	5	NA
TZD only, No.	NA	1	NA

Plus–minus data are expressed as means ± SEM.

[a] Significant difference between fasting and postchallenge value ($P < 0.001$).

[b] In the type 2 diabetes patients, glucose, insulin, HOMA and OGIS index were determined from an OGTT performed after 2 days of discontinuation of habitual use of oral blood glucose lowering medication.

($P < 0.001$). Both HOMA-IR and OGIS indicated a higher degree of insulin resistance in the type 2 diabetes patients when compared with the control group ($P < 0.001$).

4.2. Blood glucose concentrations

The 24 h glycemic profiles recorded in both the type 2 diabetes patients and healthy controls are illustrated in Fig. 1. Average blood glucose concentrations throughout the 24 h period were substantially higher in the type 2 diabetes patients compared with the control subjects and averaged 9.5 ± 0.3 and 6.3 ± 0.2 mmol/L, respectively ($P < 0.001$; Table 2). Even the diabetes patients with an HbA_{1c} level below 7.0% (53 mmol/mol; $n = 20$) showed average daily glucose concentrations that were still markedly higher when compared with the normal glucose tolerant control group (8.4 ± 0.4 and 6.3 ± 0.2 mmol/L, respectively; $P < 0.001$). Hyperglycemic glucose excursions following breakfast and lunch were largely responsible for the higher average glucose concentration during daytime (9.5 ± 0.3 mmol/L) vs. nocturnal glucose concentrations (8.9 ± 0.3 mmol/L).

Table 2 – Prevalence of hyperglycemia and glucose concentrations.

	Control ($n = 24$)	Type 2 diabetes ($n = 60$)	P value
Prevalence of hyperglycemia calculated over 3 periods, h:mm			
24 h period	0:46 ± 0:12	9:10 ± 0:52	<0.001
Daytime	0:42 ± 0:12	7:22 ± 0:39	<0.001
Nocturnal	0:04 ± 0:02	1:48 ± 0:19	<0.001
Prevalence of hypoglycemia calculated over 3 period, h:mm			
24 h period	2:02 ± 0:50	0:22 ± 0:08	0.057
Daytime	1:10 ± 0:30	0:18 ± 0:07	0.105
Nocturnal	0:52 ± 0:21	0:04 ± 0:02	0.032
Mean glucose concentrations calculated over 3 periods, mmol/L			
24 h period	6.3 ± 0.2	9.5 ± 0.3	<0.001
Daytime	6.3 ± 0.2	9.7 ± 0.3	<0.001
Nocturnal	6.4 ± 0.3	8.9 ± 0.4	<0.001

Data are expressed as means ± SEM. The prevalence of hyperglycemia and hypoglycemia are defined as total time glucose concentrations were > 10 mmol/L and < 3.9 mmol/L, respectively. Daytime period is calculated over an 18 h period (06:00 until 00:00). Nocturnal period is calculated over a 6 h period (00:00 until 06:00).

4.3. Prevalence of hyperglycemia

Type 2 diabetes patients experienced hyperglycemia for as much as $38 \pm 4\%$ of the day, representing a total duration of $9:10 \pm 0:54$ h:mm per 24 h (Fig. 2A). In contrast, hyperglycemia was negligible in the healthy control group ($3 \pm 1\%$). In the diabetes patients with an HbA_{1c} content below 7.0% (53 mmol/mol; $n = 20$) hyperglycemia was present $24 \pm 5\%$ of the day ($5:50 \pm 1:06$ h:mm), which was markedly higher compared with the control group ($P < 0.001$) (Fig. 2B). As shown in Fig. 1, hyperglycemia following breakfast and lunch markedly contributed to the greater prevalence of hyperglycemia during daytime ($7:22 \pm 0:39$ h:mm) when compared with nocturnal hyperglycemia ($1:48 \pm 0:19$ h:mm; Table 2).

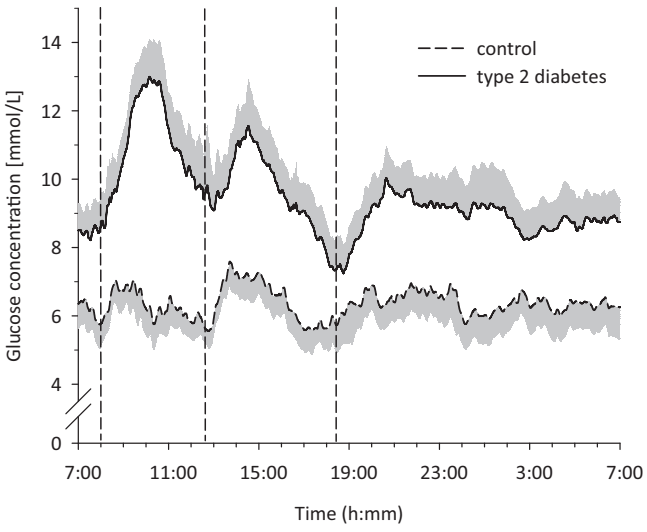

Fig. 1 – Average glucose concentrations over time in type 2 diabetes patients ($n = 60$; average 24 h glucose concentration 9.5 ± 0.3 mmol/L) and healthy, normoglycemic, control subjects ($n = 24$; average 24 h glucose concentration 6.3 ± 0.2 mmol/L) under standardized dietary, but otherwise free living conditions. The upper and lower margins of the 95% CI are indicated by the grey areas. Consumption of the main meals is indicated by the vertical dashed lines.

4.4. Prevalence of hypoglycemia

Blood glucose levels below 3.9 mmol/L were regularly observed during the day in normal glucose tolerant subjects ($2:02 \pm 0:50$; Table 2). In comparison, hypoglycemia was negligible in type 2 diabetes patients ($0:22 \pm 0:08$, $P = 0.056$). There was no difference in the prevalence of hypoglycemia between diabetes patients treated with insulin secretagogues (i.e. SUDs) ($0:14 \pm 0:07$) and those treated with other blood glucose lowering medication or diet only ($0:32 \pm 0:07$, $P = 0.271$).

4.5. Relationship between HbA_{1c} and daily glycemic control

Overall, average 24 h blood glucose concentrations correlated well with HbA1 levels ($r = 0.73$, $P < 0.001$). When calculated for the diabetes and control group separately, the correlations were $r = 0.55$ ($P < 0.001$) and $r = 0.35$ ($P = 0.097$), respectively. In agreement, the daily prevalence of hyperglycemia correlated well with HbA_{1c} levels ($r = 0.72$; $P < 0.001$), whereas the correlations for both groups separately were $r = 0.57$ ($P < 0.001$) and $r = 0.05$ ($P = 0.796$), respectively.

4.6. Relationship between hyperglycemia and insulin sensitivity parameters

For the entire population, the prevalence of hyperglycemia correlated well with HOMA-β% ($r = -0.55$, $P < 0.001$) and OGIS ($r = -0.63$, $P < 0.001$), but not with HOMA-S% ($r = -0.13$, $P = 0.241$). In the diabetes patients only, daily hyperglycemia was related to HOMA-β% ($r = -0.45$, $P < 0.001$) and OGIS ($r = -0.44$, $P < 0.001$), but not to HOMA-S% ($r = -0.12$,

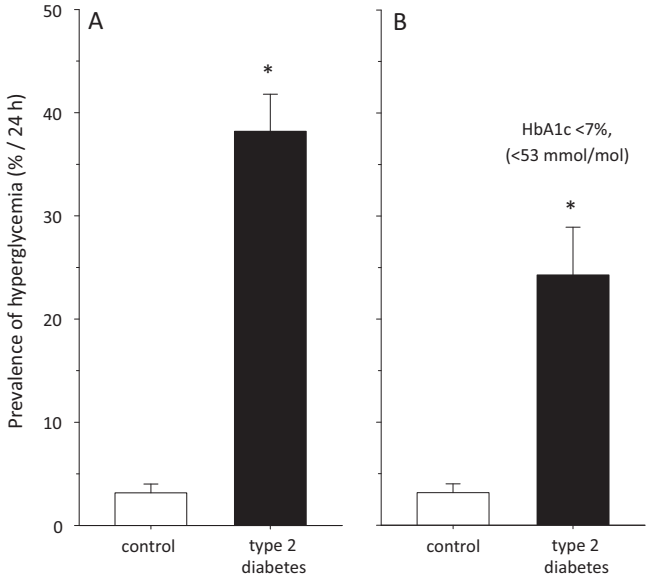

Fig. 2 – A: Daily prevalence of hyperglycemia (expressed as a percentage of the day that blood glucose concentrations exceed 10 mmol/L) in type 2 diabetes patients (n = 60, HbA_{1c} 7.5 ± 0.1% [58 ± 1 mmol/mol]) compared with healthy, normoglycemic controls. B: Daily prevalence of hyperglycemia (expressed as a percentage of the day that blood glucose concentrations exceed 10 mmol/L) in well-controlled type 2 diabetes patients (n = 20, HbA_{1c} <7.0% [<53 mmol/mol]) compared with healthy, normoglycemic controls.

$P = 0.352$). In the control group, no significant correlations were observed between hyperglycemia and HOMA or OGIS.

5. Discussion

The present study shows that hyperglycemia is highly prevalent throughout the day in relatively well-controlled type 2 diabetes patients receiving standard medical care. Type 2 diabetes patients experienced hyperglycemia more than 9 h per day (over 24 h), assessed under strict dietary standardization but otherwise free living conditions. Even those diabetes patients with apparent good glycemic control (HbA_{1c} below 7.0% [53 mmol/mol]) experienced excessive postprandial hyperglycemia for nearly 6 h per day.

To improve our insight in the glycemic abnormalities experienced by type 2 diabetes patients under normal free living conditions, we assessed 24 h glycemic profiles in 60 type 2 diabetes patients and 24 healthy control subjects under strict dietary standardization, but otherwise free living conditions (Fig. 1). Despite the fact that the type 2 diabetes patients were provided with a healthy diet based on their individual energy requirements, and continued their use of oral blood glucose lowering medication, hyperglycemia was experienced throughout a remarkably large part of the day. In fact, hyperglycemia was present for almost 40% of the entire 24 h period, representing more than 9 h per day (Fig. 2A). In contrast, hyperglycemia was nearly non-existing in the healthy, normal glucose tolerant control group. Furthermore, it should be noted that the presented data on the prevalence of hyperglycemia in the type 2 diabetes patients actually represent an underestimate of the severity of the problem. The prevalence of hyperglycemia would have been even more pronounced under (normal) conditions where habitual diet is generally less balanced, with energy intake exceeding energy expenditure. Remarkably, even when selecting patients with HbA_{1c} content below 7.0% (53 mmol/mol; n = 20), patients still experienced hyperglycemia nearly 6 h per day (Fig. 2B). This observation shows that HbA_{1c} values below 7.0% (53 mmol/mol) do not preclude the prevalence of excessive hyperglycemia throughout the day, irrespective of the strong correlation that was observed between HbA_{1c} level and the daily duration of hyperglycemic events ($r = 0.72$; $P < 0.001$).

The 24 h glycemic profiles of the type 2 diabetes patients clearly show that hyperglycemia is primarily experienced during postprandial conditions (Fig. 1). Despite the abundant postprandial hyperglycemia experienced by type 2 diabetes patients, postprandial blood glucose control is currently a secondary target, when initial treatment fails to achieve target HbA_{1c} levels. The ADA and EASD guidelines explicitly state that blood glucose management should focus on postprandial hyperglycemia when HbA_{1c} targets are not accomplished [9,11]. However, the present study shows that even well-controlled type 2 diabetes patients, achieving HbA_{1c} target values of below 7.0% (53 mmol/mol), experience substantial levels of hyperglycemia throughout the day. Since postprandial hyperglycemia significantly contributes to all-over glycemic control, particularly in type 2 diabetes patients with good HbA_{1c} levels [4,5], blood glucose management in type 2 diabetes treatment should focus more on postprandial blood glucose homeostasis independent of measured HbA_{1c} values.

In line with previous observations [20,21], the present study provides evidence that excessive hyperglycemia is most pronounced during the morning following breakfast. This observation has previously been described as the ‘‘extended dawn phenomenon’’ [21] and is likely attributable to an

elevated hepatic glucose output in the early morning [22,23], leading to an uncontrolled rise in blood glucose following breakfast. Standard treatment schemes with conventional oral blood glucose lowering medication appear to have insufficient therapeutic strength to normalize such postprandial glucose increments. Targeted interventions with an appropriate selection of therapeutic agents are warranted to reduce postprandial hyperglycemia. The pharmaceutical agents of interest include α-glucosidase inhibitors, glinides, exogenous insulin, and incretin-based therapies [10]. However, given the recent debate on the safety and effectiveness of intensive glycemic treatment with glucose lowering medication [24], additional non-pharmacological approaches should be advocated as well. In this regard, both dietary [25,26] as exercise interventions [27,28] have proven most successful to substantially reduce the prevalence of hyperglycemia throughout the day.

In conclusion, postprandial hyperglycemia is a severely underestimated problem in type 2 diabetes treatment. Even well-controlled type 2 diabetes patients receiving standard medical care experience excessive hyperglycemia (glucose levels exceeding 10 mmol/L) throughout a substantial part of the day. Obviously, standard medical care with conventional oral blood glucose lowering medication or HbA_{1c} levels below 7.0% (53 mmol/mol) do not preclude the prevalence of excessive postprandial glucose excursions. More effective pharmaceutical, nutrition and exercise intervention strategies should be defined to further improve glycemic control in type 2 diabetes patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

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