Extra-Virgin Olive Oil Reduces Glycemic Response to a High–Glycemic Index Meal in Patients With Type 1 Diabetes: A Randomized Controlled Trial

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OBJECTIVE

To evaluate whether fat quality, in the context of meals with high– (HGI) or low–glycemic index (LGI), influences postprandial blood glucose (PPG) response in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

According to a randomized crossover design, 13 patients with type 1 diabetes on insulin pump consumed two series (HGI or LGI) of meals with the same carbohydrate quantity while differing for amount and quality of fat: *1*) low in fat ("low fat"), *2*) high in saturated fat (butter), or *3*) high in monounsaturated fat (extra-virgin olive oil) (EVOO). Premeal insulin doses were based on insulin–to–glycemic load ratios. Continuous glucose monitoring was performed and 6-h PPG evaluated.

RESULTS

PPG was significantly different between HGI and LGI meals ($P = 0.005$ for time × glycemic index interaction by repeated-measures analysis [RMA]), being significantly higher during the first 3 h after the HGI meals with a later tendency to an opposite pattern. In the context of HGI meals, PPG was significantly lower after EVOO than after low fat or butter ($P < 0.0001$ for time × meal interaction by RMA), with a marked difference in the 0- to 3-h glucose incremental area under the curve between EVOO (mean ± SD 198 ± 274 mmol/L × 180 min) and either low fat (416 ± 329) or butter (398 ± 355) ($P < 0.05$). No significant differences were observed in PPG between the three LGI meals.

CONCLUSIONS

Carbohydrate quality of a mixed meal influences shape and extent of PPG. Besides, using EVOO in a HGI meal attenuates the early postprandial glucose response observed when this meal is consumed with either low fat or butter. Therefore, an optimal prandial insulin administration would require considering, in addition to the quantity of carbohydrates, the quality of both carbohydrate and fat.

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A slide set summarizing this article is available online.

Postprandial glycemic response is an important determinant of blood glucose control in type 1 diabetes. The carbohydrate content of the meal is considered the main dietary factor influencing postprandial glycemia; accordingly, current guidelines recommend calculating premeal insulin doses based on the amount of carbohydrate of the meal (1). However, carbohydrate counting may not result in optimal blood glucose control despite the best efforts of the patients, and this may depend on different factors (2).

First of all, the type of foods used, as reflected by their fiber content and/or glycemic index, influences the postprandial glycemic response (3,4). We recently observed in a real-life setting that calculating premeal insulin doses on the basis of the glycemic load—i.e., taking into account both quality and quantity of carbohydrates—improves daily blood glucose profile compared with considering only the quantity of carbohydrates (5).

Moreover, patients with diabetes eat not carbohydrates alone but meals containing, beside carbohydrates, other macronutrients that may also influence the glycemic response. There is growing evidence that the amount of fat in the meal influences the postprandial glycemic response determining a higher and more prolonged increase in blood glucose levels than carbohydrates alone (6–11). In particular, Wolpert et al. (11) showed, in a closed-loop study, that dietary fat acutely increased blood glucose concentrations and insulin requirements in patients with type 1 diabetes. According to the above results, alternative/additive methods for determining prandial insulin doses have been proposed (12,13). However, the observation that fat induces higher postprandial glycemia seems to be at odds with the notion that fat delays gastric emptying, and therefore it is expected to decrease the early postprandial glucose response; moreover, some foods rich in carbohydrate have a lower glycemic index when enriched with fat (14). Within this context, a role in modulating postprandial glycemic response may be envisaged also for fat quality, as has been shown for carbohydrate foods. There are indications that saturated fatty acids worsen postprandial insulin sensitivity and slow down gastric emptying, while monounsaturated fatty acids (MUFAs) improve postprandial insulin sensitivity and stimulate glucagon-like pepide 1 secretion; this would explain possible opposite effects of saturated and monounsaturated fat on postprandial blood glucose response (15–19).

Against this background, the aim of this study was to test the hypothesis that both the type of dietary fat and the glycemic index of the meal may affect postprandial glycemic response. Since the impact of dietary fat may vary according to whether it is consumed in the context of meals with high or low glycemic index, this was also considered in the study design. The interaction between quality of fat and glycemic index of carbohydrate foods may have clinical implication for the calculation of the prandial insulin dose in patients with type 1 diabetes; therefore, the study was undertaken in this group of patients.

RESEARCH DESIGN AND METHODS

Thirteen patients with type 1 diabetes (8 women and 5 men) were recruited at the diabetes care unit of the University of Naples Federico II teaching hospital and were enrolled in the study after giving written informed consent. Inclusion criteria were treatment with continuous subcutaneous insulin infusion, use of fast-acting insulin analogs (aspart, lispro, glulisine) for at least 6 months, and an HbA_{1c} <8.0% (64 mmol/mol). Exclusion criteria were pregnancy, celiac disease, serious microvascular and macrovascular diabetes complications including autonomic neuropathy possibly influencing gastric emptying, and any other chronic or acute disease apart from diabetes seriously affecting health status.

Patients meeting the inclusion criteria and showing a level of compliance adequate to the purpose were asked to participate in the study at their regular outpatient follow-up. The study design requirements were discussed for participation feasibility, especially concerning work schedules and recreational habits.

The study protocol was approved by the University of Naples Federico II Ethics Committee and registered at ClinicalTrials.gov (NCT02330939).

Study Design

The intervention was preceded by a 1-week run-in period during which participants underwent continuous glucose monitoring (CGM) and filled in a 7-day dietary record to optimize basal infusion rate and insulin–to–glycemic load ratio. Then, according to a randomized crossover design, participants were assigned by coin toss to a 1-week period wherein they consumed either three meals with high–glycemic index (HGI) or three meals with low–glycemic index (LGI), thereafter crossing over to the alternate series for one additional week. For each series, the sequence of meals was randomly assigned by card drawing (Supplementary Fig. 1).

In each series (HGI or LGI), meals were similar for total carbohydrate content but were different for amount and type of fat: *1*) low in fat ("low fat"), *2*) high in saturated fat (butter), or 3) high in monounsaturated fat (extra-virgin olive oil) (EVOO) (Table 1). Over the two experimental weeks, participants underwent CGM, wearing their sensors 7 days/week. They were instructed to calibrate three times per day using premeal blood glucose capillary tests. The test meals were performed between the 2nd and the 7th day of sensor life. The participants also checked capillary blood glucose 2, 4, and 6 h after test meals.

The test meals were prepared under the supervision of an expert dietitian, frozen, and then given to the patients, who kept them frozen until use. Strict instructions were given on how to defrost meals, with attentive standardization to reheating, avoiding the procedures more likely to alter the physical structure of foods (e.g., microwave) (20).

The participants consumed the test meals at lunchtime. According to the randomized crossover design (Supplementary Fig. 1), the 3 days per week were chosen on the basis of the subjects' work and recreational activities in order to keep these activities reproducible and compatible with the study design. The same procedures were followed on both experimental weeks, the HGI week and the LGI week, respectively. In case of premeal blood glucose levels outside the 5–8 mmol/L range or a rapid decrease/increase (3.3 mmol/L) of glucose levels during the last 60 min according to CGM measurement, the test meal was postponed. In the mornings preceding the test meals, patients consumed the same light breakfast in order to avoid a

Table 1—Energy content and macronutrient composition of the test meals

	HGI meals			LGI meals		
	EVOO	Butter	Low fat	EVOO	Butter	Low fat
Energy (kcal)	988	982	721	987	996	726
Carbohydrates (g)	131	131	130	130	131	131
Total fat (g)	40.5	39.4	10.6	39.8	40.4	10.8
SFA (g)	6.5	22.1	2.2	5.9	22.6	1.7
MUFA (g)	27.9	11.1	6.0	27.6	11.2	6.4
PUFA (g)	3.7	2.2	1.5	4.0	2.4	1.8
Protein (g)	33.9	34.2	33.9	35.1	35.4	35.1
Fiber (g)	7.7	7.8	8.4	20.8	20.8	20.8
Glycemic index (%)	65.5	65.5	66.2	41.1	41.1	41.1

PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

second-meal effect bias; moreover, they were asked to avoid strenuous physical activity on the day before and on the morning of the test meal and to refrain from any light/moderate physical activity or stressful unusual situations over 6 h after the meal. For improvement of protocol compliance, the participants received frequent call phones from study investigators, in particular before and over the 6 h after meal ingestion.

Premeal insulin doses, injected just before eating, were based on the individual insulin–to–glycemic load ratio determined during patients' educational sessions with the study team. Therefore, for each patient, insulin doses were the same for each series, i.e., before the butter, EVOO, or low-fat meals, but differed between the two series, i.e., before the HGI and LGI meals.

Test Meal Composition

The EVOO and butter test meals were similar in energy content; conversely, the low-fat test meal had a lower energy content, due exclusively to the lower content of fat (Table 1). While macronutrient composition was similar with respect to the amount of carbohydrate and protein in all test meals, a substantial difference in glycemic index (~25 units) and dietary fiber (~13 g) was present between the HGI and the LGI meals. On the other hand, irrespective of whether the meals were HGI or LGI, the amounts of total fat and that of saturated or monounsaturated fat were markedly different in the butter, EVOO, and low-fat test meals (Table 1).

The meals with a HGI were composed of white rice (60 g), white bread (75 g), beef minced meat (90 g), and banana (180 g), plus butter (43 g) or EVOO (37 g), with 8 g EVOO in the low-fat test meal. The meals with a LGI were composed of pasta (50 g), lentils (100 g), whole-meal bread (30 g), ham (15 g), and apple (185 g), plus butter (45 g) or EVOO (37 g), with 8 g EVOO in the low-fat test meal. The whole content of butter and EVOO was added to the meals before freezing. Apples and bananas were given fresh to the participants, who were instructed to weigh the recommended portion after peeling the fruit.

Measurements

Glucose monitoring was performed by Medtronic Enlite Sensor (n = 8 participants) and Dexcom G4 sensor (n = 5 participants). At the end of the experimental period, data from CGM and insulin pump were downloaded by dedicated informatics platforms. Participants used the CGM system integrated with their insulin pump, i.e., the one they were accustomed to. Therefore, the possible bias of differences in accuracy between the two types of CGM platforms was overcome by the crossover design that implied only within-subject comparisons.

Postprandial blood glucose incremental areas were calculated by the trapezoidal method as the area under the curve above the baseline value (iAUC). Blood glucose peak was calculated as the maximal blood glucose excursion from the fasting value over the 6-h postprandial period. Time to blood glucose peak was calculated as the time at which the maximal blood glucose excursion was observed.

To account for the few hypoglycemic events (blood glucose value $<$3.9 mmol/L) observed (LGI: EVOO = 0, butter = 1, and low fat = 2; HGI: EVOO = 2, butter = 0, and low fat = 3), we used the last sensor value before treating hypoglycemia for the calculation of iAUC and blood glucose profile.

Because of technical problems in CGM readings in one participant during the HGI meal week, data on postprandial glycemia after HGI meals were available only for 12 participants.

Sample Size

The sample size (13 patients) was calculated on the primary outcome, i.e., postprandial blood glucose iAUC. Since no data are available on the size effect of quality of fat on postprandial glycemia in patients with type 1 diabetes, we assumed that this effect would be comparable with the one observed with meals, differing only for the types of carbohydrate foods used. Therefore, our sample size was adequate to detect a 358 mmol/L $\times$ 180 min difference in postprandial blood glucose iAUC; this value corresponds to the difference in the postprandial blood glucose iAUC, with an SD of 396 mmol/L, previously observed in people with type 1 diabetes consuming two test meals differing only for glycemic index (3). This sample size would allow detection of a difference of this magnitude in the postprandial blood glucose response with an 80% power and a 5% significance level.

Statistical Analysis

Data are expressed as mean $\pm$ SD unless otherwise stated. The primary outcome was the postprandial blood glucose iAUC. The secondary outcomes were blood glucose peak and time to blood glucose peak.

In each series, i.e., LGI and HGI series, both primary and secondary outcomes were evaluated by general linear model for repeated-measures ANOVA in which outcomes were included as dependent variables and *1*) low-fat, butter, and EVOO meals or *2*) HGI and LGI meals were included as levels of the within-subjects factors test meal and glycemic index, respectively.

Differences in postprandial blood glucose profiles were evaluated by two within-subject factor repeated-measures ANOVA: *1*) postprandial glucose values

measured each 5 min over 6 hours by CGM were included as levels of the within-subject factor time and *2*) low-fat, butter, and EVOO meals or HGI and LGI were included as levels of the within-subject factors test meal and glycemic index, respectively.

Statistical analysis was performed according to standard methods using SPSS 21.0 (SPSS/PC; SPSS, Chicago, IL).

RESULTS

Participants' Characteristics

The study participants were mean ± SD 38 ± 11 years old and had a BMI of 24.8 ± 2.9 kg/m^2. The diabetes duration was 25 ± 3 years, and they had acceptable blood glucose control (HbA_{1c} 7.5 ± 1.0% [57 ± 13 mmol/mol]). Their total daily insulin dose was 41.1 ± 10.7 IU. One participant had background retinopathy, and two participants had background retinopathy and peripheral neuropathy.

Meal Insulin Dose

As determined on the basis of the individual insulin–to–glycemic load ratios, insulin doses administered before the LGI meals were significantly lower than before the HGI meals (8.3 ± 2.0 vs. 12.6 ± 3.5 IU, $P < 0.0001$).

Postprandial Glycemia

Effects of Glycemic Index

The 6-h postprandial glucose profile was significantly different between HGI meals and LGI meals ($P = 0.005$ for glycemic index × time interaction by repeated-measures ANOVA) (Fig. 1). This difference was particularly evident in the first 3 h of the postprandial response, with the blood glucose 0–3 h iAUC significantly lower after all combined LGI meals than after all combined HGI meals (112 ± 62 vs. 337 ± 76 mmol/L × 180 min, $P = 0.006$ by repeated-measures ANOVA). No significant difference was observed between HGI and LGI meals in blood glucose iAUC during the late postprandial period (3–6 h) (Fig. 2).

Time to glucose peak was significantly delayed after LGI compared with HGI meals (253 ± 27 vs. 156 ± 26 min, $P = 0.003$ for glycemic index effect by repeated-measures ANOVA). No significant differences were observed in blood glucose peak between LGI and HGI meals (4.7 ± 0.7 vs. 5.3 ± 0.9 mmol/L, $P = 0.491$).

Effects of Fat in LGI Meals

In the context of LGI meals, the quality and the amount of fat did not significantly influence postprandial blood glucose response, as shown by no significant differences between EVOO, butter, and low-fat meals in blood glucose overall profile (Fig. 1) and early (0–3 h) or late (3–6) iAUCs (Fig. 2).

Blood glucose peak and time to glucose peak were also not significantly affected by quality or amount of fat in LGI meals (Table 2).

Effects of Fat in HGI Meals

In the context of the HGI meals, a steep rise of blood glucose levels was observed in the early postprandial period after the meals with butter or low fat; conversely, the meal with EVOO showed a blunted response (Fig. 1). In the late postprandial phase, blood glucose levels returned to fasting values after the low-fat meal, while they remained elevated during the whole postprandial period with the butter meal. These differences in the shape of postprandial blood glucose responses after the three meals were highly statistically significant: $P < 0.0001$ for time × meal interaction by repeated-measures ANOVA.

Accordingly, blood glucose 0–3 h iAUC was significantly lower after the meal with EVOO (198 ± 274 mmol/L × 180 min) than after butter (398 ± 355 mmol/L × 180 min) or low fat content (416 ± 329 mmol/L × 180 min) ($P < 0.05$ for EVOO vs. butter or low-fat meals by repeated-measures ANOVA) (Fig. 2). No significant differences were observed for blood glucose 3–6 h iAUC among the three HGI test meals (Fig. 2).

The blood glucose peak was lower although not statistically significant after the EVOO meal than after butter or low fat ($P = 0.277$) (Table 2). The time to blood glucose peak was significantly

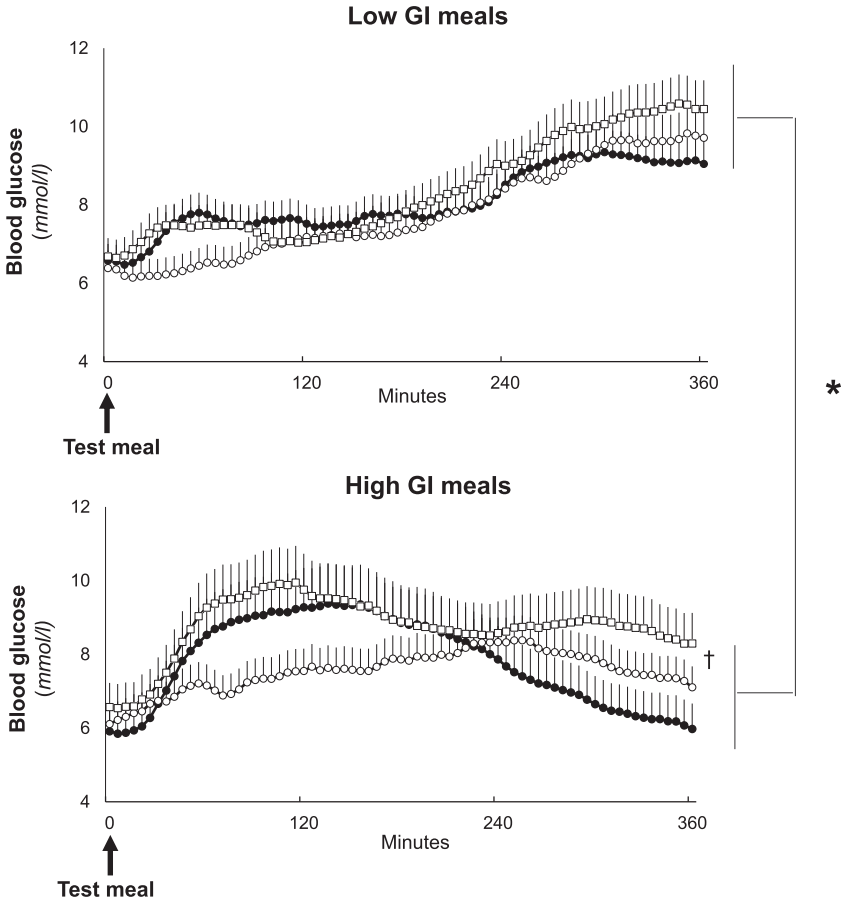

Figure 1—Postprandial blood glucose profiles after the EVOO, butter, and low-fat meals within the context of LGI or HGI meals. Empty circles, EVOO; empty squares, butter; full circles, low fat. *$P = 0.005$ for time × glycemic index interaction by repeated-measures ANOVA; †$P < 0.0001$ for time × meal interaction by repeated-measures ANOVA.

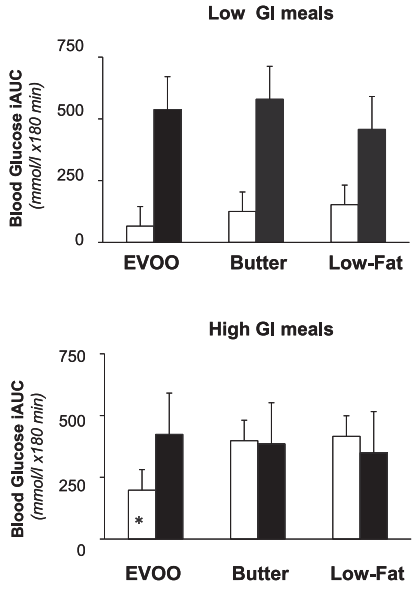

Figure 2—Postprandial blood glucose iAUCs after the EVOO, butter, and low-fat meals within the context of LGI or HGI meals. Empty bars: blood glucose iAUC 0–180 min. Full bars: blood glucose iAUC 180–360 min. *$P < 0.05$ vs. butter and low-fat meals by post hoc analysis of repeated-measures ANOVA. Blood glucose iAUC 0–180 min after all combined LGI vs. all combined HGI meals: $P = 0.006$ by repeated-measures ANOVA.

delayed after the EVOO meal than after butter or low fat ($P = 0.035$) (Table 2).

CONCLUSIONS

This study shows for the first time that the type of fat significantly influences postprandial glycemic response in patients with type 1 diabetes. In particular, our data demonstrate that *1*) the addition of EVOO to a meal with a HGI blunts the early postprandial blood glucose response observed after a similar meal with low fat or butter, *2*) neither the type nor the amount of fat influences the postprandial blood glucose response when the meal has a LGI, and *3*) the glycemic index of the meal significantly influences the shape and the extent of the 6-h postprandial blood glucose profile independently of type and amount of fat added.

In our study, the addition of 37 g EVOO to a HGI meal determined a clinically significant reduction of ~50% in the early postprandial glycemic response compared with similar meals with 43 g butter or very little fat added. Previous research focused on the influence of the amount of fat mainly showed a late postprandial hyperglycemia with dietary fat, with inconsistent findings on early postprandial glucose concentrations, which were reduced in some studies (6). Our study provides the first demonstration that in patients with type 1 diabetes, the type of fat in the meals may have more relevant effects than its quantity, particularly in the early postprandial response. This finding may contribute to explain the previous controversial results on dietary fats effects.

The results of this study have important clinical implications for patients with type 1 diabetes, as they indicate that the combination of the effects of carbohydrate foods and type of fat should be considered for timing and dose of prandial insulin administration. In our study, the addition of different types of fats to meals with a LGI did not influence postprandial blood glucose response, while it did it in the context of meals with a HGI. This finding is in line with previous observations in patients with type 1 (21) and type 2 (22) diabetes. In the first study (21), the addition of EVOO to a LGI meal did not influence postprandial glycemia, while in the study by Gulliford et al. (22) the addition of margarine influenced the postprandial glucose response to a potato meal but not to a spaghetti meal. Therefore, it is very likely that the LGI or high-fiber content of a meal is more important than fat quality in modulating carbohydrate digestion and absorption. Consequently, when the meal is based predominantly on carbohydrate foods that are rich in fiber and have a LGI, in order to decide the premeal insulin dose it may be sufficient to take into account only the glycemic load of the meal. Fat quality should, instead, be taken into consideration when the meal has a HGI.

It is noteworthy that the differences in the early postprandial (2–3 h) blood glucose levels between the LGI and the HGI meals, i.e., lower levels with LGI meals, were observed despite the fact that premeal insulin doses were based on the glycemic load of the meals, and therefore substantially lower insulin doses (>30% less than HGI) were administered before LGI meals. On the other hand, in the late postprandial period, blood glucose values increased after the LGI meals, while they tended to return to baseline after the HGI meals. These findings extend previous knowledge obtained in studies in which the observation time was often limited to 3–4 h after the meal (5,23–25) and draw attention to the limits of the definition of glycemic index that is generally calculated based on the first 2–3 h after meal. Moreover, if confirmed in future studies, these findings might have important clinical implications in relation to the timing of premeal insulin administration concerning the use of different modalities of insulin infusion (23) (e.g., dual-wave bolus) or insulin with different absorption kinetics (24), as well as modulating the amount of insulin injected according to the type of carbohydrate foods of the meal (5).

The beneficial effects of EVOO on postprandial glucose might be due to its high content of unsaturated fat and, in particular, of monounsaturated fat that is the main characteristic of olive oil; in particular, in our study MUFAs were three times higher in the EVOO than butter meals. This is also supported by the favorable glycemic effects shown

Table 2—Blood glucose peak and time to blood glucose peak after the LGI and HGI meals

	LGI			HGI			
	EVOO	Butter	Low fat	EVOO	Butter	Low fat	*P*
Blood glucose peak (mmol/L)*	4.5 ± 1.8	4.8 ± 3.6	4.5 ± 2.8	4.3 ± 0.9	6.1 ± 1.1	5.4 ± 1.2	0.491
Time to blood glucose peak (min)†	261 ± 113	265 ± 111	234 ± 114	190 ± 101‡	133 ± 104	146 ± 81	0.003

Data are mean ± SD. ‡$P < 0.05$ vs. butter or low-fat HGI meals by post hoc analysis of repeated-measures ANOVA; *maximal blood glucose excursion from the fasting value over the 6-h postprandial period; †time of maximal blood glucose excursion.

for the MUFA-rich canola oil (26). The influence of the degree of fat unsaturation on postprandial glucose and insulin responses has been evaluated in healthy people (16,27) and patients with type 2 diabetes (17) with no univocal results, with the inconsistencies mainly related to differences in the experimental design. These studies indicated that different types of dietary fat may influence the hormonal postprandial response related to gastric emptying and glucose metabolism. In particular, there is evidence that MUFAs can stimulate glucagon-like pepide 1 secretion more than saturated fatty acids (15,18,19), possibly influencing gastric emptying rate. This could contribute to explain the observed differences in postprandial responses, being of particular relevance for people with type 1 diabetes in whom the absence of insulin secretion amplifies the importance of other regulatory hormonal processes involved in the postprandial response.

Our study was performed in a real-life setting that did not allow exploration of the possible mechanisms behind the effects of dietary fat on postprandial glycemia in patients with type 1 diabetes. The evidence of a lower postprandial blood glucose response to an EVOO-rich meal and the possible involvement of the gastrointestinal hormonal patterns are of utmost clinical relevance. In fact, not only the quality of fat could be included in the algorithms predicting the premeal insulin needs—at least with HGI meals—but also their recognized effects would support the modulation in addition of counterregulatory hormones, e.g., using multihormonal pumps.

This study has some strengths and weaknesses. Strengths are the novelty of the issue addressed, the randomized controlled study design, and the use of CGM. A possible weakness could have been the real-life setting in which the experiments were conducted, as the meals were consumed at home without a direct surveillance and this may have affected the standardization of experimental procedures. However, there was an intensive communication between participants and study investigators, in particular before and during the test meal. Moreover, the evidence of significant, clear-cut differences also in conditions that may have increased the outcome variability strengthens the reliability of our observations. One more study limitation owing to the home setup was the impossibility of obtaining information on possible mechanisms. A further limit might be the possible lesser relevance of the information on olive oil in countries with gastronomic habits not including this food.

In conclusion, our study demonstrates that the addition of EVOO to a HGI meal attenuates the early postprandial glucose response observed when this meal is consumed with either low fat or butter. Moreover, LGI foods determine a blunted early postprandial response and a late rise of blood glucose levels, independently of type and quantity of fat added. Therefore, an optimal prandial insulin administration in type 1 diabetes would require considering the quality of both carbohydrate foods and fat. This result has relevant clinical implications, since limiting blood glucose fluctuations has a beneficial impact on quality of life of the patients and contributes to prevention of chronic and acute diabetes complications. Moreover, the beneficial effects of using EVOO also on postprandial glycemia represent a further motivation to prefer monounsaturated to saturated fat in order to preserve cardiovascular health in patients with type 1 diabetes. The mechanisms behind the effects of EVOO on postprandial glucose metabolism as well as the separate impact of fat quality and other functional molecules present in this food (i.e., polyphenols) should be investigated.

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