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Original article

Gastrointestinal effects of extra-virgin olive oil associated with lower postprandial glycemia in type 1 diabetes

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SUMMARY

Objective: To explore the possible mechanisms behind the lower glycemic response observed when extra-virgin olive oil (EVOO) is added to a high-glycemic index meal in patients with type 1 diabetes (T1D).

Research design and methods: According to a randomized cross-over design, eleven T1D patients (6 women, 5 men) on insulin pump consumed in the metabolic ward, one week apart, three high-glycemic index meals differing only for amount and quality of fat: high-monounsaturated fat (EVOO), high-saturated fat (Butter), and low-fat (LF). Before and after the meals, blood glucose (continuous glucose monitoring), gastric emptying rate (ultrasound technique), and plasma concentrations of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide GIP (ELISA), glucagon (RIA), and lipids (colorimetric assays) were evaluated.

Results: Blood glucose iAUC (mmol/lx360 min) was lower after the EVOO (690 ± 431) than after the Butter (1320 ± 600) and LF meals (1007 ± 990) (M ± SD, $p = 0.041$ by repeated measures ANOVA). Gastric antrum volume was significantly larger in the early (60–90 min) postprandial phase (106 ± 21 *vs.* 90 ± 16 ml, $p = 0.048$) and significantly smaller in the late phase (330–360 min) (46 ± 10 *vs.* 57 ± 22 ml, $p = 0.045$) after the EVOO than after Butter meal. EVOO significantly increased postprandial GLP-1 iAUC (261 ± 311) compared to Butter (189 ± 349) (pmol/Lx180 min, $p = 0.009$). Postprandial GIP and glucagon responses were not significantly different between EVOO and Butter. Postprandial triglyceride iAUC was significantly higher after EVOO (100 ± 53) than after Butter (65 ± 60) (mmol/l × 360 min, $p = 0.048$).

Conclusions: Changes in gastric emptying and GLP-1 secretion and reduced glucose absorption through glucose-lipid competition may contribute to lower glycemia after a high-glycemic index meal with EVOO in T1D patients.

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1. Introduction

Adding extra-virgin olive oil (EVOO) to a high glycemic index meal attenuates the postprandial glucose response observed when the meal is consumed with butter or very small amounts of fat, as previously shown in a controlled study in real life conditions, in patients with type 1 diabetes on insulin pump [1]. How EVOO influences postprandial glycemia is unknown. The main pathophysiological regulators of postprandial glucose response may be

Abbreviations: CGM, continuous glucose monitoring; EVOO, extra-virgin olive oil; GE, gastric emptying; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; LF, low-fat; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; T1D, type 1 diabetes.

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involved, including changes in gastric emptying rate and gastrointestinal hormones [2].

Gastric emptying (GE) is a major determinant of postprandial glycemia and is finely regulated by the characteristics of the meal. In particular, the amount of fat in a meal is able to slow down gastric emptying rate in healthy individuals [3] and in people with type 1 diabetes [4]. As to the quality of fat, monounsaturated fatty acids (MUFA) have been shown to slow down GE more than n-3 polyunsaturated (PUFA), n-6 PUFA, and saturated fatty acids (SFA) in healthy people [5].

The quality of meal fat could influence gastric emptying through changes in postprandial secretion of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In particular, MUFA seem to enhance GLP-1 secretion more than SFA in both healthy people [6] and in patients with type 2 diabetes [7–9], while GIP secretion seems to be increased by SFA and reduced by fish oil compared to other types of fat in healthy people [10,11]. GLP-1 could influence postprandial glucose response in people with type 1 diabetes also independently of its effects on gastric emptying, by exerting its glucagonostatic effects [12].

Another mechanism through which different types of fat could influence postprandial glycemia is by eliciting a different postprandial lipemic response, since postprandial lipid and glucose metabolism are reciprocally influenced and regulated [13].

Therefore, the aim of the present study was to explore the possible mechanisms for the reduced postprandial glucose response to a high glycemic index meal enriched with EVOO observed in our previous home-based study. For this purpose, we performed a new controlled study in the metabolic ward of our Unit, involving patients with type 1 diabetes on insulin pump, to evaluate the effects of different dietary fats on postprandial blood glucose, gastric emptying and plasma levels of gastrointestinal hormones and lipids.

2. Material and methods

Fourteen patients with type 1 diabetes (8 women and 6 men) were recruited at the outpatient diabetes clinic of the Federico II University Teaching Hospital (Naples, Italy). They were enrolled in the study after giving their written informed consent. Inclusion criteria were treatment with continuous subcutaneous insulin infusion for at least 6 months and an HbA1c less than 8.0% (64 mmol/mol). Exclusion criteria were pregnancy, celiac disease, severe microvascular and macrovascular diabetes complications including autonomic neuropathy possibly influencing gastric emptying, and any other chronic or acute disease seriously affecting health status.

Patients meeting the inclusion criteria were asked to participate in the study at their regular outpatient follow-up visits. One subject was excluded from the final analysis because of a hypoglycemic event during a test meal, and two subjects because of poor compliance to the study design. Therefore, the analyses were performed on 11 participants. The study protocol was approved by the Federico II University Ethics Committee and registered at Clinical Trials.gov, registration number: NCT02330939.

2.1. Study design

Before the intervention, patients underwent a one-week run-in period on continuous glucose monitoring (CGM), and were asked to complete a seven-day dietary record. The run-in aimed at optimizing basal infusion rate and insulin prandial dose calculation by insulin/glycemic load ratio, determined as previously described [14]. After run-in, according to a triple crossover design, participants consumed one of three experimental meals, alternating, at one-week intervals, in a random sequence determined by card drawing. The three meals had a similar carbohydrate content but different amounts and type of fat: 1) high-monounsaturated fat (EVOO), 37 g, 2) high-saturated fat (Butter), 43 g, and 3) low-fat (LF), 8 g EVOO.

The participants came to the metabolic ward in the late morning and consumed the test meals at lunchtime under the supervision of an expert dietitian. The test meals had been previously prepared in a metabolic kitchen and kept frozen until the test day, when they were defrosted and reheated on the cooker. The patients consumed the meals and drank 250 ml of water within 15 min.

In case of pre-meal blood glucose levels outside the 5–8 mmol/l range or a rapid decrease/increase of glucose levels (<3.0 mmol/l) during the previous 60 min according to CGM measurement, the test meal was postponed to the next week. On the three experimental days, the participants were asked to consume at home, no later than 7.00, the same light breakfast. They were asked to avoid strenuous physical activity on the day before and on the morning of the test meal, and to refrain from snacking or making insulin boluses or changes in insulin basal rate over the 6 h prior to the test meals. In female participants, the experiments were not performed during menses. After meals, the subjects were asked to remain in the upright position or sitting over 6 h, either reading, chatting, or watching TV. Pre-meal insulin doses, injected just before eating, were based on individual insulin/glycemic load ratio determined during the patients' educational sessions with the study team [14]. For each subject, the same insulin dose was administered before each of the three experimental meals. No changes from habitual insulin basal rate were made during the 6-h postprandial phase and between the three different test meals.

Over the whole experimental period, participants underwent CGM. Moreover, on the test days, before and over the 6 h following the meals, participants underwent gastric ultrasound for the evaluation of gastric emptying rate and venous blood sampling for the measurement of GLP-1, GIP, glucagon, and concentrations of plasma lipids.

2.2. Test meals composition

The meals consisted of white rice (60 g), white bread (75 g), minced beef (90 g), and banana (180 g) prepared with EVOO (37 g) in the EVOO meal, butter (43 g) in the Butter meal, and EVOO (8 g) in the Low-fat meal. The whole content of Butter and EVOO was added to the meals before freezing. Energy content and total amount of fat were similar for the EVOO (988 kcal; 40.5 g) and Butter meals (982 kcal; 39.4 g); conversely, the Low-fat meal had a lower energy content (721 kcal), due exclusively to the lower content of fat (10.6 g). While macronutrient composition was similar for amount of carbohydrate (130 g) and protein (34 g) in all test meals, there was a substantial difference for saturated and monounsaturated fat between the EVOO (6.5 g and 27.9 g), Butter (22.1 g and 11.1 g), and Low-fat (2.2 g and 6.6 g) meals, respectively. The small amount of fat in the Low-fat meal was necessary to allow the preparation of a meal with a similar food composition as the two fat-rich meals.

2.3. Continuous glucose monitoring

Glucose monitoring was performed using the Enlite™ Sensor Medtronic (n = 7 participants) or the Dexcom G4® (n = 4 participants) systems. 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, as it was the one they were accustomed to.

2.4. Gastric emptying rate

Gastric emptying rate was evaluated using a MINDRAY M7 digital echographer with a convex-array scan (range 2–6 MHz). Ultrasonographic scanning was done at the final portion of the stomach (antrum and pylorus) where constant viewing makes volume measurement simpler. Scanning was performed with the subjects standing up to favor air flow towards the fundus of the stomach. In order to calculate antral volume, three sagittal scans were performed to measure anteroposterior (*a*, *c* and *e*, respectively) and longitudinal (*b*, *d* and *f*, respectively) diameters. The first scan was taken on the angulus (transitional region between the body of the stomach and the pylorus); the second, at an intermediate level corresponding to the superior mesenteric vein, which is easily detectable; the third, at the level of the pyloric sphincter where the thickness of the muscle wall is visible. Finally, the antral length from the angulus to the pylorus (*h*) was measured with a transversal scan. The volume of the antrum was calculated using the formula by Bolondi et al. [15]: $0.065 \times h \times (2ab + 2ef + 4cd + cb + ad + ed + cf)$. This method has been previously validated against the scintigraphic method [16]. A limitation of the ultrasound technique is that it is unable to differentiate the relative emptying of solid, aqueous, and oil components.

2.5. Laboratory assessment

2.5.1. Plasma gastrointestinal hormones

Blood samples were drawn before and 15, 30, 60, 90, 120, and 180 min after meal for the evaluation of GLP-1, GIP, and plasma levels of glucagon. Blood in EDTA- or EDTA and aprotinin (for the GLP-1 assay) tubes was centrifuged and plasma stored at −80 °C until measurement. Active GLP-1 was assayed by a nonradioactive, highly specific sandwich ELISA (Merck- Millipore, Darmstadt, Germany), which has a 100% cross-reactivity with the active isoforms of GLP-1 (7–36 amide and 7–37 glycine extended) but no reactivity with inactive isoforms (9–36 amide and 9–37 glycine extended), GLP-2 or glucagon [17]. Total GIP was assayed by a nonradioactive, highly specific sandwich ELISA (Merck-Millipore, Darmstadt, Germany) with 100% cross reactivity with human GIP (1–42) and GIP (3–42). The intra- and interassay coefficients of variation of the GLP-1 and GIP assays were <5% and <10%, respectively. Plasma glucagon was assayed by competitive RIA using a rabbit antiserum against a glucagon–albumin conjugate (Euria-Glucagon, Euro-Diagnostica, Malmö, Sweden). Glucagon in standards and samples compete with 125I labeled glucagon in binding to the antibodies in a two-step incubation. Antibody-bound ^{125}I-glucagon is separated from the unbound fraction using double antibody solid phase and measured in a gamma counter. The limit of sensitivity for the glucagon assays was 3 pmol/l. The intra- and interassay coefficients of variation were <10%.

2.5.2. Other measurements

Plasma triglyceride (Roche Molecular Biochemicals, Mannheim, Germany) and FFA (Wako Chemicals GmbH, Neuss, Germany) were measured before and 60, 120, 180, 240, 300 and 360 min after meals by a Roche Cobas Mira autoanalyzer (ABX Diagnostics, Montpellier, France) using a colorimetric assay. All laboratory analyses were performed blinded to the assigned treatment.

2.6. Statistical analysis

A sample size of 13 participants with a randomized crossover design was determined. In our previous study, this size had been sufficient to discriminate the postprandial blood glucose patterns between EVOO and butter [1]. Being a mechanistic study, multiple endpoints were selected, namely postprandial changes in gastric emptying rate, gastrointestinal hormones, and blood lipids.

Data are expressed as mean ± standard deviation (SD) unless otherwise stated. Differences in postprandial glucose, hormones, and lipid profiles were evaluated by two-way repeated-measures ANOVA. Postprandial concentrations were included as levels of the within-subject factor *time*, and EVOO, Butter, and Low-fat were included as levels of the within-subject factor *test-meal*. Postprandial incremental area (iAUC) was calculated by the trapezoidal rule as the area under the curve above the baseline value. Differences between the three experimental meals in iAUCs or single time-point values were evaluated by one-way repeated measures ANOVA or, when data were not normally distributed, by Friedman's analysis of variance by ranks. A p-value <0.05 was considered significant. Statistical analysis was performed according to standard methods using the Statistical Package for Social Sciences software 21.0 (SPSS/PC; SPSS, Chicago, IL, USA).

3. Results

3.1. Participants' characteristics

The study participants (5 men and 6 women) were 41 ± 9 (mean ± SD) years old and had a BMI of 24.9 ± 2.2 kg/m^2. Diabetes duration was 25 ± 9 years, and blood glucose control was acceptable (HbA1c 7.0 ± 0.6%; 53 ± 6 mmol/mol). Their total daily insulin dose was 41.9 ± 10.9 IU. As determined based on the individual insulin/glycemic load ratios, insulin doses administered before the three experimental meals were the same for each subject, ranging between 5 and 16 IU. One participant had background retinopathy and two had both background retinopathy and peripheral neuropathy.

Gastric volume and plasma concentrations of glucose, gastrointestinal hormones, and lipids did not differ before the EVOO, Butter, and Low-fat meals. Data are reported in Supplemental Table S1.

3.2. Postprandial glycemia

Postprandial blood glucose response to the EVOO meal was blunted compared with the Butter and Low-fat meals ($p < 0.037$ for *time* × *meal* interaction by two-way repeated measures ANOVA) (Fig. 1). Blood glucose progressively increased in the later time of observation (3–6 h) after the two fat meals, at variance with the Low-fat meal, which peaked at 2 h. Differences between the EVOO and Butter meals were also evident in the later postprandial phase. Blood glucose iAUC was significantly lower after the meal with EVOO (690 ± 431) than with Butter (1320 ± 600) or Low-fat (1007 ± 990) (mmol/l × 360 min; $p = 0.041$, repeated measures ANOVA; EVOO *vs*. Butter, $p = 0.004$).

3.3. Gastric emptying

Gastric antrum volume in the early postprandial phase was significantly larger after the EVOO than after the Butter meal (mean values 60–90 min: 106 ± 21 *vs.* 90 ± 16 ml, $p = 0.048$), indicating a slower gastric emptying after EVOO (Fig. 2). Conversely, at the end of the observation, antrum volume was significantly smaller after the EVOO than after the Butter meal (mean values 330–360 min: 46 ± 10 *vs.* 57 ± 22 ml, $p = 0.045$).

Combining all meals, in the late postprandial phase, blood glucose levels (mean values 300–330 min) were significantly and positively correlated with gastric antrum volumes at 330 min ($r = 0.528$, $p = 0.002$) and 360 min ($r = 0.493$, $p = 0.004$).

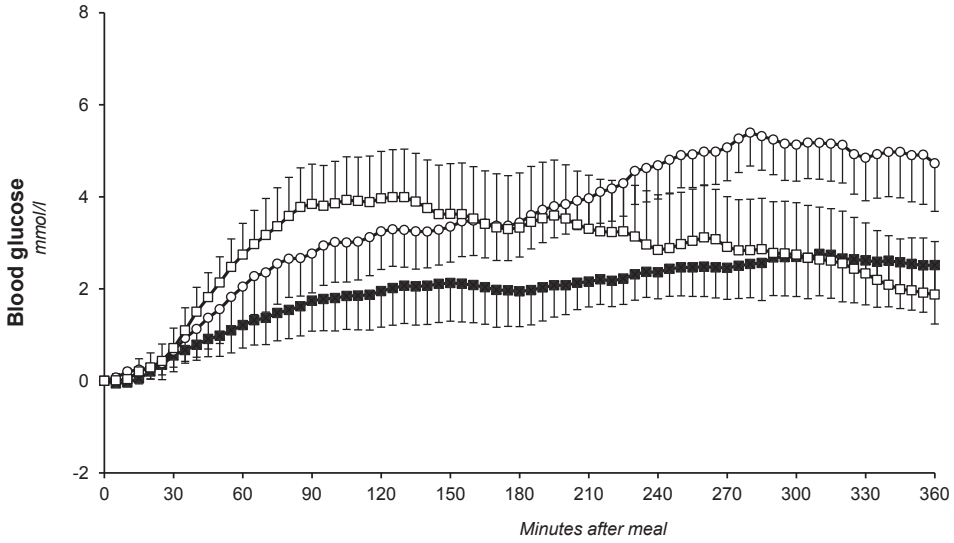

Fig. 1. Absolute changes vs. baseline (t0) in blood glucose concentrations after EVOO (full squares), Butter (empty circles), and Low-fat (empty squares) meals ($p = 0.037$ for *time* × *meal* interaction by two-way repeated measures ANOVA; EVOO *vs.* Butter, $p = 0.004$).

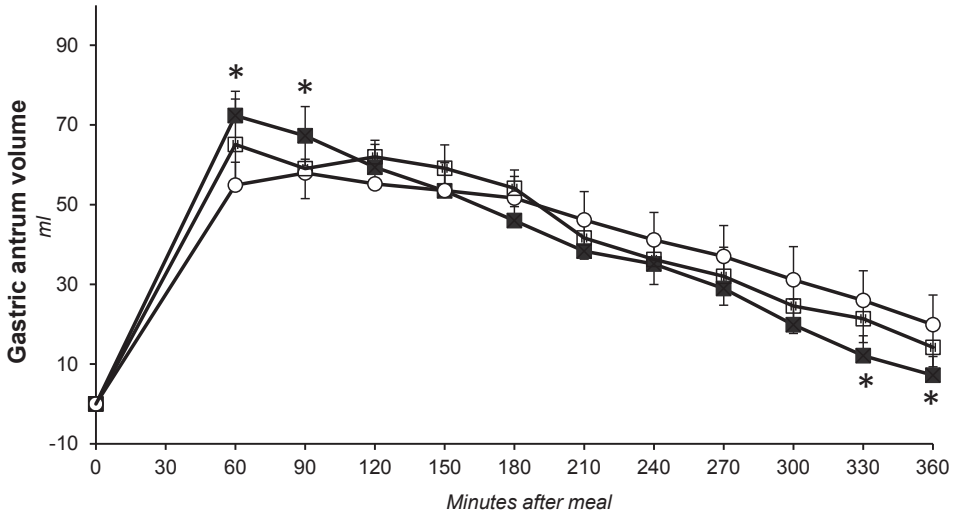

Fig. 2. A. Absolute changes vs. baseline (t0) in gastric antrum volume after EVOO (full squares), Butter (empty circles), and Low-fat (empty squares) meals. Data in the figure are means and SEM. *$p < 0.05$ EVOO *vs.* Butter.

3.4. Postprandial hormones

GLP-1 plasma concentrations at 15, 30, and 60 min increased significantly more after the EVOO than after the Butter and LF meals (Fig. 3A). Postprandial GLP-1 iAUC was significantly higher after the EVOO (261 ± 311) than after the Butter (189 ± 349) and LF meals (180 ± 337) (pmol/l × 180 min; $p = 0.009$ by repeated measures ANOVA; $p = 0.028$ EVOO *vs.* Butter, $p = 0.004$ EVOO *vs.* LF) (Fig. 3B).

There was a two-fold increase in plasma GIP concentrations after the EVOO and Butter meals than after LF meal, with significant differences between the two fat-rich meals and the low fat meal at all postprandial time-points (Fig. 3C). Postprandial GIP iAUC was significantly higher after the EVOO (18873 ± 7250) and Butter (17217 ± 5344) than after LF meals (10634 ± 3680) (pmol/l × 180 min; $p < 0.001$ by repeated measures ANOVA; $p = 0.001$ EVOO *vs.* LF, $p = 0.001$ Butter *vs.* LF) (Fig. 3D).

Plasma glucagon concentrations increased only slightly after the three meals (on average less than 10%) with a polyphasic pattern and without an evident peak. The high variability due to the small postprandial changes could explain some differences between the statistical tests. The postprandial concentration of glucagon increased significantly after EVOO at 15, 60, and 120 min when compared to LF, and at 15 and 120 min when compared to the butter meal. The mean concentration at all time-points (15–180 min) was significantly higher after both the EVOO and Butter (46.3 ± 8.0 and 47.0 ± 8.7, respectively) than after the LF meal (42.5 ± 8.0) (pmol/l, $p = 0.013$ by repeated measures ANOVA) (Fig. 3E). However, glucagon postprandial iAUCs were not significantly different between the three meals ($p = 0.503$) (Fig. 3F).

3.5. Postprandial lipids

Plasma triglyceride concentrations increased significantly more after the two fat-rich meals than after the low-fat meal, with a significantly higher increase after EVOO than after Butter at 60, 120, and 360 min ($p = 0.005$ for time × meal interaction by two-way repeated measures ANOVA) (Fig. 4A). Postprandial triglyceride iAUC was significantly higher after EVOO (100 ± 53) than after the

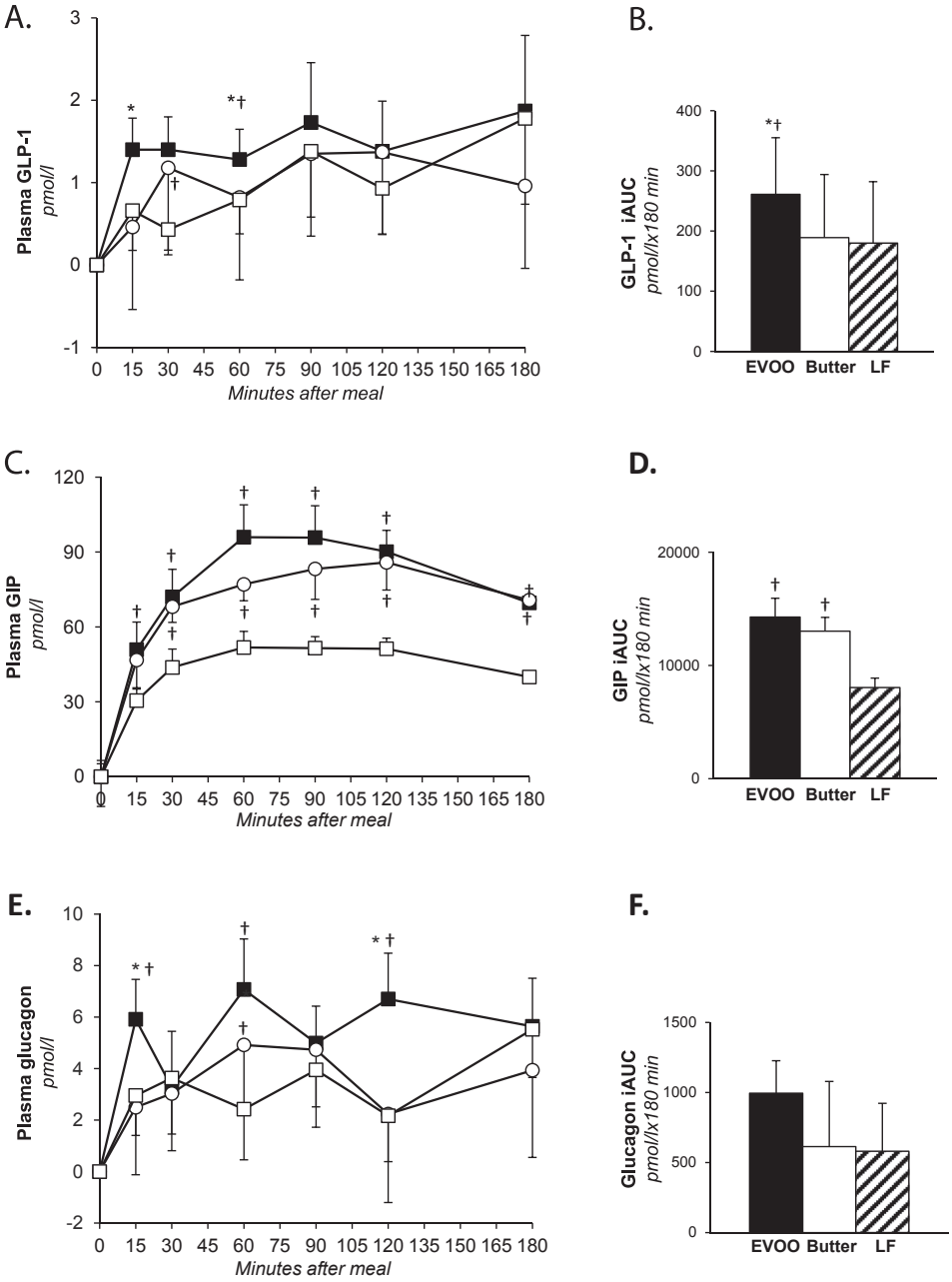

Fig. 3. Absolute changes vs. baseline (t0) in plasma concentrations of GLP-1 (**A**), GIP (**C**), and glucagon (**E**) after EVOO (full squares), Butter (empty circles), and Low-fat (empty squares) meals. GLP-1 (**B**), GIP (**D**), and glucagon (**F**) postprandial iAUCs after the three test meals. Data in the figure are means and SEM. *p < 0.05 *vs*. Butter; †p < 0.05 *vs*. Low-fat.

Butter (65 ± 60) and LF meals (23.9 ± 23.7) (mmol/l × 360 min; p < 0.001 by repeated measures ANOVA; p = 0.048 EVOO *vs*. Butter, p < 0.001 EVOO *vs*. LF, p < 0.014 Butter *vs*. LF) (Fig. 4B).

Postprandial FFA concentrations were less suppressed after the EVOO meal than after the Butter and LF meals, with significant differences at 60 and 120 min (Fig. 4C). The difference in postprandial FFA iAUCs after the EVOO and Butter meals tended to be statistically significant (−80 ± 91 *vs*.−203 ± 174 mEq/L × 360 min, respectively; p = 0.066) (Fig. 4D).

4. Discussion

The present study confirms, in a controlled setup, our previous home-based findings that the addition of EVOO to a high-glycemic index meal reduces postprandial glycemia, and shows that differential changes in gastric emptying, increased GLP-1 secretion, a more pronounced postprandial triglyceride response and lower postprandial free fatty acids inhibition may contribute to this effect.

In our study, EVOO slowed down early gastric emptying, as shown by significant differences in early postprandial gastric volumes between EVOO and butter intake. This suggests that only early postprandial changes in gastric emptying contributed to reducing postprandial glycemia. During the late postprandial phase, in line with a bidirectional relationship between gastric emptying and hyperglycemia [18], a more relevant factor slowing down gastric emptying may became the higher blood glucose levels. This is also suggested, in our study, by the significant and positive correlations between blood glucose concentrations and gastric volumes observed 6 h after the meals.

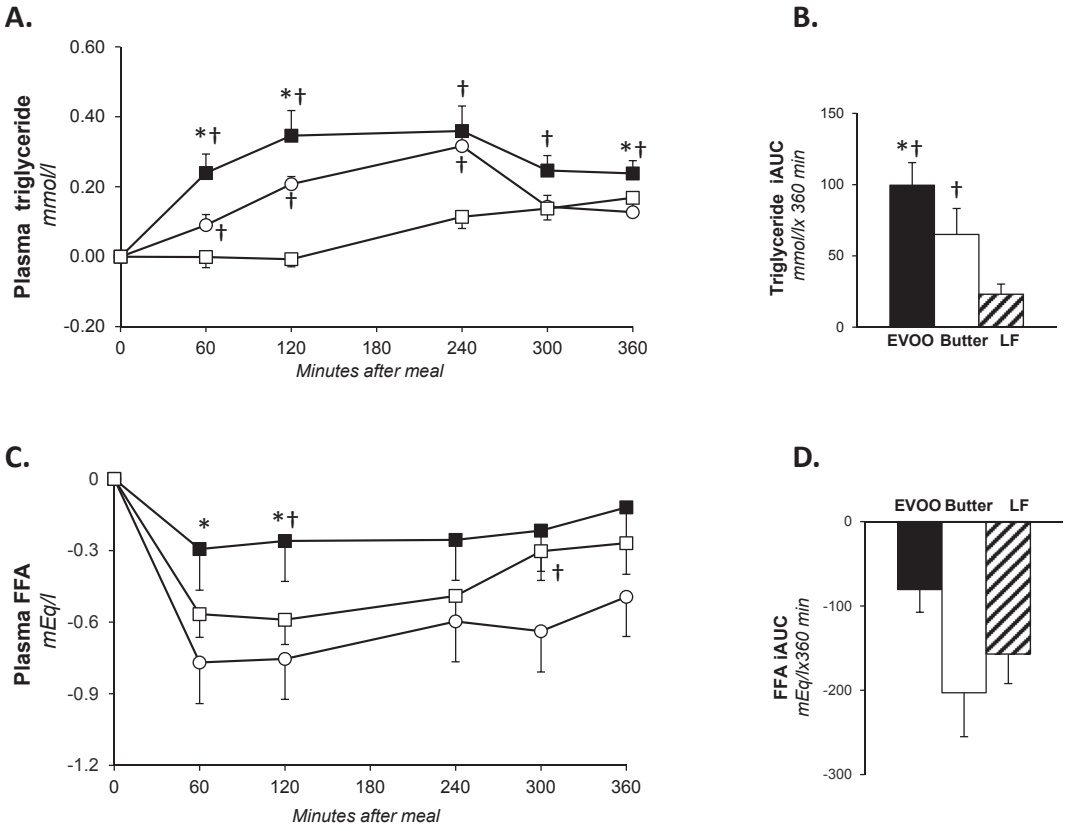

Fig. 4. Absolute changes vs. baseline (t0) in plasma concentrations of triglyceride (**A**) and FFA (**C**) after the EVOO (full squares), Butter (empty circles), and Low-fat (empty squares) meals. Triglyceride (**B**) and FFA (**D**) postprandial iAUCs after the three test meals. Data in the figure are means and SEM. *p < 0.05 *vs.* Butter; †p < 0.05 *vs.* Low-fat.

In our cohort of patients with type 1 diabetes, EVOO induced a higher postprandial increase in plasma GLP-1 concentrations than did the butter or low fat meals. Although GLP-1 is mainly a glucose-dependent insulin secretagogue, its postprandial secretion is preserved in people with type 1 diabetes [12,19], and the extent of postprandial GLP-1 response is influenced by meal size and fat content meal [4,9,19,20]. There is also evidence that the quality of fat may influence postprandial GLP-1 secretion. In particular, monounsaturated fatty acids given either as fat emulsion in healthy people [21] or as olive oil in healthy people [6] and in patients with type 2 diabetes [7] increased postprandial GLP-1 secretion compared to butter. Conversely, EVOO increased postprandial GLP-1 secretion to the same extent as butter compared with carbohydrate alone in insulin resistant individuals [22]. Our study shows that the quality of fat added to a high glycemic index meal modulates the postprandial increase in GLP-1 concentrations also in people with type 1 diabetes, possibly contributing to the lower postprandial blood glucose response observed after EVOO consumption. Considering that GLP-1 increased in the very early postprandial phase, we can speculate that this was due to indirect stimulation, likely through a neuro/endocrine pathway. While in healthy people and in patients with type 2 diabetes blood glucose lowering by endogenous or exogenous GLP-1 is mainly related to the stimulation of insulin secretion, this mechanism of action unlikely played a role in our patients with type 1 diabetes of long duration. The concomitant increases in plasma GLP-1 and gastric volume during the early postprandial phase in our study support the possibility that EVOO may have reduced postprandial glycemia by slowing down gastric emptying through the stimulation of GLP-1 secretion [23].

As another potential mechanism, we investigated the glucagonostatic effect of GLP-1 shown with exogenous GLP-1 in patients with type 1 diabetes [24]. In our study, in line with Kielgast et al. [12], we observed a slight postprandial increase in glucagon levels, which tended to be even higher after EVOO. Consequently, it is unlikely that the higher GLP-1 concentrations due to EVOO acted through glucagon suppression. Possibly, the postprandial glucagon increase in our patients was, instead, a consequence of the postprandial GIP increase, which was significantly higher after both high-fat meals than after the low-fat meal, as previously observed by Lund et al. [25] in patients with type 2 diabetes.

EVOO may have exerted its postprandial hypoglycemic effects also by influencing carbohydrate absorption at the intestinal level. The consistent increases in GIP, GLP-1, and glucagon in response to the fat-meals suggests that dietary fats stimulate the regulation of postprandial hormonal response more than carbohydrates. In the intestine, the absorption of fat competes with the absorption of carbohydrates, thus blunting the latter [13]. This may hold particularly true for monounsaturated fatty acids, which are preferentially absorbed compared with other types of fat [26]. Consistent with this, we observed a higher triglyceride response and a lower FFA suppression after EVOO meals. A higher postprandial increase in plasma triglyceride and free fatty acids with EVOO than with butter has been observed in studies on healthy people [27]. Likewise, in patients with type 2 diabetes, despite its beneficial chronic effects on fasting parameters, EVOO determined a higher postprandial triglyceride response mainly related to an increase in lipoproteins of intestinal origin and, therefore, to a direct effect of dietary fatty acids [28,29].

5. Conclusions

The present study explored for the first time the possible mechanisms underlying the reduced postprandial glycemic response determined by the addition of EVOO to a high glycemic index meal. These results indicate that EVOO improves postprandial glucose response in patients with type 1 diabetes through complex interactions between the macronutrient composition of the meal and gastro-intestinal sensing that involve gastric emptying, incretins secretion, and lipid metabolism. Moreover, this study confirms, in well-controlled experimental conditions, the differences in postprandial blood glucose profiles observed in our previous home-based study. This has relevant direct implications in the treatment of patients with type 1 diabetes, as it shows that insulin doses and time/duration of administration may differ consistently after meals with a similar amount of carbohydrates and total fat. This information may be especially useful for patients on insulin pump and can be of help in defining algorithms for the determination of prandial insulin administration.

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Declaration of interest

None.

Author contributions

L.B. designed the experiment, acquired, analyzed and interpreted data, and wrote the manuscript. A.A., M.G., and F.B. acquired and interpreted data and edited the manuscript. G.C., E.G., C.V., and P.C. acquired data and edited the manuscript. A.G. interpreted data and contributed to discussion. G.R. contributed to the conception of the study and reviewed and edited the manuscript. A.A.R. designed the experiment, contributed to the discussion, and reviewed and edited the manuscript. G.A. designed the experiment and wrote the manuscript. G.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.11.015.

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