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Effect of Extra Virgin Olive Oil on Postprandial Blood Glucose in Patients with Type 2 Diabetes Mellitus

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Abstract

INTRODUCTION: The burden of diabetes despite the emergence of new medications continues to rise. Hence, all possible treatment modalities including the use of our readily available herbs and oils are explored. Extra virgin olive oil (EVOO) is known for its cardiovascular effects and its effect on glucose lowering. However, there has been no study on the efficacy of extra virgin olive oil and Type 2 Diabetes Mellitus Filipino patients.

OBJECTIVES: The primary objective of this study is to determine whether a significant difference exists in the 2-hour postprandial blood glucose of meals containing EVOO and meals without EVOO in Type 2 Diabetes Mellitus.

METHODS: Thirteen patients were included in this randomized controlled cross-over trial. They received a test meal with EVOO or no EVOO followed by a one week wash out period, in which the subjects were given the other intervention. The primary outcome is the trans-meal blood glucose, which is calculated as the percent change in 2-hour postprandial blood glucose.

RESULTS:
In group A, there was a noted 88.55% increase in 2-hour post prandial blood glucose in taking meals with EVOO, compared to 72.11% change in meals without EVOO. The same was observed in Group B, where there was a 71.08% and 49.22% increase in 2-hour postprandial blood glucose in meals with EVOO and without EVOO, respectively. The difference was significant with a p-value of 0.044. Free fatty acids inhibit glucose transport and insulin secretion, this effect may be more predominant in Asian Type 2 Diabetes Mellitus patients.

CONCLUSION: This study found that adding extra virgin olive oil on top of meals provided no additional benefit in terms of post-prandial glucose excursion.

INTRODUCTION

Diabetes mellitus is a devastating global pandemic that poses an enormous public health challenge. Despite the numerous efforts of the public, and the current available drugs in the market, the burden of diabetes mellitus remains at large. Epidemiologic studies show that about 3.7 million Filipinos have the disease, and the Philippines ranks 15 in the world when it comes to diabetes prevalence.[1, 2] Just like people with diabetes, individuals with chronic medical conditions are turning to complementary and alternative medicines, to serve as adjuncts in the treatment of their diseases. Hence, efforts are made to find the most effective and safe options for these patients.

Olive oil, believed to be the most powerful factor in the Mediterranean diet, has long been known for its health benefits. However, the fascination with olive oil came only in the last decade, when epidemiological research confirmed its protective role against several chronic diseases.[3] A large randomized controlled trial[4] provided evidence, a higher baseline total olive oil consumption was associated with improved lipid profile, decreased blood pressure and reduced the risk of major cardiovascular events.[4] Extra virgin olive oil intake was also associated with a decreased risk to develop Type 2 Diabetes Mellitus in healthy individuals, as found by a systematic review involving 29 randomized controlled trials.[5]

Indeed, the olive oil market has been growing steadily over the decade, especially catering to the health conscious, and patients with Type 2 Diabetes Mellitus are no exempt. Questioning what has been dubbed “a good fat”, this study explored the effect of

extra virgin olive oil on the glucose control of patients with Type 2 Diabetes Mellitus, specifically on their postprandial blood glucose. Specifically, this study determined if there is a significant difference in the trans-meal blood glucose 2 hours after a test meal with EVOO versus without EVOO.

RESEARCH QUESTION

Is there a significant difference in the postprandial blood sugar between meals with extra virgin olive oil (EVOO) and without EVOO among Type 2 Diabetes Mellitus patients?

METHODOLOGY

Study design and population

This study was a randomized controlled crossover trial conducted from September to November 2018. All adult patients aged 30-65 years old, diagnosed with Type 2 Diabetes Mellitus were recruited to participate in this study, with body mass index under the overweight or obese class I category (by Asia Pacific guidelines). All prescription medications for their diabetes, including insulin and other oral hypoglycemic medications were kept stable throughout the duration of the study.

Excluded in the study were: 1) pregnant patients, 2) patients with history of frequent hypoglycemic episodes, 3) those at high risk of developing ketoacidosis and hyperglycemic hyperosmolar syndrome, 4) those with identified acute stress during the

study (illness, fever, trauma leading to hospitalization), 5) current intake of steroids, 6) olive oil allergy or intolerance and 7) digestive disorders.

Study design

The participants were selected from a pool of patients with Type 2 Diabetes in the outpatient Diabetes Clinic of Makati Medical Center, Philippines.

During their first visit, the participants were oriented on the conduct of the study. They were advised to be compliant with their medications throughout the duration of the trial.

On their second visit, participants were asked to do a six to eight-hour overnight fast, and their fasting blood sugar was drawn. Serum samples were analyzed through the hexokinase method. The participants were then randomly allocated (first allocation) through a coin toss to receive a standard breakfast without EVOO or a meal admixed with one tablespoon of EVOO. The standard meals were labeled with serial numbers, and both the participants and the investigator were blinded to the intervention. The meals were consumed steadily in 15 to 20 minutes, after which, the food containers were collected to ensure its full consumption. Breakfast was chosen in order to avoid a second meal bias. The participants were asked to sit in the waiting area of the laboratory until the 2-hour postprandial blood sugar was due to be drawn.

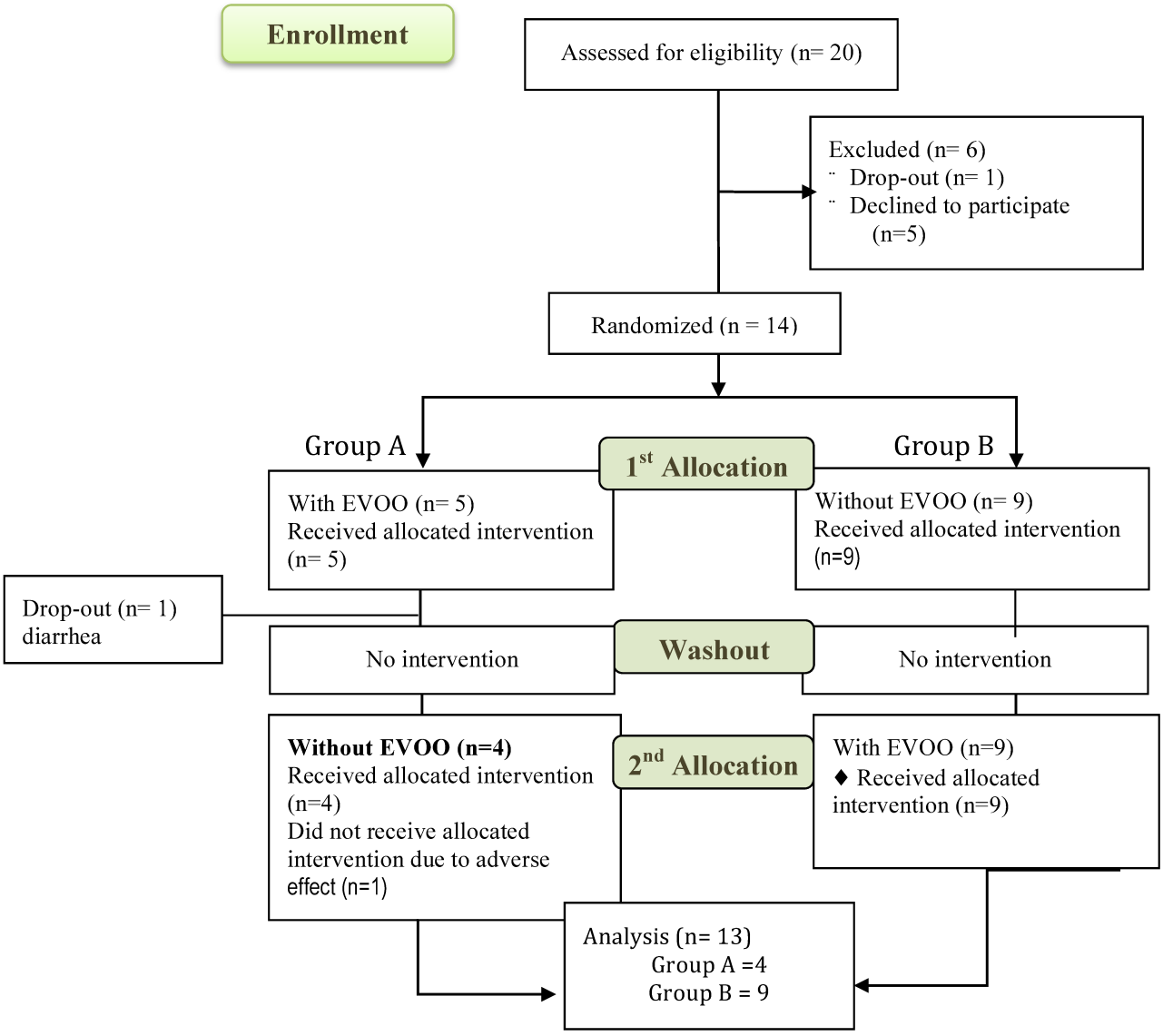

Figure 1. Flow diagram of the conduct of the study
Group A: With EVOO to Without EVOO = 4
Group B: Without EVOO to With EVOO = 9

After a one-week washout period, the participants were asked to come back for a cross over to the other treatment arm (second allocation). The participants were given the same test meal to ensure that that the glycemic index of the food remained constant.

Standard meal

The standard meal was prepared by a registered dietician. Calories were calculated based on the ideal body weight of each participant multiplied by a factor of 25 for obese or overweight individuals divided by 3. The meal was composed of 50% carbohydrates, 20% protein and 30% fat. Water (250 ml) was served with each meal.

Extra Virgin Olive Oil (EVOO)

According to the International Olive Oil Council[16], virgin olive oils are obtained from the fruit of the olive tree (*Olea eurpaea)* exclusively by cold-press technique under conditions that do not alter the oil. Extra virgin olive oil (EVOO) differs from ordinary olive oil in its free acidity, which is not allowed to exceed 0.8 g per 100 grams.

This study used the FDA approved Doña Elena Extra virgin olive oil, which is readily available in local supermarkets. Its free acidity expressed as oleic acid was found to be 0.26%, comparable with the International food standards.[15]

Outcomes

The main outcome measured in the study was the trans-meal blood glucose, which is expressed as percent change in 2-hour postprandial blood glucose. This was calculated as the fasting blood sugar subtracted from the 2-hour postprandial glucose divided by the fasting blood sugar multiplied by 100.

Sample size calculation

A minimum total of 12 patients were needed for this RCT study with cross-over design, setting a two-sided significance level of 0.05, power of 90% to detect a significant difference between the two interventions, and population variance taken from the study of Violi et al.[8]

Formula:

$$n = \frac{\left(z_\alpha + z_\beta\right)^2 \sigma^2}{2\left(\mu - \mu_0 - \delta\right)^2}$$

Legend:
n=sample size per arm
z_α = critical value for 2-sided alpha of 0.05
z_β = critical value for power of 90%
μ-μ_0 = true difference between the two mean values at which the power is calculated
δ = superiority margin or non-inferiority margin
σ = population variance

Calculation:

$$n = \frac{\left(1.96 + 1.282\right)^2 23.33^2}{2\left(0 - 5\right)^2}$$

$$n = 5$$

The minimum number of participants needed per arm is 5, or a study population of 10. To compensate for a possible dropout rate of 20%, the sample size is recalculated as follows:

Adj. N = 10 (120%) = 12

Analysis of Data

Univariate analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion was used for nominal data, median and range for nonparametric data, and mean and standard deviation for parametric data.

Crossover data analysis

ANOVA for crossover studies was used to determine relative effect of EVOO or no intervention, magnitude of treatment effect, period effect, and treatment or period interaction.

Ethical Considerations

Data gathered from this study were treated in conformance with the principles of confidentiality, codes were used in data collection forms and documents accessible only by the primary investigator.

The technical aspect of this study was reviewed and approved by the Institutional Review Board (IRB) of Makati Medical Center. The ethical principles based on the Declaration of Helsinki and the National Guidelines for Biomedical Research of the

National Ethics Committee (NEC) of the Philippines were considered in the conduct of this study.

No monetary compensation was given to participants for recruitment. However, a reasonable transportation allowance of Php 200.00 each, to cover for their every visit was provided. Assurance was made that exclusion or withdrawal from this study will not result in any form of denial to any future medical service or assistance.

RESULTS

Table 1. Baseline characteristics of participants with type 2 DM (n = 13)

	Mean ± SD; Frequency (%)
Age (years)	57.92 ± 5.01
Sex	
Male	6 (46.15)
Female	7 (53.85)
Weight (kg)	61.75 ± 5.04
Height (cm)	155.72 ± 8.79
BMI (kg/m^2)	24.56 (23.51 – 31.07)
Normal	0
Overweight	7 (53.85)
Obese	6 (46.15)
Comorbidities	
Hypertension	9 (69.23)
CAD	4 (30.77)
Liver disease	0
Renal disease	0
COPD	0
Others	0
Smoking history (pack-years)	2
Never smoker	10
Current smoker	0
Quit smoking	1 (7.69)
Alcohol drinking	0

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

A total of 14 patients were randomized to the first allocation in the study, however, one patient withdrew from the study due to watery diarrhea experienced one hour after eating the meal with extra virgin olive oil.

Table 2. Clinical and laboratory profile of participants with Type 2 Diabetes Mellitus (n = 13)

	Mean ±SD; Median (Range); Frequency (%)
Vital signs	
Heart rate (/min)	76.77 ± 7.00
Respiratory rate (/min)	20 (16 – 20)
Systolic blood pressure (mmHg)	115.38 ± 11.98
Diastolic blood pressure (mmHg)	74.62 ± 7.76
Medications used	
Metformin	11 (84.62)
DPP4 inhibitor	8 (61.54)
Insulin	5 (38.46)
SUR	5 (38.46)
Pioglitazone	1 (7.69)
SLGT2 inhibitors	1 (7.69)
Lipid profile (mg/dL)	
Total cholesterol	183.35 ± 37.40
LDL-C	97.77 ± 33.37
HDL-C	56.07 ± 15.63
Triglyceride	102 (54.91 – 708.85)
Blood glucose control	
HbA1c (%)	7.7 (6.77 – 11.12)
Serum creatinine (mg/dl)	0.89 ± 0.25
Liver profile (U/L)	
Alanine transaminase	26 (13 – 117)
Aspartate transaminase	30 (17 – 88)

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

Of the 13 patients included in the final analysis, four were assigned to Group A (with EVOO to without EVOO) and nine were assigned to Group B (without EVOO to

with EVOO). The mean age of these patients was 57.92 (±5.01) years, seven (53.85%) were female, all were either overweight (53.85%) or obese (46.15%), and nine (69.23%) have hypertension, while four (30.77%) have CAD (Table 1).

The average vital signs values were within normal (Table 2). The most common medications used were metformin (84.62%), DPP4 inhibitor (61.54%), insulin (38.46%), and SUR (38.46%). The median HbA1c (%) was at 7.7 (range 6.77 – 11.12).

A significant difference was found between groups, with treatment effect at p = 0.044. For both groups and both periods, whenever EVOO was used, the percent increase was significantly higher with the use of EVOO. See Table 3.

Table 3. Serum glucose before and after interventions (n = 13)

	Period 1			**Period 2**		
	Fasting	**2 hours post-prandial**	**% Change**	**Fasting**	**2 hours post-prandial**	**% Change**
				Mean ± SD		
With-Without EVOO	144.57 ± 17.48	275.80 ± 71.22	88.55 ± 26.92	138.87 ± 27.35	241.28 ± 68.15	72.11 ± 20.34
Without-With EVOO	148 ± 71.17	208.79 ± 65.02	49.22 ± 36.08	125.87 ± 13.80	214.38 ± 43.50	71.08 ± 34.88
p-value	0.928	0.123	0.079	0.267	0.403	0.958
Sequence effect (p-value):				0.280		
Period effect (p-value):				0.754		
Treatment effect (p-value):				**0.044**		
Interaction of sequence and treatment (p-value):				0.754		
Interaction of period and treatment (p-value):				0.161		
Normality:		With-Without: 0.986			Without-With: 0.552	

The sequence by which EVOO was given had no statistical effect on the blood glucose levels (p = 0.280) and no interaction with treatment effect (p = 0.754). The period effect, or the carryover effect, likewise had no statistical effect on the blood glucose levels (period effect, p = 0.754) and no interaction with treatment effect (p = 0.161). We verified normality of the data for both EVOO-first (p = 0.986) and EVOO-second groups (p = 0.552). See Table 3.

DISCUSSION

Although olive oil has long been part of the Mediterranean diet, its popularity soared only over the last decade, as studies[4] have linked it to benefits on cardiovascular health. Recent studies[8, 10] further explored its effect on glucose metabolism. A study[8] on healthy subjects found that 10 grams of EVOO compared to placebo lowered the postprandial blood glucose after a standard meal. Another study[10] was done among among Type 1 Diabetes Mellitus patients, and found that 37 grams of EVOO added to meals significantly lowered the postprandial glucose. This effect was attributed to the high content of monosaturated fats (MUFAs) in EVOO, which improves postprandial insulin sensitivity by prolonging the effect of incretins. This effect was mainly achieved through the inhibition of the enzyme dipeptidyl peptidase- 4 (DPP-4), which degrades incretins. Incretins are substances that heighten glucose-induced insulin release, causing 70% of the postprandial insulin increase.[18] Insulin-independent glucose-lowering actions of incretin include the inhibition of hepatic glucose production, suppression of glucagon

release and the prolongation of gastric emptying[19], explaining its benefits even in Type I Diabetes Mellitus patients, where the defect is insulin deficiency.

However, in contrast to these studies, our study found a significantly higher percent change in the 2-hour postprandial blood sugar of patients taking EVOO with meals compared to those taking meals without EVOO ($p = 0.044$). These results can be explained by the effect of an elevated free fatty acid on glucose metabolism. A tablespoon (15 ml) of EVOO contains 120 calories and 13.5 g of fat, which is an added 15.75% to the recommended daily allowance compared to meals without EVOO. Elevated free fatty acids can impair the glucose metabolism.[19] Free fatty acids compete with glucose for substrate oxidation, causing a 50% reduction in glucose oxidation. Aside from this, they also affect insulin signaling at the level of Protein Kinase C, with resultant reduction in insulin-mediated glucose uptake.

The difference in our findings may be explained by the difference in ethnicity between the study populations. These metabolically adverse effects of extra virgin olive oil may be more dominant in the Asian Type 2 Diabetes population compared to its agonist effects on incretin, as exhibited by Caucasian patients. Compared to Caucasians, Asian Type 2 Diabetes Mellitus patients are known have more visceral adiposity, which contributes to lipotoxicity and insulin resistance. Hence, it is plausible that the difference in ethnicity may account for the nuances of insulin and fat metabolism in these populations. Data addressing the role of insulin secretion in meals with and without EVOO, however, was not explored in this study and should be investigated.

Another limitation of this study is that the effect of EVOO added to meals was only measured at one point. Although other studies[8] have estimated their outcomes with just one dose of EVOO, it is recommended that a long term EVOO consumption be employed in future studies, as it remains to establish if changes in the glucose profile will be observed if EVOO is to be taken longer. This study design will also enable the measurement of HbA1c.

Another limitation of this study is in the profiling of the phenolic content of EVOO. Some studies have suggested that the anti-oxidant effect of EVOO is mainly responsible for lowering the post-prandial blood sugar, and this is mainly accounted for by its phenolic acid content. Oxidative stress has been found to lead to insulin resistance and the generation of the advanced glycosylated end-products (AGEs) from reactive oxygen species (ROS). Apart from the formation of AGEs, the generation of ROS has been known to upregulate DPP_4 concentrations, the enzyme known to breakdown incretins, which eventually inhibits the secretion of insulin. Profiling the phenolic content of the EVOO may explain the difference in the results, especially that much of the mechanism for the effects of EVOO are attributed to their antioxidant effects, however further studies are needed.

Despite its limitations, however, this study was able to demonstrate a disadvantageous increase in postprandial blood sugar when EVOO is added to a standard meal among patients with Type 2 Diabetes Mellitus. These findings do not alter the current dietary recommendations: to reduce saturated and trans fat intake in general,

however highlights the need for further elucidation of the effects of different dietary fats and our carbohydrate metabolism.

CONCLUSION

The postprandial glycemic response is hugely influenced by the fat content of a meal. In this study, the authors have demonstrated a significantly increased postprandial glucose levels in Type 2 Diabetes Mellitus patients who added a tablespoon of EVOO on top of meals compared to the same meal without EVOO.

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