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Effect of Extra Virgin Olive Oil on Glycemic Control, Insulin Resistance and Insulin Secretion in Patients with Type 2 Diabetes.

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Abstract. Type 2 diabetes mellitus (T2DM) is a common disease all over the World and may lead to serious outcome. Several health benefits are contributed to extra virgin olive oil (EVOO). The polyphenol fraction of EVOO may be responsible for its cardioprotective impacts. The current study aimed to assess effect of EVOO on glycemic control in patients with T2DM. A randomized controlled trial was conducted in the period May 1st 2019 to November 1st 2020. A total of 100 patients with T2DM were enrolled in the study and were randomly subdivided into either study group (50 patients) where patients received extra virgin olive oil with conventional therapy of DM or control group (50 patients) where patients only conventional therapy of DM. Lipid profile and glycemic control were assessed at baseline and after 3 months in both groups. The main findings in the current study included; both groups had insignificant differences as regard patients' characteristics and baseline laboratory data. During the follow up; the study group had significantly lower Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), cholesterol and triglycerides with significant increase in Homeostatic Model Assessment of beta cells (HOMA-B). Also, the study group had improvement in the glycemic control and lipid profile during follow up in comparison to baseline data. Meanwhile, the control group showed no significant differences between baseline and follow up laboratory data. EVOO seems a promising hypoglycemic effects and lipid profile. And yet, well-designed randomized trials with longer durations are still needed to evaluate the EVOO's efficacy on glycemic parameters.

Keywords: diabetes mellitus; glycemic control; Extra virgin olive oil

Introduction

Type 2 Diabetes mellitus (T2D) describes a group of metabolic disorders characterized by chronically elevated glycemia. It represents one of the fastest-growing health challenges of the 21st century, with the number of adults living with diabetes having more than tripled over the past 20 years. The International Diabetes Federation estimated 451 million (age 18–99 years) people with diabetes worldwide in 2017, with the estimation going up to 693 million for 2045 **[1]**.

Extra virgin olive oil (EVOO) is a major component of the Mediterranean diet and is appreciated worldwide because of its nutritional benefits in metabolic diseases, including T2D. Traditionally, the high content of monounsaturated fatty acids (MUFAs), particularly oleic acid, was considered to be responsible for the beneficial effects of EVOO **[2]**.

Indeed, recent meta-analyses of randomized controlled trials have reported beneficial effects on metabolic parameters in T2D patients after replacing carbohydrates (~5–10% of total energy intake) with MUFAs **[3, 4]**. It has been suggested, however, that most of the metabolic benefits of EVOO could be due to its minor components, particularly phenolic compounds (PCs)**[2]**.

There is paucity in literature about effects of EVOO on glycemic control and lipid profile in patients with T2D. So, we conducted this work to evaluate the effect of EVOO on glycemic control in patients with T2DM.

Patients and Methods

Study setting and design

A randomized controlled clinical trial was carried out in the Outpatient Diabetic Clinic at the Department of Internal Medicine, Assuit University Hospital in the period May 1st 2019 to November 1st 2020.

Inclusion criteria

Any patient with type 2 diabetes with the following criteria was enrolled in the study;

- age 30-60 years regardless of their gender.
- Duration of diabetes less than 5 years.
- On oral antihyperglycemic medication.

- Glycosylated hemoglobin (Hb A1c) more than 7%.

Exclusion criteria

Any patient with one or more of the following criteria was excluded;

- Type 1 diabetes
- Insulin treated type 2 DM patients.
- Pregnant women
- Patients on cholesterol-lowering drugs, steroids and other drugs that affect the fat metabolism.
- Patients on regular supplement that contain olive oil
- Patients have aversion or allergy to olive oil.
- Smokers.
- Patients have gall bladder disease, gastrointestinal disease (e.g. malabsorption), liver, kidney, heart and thyroid diseases

Participants

The study 100 patients with type 2DM. Those patients were randomly subdivided into either study group (50 patients) where patients received extra virgin olive oil with conventional therapy of DM or control group (50 patients) where patients only conventional therapy of DM.

Methodology

All patients were subjected to thorough history taking and clinical evaluation included age, sex, duration of DM and body mass index.

EVOO intake

During the experimental period (3 months), participants were requested to consume daily dose of 30 mL (3 tablespoons) of EVOO. All patients should already be following a controlled Diet. The participants were asked to maintain their habitual lifestyle and to report any illness or abnormality occurring during the study. Throughout the study, participants received a 1-week recall to evaluate the compliance with diet and physical activity.

Anthropometric and blood pressure measurements

At the beginning and after three months intervention period, all patients underwent physical examination and blood pressure evaluation. Height and weight were measured in the morning with cloths, but not shoes. After 5 min of rest, blood pressure was measured in a sitting position. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m). Waist circumference was measured at the umbilical level with the participants standing after normal expiration.

Biochemical measurements

At baseline and after three months intervention, routine haematochemical parameters were determined according to institutional guidelines. Fasting blood samples were collected. Serum and EDTA plasma were stored at −80 °C until assayed.

For each subject, the analyses, carried out in frozen samples of whole serum or plasma as appropriate, were the following: blood glucose, glycated haemoglobin (HbA1c), lipid profile (total cholesterol, HDL and LDL cholesterol, triglycerides), liver function markers (alanine aminotransferase, ALT and aspartate aminotransferase, AST). All parameters were assayed with standard laboratory methods.

Homeostatic model assessment for insulin resistance (HOMA-IR) and for beta cell (HOMA-B)

HOMA is a method for assessing β-cell function (HOMA – B) and insulin resistance (HOMA –IR) from basal (fasting) glucose and insulin. Insulin resistance was calculated on the basis of fasting glucose (mg/dL) and insulin levels (μU/mL) according to the homeostasis model assessment (HOMA-IR) method: glucose x insulin / 405 **[5]**.

The HOMA-beta cell function (HOMA-B) was calculated by using the following formula: 360 x fasting insulin (μU/mL) / (fasting glucose (mg/dL) - 63) **[6]**.

Ethical consideration

The study protocol was approved by the local ethics committee, and all subjects gave an informed consent to participate in the study. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was registered on ClinicalTrials.gov Identifier: NCT03891927

Statistical analysis

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). The Shapiro test was used to determine compliance of the data to normal distribution. Quantitative data with normal distribution are expressed as mean ± standard deviation (SD) and compared with Student t test and paired t test.

Nominal data are given as number (n) and percentage (%). Chi^2 test was implemented on such data.

Level of confidence was kept at 95% and hence, P value was considered significant if < 0.05

Results

Baseline data of the studied groups (table 1):

Both study groups had insignificant difference as regard age (51.40 ± 6.22 vs. 52.30 ± 5.16 (years); p= 0.93), body mass index (27.87 ± 2.30 vs. 28.90 ± 2.90 (kg/m^2); p= 0.26) and waist circumference (94.24 ± 3.45 vs. 95.80 ± 3.57 (cm); p= 0.54).

Table 1. Baseline data of the studied groups

	Study group (n= 50)	**Control group (n= 50)**	**P value**
Age (year)	51.40 ± 6.22	52.30 ± 5.16	0.93
Sex			0.27
Male	27 (54%)	31 (62%)	
Female	23 (46%)	19 (38%)	
BMI (kg/m^2)	27.87 ± 2.30	28.90 ± 2.90	0.26
WC (cm)	94.24 ± 3.45	95.80 ± 3.57	0.54
Residence			0.15
Rural	26 (52%)	30 (60%)	
Urban	24 (48%)	20 (40%)	
Marital status			0.50
Married	40 (80%)	41 (82%)	
Singe	10 (20%)	9 (18%)	
Education level			0.73
Illiterate	13 (26%)	10 (20%)	
Primary level	21 (42%)	23 (46%)	
Secondary level	10 (20%)	13 (26%)	
University/above	6 (12%)	4 (8)	
Family of DM	17 (34%)	11 (22%)	0.13

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05. BMI: body mass index; WC: waist circumference

Characteristics of diabetes mellitus among the studied groups (table 2)

Both groups had insignificant differences as regard age of diagnosis (47.46 ± 6.21 vs. 48.34 ± 4.69 (years); p= 0.42) and duration of DM (2.21 ± 1.05 vs. 2.52 ± 0.91 (years); p= 0.10). Also, other data showed no significant differences between both groups.

Table 2. Characteristics of diabetes mellitus among the studied groups

	Study group (n= 50)	**Control group (n= 50)**	**P value**
Age of diagnosis (year)	47.46 ± 6.21	48.34 ± 4.69	0.42
Duration of DM (year)	2.21 ± 1.05	2.52 ± 0.91	0.10
Frequency of monitoring			0.73
Not at all	19 (38%)	19 (38%)	
Regular	18 (36%)	21 (42%)	
Sometimes	13 (26%)	10 (20%)	
Diet control			0.35
Poorly controlled	22 (44%)	21 (42%)	
Well controlled	28 (56%)	29 (58%)	
Practicing exercise			0.50
Not at all	22 (44%)	20 (40%)	
Regular	12 (24%)	12 (24%)	
Sometimes	16 (32%)	18 (36%)	

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05. DM: diabetes mellitus

Baseline laboratory data among the studied groups (table 3): Both groups had insignificant differences as regard baseline laboratory data (p> 0.05).

Table 3. Baseline laboratory data among the studied groups

	Study group (n= 50)	**Control group (n= 50)**	**P value**
Alanine transaminase (u/l)	38.64 ± 7.45	37.47 ± 8.23	0.83
Aspartate transaminase (u/l)	44.48 ± 9.42	44.29 ± 8.40	0.94
Urea (mg/dl)	9.38 ± 2.21	10.58 ± 2.50	0.09
Creatinine (mg/dl)	1.18 ± 0.26	1.07 ± 0.45	0.53
Cholesterol (mg/dl)	201.94 ± 47.42	191.62 ± 41.11	0.24
Triglycerides (mg/dl)	151.26 ± 47.98	183.56 ± 55.64	0.06
HDL (mg/dl)	43.16 ± 9.75	45.54 ± 14.67	0.34
LDL (mg/dl)	124.76 ± 37.39	110.50 ± 34.88	0.06

FPG(mg/dl)	176.98 ± 34.78	166.11 ± 45.90	0.96
2h.PPG (mg/dl)	234.08 ± 70.59	256.99 ± 90.73	0.17
Glycosylated hemoglobin (%)	10.36 ± 1.72	9.99 ± 2.22	0.92
HOMA-IR	2.64 ± 0.67	2.84 ± 0.44	0.08
HOMA-B (%)	54.85 ± 16.04	50.41 ± 7.79	0.09

Data expressed as mean (SD). P value was significant if < 0.05. HDL: high density lipoproteins; LDL: low density lipoproteins; FPG: fasting plasma glucose; 2h.PPG: two-hours post-prandial glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

Follow up laboratory data among the studied group (table 4, figures 1-2)

During follow up; the study group showed better glycemic improvement as regard FPG (162.45 ± 18.90 vs. 188.11 ± 21.98 (mg/dl); p= 0.01), 2h-PPG (182.76 ± 39.01 vs. 253.20 ± 55.56 (mg/dl); p< 0.001) and HbA1C (7.13 ± 1.12 vs. 8.90 ± 2.11 (%); p= 0.04).

Also, the study group showed significant decrease in HOMA-IR (1.74 ± 0.60 vs. 2.38 ± 0.37; p< 0.001) and significant increase in HOMA-B (71.90 ± 8.58 vs. 51.13 ± 7.06 (%); p< 0.001). There was significant decrease in cholesterol (159.18 ± 29.21 vs. 198.26 ± 20.87 (mg/dl); p< 0.001) and triglycerides (121.54 ± 32.64 vs. 186.44 ± 67.88 (mg/dl); p< 0.001).

Table 4. Follow up laboratory data among the studied group

	Study group (n= 50)	**Control group (n= 50)**	**P value**
Alanine transaminase (u/l)	38.97 ± 5.99	34.12 ± 4.04	0.53
Aspartate transaminase (u/l)	42.34 ± 11.09	41.41 ± 10.11	0.08
Urea (mg/dl)	8.84 ± 2.01	8.80 ± 2.15	0.92
Creatinine (mg/dl)	0.99 ± 0.28	1.01 ± 0.33	0.80
Cholesterol (mg/dl)	159.18 ± 29.21	198.26 ± 20.87	< 0.001
Triglycerides (mg/dl)	121.54 ± 32.64	186.44 ± 67.88	< 0.001
HDL (mg/dl)	43.22 ± 9.01	44.33 ± 11.11	0.34
LDL (mg/dl)	119.10 ± 34.57	124.33 ± 24.45	0.08
FPG (mg/dl)	162.45 ± 18.90	188.11 ± 21.98	0.01
2h.PPG(mg/dl)	182.76 ± 39.01	253.20 ± 55.56	< 0.001
Glycosylated hemoglobin (%)	7.13 ± 1.12	8.90 ± 2.11	0.04
HOMA-IR	1.74 ± 0.60	2.38 ± 0.37	< 0.001
HOMA-B (%)	71.90 ± 8.58	51.13 ± 7.06	< 0.001

Data expressed as mean (SD). P value was significant if < 0.05. HDL: high density lipoproteins; LDL: low density lipoproteins; FPG: fasting plasma glucose; 2h.PPG: two-hours post-prandial glucose ; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

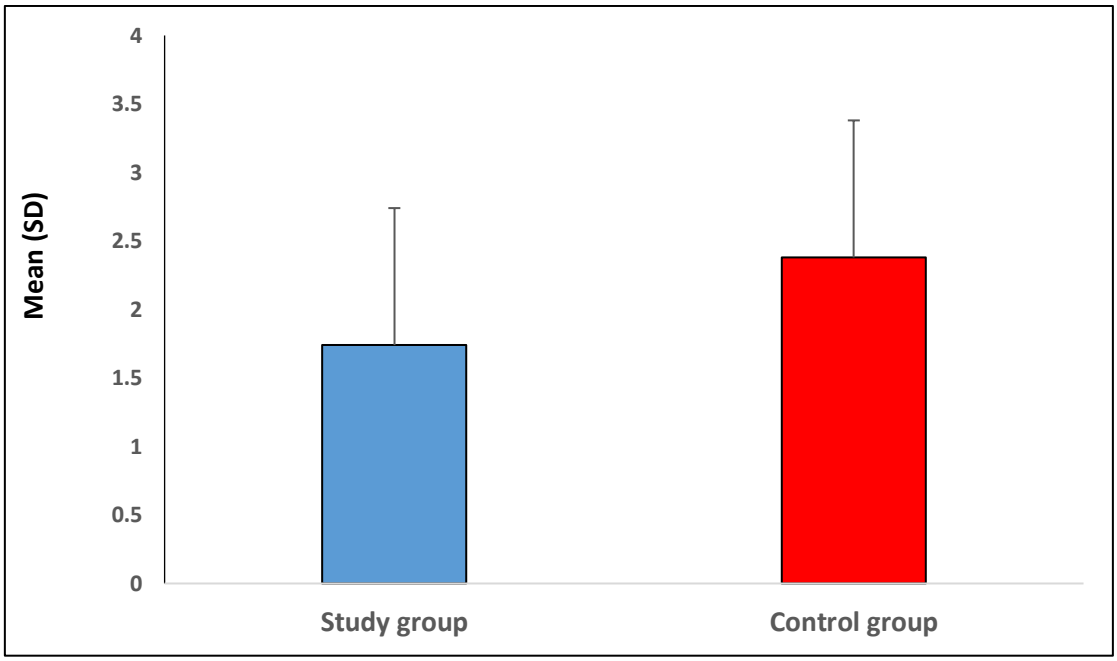

Figure 1. Mean follow up HOMA-IR among the studied groups

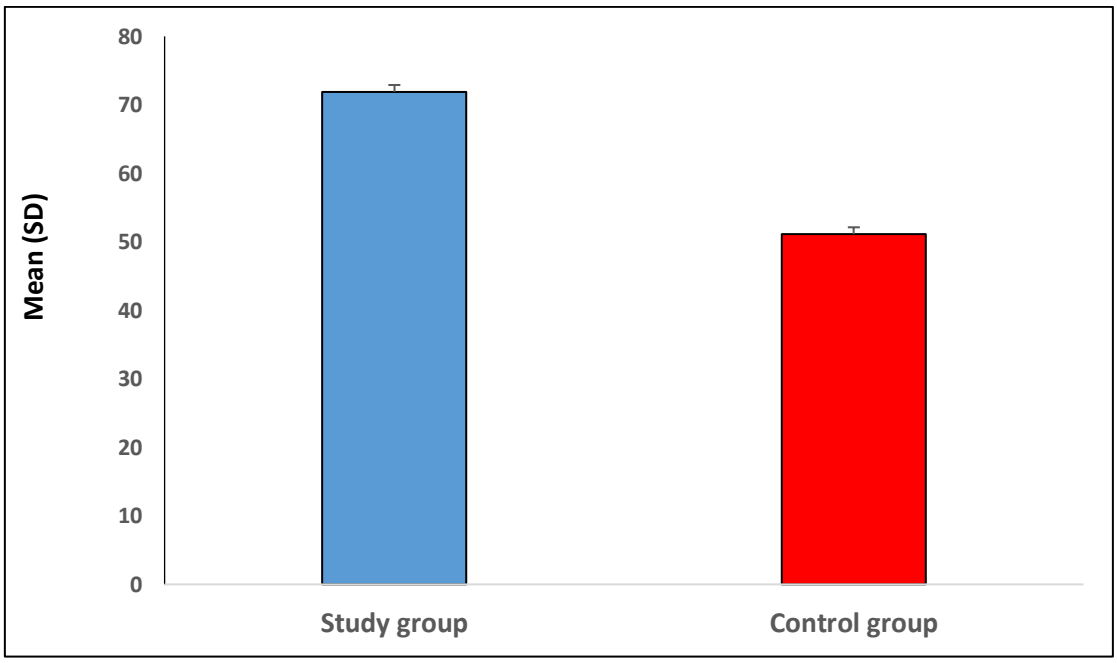

Figure 2. Mean follow up HOMA-B among the studied groups

Baseline and follow up laboratory data in each separate group (tables 5-6)

In the study group; there was significant improvement in the glycemic control during follow up in comparison to baseline data. Also, there was significant reduction in cholesterol and triglycerides. In contrast, the control group showed no significant differences between baseline and follow up laboratory data.

Table 5. Baseline and follow up laboratory data among the study group

	Baseline (n= 50)	**Follow up (n= 50)**	**P value**
Alanine transaminase (u/l)	38.64 ± 7.45	38.97 ± 5.99	0.09
Aspartate transaminase (u/l)	44.48 ± 9.42	42.34 ± 11.09	0.30
Urea (mg/dl)	9.38 ± 2.21	8.84 ± 2.01	0.08
Creatinine (mg/dl)	1.18 ± 0.26	0.99 ± 0.28	0.20
Cholesterol (mg/dl)	201.94 ± 47.42	159.18 ± 29.21	< 0.001
Triglycerides (mg/dl)	151.26 ± 47.98	121.54 ± 32.64	< 0.001
HDL (mg/dl)	43.16 ± 9.75	43.22 ± 9.01	0.06
LDL (mg/dl)	124.76 ± 37.39	119.10 ± 34.57	0.07
Fasting plasma glucose (mg/dl)	176.98 ± 34.78	162.45 ± 18.90	0.04
2h.PPG (mg/dl)	234.08 ± 70.59	182.76 ± 39.01	< 0.001
Glycosylated hemoglobin (%)	10.36 ± 1.72	7.13 ± 1.12	< 0.001
HOMA-IR	2.64 ± 0.67	1.74 ± 0.60	0.01
HOMA-B (%)	54.85 ± 16.04	71.90 ± 8.58	0.02

Data expressed as mean (SD). P value was significant if < 0.05. HDL: high density lipoproteins; LDL: low density lipoproteins; 2h.PPG: two-hours post-prandial glucose; HOMA-IR: homeostatic model assessment for insulin resistance

Table 6. Baseline and follow up laboratory data among the control group

	Baseline (n= 50)	**Follow up (n= 50)**	**P value**
Alanine transaminase (u/l)	37.47 ± 8.23	34.12 ± 4.04	0.06
Aspartate transaminase (u/l)	44.29 ± 8.40	41.41 ± 10.11	0.20
Urea (mg/dl)	10.58 ± 2.50	8.80 ± 2.15	0.09
Creatinine (mg/dl)	1.07 ± 0.45	1.01 ± 0.33	0.22
Cholesterol (mg/dl)	191.62 ± 41.11	198.26 ± 20.87	0.06
Triglycerides (mg/dl)	183.56 ± 55.64	186.44 ± 67.88	0.33
HDL (mg/dl)	45.54 ± 14.67	44.33 ± 11.11	0.10
LDL (mg/dl)	110.50 ± 34.88	124.33 ± 24.45	0.20
Fasting plasma glucose (mg/dl)	166.11 ± 45.90	188.11 ± 21.98	0.09
2h.PPG (mg/dl)	256.99 ± 90.73	253.20 ± 55.56	0.18

Glycosylated hemoglobin (%)	9.99 ± 2.22	8.90 ± 2.11	0.06
HOMA-IR	2.84 ± 0.44	2.38 ± 0.37	0.08
HOMA-B (%)	50.41 ± 7.79	51.13 ± 7.06	0.14

Data expressed as mean (SD). P value was significant if < 0.05. HDL: high density lipoproteins; LDL: low density lipoproteins; 2h.PPG: two-hours post-prandial glucose ; HOMA-IR: Homeostatic Model Assessment for Insulin Resistanc

Discussion

There is increasing data support the beneficial role of MD and its components on T2D, the exact mechanisms responsible for these effects remain only partially elucidated [7]. There is paucity in literature about effect of extra virgin olive oil on glycemic control, insulin resistance and insulin secretion in patients with type 2 diabetes.

The current study enrolled 100 patients with type 2DM. Those patients were randomly subdivided into either study group (50 patients) where patients received extra virgin olive oil with conventional therapy of DM or control group (50 patients) where patients only conventional therapy of DM.

The main findings in the current study included; both groups had insignificant differences as regard patients' characteristics and baseline laboratory data. During the follow up; the study group had significantly lower HOMA-IR, cholesterol and triglycerides with significant increase in HOMA-B. Also, the study group had improvement in the glycemic control and lipid profile during follow up in comparison to baseline data. Meanwhile, the control group showed no significant differences between baseline and follow up laboratory data.

There are many previous animal studies that discussed such issue and reported that EVOO improves glycemic indices [8]. In an animal study in type 2 diabetes mellitus (T2DM) mice, EVOO consumption for 24 weeks significantly reduced blood glucose and insulin [8, 9]. Another animal study in diabetic rats showed that EVOO oral administration significantly reduced blood glucose [9].

Mechanisms in which EVOO can exert its hypoglycemic effect in animal studies are as follows: higher protection in islets of Langerhans as it has straight effect against oxidation, stimulating glucagon-like peptide-1 (GLP-1) which trigger insulin secretion based on glucose detection and sending a satiety signal to the brain, and phenolic compound such as Oleacein decrease circulating insulin levels, improve insulin sensitivity, and can prevent metabolism dysfunction [10-12].In a meta-analysis included 13 trials that evaluated role of EVOO on glycemic control in type 2DM. The authors concluded that glucose, insulin, and HOMA-IR slightly reduced in the groups receiving EVOO compared with their control groups, although these reductions were not statistically significant. High heterogeneity and an insufficient number of articles might be the most critical factors that lead to statistically insignificant results. [13].

Another meta-analysis included four cohort studies including 15 784 T2D cases and 29 trials. The highest EVOO intake category showed a 16% reduced risk of T2D (RR: 0.84; 95% CI: 0.77, 0.92) compared with the lowest. In T2D patients EVOO supplementation resulted in a significantly more pronounced reduction in HbA1c and fasting plasma glucose as compared with the control groups [14].

In postprandial studies, EVOO showed a noticeable improvement in glycemic indices [15, 16]. In Violi et al. (2015)‘s study, a Mediterranean-type meal added with 10 g EVOO significantly decreased blood glucose and increased insulin in 25 healthy subjects compared with the control group [15].

In another study, a meal containing 10 g EVOO in patients with impaired fasting glucose was related to a significant decrease in glucose and an increase in insulin compared with the control group [16]. In a crossover study in T1DM, consuming three high-glycemic index differing in fat types showed that blood glucose was lower after the EVOO than after the butter or low-fat meals [17].

Wijayanthie et al. (2019) studied the effect of extra virgin olive oil (EVOO) and rice bran oil (RBO) on glycemic control and lipid profiles in patients with type-2 diabetes mellitus (T2DM). The authors found that changes in levels of FPG, PPG, TC, LDL-C, and TGs were not significantly different in the two groups. However, significantly decreased the levels of HDL-C were observed in both groups [18].

A major component of olive oil is oleic acid, a compound which belongs to the class of monounsaturated fatty acids. In a recent meta-analysis of randomized controlled trials performed by Qian et al. (2016) reductions in fasting glucose levels were significantly more pronounced following a high-mono unsaturated fatty acid (MUFA) diet as compared with a regimen high in

carbohydrates as well as high-poly unsaturated fatty acid diets [19].

However, improvements in parameters of glycemic control following high-MUFA diets could be confirmed in other studies as well. As potential mechanism of action, reductions in glycemic load and the consecutive attenuation in insulin secretion as well as increased insulin sensitivity may explain the beneficial effects of MUFA on glycemic control. Although there is some evidence of a beneficial effect of plant-based monounsaturated fatty acids, it is still not clear whether these effects are due phenolic compounds of extra virgin olive oil or the fatty acid composition [20-22].

In particular, Mediterranean diet (MD) supplemented with extra-virgin olive oil strongly reduces the risk of T2D in Mediterranean population at high risk of CVD [23] and downregulates the expression of atherosclerosis-related genes in peripheral blood mononuclear cells, in healthy subjects. Moreover, higher olive oil intake has been associated with a reduced T2D risk in a large women population as well. Although it is difficult to separate the effects of EVOO within a total diet, increasing evidence supports the benefits of olive oil polyphenols in human health [24, 25].

There are several reports indicate the existence of an association between elevated serum levels of liver enzymes and T2D. According to previous data reporting beneficial effects of olive oil consumption on fatty liver, the decreased levels of AST and ALT, indirect circulating markers of liver injury, seem to be a further positive response to the EVOO consumption [26-28].

A meta-analysis stated that olive oil interventions resulted in a significantly more pronounced reduction in HbA1c as compared with the respective control groups. No significant differences could be observed comparing olive oil interventions vs fish oil and PUFA-rich oils. Stratified analyses for age, study design, study length, administration of olive oil and type of olive oil confirmed the results of the main analysis [14].

Another finding in this meta-analysis; FBS values were more decreased in T2D in the olive oil intervention groups compared with controls. With respect to subgroups, comparing olive with fish oil and PUFA-rich oils, changes in fasting glucose were significantly more pronounced in the olive oil groups when compared with their respective controls as well [14].

Galvão Cândido et al. (2018) designed study to assess the effects of EVOO incorporated into an energy-restricted non-Mediterranean diet program on body weight, body composition and metabolic biomarkers in women with excess body fat. The main finding of their study was that the consumption of EVOO increases total fat loss and reduces diastolic blood pressure compared to the control soybean oil group [29].

It has been widely suggested that the consumption of a MD rich in olive oil can prevent type 2 diabetes mellitus, metabolic syndrome and obesity [30, 31]. However, randomized clinical trials in which the effect of olive oil on body weight/fat was investigated are scarce and presented conflicting results [32-34].

The main limitations of the current study included; relatively small sample size. Also, given the usually extended time scope, cohort studies not RCTs are better suited to investigate nutritional effects on incidence of T2D. However, they are not limitation-free (variations in dietary assessment methods making it difficult to compare actual intake of olive oil, recall bias etc.). Moreover, several of the included studies did not specify the type of olive oil used, limiting the interpretation of the present meta-analysis.

In conclusion, the present study provided evidence of favorable effects of olive oil on T2D risk and parameters of glycemic control. In light of other benefits, especially reported for extra virgin olive oil as an integral part of a Mediterranean diet, this vegetable oil represents a suitable component of a balanced diet. It's recommended to perform such studies on large number of patients in multiple centers to draw firm conclusion.

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