Supplementation with rich-polyphenols olive tree powder improves fasting blood glucose and insulin resistance in patients with type 2 diabetes mellitus: a 14-weeks randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Background- Despite the fact that olive tree extracts have been used for long time as antidiabetics in Mediterranean folk medicine, there are few studies on olive polyphenols providing support to this view.

Objectif- To assess the effect of rich-polyphenols olive extract on glucose metabolism and cardiovascular risk factors, a randomized, double-blinded, placebo-controlled trial was conducted in human subjects with type 2 diabetes.

Methods- Eighty T2D patients were randomized to receive either a daily dose of 3 g of olive tree powder

(6 capsules, 500 mg each) or placebo during 14 weeks. Anthropometric measures, glucose and insulin profiles, lipid profile and questionnaires administration were determined at the baseline and at the end of the trial. Doctors assessed potential adverse effects of olive tree powder through the period of study.

Results- Good compliance (over 94%) with the treatment was observed, without any study-intervention adverse and without any side effect observed. The lipid profile levels of treated group decrease significantly ($p < 0.0001$ vs. placebo group), while the value of HDL-cholesterol raise to 51.5 ± 9.4 mg/dL ($p = 0.007$ vs. placebo). The daily administration of rich-polyphenols olive tree powder results in a significant reduction (vs. placebo) in HbA1c ($p < 0.0001$), fasting glucose ($p < 0.0001$), insulin resistance ($p = 0.0002$). The average value of fasting glucose decreases to 114.2 ± 15.2 mg/dL, which is under to the normal range defined by the American Diabetic Association.

Conclusion- The supplementation with a rich-polyphenols powder from the olive tree was associated in a net improvement in fasting plasma glucose, insulin resistance and lipid profile in subjects with type 2 diabetes, suggesting the potential therapeutic effect of this extract as an antidiabetic.

Keywords: Type 2 diabetes mellitus; Olive tree powder; Olive tree extract; Glucose control; Randomized clinical trial.

INTRODUCTION

The most recent data published by the World Health Organization suggest that 422 million people already had diabetes by 2014 [1], while the projections predict

a continuous increase in the global incidence of diabetes to reach 552 million patients by 2030 [2]. This makes the pandemic of type 2 diabetes one of the enormous public health problems. T2DM is a chronic degenerative disease of metabolic disorders (most notably glucose metabolism), that progressively affects the optimal function of cardiovascular system, eyes, kidneys, nervous system and other organs such as the skin, liver and gut[2].

Regarding T2DM, one third of patients use alternative medicine to delay the disease outcomes, even without any scientific evidence supporting these uses (Yeh *et al.*, 2003). Data from comprehensive meta-analyses reported, in fact, inverse correlations between adherence to Mediterranean diet and risk of type 2 diabetes, as well as significant improvements in glycemic control (Babio *et al.*, 2014; Esposito *et al.,* 2009). The main features of this kind of diets is the predominance of plant foods and -notably- the high consumption of olive products (REF). Olive polyphenols are reportedly responsible for the health benefits associated with the Mediterranean diet (Martínez- González *et al.*, 2012; Babio *et al.*, 2009; Esturch *et al.*, 2006), as the analysis of the results from the PREDIMED trial showed an inverse correlation between polyphenol excretion and fasting glucose (Medina-Remón *et al.,* 2015). The most well studied phenolic compounds present in olive tree products are the catecholic derivatives, oleuropein and hydroxytyrosol, which show -according to in vitro and animal studies- antioxidant, anti-inflammatory, hypoglycemic, antihypertensive, antimicrobial, and anti-atherosclerotic properties (El and Karakaya, 2009).

For this reason, – in 2012 – the European Union recognize that a daily intake of 20 g of virgin olive oil containing, at least, 5 mg of hydroxytyrosol and its derivatives (notably,

oleacein), contributes to improve human health and well-being (EEC, 2012).

Additionally, the European Food Safety Authority has already endorsed the health claim that "the consumption of olive oil polyphenols contributes to the protection of blood lipids to oxidative damage" in 2006 (Bach-Faig *et al.,* 2011). This make exploring of the potential health benefits of olive products (rich in polyphenols) an expanding nutraceutical market. However, more studies on cultured cells, animals and - notably - humans are needed to provide compelling evidence that olive polyphenols are possible candidates for prevention and therapy of metabolic syndrome, particularly T2D.

For this purpose, we conducted a randomized, double-blinded, placebo-controlled, trial to assess the effect of olive tree powder on glucose metabolism in human subjects with T2DM. The main monitored outcomes were glycemic control and plasma biomarkers involved in the development of cardiovascular disease.

MATERIALS AND METHODS

Subjects

Men and women were recruited from October 2016 to February 2017 among of those referred to an outpatient clinic in Fez, Morocco. To be enrolled in the current study, subjects had to have been diagnosed with Type 2 Diabetes (T2DM) since at least one year based on the American Diabetes Association (ADA) criteria for the diagnosis of diabetes (A hemoglobin A1c (HbA1c) level of 6.5% or higher; A fasting plasma glucose (FPG) level of 126 mg/dL or higher; A 2-hour plasma glucose level of 200 mg/dL or higher during a 75-g oral glucose tolerance test (OGTT); A random plasma glucose of 200 mg/dL or higher

in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis). Study was thoroughly explained to the voluntary participants. Patients were not eligible if :

- they were under the age of 20 years or over the age of 80 years;
- >1 hour of physical activity per week with participation in weight-reduction programs;
- on insulin therapy;
- they had hepatic or renal dysfunction;
- they had history of malignancy;
- they had a clinically important hematological disorder or severe autoimmune disease;
- they were pregnant (or planned to be), or breastfeeding during the trial period; lactating;
- they were receiving contraceptive;
- they were smoking; drug or alcohol abuse.
  Exclusion criteria involved also the consumption of olive antioxidants or other antioxidant supplements ≤3 weeks before the intervention, history of allergy or intolerance to olive products. Before to be enrolled to this study, written informed consent was obtained from all voluntary participants.

Study design and intervention

The current study was planned as a double-blind, randomized, placebo-controlled trial (Fig. 1). It was directed according to the guidelines approved by Helsinki Declaration and the protocol was approved by the local ethics committee of the University Sidi Mohammed Ben Abdellah. Eligible participants were randomly assigned to Olive Tree Powder (OTP) supplement group or placebo group using a computer-generated random-number sequence. Researchers, participants and clinical staff

were blinded to the treatment codes of each group. The enrolled participants were invited by telephone to the clinic after an overnight fasting (between 8 and 14 h) to attend a screening visit (baseline analyses) including the assessment of adherence to the Mediterranean Diet (according to the modified questionnaire of Estruch *et al.* (2006)) and the evaluation of physical exercise by the International Physical Activity Questionnaire (Physical exercise was categorized as high, moderate, or low).

Participants were asked to maintain their habitual diet during the period of study, and avoid the consumption of olive products (including olive oil, olive table), and the use of all herbs or products known to affect glucose metabolism (synthetic or natural antioxidants). Dietary changes were monitored trough a 3-day dietary records at baseline and 14 weeks after intervention. Necessary explanations were provided about how to estimate food intake and record the estimations. We repeated all examinations and measurements after 14 weeks.

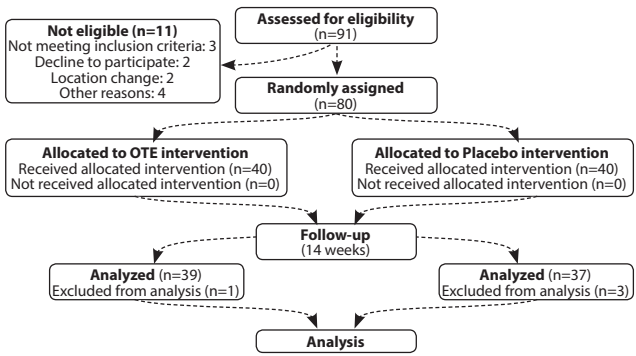

Figure 1. Study flow diagram.

During the study, all participants and investigators had free and continuous access to clinic for advice and consultation.

Participants who fulfilled all the inclusion criteria were received 500-mg study capsules (identical capsules for supplement and placebo group). Participants received also instructions concerning capsules taking and storage. Patients were asked to administrate 6 capsules per day before each meal and they were contacted every week to monitor supplement intake. Olive tree powder (OTP) was enclosed in soluble vegetal capsules. The placebo capsules contained only maltodextrin. OTP was obtained from different olive tree parts, fruits, olive tree young branches, and leaves using a purely natural and physical extraction (Laaboudi *et al.*, 2015). These specific olive trees are planted in the middle a rocky desert of Morocco, free of pollution, free of industrial activity, and under drought-stress (with temperatures up to 52°C). OTP is encapsulated in slight variations through the brand OLIVIE such as for example OLIVIE RICH/FORCE and marketed in Belgium as OLIVIE RICHE (see more in www.olivie.ma). Table 1 illustrate the main components of OTP extract.

LABORATORY MEASUREMENTS

Anthropometric measures were performed using calibrated scales and wall-mounted stadiometer with a precision of 0.1 cm; systolic and diastolic blood pressure were measured using a semi-automatic oscillometer (BosoMedicus smart Semi automatic Blood Pressure Monitor, Germany). Energy, nutrient intake and participants' diets assessment was carried out by Nutritionist 4.3 software (First Databank, Hearst Corp, San Bruno, CA). Blood samples were collected in EDTA and SST tubes. The obtained erythrocytes, plasma, serum and urine samples were aliquoted into 1 mL microtubes and stored at -80°C until further analysis. The fasting plasmaglucose(mg/dl) was assayed by the glucose oxidase method (Beckman Glucose Analyzer).The following parameters were measured: HbA1C (%), TC (mg/dl),

HDLcholesterol (HDL-c) (mg/dl), LDL cholesterol (LDL-c) (mg/dl), TGs (mg/dl), hemoglobin (g/dl), hematocrit (%) and erythrocytes (mil./mm3). TC, VLDL and TG were measured using enzymatic tests in a contract clinical laboratory. LDL-c levels were calculated by the Friedewald equation, HDL-c was measured by using theheparin-manganese precipitation method. High- sensitivity enzyme-linked imminosorbent assay kits (DiaSource, Belgium) were used to quantify serum levels of insulin according to the manufacturer's guidelines. Fasting insulin resistance was assessed with homeostasis model assessment and calculated with the following formula, according to Matthews *et al.* (1985): fasting plasma glucose (mg/dL) *fasting serum insulin (μU/mL)/405. High scores indicate high insulin resistance. Urinary hydroxytyrosol was quantified by High Performance Liquid Chromatography (HPLC) as markers of OTP intake. Briefly, hydroxytyrosol was extracted from acidified urine (hydrochloric acid, 0.6 N of final concentration) as described previously (Visioli et al., 2000) and analyzed in a Shimadzu chromatograph device equipped with a reverse phase C18 column (250 mm L. × 4.6 mm I.D., 5 μm).

Doctors assessed potential adverse effects of OTP administration over the period of study including mouth symptoms, digestive disorders, fullness, allergic skin response, and other intervention-related symptoms. Finally, global satisfaction assessment in response to treatment (GAST) (including anxiety) was evaluated using a 5-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent).

STATISTICAL ANALYSIS

Data were statistically analyzed using GraphPad Prism version 5.00 (GraphPad Prism Inc, San Diego, California). For the baseline characteristics, continuous variables are

expressed as mean values ± standard deviation (SD), and categorical variables are expressed as frequencies (percent). Normal distribution of data was checked using the Kolmogorov-Smirnov test. The difference between baseline groups characteristic was performed by, the independent t test, the Mann-Whitney U test, and the $\chi 2$ test for normally continuous data, not normally continuous data, and categorical data, respectively. the independent t test was also used to compare the mean changes from baseline to the end of the study between treated and placebo groups. Results with two- sided P values of <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Ninety-one eligible patients were enrolled, and 11 were excluded from the study for several reasons (Figure 1). Four participants were dropped out of analysis because they were unable to follow study protocol (Figure 1), due to higher fasting plasma glucose, total cholesterol and LDL-C levels than participants who completed the study. Good compliance was showed in treated-group (94.6%) and placebo-group (92.3%), without any observed study-intervention adverse. Urinary hydroxytyrosol determined as biomarker of compliance was quantified by HPLC. Results of the Figure 2 graph illustrate the changes from pre-intervention periods for placebo and treated (at 4 and at the end of study) group. The concentration of hydroxytyrosol founded in urine of treated participants was significantly higher ($P<0.0001$) compared to that of placebo group. However, it is worth noting that literature data on olive phenols absorption, metabolism, and excretion are not in agreement (Covas *et al.,* 2006; Visioli *et al.,* 2003).

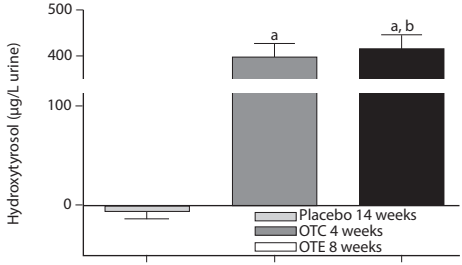

Figure 2. Change from baseline in urinary hydroxytyrosol excretion. Mean with SD. [a]P<0.0001, between OLF-group (at 4 or 8 weeks); [b]P=0.003, between OLF-group at 4 and 8 weeks.

Table 2 shows the baseline characteristics of the 80 participants who randomized into the treated and placebo group. Statistical analysis reveals no significant differences in demographic and clinical measurements among the two study groups, including the degree of adherence to Mediterranean Diet (*P*=0.326).

Table 1. Baseline characteristics of participants.

Parameter	Intervention group (n=40)	Placebo group (n=40)	*P* value[a]
Age (years)	53.27 ± 1.61	55.73 ± 1.97	0.346
Female, n (%)	17 (42.5)	15 (37.5)	0.915
Weight (Kg)	88.81 ± 3.55	86.15 ± 4.06	0.631
BMI (Kg/m^2)	30.5 ± 5.1	29.8 ± 4.7	0.175
BMI >30 (Kg/m^2), n (%)	28 (70)	24 (60)	0.632
BMI <25 (Kg/m^2), n (%)	7 (17.5)	9 (22.5)	0.539
Disease duration (y)	4.67 ± 1.4	3.50 ± 0.7	0.366
Family history of disease, n (%)	9 (22.5)	10 (25.0)	0.699
Diet, n (%)	7 (17.5)	9 (22.5)	0.813
OAH + Diet, n (%)	33 (82.5)	31 (77.5)	0.784
Hb$_{A1C}$ (%)	7.79 (0.8)	7.46 (1.1)	0.663

Hb_{A1C} level > 7%, n (%)	27 (67.5)	23 (57.5)	0.558
Glucose (mg/dL)	166.9 ± 10.8	162.4 ± 9.8	0.764
Insulin (µU/mL)	13.1 (5.6)	14.1 (6.4)	0.432
HOMA-IR	5.4 (2.8)	5.7 (3.1)	0.698
Total cholesterol	201.7 ± 14.6	199.3 ± 18.3	0.923
LDL-C	127.7 ± 13.8	133.9 ± 14.9	0.765
HDL-C	45.9 ± 6.2	43.6 ± 5.2	0.784
TGs	131.5 ± 11.7	127.1 ± 11.5	0.799
Systolic BP (mm Hg)	130.9 ± 11.4	129.3 ± 12.4	0.589
Diastolic BP (mm Hg)	81.3 ± 7.2	80.7 ± 7.7	0.643
15-item Mediterranean diet score	2.05 ± 0.15	2.40 ± 0.20	0.326

Value are expressed as mean ± standard deviation or in percentage.

[a]P value (<0.05) by independent t-test or Mann-Whitney test.

BP: Blood Pressure; BMI: Body Mass Index; Hb_{A1c}: Hemoglobin A1c; HDL: High-Density Lipoprotein; HOMA-IR : Homeostasis Model Assessment of Insulin Resistance; OAH: Oral Antihyperglycemic agents.

Results of dietary questionnaires represented in table 3 show that there was no significant difference in diet intake at the baseline and after 14 weeks of OLF and placebo supplement. The MUFAs and PUFAs – main components of the Mediterranean Diet – intake was maintained constant, which was good for the study since these nutrients affect (positively) plasma lipids and glucose metabolism of T2DM patients (Schwingshackl et Strasser, 2011; Esposito *et al.,* 2009). We also reported in table 3 change in participant's weight, with a slight decrease observed at the end of the intervention period in participant of treated group (but still not significant, P = 0.176). The level of macronutrient intakes was held constant during the study course and all participants met the daily diet recommended by the researchers by avoiding consumption of olive products and any other products known to affect glucose metabolism.

Table 2. Change in energy and macronutrients intake at baseline and end of the study for tow study groups. Data are expressed as mean ± standard deviation.

Parameter	OLF group (n=45)	Placebo group (n=45)
Energy (cal)		
Baseline	1755 ± 209.8	1809 ± 200.7
14 weeks	1832 ± 202.3	1445 ± 318.6
P value a	0.506	0.695
Fat (g)		
Baseline	75.90 ± 9.9	69.2 ± 12.4
14 weeks	69.7 ± 12.4	71.4 ± 15.4
P value[a]	0.507	0.680
PUFAs (g)		
Baseline	9.2 ± 1.4	8.9 ± 1.3
14 weeks	9.7 ± 2.9	10.7 ± 1.9
P value[a]	0.711	0.651
MUFAs (g)		
Baseline	22.7 ± 1.5	20.1 ± 1.7
14 weeks	21.7 ± 2.9	21.6 ± 1.2
P value[a]	0.510	0.450
SFAs (g)		
Baseline	15.3 ± 1.9	13.6 ± 2.7
14 weeks	15.2 ± 1.6	14.1 ± 2.9
P value[a]	0.655	0.844
Weight (kg)		
Baseline	88.81 ± 3.55	86.15 ± 4.06
14 weeks	86.31 ± 3.87	87.31 ± 3.46
P value[a]	0.176	0.359

PUFAs, polyunsaturated fatty acids; MUFAs, monounsaturated fatty acids; SFAs, saturated fatty acids.a Paired Student t test ($p<0.05$).

CLINICAL MEASUREMENT

At the end of the 12-week study period, weight and BMI were reduced in the intervention group, but with no significant difference compared to the control group (Table).

Table 3. Results from generalized linear model analysis describing changes in clinical and laboratory measurements between baseline and 14-monthfollow-up examinations. See legend of table 1 for the abbreviations.

Variable	Intervention group (n=39)		Placebo group (n=37)		*P* value[a]
	14-weeks	Δ study end	14-weeks	Δ study end	
Weight (Kg)	86.3 ± 3.8	↓ 2.5	87.3 ± 3.4	↑ 1.2	0.593
BMI (Kg/m^2)	28.1 ± 4.6	↓ 2.4	30.8 ± 3.9	↑ 1	0.332
HbA1C (%)	6.08 ± 1.2	↓ 1.3	8.6 ± 1.3	↑ 1.04	<0.0001
Glucose (mg/dL)	111.2 ± 15.2	↓ 55.7	172.7 ± 17.1	↑ 10.3	<0.0001
Insulin (μU/mL)	14.5 ± 2.5	↑ 1.4	13.6 ± 3	↓ 0.5	0.251
HOMA-IR	3.9 ± 1.2	↓ 1.4	5.8 ± 2.0	↑ 0.1	0.0002
Total cholesterol (mg/dL)	150.9 ± (26.4)	↓ 50.8	234.8 ± 37.3	↑ 35.5	<0.0001
LDL-C (mg/dL)	106.9 ± 20.1	↓ 20.8	150.9 ± 26.4	↑ 17	<0.0001
HDL-C (mg/dL)	51.5 ± 9.4	↑ 5.6	41.7 ± 11	↓ 1.9	0.007
TGs (mg/dL)	87.1 ± 11.2	↓ 44.4	148.8 ± 19.4	↑ 21.7	<0.0001
GAST	3.4 ± 0.6		2.2 ± 0.4		0.04

However, the lipid profile levels of treated group decrease significantly (vs placebo group) for Total cholesterol ($p < 0.0001$), LDL-C ($p < 0.0001$), and TGs ($p < 0.0001$), while the value of HDL-C raise to 51.5 ± 9.4 mg/dL ($p = 0.007$). The daily supplementation with the rich-polyphenols olive tree extract was associated to a significant reduction (vs. placebo) in HbA1c($p< 0.0001$), fasting glucose ($p < 0.0001$), HOMA ($p = 0.0002$). The average value of fasting glucose raises to 114.2 ± 15.2 mg/dL at the end the intervention, which is to the normal range defined by the ADA (13). The fasting insulin levels increased over time for the treated group (even the difference still no significant compared to the placebo

group p = 0.251), suggesting an improve in insulin secretion as well (taking together with the decrease in fasting glucose).

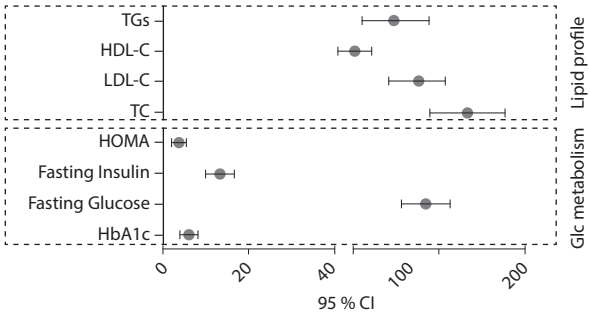

Figure. The horizontal line joins the lower and upper limits of the 95% Clof each corresponding parameter measured in the intervention group.

Additionally, almost all of the treated group participants have reported a very good satisfaction of the treatment, evaluated by the GASTquestionnaire (Table 3).

DISCUSSION

In this placebo-controlled trial, patient with T2D were allocated to a treatment by an aqueous olive tree extract during 14 weeks, by receiving a daily dose of 3 g (6 capsules, 500 mg each). No adverse signs and laboratory parameters fluctuation have been observed during the study period and within the three post-intervention weeks (data not shown). We found that the supplementation with rich-polyphenols OTE modulates carbohydrate and lipid metabolism, attenuate hyperglycemia, dyslipidemia and insulin resistance.

T2DM is an endocrine disease related impaired carbohydrate metabolism and insulin resistance [4]. Several authors reported that Mediterranean Diet (rich

in olive polyphenols) and polyphenol-rich foods (olive oil, tea, cocoa, cinnamon, grapes, and berries) modulate carbohydrate metabolism, and attenuate hyperglycaemia, dyslipidemia and insulin resistance [Elhayany *et at.,* Esposito *et al.,* 2009; 21, 22]. We have already shown -as well as many others authors- that a daily supplementation with olive polyphenols exert a hypoglycemic response in animal models [Laaboudi *et al.,* 2016; 23,24,25]. Furthermore, diabetic rats consuming 0.5 mg/kg olive leaf extract for 30 days showed improved blood glucose, and insulin secretion (26). More interesting, the anti-hyperglycemic effects of olive polyphenols were also demonstrated in prediabetics and diabetics human volunteers by several research groups [27,28,29,76].

The first goal of T2D treatment is to target glycemic control by maintaining HbA1c as close as possible to normal value (≤ 7%). Here, OTP supplementation for 14 weeks was associated with a reduction of HbA1c by ≈22% (more than 62% of participants have had a normal value at the end of the intervention). Similar effect was also observed in diabetic patients consuming a daily dose of olive leaves extract of 500 mg for 14 weeks, but the HbA1c values decreased only by 10% (Wainstein *et al.,* 2012). It is to be noted that the OTP represent the full spectrum of the tree, not only a single part of the olive tree such as isolated leafs. As we said in the beginning, OTP comes from olive tree leafs, baby leafs, olive fruit as well as olive oil. There is a positive synergetic effect produced by the mix of all the polyphenols present inside the olive tree in their natural proportions. How polyphenols influence the level of circulating glycatedplasma proteins is still not so clear. However, it was suggested that the antioxidant properties might diminish the production of advanced glycosylated end products such as HbA1c (Xiaoand Högger, 2015). T2DM is also associated with

deregulation of lipid metabolism, which can be positively targeted by olive polyphenols. In the well-known large multi-centre crossover trial (200 healthy men), Estruch et al. demonstrated the dose dependent improvements in plasma HDL status after administration of increasing polyphenol concentrations in olive oils. Supplementary, modulation of glucose metabolism would reduce the accumulation of lipids in the liver (as observed in a cholesterol fed rat model) and potentially offset de-novo lipogenic pathways (Jemai *et al.,* 2008). This might explain reduced dyslipidaemia (reduction in total cholesterol, LDL-C, TGs, and improvement in HDL-C) of the participants allocated to OTE. The supplementation with rich-polyphenols olive leaf extract improves fasting glucose in T2D diabetic subjects (Wainstein *et al.,* 2012), and both insulin sensitivity and secretion in overweight middle-agedmen (deBock *et al.,* 2013). Similar effects were observed at the end of this intervention with an improvement in fasting glucose, insulin resistance, and insulin secretion by over 33, 27 and 11%, respectively. We should underline, in fact, that we have used an olive tree powder (not an olive leaf extract) at high daily dose in comparison to de Bock' and Wainstein' studies. Additionally, the treatment by OTP might have an exaggerated response in patients who had already T2D compared to prediabetic subjects (deBock *et al.,* 2013), which can explain the results herein obtained. However, we all assume that polyphenols contained in our powder are responsible of the observed hypoglycemic effects. In this sense, it has been reported that a daily supplementation with rutin (500 mg) reduces fasting glucose levels by over 10% in diabetic patients at 4 and 8 weeks.

Because T2DM is a multifactorial disease, olive polyphenols might have multifaceted anti-hyperglycemic effects. Firstly, hydroxytyrosol and oleuropein have been

shown, *in vitro,* a strong inhibition of amylase andα-glucosidase (Adefegha *et al.,* 2012; Xiao *et al.,* 2013). Actually, our unpublished data show the same effect of the studied olive tree extract (rich in hydroxytyrosol) on α-glucosidase and α-mannosidase. On the other hand, polyphenols can act as direct suppressors of the proteins involved in the intestinal transport of dietary carbohydrate (Hanhineva *et al.,* 2010).This would result in the suppressed digestion of starch and therefore a lower glycemic response to foods. Furthermore, Polyphenols might affect glucose metabolism via a reduction of glucose release from the liver or a stimulation of cellular glucose uptake, which lead to reduced plasma glucose (Hanhineva *et al.,* 2010; Gonzalez *et al.,* 1992). Oleuropein and hydroxytyrosol (two phenols abundant in the studied extract) enhance glucose induced insulin secretion following oral glucose challenge in human subjects (de Bock *et al.,* 2013), and protect insulin-secreting β-cells against toxic H2O2 by maintaining normal redox homeostasis during an oxidative stress (Cumaôglu *et al.,* 2011).

CONCLUSION

Overall, results herein obtained demonstrate that the administration of rich- polyphenols extract from olive tree was associated to significant hypoglycemic effects in patients with type 2 diabetes. We suggest that olive polyphenols -as natural components of olive tree powder- exert an hypoglycemic effect, mainly by i) improving glucose-induced insulin secretion, and ii) increasing peripheral glucose uptake. Further research should compare hypoglycemic effect of pure polyphenols (from this olive tree powder) to conventional T2DM therapy (e.g. metformin) to better understanding the mechanism(s) by which these molecules contribute to glucose metabolism control.

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