Consumption of Virgin Olive Oil Influences Membrane Lipid Composition and Regulates Intracellular Signaling in Elderly Adults With Type 2 Diabetes Mellitus

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We aimed to define changes in membrane fatty acids and signaling proteins induced by virgin olive oil (VOO) consumption in elderly persons with type 2 diabetes (n = 16) compared to a control group (n = 28). The fatty acid composition was determined by gas chromatography and G-protein subunits and protein kinase C alpha (PKCα) by immunoblotting. VOO consumption increased the monounsaturated fatty acid content in phospholipids and cholesterol esters in both groups. In contrast, saturated fatty acids were decreased only in phospholipids. The levels of Gαo, Gβ, and PKCα were significantly lower in diabetics than in controls. However, whereas VOO consumption reduced Gαs, Gβ, and PKCα in both groups, reduction in Gαi was observed only in diabetics. These results indicate that long-term VOO consumption modifies the fatty acid composition of plasma membrane, which influences the association of G proteins and PKCα with the lipid bilayer. These combined effects probably account for the positive effects of VOO on glycemic homeostasis.

Type 2 diabetes mellitus is becoming one of the major health risks for elderly people in industrialized countries. Like hypertension and obesity, diabetes increases the probability of severe vascular pathologies, such as atherosclerosis, the consequences of which account for about 80% of premature deaths among diabetic patients (1). Although the origins of the increased prevalence of type 2 diabetes appear to be multiple, the nutritional impact of the so-called Western diet could be a major risk factor. Formerly, nutritional recommendations for diabetic patients were mainly focused toward high carbohydrate diets, primarily to avoid the increased cardiovascular risk associated with high levels of saturated fats (2). However, diets high in carbohydrates may make it difficult to achieve glycemic control (3). It has been demonstrated that virgin olive oil (VOO), a natural source of monounsaturated fatty acid (MUFA) consumption, has beneficial effects on glycemic tolerance (4,5) and cardiovascular parameters (6) in diabetic individuals. As a consequence, diets rich in MUFA are being increasingly advocated for patients with type 2 diabetes, because they contribute not only to lowering plasma glucose concentrations but also to reducing blood pressure, another cardiovascular risk factor (7,8).

It has already been established that the fatty acid composition of the cell membrane phospholipids is altered in individuals suffering from diabetes mellitus (9,10). Interestingly, dietary intake of VOO normalizes the fatty acid composition of cell membranes in healthy and hypertensive persons (11,12), and of plasma when those persons become elderly (13,14). We have recently demonstrated that fatty acids, either free or esterified, contribute significantly to the biophysical properties of membranes (15,16). Moreover, it has been shown in vitro that altered membrane properties provoke variations in membrane lipid–protein interactions. These alterations can provoke changes in the cellular localization and activity of important membrane-associated signal transduction proteins, such as G proteins and protein kinase C (PKC) (17–20). Interestingly, members of the glucagon receptor family, such as the important antidiabetic intestinal hormone glucagon-like peptide-1 or the glycogenolytic pancreas hormone glucagon, mediate their physiological effects through G protein-coupled receptors (21). Furthermore, PKC activation by hyperglycemia may be responsible for the progress of atherosclerosis, thereby promoting vascular pathologies in diabetic patients (22).

In the present study, we have analyzed the differences in the fatty acid composition of erythrocyte membranes from healthy elderly persons and elderly persons with type 2 diabetes. We have also examined the changes brought about in these persons by long-term VOO consumption in association with the key signaling proteins (PKC and G proteins) in the membrane in vivo. These results could in part explain the cardiovascular alterations associated with diabetes and some of the benefits of VOO consumption as part of the Mediterranean diet with respect to the development of cardiac complications of diabetic patients.
METHODS

Participants and Diets

This study was performed at the Residencia Heliópolis (Junta de Andalucía, Sevilla, Spain), a residential home for elderly persons where the diet of all the participants was controlled. All persons gave their written informed consent to participate in the study, and the protocol was previously approved by the Institutional Committee for Research on Humans (Virgen del Rocio University Hospital, Seville, Spain). During the study, the participants first consumed a diet enriched with sunflower oil (SO) (basal values), and then, for 4 weeks, a diet rich in VOO of the hojiblanca variety (Olea europaea var. hojiblanca). SO was chosen as baseline dietary oil as it was habitually consumed at the residence. Before the study, the health officers recorded the regular dietary intake of the participants over 4 consecutive weeks using 24-hour recall and food-frequency questionnaires. The energy consumption and nutrient intake of the participants were calculated and approved by a dietician. Diets were revised weekly and adjusted so that 30% of their energy was obtained from fats, 55% from carbohydrates, and 15% from proteins. The diets for each experimental group and period were analyzed in triplicate to determine the fat content and that of other nutrients. The energy consumption was approximately 1800 kcal/day in both experimental groups. The fatty acid composition of SO and VOO is shown in Table 1.

The participants included in this study were elderly type 2 diabetic patients or normoglycemic controls. The diabetic group consisted of 16 individuals (2 men, 14 women) with a mean age of 81.8 ± 6.9 years, and with mean plasma glucose and insulin values of 180.9 ± 17.1 mg/dL and 10.0 ± 1.6 mg/dL, respectively. Their creatinine and uric acid values were 1.0 ± 0.4 mg/dL and 4.3 ± 0.4 mg/dL, respectively. Diabetic patients were treated with sulfonylurea, biguanides, acarbose, insulin, and insulin analogues. The control group consisted of 28 persons (6 men, 22 women) with a mean age of 86 ± 1 years, and with mean plasma glucose and insulin values of 101.1 ± 14.9 mg/dL and 8.1 ± 1.0 mg/dL, respectively. Creatinine and uric acid values were 0.97 ± 0.03 mg/dL and 4.9 ± 0.3 mg/dL, respectively. The medical histories of all participants were reviewed before recruitment into the study, and a physical examination and a clinical biochemical analysis were performed to exclude possible secondary causes of diabetes. None of the participants in the study had hypothyroidism, and no history of alcohol abuse or cigarette smoking was found.

Preparation of Erythrocyte Membranes

Erythrocyte membranes were prepared as described previously (23). Briefly, blood samples obtained after overnight fasting were collected in heparinized tubes and centrifuged at 1750 g at 4°C for 10 minutes. The plasma and buffy coat were removed, and the erythrocyte pellet was washed twice with MgCl₂ at 110 mmol/L.

Analysis of Lipid Classes and Fatty Acid Methyl Esters

Total lipids were extracted following a modified version of the method of Rose and Oaklander (24), using butylated hydroxytoluene (BHT) as the antioxidant. Lipids were separated by thin-layer chromatography on silica gel plates (Kieselgel 60 F254; Merck, Darmstadt, Germany) using a mixture of hexane, diethylether, and acetic acid as the mobile phase (80:20:1, vol/vol/vol). The phospholipid and cholesteryl-ester fractions were scraped off the silica and transmethylated, and the resulting fatty acid methyl ester species were analyzed by gas chromatography using a model 5890 series II gas chromatograph (Hewlett-Packard, Avondale, PA) equipped with a flame ionization detector and a capillary silica column Supelcowax 10 (Supelco, Bellefonte, PA) 60 m in length with a 0.25 mm i.d. Injector and detector temperature were set to 250°C, and oven temperature ranged from 180°C at initial time to 205°C at the end of the chromatogram (25). Individual species were identified by comparison with known standards or by gas chromatography–mass spectrometry.

Immunoblot Analysis and Quantification of G Proteins and PKCα

Immunoblotting of G proteins and PKCα from erythrocyte membranes of elderly normoglycemic (control) and diabetic participants was performed as described previously (14). Briefly, membrane proteins were solubilized and fractionated by sodium dodecyl sulfide–polyacrylamide (10%) gel electrophoresis, and then immunoblotted. The following primary antibodies were used to detect the distinct proteins: anti-Gₛ₁₂ (1:5000), anti-Gₛ₁₆ (1:3000), anti-Gₛ₂₀ (1:3000), anti-Gβ (1:3000) (all obtained from New England Nuclear Corporation, Bad Homburg, Germany), and anti-PKCα (1:1000) (obtained from BD Transduction Laboratories, Heidelberg, Germany). Quantification was performed by regression analyses of the densitometric intensities of the immunolabeled bands of the samples versus standard curves from control participants (100%).

Statistical Analysis

The results of the statistical analyses are expressed as the mean ± standard error of the mean. The differences between experimental groups were determined by two-tailed t test and were considered statistically significant at a value of the method and of Rose and Oaklander (24), using butylated hydroxytoluene (BHT) as the antioxidant. Lipids were separated by thin-layer chromatography on silica gel plates (Kieselgel 60 F254; Merck, Darmstadt, Germany) using a mixture of hexane, diethylether, and acetic acid as the mobile phase (80:20:1, vol/vol/vol). The phospholipid and cholesteryl-ester fractions were scraped off the silica and transmethylated, and the resulting fatty acid methyl ester species were analyzed by gas chromatography using a model

### Table 1. Fatty Acid Composition of Sunflower (SO) and Virgin Olive (VOO) Oils

<table>
<thead>
<tr>
<th>Fatty Acid Species</th>
<th>SO</th>
<th>VOO</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:0</td>
<td>6.4 ± 0.4</td>
<td>10.9 ± 1.8*</td>
</tr>
<tr>
<td>16:1, n-7</td>
<td>0.1 ± 0.0</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>18:0</td>
<td>1.6 ± 0.3</td>
<td>2.4 ± 1.3*</td>
</tr>
<tr>
<td>18:1, n-9 t</td>
<td>ND</td>
<td>0.3 ± 0.2</td>
</tr>
<tr>
<td>18:1, n-9</td>
<td>25.1 ± 1.4</td>
<td>74.6 ± 0.6*</td>
</tr>
<tr>
<td>18:1, n-7</td>
<td>1.6 ± 0.3</td>
<td>3.5 ± 0.1</td>
</tr>
<tr>
<td>18:2, n-6</td>
<td>64.5 ± 1.2</td>
<td>4.5 ± 0.4*</td>
</tr>
<tr>
<td>18:3, n-3</td>
<td>ND</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>18:3, n-6</td>
<td>0.9 ± 0.1</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>20:1, n-9</td>
<td>0.4 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>22:6</td>
<td>ND</td>
<td>0.8 ± 0.12</td>
</tr>
</tbody>
</table>

Notes: Values are expressed as the mean ± standard error of the mean (n = 3).
* p < .05.
ND = Not detectable.
of $p < .05$. The differences among groups for phospholipids and cholesterol ester fatty acid compositions were analyzed by two-way analysis of variance with Tukey’s test for comparison of the means.

**RESULTS**

**Effects of Chronic VOO Consumption on Fatty Acid Composition in Erythrocyte Membranes of Elderly Type 2 Diabetic Individuals**

VOO consumption did not modify glucose levels in either type 2 diabetic participants or control participants (182.5 ± 19.4 mg/dL and 99.0 ± 8.1 mg/dL, respectively). The long-term consumption of VOO induced changes in the fatty acid content of erythrocyte membranes isolated from elderly type 2 diabetic participants. Prior to VOO consumption, the proportion of MUFA observed in erythrocyte membranes was generally between 21% and 25% of the total fatty acids. Following a 4-week period of VOO consumption, the proportion of MUFA increased between 2.5% and 3.1%, a relative change of at least 10% in all the lipid species and in both experimental groups studied (Tables 1 and 2). This change was mainly due to an increase in the proportion of oleic acid in the membranes (18:1 n-9). In contrast, VOO consumption induced a decrease of about 1.2%–5.5% in the levels of polyunsaturated fatty acids (PUFAs), a relative change of 3%–10% across all lipid species and in both experimental groups (Tables 1 and 2). In cholesterol esters, this decrease was mainly due to changes in the concentrations of 18:2 fatty acids (n-6), whereas among the phospholipids, it was produced by the contribution of various long-chain species with 20–24 carbons.

Interestingly, VOO consumption decreased the content of saturated fatty acids (SFA) in phospholipids by 1.1%–2.8%, which represented a relative change of 3%–7%, mainly due to a decrease in the stearic acid content (18:0). In contrast, the SFA content in cholesterol esters from erythrocyte membranes increased in both control and diabetic participants after consumption of VO. This increase represented an absolute variation of 1.5%–2.1% or a relative change of 9%–11%. As a result, the MUFA/PUFA and MUFA/SFA ratios were higher in membrane phospholipids after VOO consumption, both in normoglycemic and diabetic participants (Table 2).

In contrast, the PUFA/SFA ratio did not significantly change in membrane phospholipids from the control group, although they marginally increased in the diabetic group. Because phospholipids contribute approximately 75% of the total fatty acid content in membranes, these changes are particularly relevant to the biophysical properties of the membranes. With regard to cholesterol esters, the increase in MUFA only caused a significant increase in the MUFA/PUFA ratio after VOO consumption, and was only observed in the control group (Table 3). Neither eicosapentaenoic (20:5, n-3, EPA) nor docosahexaenoic acid (DHA) (22:6, n-3) could be found in cholesterol esters.

It is particularly interesting that, although diabetic participants presented significantly lower amounts of DHA...
and a higher proportion of lignoceric acid (24:0), the concentrations of these moieties were restored to normal levels after long-term consumption of VOO (Table 2).

Effects of VOO Treatment on the G Proteins and PKCα Density at the Membrane

The amounts of Gzα, Gβ, and PKCα associated with cell membranes from diabetic participants were significantly lower than those of membranes from normoglycemic participants, reaching 66 ± 7%, 51 ± 6%, and 73 ± 6%, respectively (Figures 1 and 2). In contrast, no significant differences in the levels of Gzα and Gzβ were observed between the two groups (Figure 1). Long-term VOO consumption induced a significant reduction in the membrane concentrations of Gzα, Gβ, and PKCα in the control group, registering decreases of 46 ± 10%, 52 ± 12%, and 59 ± 12%, respectively (Figure 1). In contrast, VOO consumption resulted in significant decreases in the membrane levels of Gzα, Gzβ, and Gβ in diabetic participants, decreases of 27 ± 10%, 72 ± 12%, and 65 ± 12%, respectively (Figure 1). In this group of individuals, the levels of PKCα also showed a tendency to decrease, although this finding did not prove to be statistically significant at the degree of stringency established (a decrease of 17 ± 8%). No significant changes were observed in the levels of Gzδ in elderly diabetic patients, or of Gzα and Gzδ in the control group after VOO consumption.

DISCUSSION

Diabetes mellitus is a condition that is usually accompanied by multiple metabolic disorders such as hyperglycemia or dyslipidemia, and as a consequence, changes in the microviscosity of the cell membrane in both type 1 and 2 diabetes (26,27). In the case of type 2 diabetes, a relationship has been demonstrated between membrane fluidity, the fatty acid composition of erythrocyte membranes, and diabetic retinopathy (a microangiopathic complication) (28). Besides the pharmacological approach to avoid hyperglycemia, another way to improve the metabolic state of diabetic patients that is less prone to side effects would be to directly influence membrane lipid composition through diet. For this reason, we have analyzed the effect of long-term VOO consumption, a characteristic of the Mediterranean diet, on the fatty acid composition of erythrocytes in elderly diabetic patients. The biophysical properties of the plasma membrane are determined not only by their polar headgroups but also by the fatty acid composition. Both the presence and configuration (cis or trans) of double bonds in fatty acids greatly influence the physical properties of membranes (15,16) and, as a consequence, the associated membrane–protein interactions (19). For this reason, we analyzed the fatty acid concentration in phospholipids and cholesterol esters from erythrocyte membranes of control and type 2 diabetic participants before and after long-term VOO consumption.

After consuming VOO for 4 weeks, the most apparent difference was a significant increase in the total amount of MUFA. This increase was mostly due to a rise in the proportion of oleic acid, probably caused by the high amount of oleic acid present in VOO. A more surprising finding was the decrease in SFA that was also detected, particularly because it is well known that the ratio of PUFA or MUFA to SFA in membrane lipids influences membrane fluidity (29). Higher PUFA/SFA ratios reduce the microviscosity of membranes (they become more fluid). In this context, the observed increase in the PUFA/SFA ratio could account for at least some of the beneficial effects of VOO, probably by reverting the pathologically diminished membrane fluidity in diabetic individuals.
The most significant contribution to the increase in PUFA content after VOO in diabetic participants was detected in DHA. Diabetes impairs fatty acid metabolism by decreasing the activity of Δ6 and Δ5 desaturases. These enzymes convert dietary linoleic acid and α-linolenic acid to PUFA, including arachidonic acid (AA) (20:4 n-6), eicosapentaenoic acid (20:5, n-3), and DHA (30). As a result, AA and DHA levels are reduced in the membrane phospholipids of several tissues, including erythrocytes (31,32). Whereas the AA content in phospholipids from erythrocyte membranes isolated from the diabetic patients was only slightly diminished, a very significant deficiency in DHA content was detected when compared with the controls. VOO consumption restored the DHA content in phospholipids and reduced the AA content in cholesterol esters without altering the AA content in phospholipids. As AA and DHA are formed through the Δ6 and Δ5 desaturase pathway, the AA decrease in cholesterol esters of diabetic persons might be compensatory for the DHA increase in phospholipids. It has been shown that supplementing the diet with n-3 fatty

![Figure 1](https://academic.oup.com/biomedgerontology/article-abstract/62/3/256/655788)
acids increases the content of DHA in the cell membranes of type 2 diabetic persons (33). We now report that VOO consumption also restores the concentration of DHA in the erythrocyte membrane phospholipids of these patients. This influence of VOO has previously been observed in healthy (34) and hypertensive (35) individuals, and it has been related to enhanced membrane fluidity and a decrease in systolic and diastolic blood pressures. Although it has not been proven, we have suggested that VOO stimulates the elongation and desaturation of ω-linolenic acid (18:3, n-3) to docosapentaenoic acid (DPA) (22:5, n-3) and DHA and their incorporation into membrane phospholipids (34). Therefore, VOO consumption might facilitate the competitive formation of n-3 PUFA at the expense of n-6 PUFA, which has been related to improvements in homeostasis and blood pressure (34,35).

Membrane microviscosity is only one of the characteristic biophysical properties of membrane bilayers. Other membrane properties include the propensity to form nonlamellar membrane structures, which also depends on membrane fatty acid composition. In fact, it has been demonstrated that an increase in the MUFA oleic acid (either free or as a part of other lipids) markedly augmented the nonlamellar, an increase in the MUFA oleic acid (either free or as a part of fatty acid composition. In fact, it has been demonstrated that membrane structures, which also depends on membrane biophysical properties of membrane bilayers. Other membrane-related mechanisms exist.

The reduction in the association of G proteins most likely affects signaling through hormones of the glucagon family that regulate glycemic clearance and glycogenolysis (21). Although other studies have shown higher serum concentrations of the antidiabetic glucagon-like peptide-1 after VOO consumption (4), our findings would lead us to expect that the physiological effect of this hormone would be diminished. This decrease would reflect the reduced amount of the signal transducing Gα proteins at the membrane, which should lower the concentration of the second messenger cAMP in the target cells and thereby impair insulin secretion. However, this apparently negative molecular effect of VOO could be more than compensated for by the inhibition of another key hormone in glycemic homeostasis, namely glucagon. Because glucagon also propagates its signal through Gα proteins, glycogenolysis and the ensuing increase of plasma glucose concentrations would also be inhibited, which leads to the conclusion that the physiological benefits of VOO consumption for diabetes are most probably achieved through antagonism of glucagon and not of its counterpart the glucagon-like peptide-1.

Like G proteins, the cellular localization and activity of PKCα is modulated by the lipid composition of the membrane (17,38). This enzyme is a key element in many G protein-coupled receptor-associated signaling pathways, including those involved in the progression of atherosclerosis, a common vascular complication among diabetic patients (22). We found that basal concentrations of PKCα were significantly reduced in elderly diabetic participants (Figure 2). Whereas the reduction in membrane PKCα concentrations was only slight after VOO consumption in the diabetic group, a significant decrease was detected in the control group. Therefore, it is likely that the lower basal levels of PKCα in diabetic patients also constitute an adaptive desensitization mechanism to circumvent the constant activation caused by hyperglycemia. Although the reduction of membrane-bound PKCα in diabetic participants was not as strong as that in the control group,
both groups showed the same tendency to reduce the associated PKCα after VOO intake. This result is in accordance with the need to inhibit prolonged PKC activation, an important molecular mechanism in the progression of atherosclerosis (39).

Because most of the molecular modifications induced by VOO consumption appeared both in diabetic and in control participants, the observed changes seem to be caused by a general beneficial effect that is not limited to the pathophysiological condition of diabetics. Therefore, the nutritionally induced alterations in membrane fatty acid composition, and as a consequence, in biophysical membrane properties, are most likely to cause the biochemical changes in the amount of signaling proteins. Furthermore, these data are of special relevance in the field of cell signaling, because a direct relationship between membrane lipid levels in human erythrocytes and neurons has been reported (40). As a result, the effects of a diet rich in VOO on membrane lipids and signaling proteins could also occur in neurons and other cells implicated in the control of glycemic homeostasis.

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