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Olio extravergine d'oliva, acido oleico, patologia Coronarica e Depressiva. Ruolo di una rete neurale artificiale

Extra virgin olive oil, oleic acid, coronary heart disease and depressive disorder. Role of an artificial neural net

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Key words : olive oil, oleic acid, platelets, coronary heart disease, depression, G protein, artificial neural net.

Riassunto

Per molti anni i ricercatori hanno studiato i rapporti fra stato di salute e assunzione di olio extra vergine d'oliva (e l'acido oleico) che viene considerato importante per la prevenzione della patologia cardiaca ischemica e di altre malattie. Gli aspetti biomolecolari che interessano la proteina G necessitano di ulteriori ricerche ma i livelli di acido oleico presenti nelle piastrine sembrano essere, con l'acido linoleico e l'acido arachidonico, un fattore discriminante di una cardiopatia ischemica anche se vi è un ampio dibattito sul ruolo svolto esclusivamente dall'acido oleico o in associazione con gli antiossidanti. Scopo dello studio è stato quello di evidenziare quali acidi grassi potrebbero essere utilizzati come markers di una patologia cardiovascolare ischemica e di una patologia depressiva ricorrendo all'uso di una rete neurale artificiale (RNA).

Abstract

For many decades, researchers have investigated the relationships between health status and consumption of extra virgin olive oil. Extra virgin olive oil (and oleic acid) is considered important for the prevention of coronary heart disease and other diseases. While the biomolecular aspects involving G protein need further research, oleic acid levels in platelets may be a discriminating factor, together with linoleic and arachidonic acid, for coronary heart disease. There is still ample debate regarding the effects of oleic acid alone or in combination with antioxidants.
The aim of the study was to understand which fatty acid could be utilized as markers of ischemic cardiovascular pathology and depressive disorder, and to classify subjects using an artificial neural net (ANN).

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Introduction

Diseases of the cardiovascular system, hypertension, aneurysms, thrombosis, heart attack, stroke, etc., in addition to being the leading cause of death in all developed nations are often debilitating diseases and are designed to grow with the increase of expectation of life. At one time it was thought that these illnesses affect only the industrialized nations, but today's data show that 80% of deaths occur in developing countries or those with emerging economies.
The major known risk factors are mainly related to inappropriate lifestyles such as smoking tobacco, reduced physical activity, obesity and eating mostly incorrect: the presence simultaneously of two or more factors multiplies the risk of experiencing cardiovascular disease.
According to the World Health Organization in 2005 there were 17.5 million deaths in the world for cardiovascular disease, representing 30% of all deaths. Of these, 7.6 million are due to heart disease and 5.7 million to stroke[1]. It is estimated that by 2015 the number of deaths from these diseases will increase, globally, to reach 20 million units, confirming its position as the leading cause of death in the world[1].
In 2005 the United States, 865 thousand people have died from cardiovascular diseases (35.3% of the total, ie one death every 2.8), with coronary heart disease known to be the leading cause of death overall with 445 thousand deaths. The number of deaths was far greater than the sum of deaths from cancer, accidents and HIV / AIDS[2]. In the United States it is estimated that in 2006 80 million people have been affected by one or more cardiovascular diseases.
Despite a death toll so high, if one examines the period between 1995 and 2005 there is a decline from previous years with a reduction of 9.6% in the number of deaths in absolute terms, while the standardized mortality rate decreased by 26.4%.

As for the near future, however, estimates derived from a report on demographic changes and cardiovascular disease in the period 1950-2050 indicate that mortality from cardiovascular disease in the U.S. could increase between 2000 and 2030[2,3]). This latest analysis suggests the need for a strong and immediate preventive action.

An analysis of cardiovascular diseases in the European Union indicates that these are responsible for 2 million deaths each year and, throughout the European continent, 4.3 million[1,4]. Coronary artery diseases are the diseases most responsible for fatalities from 741 thousand in the European Union member states and 1.9 million across Europe.

One thing is comforting only in part from the analysis of mortality rates in 20 years that have fallen in Western Europe and North America (37% in Finland and 42% in the United Kingdom), but have grown rapidly in some countries of Central and Eastern Europe (57% in Albania and 19% in Ukraine)[1,5].

In Italy, cardiovascular diseases still represent the leading cause of death, although the mid-'70s to today, the death rate is slowly decreasing.

The importance of health and socio-economic on data reported seems obvious and requires more effort because, according to available estimates, at least 50% of the risk factors of cardiovascular diseases can be prevented, attenuated or terminated by changing habits and lifestyle of the subject, with considerable health and socio economic advantages[6].

In fact, the cardio-vascular disease is, after parturition, the second leading cause of hospitalization but with much higher costs: these should be added to the potential years of life lost for death and in case of survival, the abandonment of work, rehabilitation, home care and continuous medical care[7].

Taken together, the health costs are fairly high: in Europe in 2006 the total economic impact of cardiovascular diseases has reached 192 billion euro, equivalent to 391 euros per capita, 57% of which were for direct health care costs and 43% for indirect costs for lost productivity and other costs in health care[1].

Health expenditure per capita average for cardiovascular disease in Europe amounts to 223 euros, but in Germany amounts to 413 euros, the United Kingdom to 313 euros to 235 euros in Italy, France and Spain at 207 euros to 130 euros. The total costs of cardiovascular diseases in Italy have been calculated at around 21.8 billion euros for 2006[1,8]. As part of the habits and lifestyle, the nutritional aspect of the quantity and quality of food given daily, plays a major role.

The incidence of myocardial infarction, however, is highly variable, with lower rates in Mediterranean countries compared to those in northern Europe, USA, or Australia[9]. Paradoxically, the low incidence of myocardial infarction occurs in spite of a high prevalence of classical cardiovascular risk factors[10].

Olive oil is the primary source of fat in the Mediterranean diet. The beneficial effects of olive oil on CHD have now been recognized, and are often attributed to the high levels of monounsaturated fatty acids (MUFA)[11]. Indeed, in November 2004, the US Federal Drug Administration (FDA) allowed a claim on olive oil labels concerning "the benefits on the risk of coronary heart disease of eating about two tablespoons (23 g) of olive oil daily, due to the MUFA in olive oil"[12].

A crucial element for a healthy heart: oleic acid and platelets

Oleic acid, and especially that obtained from pressing olives, is a crucial element in prevention of ischemic cardiovascular disease, as has been demonstrated by a series of international scientific activity. Fatty acids other than n-3 Polyunsaturated Fatty Acids (PUFAs) can interact with metabolism of eicosanoids and potentially influence platelet function. For example, there is evidence that diets rich in unsaturated fatty acids, such as linoleic acid and oleic acid, can also decrease thromboembolic risk by replacing arachidonic acid in platelet phospholipids, decreasing, at least in vitro, the production of thromboxane A_2 [TXA2] and platelet aggregation. However, there is little conclusive evidence that platelet function in vivo is affected by diet[13].

Oleic acid has been found to be a potent inhibitor of platelet aggregating factor (PAF) induced platelet aggregation and serotonin secretion. Consequently, in order to understand the molecular mechanisms of oleic acid action, the effects of this fatty acid on several biochemical events associated with platelet aggregation induced by PAF have been investigated. In particular, it has been found that oleic acid causes a decrease in the levels of phosphatidylinositide (PIP) and phosphatidylinositol bisphosphate hydrolysis (PIP2), which is associated with an inhibition of platelet aggregation induced by PAF. These results suggest that inhibition of the PAF response by oleic acid may be at least one of the steps involved in signal transduction[14].

Several reports in the literature have further suggested that olive oil may inhibit platelet function. This possible effect is of interest for two reasons. First, it may contribute to the apparent anti-atherogenic effects of olive oil, and second, it may invalidate the use of olive oil as an inert placebo in studies of platelet function. After exposure to olive oil, platelet aggregation and TXA2 release decreased, and the content of platelet membrane oleic acid increased significantly; platelet membrane arachidonic acid content was found to significantly decrease. This suggests that excess of oleic acid impairs the incorporation of arachidonic acid into platelet phospholipids. Olive oil also has an inhibitory effect on various aspects of platelet function, which might be associated with decreased risk for heart disease, although fish intake also plays a protective role[15].

The beneficial effects of olive oil can be attributed to its high content of oleic acid (70-80%). The consumption of olive oil increases the levels of oleic acid in cell membranes, which helps to regulate the structure of membrane lipids through control of signal-mediated G-protein, causing a reduction in blood pressure[16].

In rats, cardiovascular tissues treated with 2-OHOA (hydroxy oleic acid) show activation of cAMP in response to activation of Gs protein, which can be attributed to increased expression of Gs proteins. As a result, there is significant reduction in systolic blood pressure[17]. The involvement of Gs alpha protein is also of interest considering the hypothesis forwarded by Cocchi, Tonello, Rasenick and Hameroff in psychiatric disorders as depression, suicide etc. (private meeting, 2008). In light of the below model, the role of Gs protein in ischemic heart disease merits further investigation.

In figure 1, the molecular depression hypothesis described by Cocchi et al. [18], Donati et al. (19) and Hameroff and Penrose (20) is shown. Because of the possible similarity of the platelet to neurons, membrane viscosity can modify Gs protein status. The Gs protein is associated with tubulin. Depending on local membrane lipid composition, tubulin may serve as a positive or negative regulator of phosphatidylinositol bisphosphate hydrolysis (PIP2) similar to G proteins. Tubulin is known to form high-affinity complexes with certain G proteins. The formation of these complexes

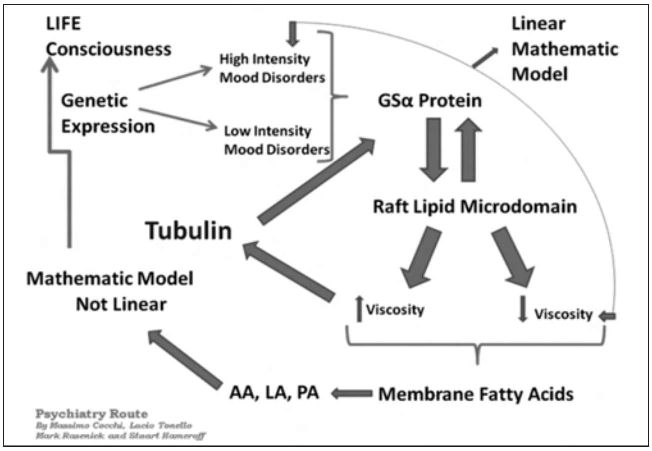


Figura 1
Description of selected biochemical and biomolecular events potentially involved in psychiatric disorders.

allows tubulin to activate G alpha protein and creates a system whereby elements of the cytoskeleton can influence G-protein signaling. Rapid changes in membrane lipid composition or the cytoskeleton can modify neuronal signaling through such a mechanism.

Protein kinase C (PKC) activation (Figure 2) is preceded by a number of steps, originating from the binding of an extracellular ligand that activates a G-protein on the cytosolic side of the plasma membrane. This G-protein, using guanosine triphosphate (GTP) as an energy source, then activates protein kinase C (PKC) via the phosphatidylinositol bisphosphate (PIP2) intermediate, which is shown as the diacylglycerol DAG/IP3 complex. Several studies have shown reduced functionality of the serotonin (5-HT) transporter in some psychiatric disorders, such as obsessive-compulsive disorder (OCD), may be related to alterations in its regulation at an intracellular level. PKC has also been reported to provoke a decrease in the number of 5-HT transporter proteins. The increased activity of PKC in OCD may be the result of increased activity of the phosphatidylinositol pathway.

The exclusive use of olive oil during food preparation seems to offer significant protection against ischemic heart disease, in spite the poor clinical, lifestyle and other characteristics of individuals[22]. In addition, several historical papers have reported on the positive effects of olive oil on CHD. In 1985, Mattson and Grundy[23] reported that olive oil reduces HDL cholesterol, which plays a protective, anti-atherogenic function, favoring the elimination of LDL-cholesterol. In 1986, Sirtori et al.[24] have shown that in addition to its effects on cholesterol and atherosclerosis, olive oil has preventive action on thrombosis and platelet aggregation. High intake of olive oil is not harmful, and reduces the levels of LDL-cholesterol, but not HDL[25, 26, 27, 28, 29, 30, 31, 32, 33].

Depression and Ischemic Heart Disease: a common role for oleic acid?

Because of the particular role of platelets in control of depressive and thrombogenetic risk, our group has investigated the platelet fatty acid profile in three groups of subjects: healthy (n=60), ischemic (n= 50) and depressive (n= 84). The aim of the study was to understand which fatty acid could be utilized as markers of ischemic cardiovascular pathology and depressive disorder, and to classify subjects using an artificial neural network (ANN). All the ANNs tested gave essentially the same result. However, one type of ANN, known as a self-organizing map (SOM),[34,35,36], gave additional information by allowing the results to be described in a two-dimensional plane with potentially informative border areas. The central property of the SOM is that it forms a nonlinear projection of a high-dimensional data manifold on a regular, low-dimensional (usually 2D) grid. A series of repeated and independent SOM simulations, with the input parameters being changed each time, led to the finding that the best discriminate map was that obtained by inclusion of the following three fatty acids: palmitic acid (C16:0), linoleic acid (C18:2 *n*-6) and arachidonic acid (C20:4 *n*-6) for depressive subjects and oleic acid (C18:1), linoleic acid and arachidonic acid for ischemic subjects[18, 37, 38, 39] (Figures 3, 4).

Commonalities between CHD and Depression

To demonstrate the powerful grouping capacity of the SOM, a new network has been created where all three groups were inserted and grouped simultaneously on the basis of the characteristics of the triplets previously highlighted, which were all different from one another[40] (Figure 5).

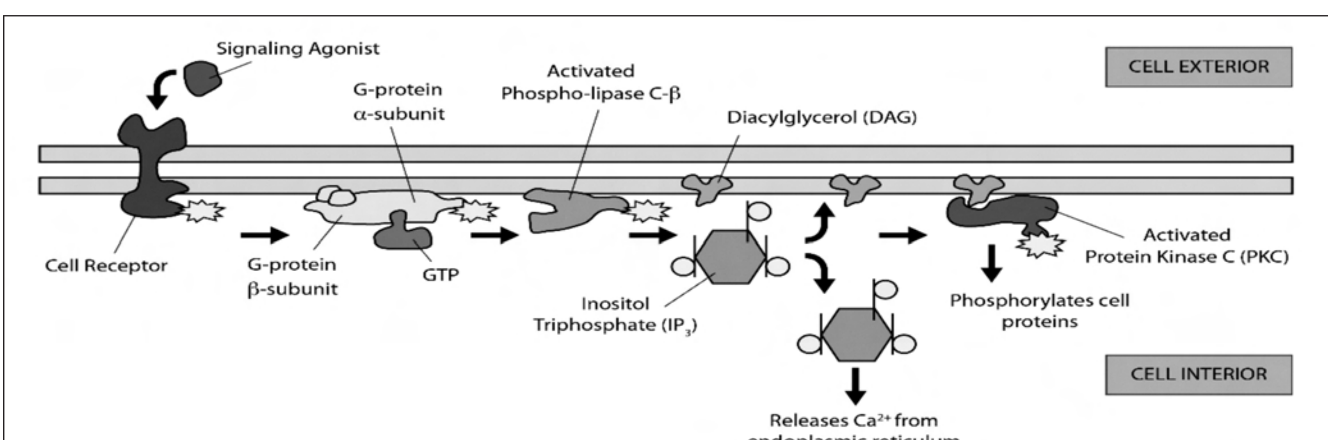


Figura 2
description of PKC activation. Adapted and modified from Alberts et al. (21)

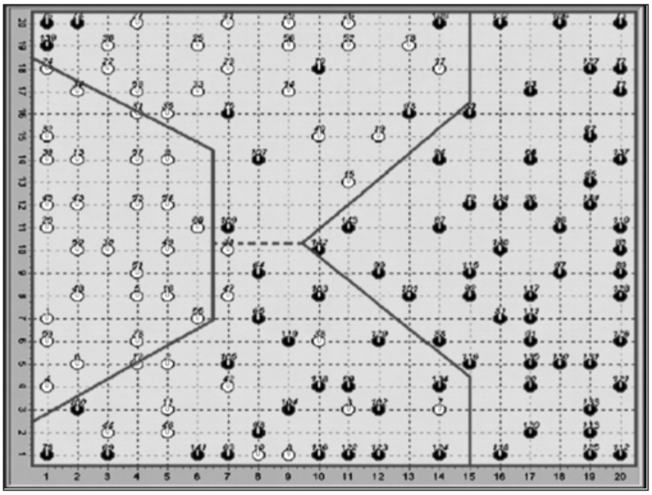


Figura 3
SOM classification of depressive subjects (black) against normal subjects (white). Platelet arachidonic acid (C20:4), palmitic acid (C16:0), and linoleic acid (C18:2) can discriminate depression and have diagnostic power.

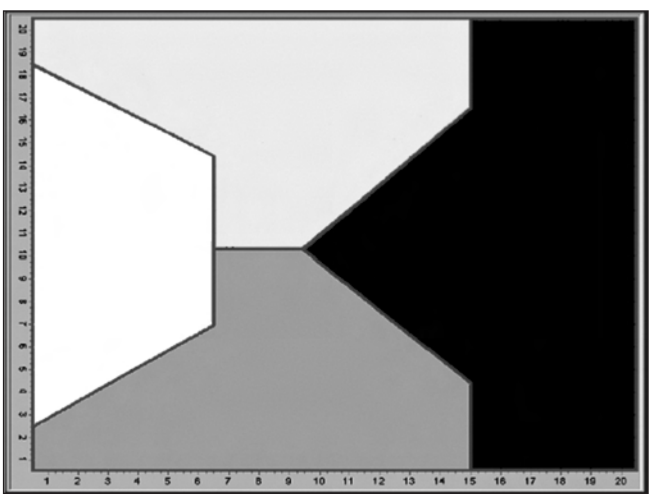


Figura 4
SOM classification of ischemic subjects (black) against normal subjects (white). Platelet oleic acid (C18:1), arachidonic acid (C20:4), linoleic acid (C18:2) can discriminate ischemia and have diagnostic power.

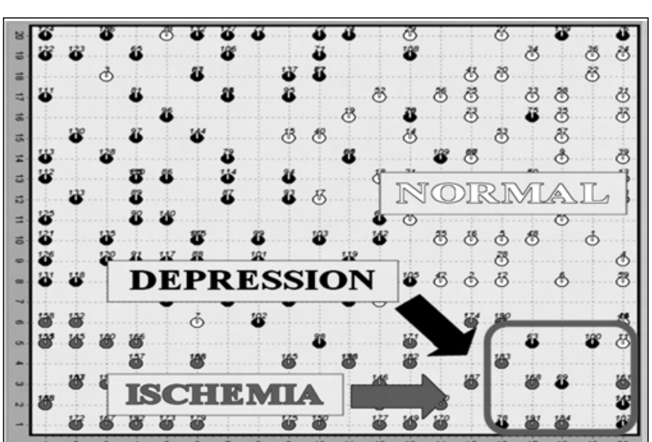
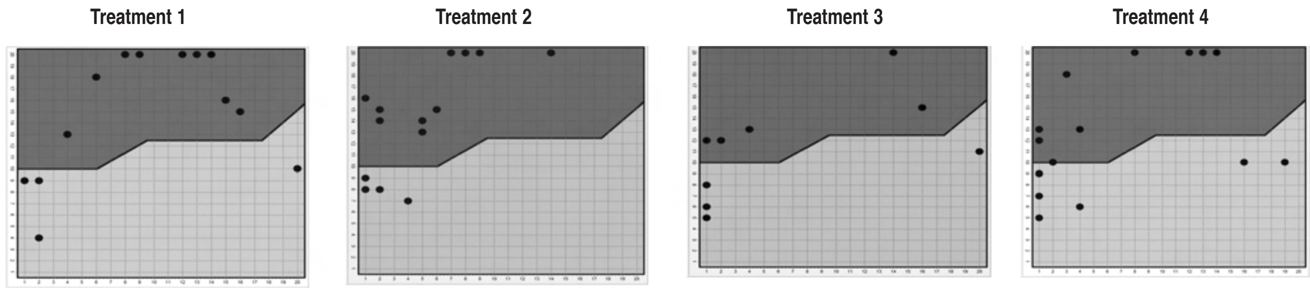


Figura 5
Simultaneous classification, using the SOM, of three groups of subjects (normal, depressive and ischemic). In the right corner of the map, ischemic and depressive subjects are mixed and have, in common, a low level of platelet oleic acid.

As shown by the SOM, it is possible that reduced amounts of oleic acid not only are critical in the biochemical classification of ischemic heart disease, but are also common to a condition that characterizes a relationship between depression and ischemia[41]. It seems possible that levels of C18:1 in platelets dominates in ischemia, and are linked to depression. Furthermore, it can be conjectured that there are two different types of depression, namely classical and ischemia-induced according to the findings of different platelet membrane viscosity and its effect at the biomolecular level[18, 19, 20]. The relationships between depression and ischemic heart disease have been widely studied[42,43]. Interestingly, Weyers and Colquhoun[44] reported improvements in depressive symptoms in patients with CHD after consumption of olive oil.

Do we eat enough extra virgin olive oil?

The question then arises as to whether there is sufficient consumption of olive oil and oleic acid in the Italian population. Knowing that oleic acid can significantly change the composition of platelet fatty acids, which are crucial in the genesis of plaque formation, and can significantly alter the amount of oleic acid in platelet membranes, an experiment on a large group of pigs (80 Duroc x Large White) was performed[45]. Four groups of pigs were studied, 20 animals each, which received four diets containing different lipid fractions, as follows:
Diet 1: corn oil (low linoleic acid.), diet 2: corn oil (medium linoleic acid.), diet 3: sunflower oil (high oleic acid.), diet 4: sunflower oil (high oleic acid) + palm oil (high palmitic acid). Significant changes in platelet fatty acid composition were seen in the different groups.
The modifications in fatty acid platelet composition were plotted as for ischemic and normal human subjects in the SOM for ischemia (Figure 6). It is feasible to obtain similar results in humans. If one considers the characteristics described for the pig model of atherosclerosis[46], and applying similar characteristics to humans, it can be assumed that we should consume a quantity of oleic acid, and consequently, extra virgin olive oil, that is at least twice that of current levels. To demonstrate this, we made simple considerations based on data on the consumption of olive oil in Italy (Table 1).
Based on data provided and taking into account that the value derived from the table should be increased by 40%, since about 40% of purchase data were excluded, the consumption of extra virgin olive oil for each Italian is on average, about 11.76 grams of oleic acid daily, considering an that olive oil is on average value about 70% oleic acid. This value is even likely to be less, as much oil is also used for frying, and therefore cannot be included as part of raw consumption. While this quantity is very small, there are also regional differences between the north and south of Italy.
This observation is also related to the observation that current eating behavior does not allow large consumption of olive oil. It should be remembered that meals eaten out of the household, often consisting of a sandwich, make it difficult to consume extra virgin olive oil in larger quantities. While the eating habits of rural areas may still be able to compensate for the problem, there is an increasing trend to gradually move away from such traditions.
Given this, as Ancel Keys pointed out, one wonders if the Mediterranean diet is still a model of health, considering the consumption of extra virgin olive oil.



Summary	N	%
Normal Area	5	25
Ischemic Area	15	75
Border line	0	0
Total	20	100

Summary	N	%
Normal Area	5	25
Ischemic Area	15	75
Border line	0	0
Total	20	100

Summary	N	%
Normal Area	8	40
Ischemic Area	12	60
Border line	0	0
Total	20	100

Summary	N	%
Normal Area	8	30
Ischemic Area	12	65
Border line	0	5
Total	20	100

Figura 6

By increasing the oleic acid content in diets is possible to move pig platelets, in agreement with the fatty acid triplet [31, 32], from the pathologic (dark gray area) to the normal (light gray area) area.

Tabella 1

PURCHASE OF OLIVE OIL IN ITALY, BY REGION, PROVIDED BY THE ISTITUTO DI SERVIZI PER IL MERCATO AGRICOLO ALIMENTARE (ISMEA).

	1000s liters	
	2008	2007
Total domestic purchases of olive oil in Italy	302,554	296,150
Piemonte, Val d'Aosta, Liguria	31,009	30,763
Lombardia	40,344	42,232
Triveneto	31,855	31,275
Emilia Romagna	19,890	18,712
Toscana, Sardegna, Umbria, Marche	41,647	39,965
Lazio	26,482	23,442
Campania, Abruzzo, Molise, Puglia	64,022	66,608
Sicilia, Calabria, Basilicata	47,301	43,156
Source: Ismea-Nielsen		

Conclusion

Olive oil, and, particularly an extra virgin olive oil-rich diet, decreases prothrombotic activity, and modify platelet adhesion, coagulation, and fibrinolysis. The wide range of antiatherogenic effects associated with olive oil consumption can help to justify the low rate of cardiovascular mortality found in southern European Mediterranean countries, in comparison with other western countries, despite a high prevalence of CHD risk factors. Experimental evidence confirms a critical role of reduced levels of oleic acid in platelets in ischemic subjects with a diagnostic discriminant capacity from normal subjects. At present, although traditional cardiovascular risk factors are under revision, a new field of research in platelets, and in particular oleic acid and its relationship with linoleic and arachidonic acid, should be pursued. The mechanisms by which olive oil exerts its beneficial effects merit further investigation, and additional studies are required to document the benefits of olive oil consumption on primary endpoints for cardiovascular disease. In this regard, consumption of extra virgin olive oil and daily intake of oleic acid should however be promoted.

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