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Review

Obesity and the metabolic syndrome in Mediterranean countries: A hypothesis related to olive oil

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In Mediterranean countries people would previously have consumed a diet with a high proportion of MUFA. Physical activity would have been intense with a low level of stress. The stearoyl-CoA desaturase (SCD1) system selected over thousands of years of this type of behavior must have adapted to a particular capacity of self regulation. Now, this pattern, called the "Mediterranean diet", has been broken and many people living by the Mediterranean consume a high quantity of calories, mainly from saturated or n-6-rich fats and the relative intake of MUFA has decreased. Simultaneously, physical activity has decreased and the pattern of stress has changed towards what is called a western lifestyle. In this new context, if people have a favorable, genetically conditioned SCD1 activity that will let them confront the new situation or else have some other compensatory mechanism, such as being keen on sport, etc, then they can prevent the appearance of some of the complications associated with the metabolic syndrome. If, on the other hand, the SCD1 pattern is genetically unfavorable for this new situation and they have a new cultural context, then they do not have the alternative compensatory mechanisms and the probability of developing the metabolic syndrome is high.

Keywords: Adipose tissue / Mediterranean diet / Metabolic syndrome / Obesity / Olive oil

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1 Introduction

The increased prevalence of obesity is one of the greatest public health problems in the industrialized world. The rapid adaptation to the current lifestyle, the reduction in physical exercise and the increased consumption of tasty, affordable food that has a high energy density are among the causes of this increase in most industrialized countries, as well as in developing countries that adopt a similar lifestyle. Obesity increases the risk of diabetes, hypertension, coronary disease and non-alcoholic hepatic steatosis, either independently or within the context of the metabolic syndrome [1, 2]. A new concept, lipotoxicity, has emerged as one the mechanisms explaining some of the pathophysiological disorders associated with the metabolic syndrome [3].

Humans are generally accepted to have a particular genotype. This genotype, which is the result of evolution, has remained unchanged for thousands of years and the increase in the prevalence of obesity is considered to be the result of the interaction between this genotype and the changing lifestyle of the industrialized countries [4]. Two of the most important recent changes are a reduction in physical activity and an increased consumption of calories from fat. However, the role of fat in the genesis of this epidemic is unclear. Some authors defend the importance of fat [5], whereas others doubt it [6], and some studies have even found a negative correlation between fat intake and the increased prevalence of obesity [7]. Other studies that have examined the type of dietary fat have found a weak positive association with the intake of animal fat and a negative association with vegetable fat [8], with yet others detecting no association between the type of dietary fat and the prevalence of obesity [9]. Experimental animal models (rats)

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Abbreviations : **LA**, linoleic acid; **LNA**, linolenic acid; **PPAR**, peroxisome proliferator-activated receptor; **SCD**, stearoyl-CoA desaturase

have shown that a diet having a 2:1 ratio of n-6:n-3 PUFA results in a greater increase in weight and adipocyte volume than a diet based on a linoleic:linolenic acid (LA:LNA) ratio of 59:1 [10]. Most studies have examined the role of saturated fatty acids and n-6 and n-3 PUFA [11–13], with the role of MUFA in body weight being less well known. Recent studies in rats suggest that an increase in MUFA increases adipocyte lipolytic activity [14], and that diets with different fatty acids can influence the increase in weight and the redistribution of body fat [15]. Clinical and epidemiological studies have shown that a diet rich in MUFA reduces peripheral resistance to the action of insulin [16]. However, the role of a diet with different fatty acids (though with the same level of energy) on the increase in body weight in humans is not yet fully established [5–7].

2 White adipose tissue during the initial stages of development

One factor determining the size of the fat depot could be related with adipocyte changes during development. The first traces of white adipose tissue in a human fetus appear between weeks 14 and 16 of prenatal life. Adipocytes, as functional cells, are already present in almost all parts of the body by week 23 of gestation [17]. Adipose tissue in humans grows in cell size (hypertrophy) and cell number (hyperplasia), although not linearly, at least during the early years [17–22]. Consideration of these studies, together with others related with adipocyte precursors [23, 24], shows that the early stages of life are especially sensitive to changes in adipocyte resources and thus the size of the adipose organ [10].

3 n-6 fatty acids and obesity

In 1996, our research group found that the growth of adipose tissue in humans during the early years of life was correlated with the tissue composition of n-6 PUFA; these fatty acids are not synthesized by the organism but come instead from the diet [18]. Numerous studies have suggested that n-6 PUFA, unlike n3 PUFA, are powerful promoters of *in vitro* adipogenesis and of the development of adipose tissue *in vivo* during gestation and nursing. Adipogenesis is dependent on glucocorticoids, insulin and IGF-1. Fatty acids act as adipogenic hormones *via* activation of a group of nuclear receptors, important among which is peroxisome proliferator-activated receptor gamma (PPARγ), which establishes a clear link relating diet with increased fat mass [25]. Other lipid mediators able to activate this pathway include prostaglandins and endoperoxides, derived from arachidonic acid. Arachidonic acid, a product of dietary linoleic acid, promotes the differentiation of preadipocytes, an effect that is blocked by cyclooxygenase inhibitors. Additionally, a great body of evidence exists concerning the role of fatty acids in the regulation of adipocyte proliferation and differentiation [10]. The biological effects resulting from changes in nutritional habits concerning dietary fats are difficult to assess in populations, as an increase in one type of dietary fatty acid is always accompanied by a relative decrease in one or more of the other fatty acids and the biological effects may be the consequence of either the increase in one or the decrease in the other.

In USA, in the second half of the 20th century, there was a continuous increase in the amount of α-linoleic acid in the diet and in breast milk [26]. This increase, together with the results of experimental studies, led Aillaud *et al*. [10] to propose the hypothesis that an increased consumption of n-6 PUFA in association with a high LA/LNA ratio, encourages the continuous development of adipose tissue during pregnancy and the nursing period, a period that is especially sensitive to nutritional stimuli, and during which physical activity is similar for all. This early stimulation of adipocytes and their precursors could be the start of obesity in the adult, especially if the intake of diets rich in n-6 PUFA continues during life.

4 Nature *versus* Nurture: What is the importance of environmental factors in the development of the obese phenotype?

It was probably Francis Galton who introduced the expression Nature *versus* Nurture in biological nomenclature [27]. It is a simple, clear and even poetic phrase, but looking back and with no intent to offend, may have done more harm than good as it highlights the dying aspect between nature and culture (biology *versus* culture or environment). It oversimplifies in a competitive manner the opposing aspects of genetics and the environment, suggesting that the relationship between genotype and phenotype is a simple question of causality. Nevertheless, during the whole of the 20th century a vast amount of information has been accumulated concerning the collaborative aspects of a model of co-action, interaction, and even collaboration between the genome and the environment. In this discussion, both social sciences and the environment, as well as genetics itself, have all lost. At times, it was the environmentalists who saw in the radicalization of the biological or genetic thesis the seeds of a radical biologicism that threatened an open conception of human nature. At other times, it was the biologicists who saw in the radical environmentalists the seeds of a prescientific, if not openly antiscientific model. Nowadays, we know that a good part of the human phenotype (physical appearance, disease, behavior) is based not only on the type of genes inherited, but also on the fact that the environment can modify the expression or behavior of these genes. For example, few doubt the existence of a genetic predisposition to cardiovascular disease, that smoking is an important

environmental cause of cardiovascular disease and that certain persons may be genetically predisposed to acquire the habit of smoking [28]. Establishing a relationship of causality between the multiple factors is an opportune strategy if we wish to arrange the causative factors in order of importance when attending a patient with coronary disease who is also a smoker. Similar examples exist between diet and metabolic or cardiovascular diseases. The influence, therefore, of genes in the acquisition of a particular habit, or the influence of the habit on the expression of certain genes, or the interaction of different genes, have complicated even more than initially expected the simple phrase of nature *vs*. nurture. Furthermore, from the agonic perspective between biology and environment, it is difficult to understand how we managed to reach this point in life in general and human life in particular. Contemporary Darwinian thought covers equally both competence and cooperation, and in the case of human behavior, even altruism [29].

5 Thrifty genotype theory

Modern man in industrialized countries lives in a world of energy abundance where the phylogenetically developed capacity to accumulate fat in adipose tissue to cope with times of shortage has little sense. Theoretically, there is little evidence to suggest that humans have developed mechanisms to prevent obesity; indeed, the opposite may well have occurred, as obesity could have been the tool that many animals, including man, developed to survive during famine, as suggested by Neel in his theory of the "thrifty gene" [30]. In fact, some of these genes that permit the rapid adaptation to times of readily available high-energy foods (fats), allowing storage or consumption of the energy from dietary fatty acids, such as the mu-opioid receptor [31], have already been identified.

6 The increased prevalence of obesity in Mediterranean countries

The increase in obesity has arisen not only in USA [32] but also in most European countries [33], especially those around the Mediterranean and in eastern Europe [33]. Studies carried out in certain regions of Spain show obesity figures of over 28% for the general population [34, 35]. Since the pioneering studies of Ancel Keys in Crete [36] the patterns of the Mediterranean diet have changed substantially. Many Mediterranean countries, especially the European countries, have undergone very important changes in lifestyle, eating habits and physical activity, both work and non-work related. Different studies agree that all the countries have seen an increase in the dietary consumption of energy, animal proteins and saturated fats. On the other hand, calorie expenditure has decreased substantially, although important differences exist between countries. One recent study [37] showed that persons from northern European countries undertake more exercise in their free time than persons from countries in the south of Europe. The greatest percentage of adults who undertook some form of physical activity in their free time was from Finland (91.9%) and the least from Portugal (40.7%), with Spain occupying an intermediate position (64.0%). Other studies have compared the evolution of food consumption and the prevalence of obesity over the last four decades in Spain [38, 39]. The Spanish diet has undergone a remarkable increase in the consumption of fats, fruits and dairy products. The intake of dairy products is now the highest in Europe, as is the proportion of energy in the form of fat. The consumption of olive oil, however, especially between 1960 and 1991 has decreased markedly. At the same time, overweight and obesity have both risen a lot, especially over the last decade, with levels as high as those of Italy and above those seen in France. Overweight in children aged 6–7 years is even above that found in USA and overweight in adolescents is among the highest in the world [40].

7 Biological value of the Mediterranean diet

The traditional Mediterranean diet is characterized by a high intake of vegetables, legumes, fruit, nuts and cereals (previously unrefined) and a high intake of olive oil, a low intake of saturated fats and a varied intake of fish, depending on the proximity to the sea, as well as a low or moderate intake of dairy products, especially those derived from goat's milk, a low intake of meat and a moderate intake of alcohol, usually wine during meals [40]. Since the classic studies of Keys [36], much ecological evidence has confirmed the beneficial effects on health of the Mediterranean diet. Trichopoulos *et al*. [40] recently showed that a greater adherence to a traditional Mediterranean diet is associated with a significant reduction in mortality. These results agree with the protective role of variations of the Mediterranean diet found in certain randomized clinical trials of the secondary prevention of coronary disease [41, 42]. Numerous clinical and experimental studies have found the mechanisms whereby olive oil, the common denominator in the Mediterranean diet, exerts its biological effects [43–46].

8 SCD1: A new link between dietary fatty acids and obesity?

As seen above, some dietary fatty acids (linoleic and linolenic) or their metabolites (endoperoxides derived from arachidonic acid) are activators of the nuclear receptors (PPAR) that regulate adipocyte differentiation and lipogenic-lipolytic capacity. However, other biochemical targets have been discovered that seem to increase the links

between diet and phenotype. One of these is the key enzyme in the synthesis of MUFA, stearoyl-CoA desaturase (SCD). This enzyme from the ER catalyses a key step in the biosynthesis of MUFA from saturated fatty acids. In rodents there are four genes and in humans two, the most relevant of which is *SCD1* [47]. The preferential substrates are palmitic acid and stearic acid, which are transformed by SCD1 into palmitoleic acid and oleic acid, respectively [48] by the introduction of a double cis bond at position 9 of the substrate acyl CoA. The biological importance and the possible clinical role of SCD1 have recently been reviewed [49]. These two fatty acids, especially oleic acid, are the most important MUFA in the various lipid structures of numerous tissues, including triglycerides, phospholipids, cholesterol esters, ceramides and others [50]. Apart from their structural function, MUFA are transduction signal mediators of several genes, acting on cell differentiation and apoptosis [51]. As SCD1 is a key enzyme in the endogenous composition of MUFA, it is expected to have a great variety of actions within the different metabolic pathways related to carbohydrate and lipid metabolism and, by extension, *SCD1* could be a target gene for the treatment of diseases such as obesity, diabetes or arteriosclerosis [49]. Most information about *SCD1* comes from mice with natural or *SCD1*-directed mutations [47]. SCD1-deficient mice consume 25% more food but accumulate less fat and are considerably thinner than their normal littermates [52, 53]. SCD1-deficient animals have a greater consumption of oxygen, a higher rate of β-oxidation in liver and fatty tissue [54], a greater increase in the expression of UCP1 [55] and a greater response to stimuli of the β3 adrenergic-adenyl cyclase cAMP system [55]. Taken together, these biological actions explain the increase in thermogenesis and the decrease in adiposity.

SCD1 activity has been related to both obesity and the appearance of disorders in specific organs such as the liver or striated muscle (triacylglycerol deposits in both, resulting in steatosis) [56, 57]. Animals and humans with hepatic steatosis have raised levels of oleic acid in the liver [56] and muscle [57], indicating an increased activity of SCD1. SCD1-deficient animals have a lower liver content of triglycerides and cholesterol esters [58, 59], as well as reduced levels of VLDL and LDL plasma triglycerides [59], and are more resistant to a diet-induced fatty liver [53].

Multiple mechanisms of action of SCD1 regulate the synthesis, storage and β-oxidation of lipids. They come from the products of enzyme activity (oleic acid, palmitoleic acid) and from their capacity as a protein to interact directly or indirectly with other signal transducer proteins or specific transcription modulators of genes such as leptin, the kinases AKT or AMPK, or the phosphatase PTP1B. Recent studies have shown that part of the ability of leptin to inhibit the accumulation of fat in the liver and in other tissues is mediated by its ability to repress the expression of *SCD1*, as witnessed by the fact that in obese *ob/ob* mice

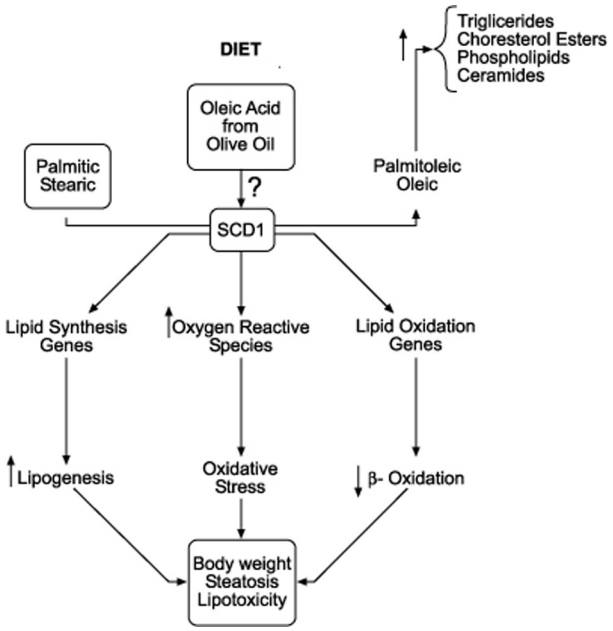

Figure 1. Role of SCD1 in body weight regulation, steatosis and lipotoxicity.

deficient in leptin, the accumulation of lipids in the liver and other tissues is normalized when these mice are also deficient for SCD1 [52]. A similar effect can be seen in the steatosis of PPAR-α-deficient mice that are also deficient for SCD1 [60]. The mechanisms by which a deficiency of SCD1 protects from hepatic steatosis are not well known. Possible mechanisms, which either reduce lipogenesis or increase oxidation of fats, include a reduction of malonyl Co-A *via* increased activation of AMP-AMPK; action at the level of the lipogenic transcription factors, reducing the expression of enzymes such as fat synthetase, acetyl Co-A carboxylase 2 or the glycerophosphate acyltransferase; or up-regulation of genes related to β-oxidation, such as carnitine-palmitoyl-transferase 1, acyl CoA oxidase or acyl-CoA dehydrogenase [49]. An additional factor is the oxidative stress resulting from the increased activity of SCD1, as its biochemical cycle generates reactive oxygen species. We have recently been able to show that induction of *SCD1* in the liver *via* the administration of detergents such as Tween-20 produces hepatic steatosis and oxidative stress. The reversion of the oxidative stress by means of antioxidants or inhibition of *SCD1* expression improves the steatosis ([61], Serrano *et al.*, personal communication) (Fig. 1).

9 SCD and plasma lipids

Oleic acid is the largest product of the activity of SCD1, and it is the most important substrate of acyl-CoA cholesterol acyltransferase (ACAT), the enzyme limiting cholesterol esterification [56]. In hyperlipidemic mice models,

hypertriglyceridemia is associated with increased activity of SCD1 [62]. In human cohort studies, SCD1 activity accounts for 41% of the variance in plasma triglycerides [62]. Mice deficient in SCD1 have reduced levels of VLDL production and secretion [63]. Finally, SCD-deficient mice have improved glucose tolerance and a higher insulin sensitivity than controls, an effect that could be related to the phosphorylation of the insulin receptor substrates IRS1 and IRS2, as well as the greater content of GLUT4 seen in SCD1-deficient mice [63]. The ceramides, non-oxidative derivatives of palmitoyl-CoA, are probably the intermediaries in the lipotoxic effect of the accumulation of triglycerides in the muscle and other tissues [3, 64]. Of particular interest are the recent findings that suggest that SCD1-deficient mice reduce the synthesis of ceramides, decreasing the expression of serine palmitoyltransferase (SPT) and increasing the beta-oxidation rate in the muscle [65].

SCD is a highly regulated enzyme and has been shown to be modulated by a number of dietary, physiological and hormonal factors including insulin, fructose, glucose, cholesterol, PUFA, and vitamin A, as well as exercise [66]. This high degree of regulation despite the dietary abundance of the monounsaturated products of SCD suggests that SCD may be critical to various cellular processes.

Feeding a high fructose diet to wild-type animals results in up-regulation of lipogenic genes including FAS, ACC, LFAE, as well as SCD1 [67]. These changes seemed to be mediated through increases in SREBP-1c transcription as well as maturation. However, $SCD1^{-/-}$ mice, placed on the high-fructose diet were protected from this effect. Consequently, they were protected from increases in lipogenic gene transcription and were therefore protected from the hyperlipidemic effect of the high-fructose diet. This effect was partially rescued by supplementing the fructose diet with high levels of oleate for 7 days [67].

10 A hypothesis

The expression of *SCD1* is sensitive to dietary factors, including PUFA, cholesterol and vitamin A, temperature changes, thiazolidindiones, metals, alcohol and phenolic components [68]. Its activity is regulated by the amount of substrate and final product. This accounts for the interest in the role of the SCD1 substrates or products present in the diet, like oleic acid from olive oil, and its genesis of population obesity in Mediterranean countries.

The cultivation of the olive tree probably originated over 6000 years ago in the Middle East. The ease of multiplication of the olive tree by rooting of large propagules, and also its ability to sprout latent buds on older wood as a consequence of diverse stimuli, led to it being among the first trees man started to cultivate [69]. The consumption of olive oil and olives, however, probably started in the Mediterranean many years before there was any historic evidence of it.

For thousands of years olive oil formed a substantial part of the daily calorie intake of the inhabitants of the shores of the Mediterranean. Humans from around the Mediterranean evolved within a nutritional context of abundance of MUFA from this vegetable source. The first consequence was that, over many generations, they probably maintained a SCD1 activity in relation to their dietary intake of MUFA/PUFA. However, this hypothesis has not been studied at the population level in comparison with other communities with other dietary habits. Most scientific research on the biological effects of fatty acids has focused on the n-6 and n-3 saturated fatty acids. Reasons for this included the finding of a close association between the intake of saturated fat and the risk of cardiovascular disease, which led to numerous studies in the second half of the last century that provided a solid support to the pioneering observations of Keys [70]. Additionally, the essential character of the n-6 and n-3 fatty acids [71, 72] and their condition as precursors of the metabolic chains and pathways of endoperoxides, prostacyclines and prostaglandins [73] have generated abundant manuscripts providing better awareness of the biological importance of both groups of PUFA. The role of MUFA, however, has been less well studied and it is only very recently that the biological importance of the MUFA has been considered. This is very relevant, considering the attempts to recover the biological value of the Mediterranean diet, of which a high intake of MUFA is the common denominator in the Mediterranean countries [43].

Unlike the n-6 and n-3 fatty acids, which are essential fatty acids that cannot be synthesized by the organism, MUFA can be synthesized due to the presence of delta-9 desaturase in most tissues.

Nevertheless, this non-essential character of MUFA, far from reducing their biological importance as compared with PUFA, may well increase it. In many tissues MUFA constitute the majority of the fatty acids and their key functions in cell regulation are now better known. Indeed, in those situations involving a deficit of essential fatty acids, the first thing noted is an increase in the activity of SCD1 and increase in the concentration of MUFA. Notably, the system used to defend against a deficit of PUFA is an endogenous increase of MUFA. Teleologically, it is possible that evolution has provided the superior organisms with a system able to supply the cell biology with better guarantees of stability in the concentration of MUFA. SCD1 would form part of this system. The recent findings that correlate the activity of the SCD1 system with the pathophysiology of the metabolic syndrome provide this hypothesis with a final sense.

In a theoretical model, the dietary increase of saturated fats should increase the activity of SCD1 but the increase of MUFA, on the other hand, should reduce it. In Mediterranean countries the intake of saturated fat has habitually been low, with a high intake of n-9 and a sufficient intake of n-6 to avoid its deficit. The activity of the SCD1 system would thus be adapted to this nutritional pattern.

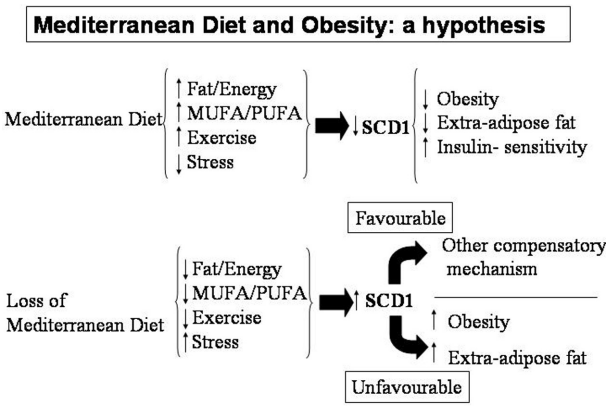

Figure 2. Mediterranean diet and obesity: a hypothesis. In Mediterranean countries subjects would, historically, have consumed a moderate amount of calories from a diet with a high proportion of fat in which the proportion of MUFA was very high and that of saturated fatty acids and n-6 fatty acids very low. At the same time physical activity would have been intense with a low level of stress associated with a particular way of understanding life. The SCD1 system selected over thousands of years of this type of nutritional behavior must have adapted to a particular activity and capacity of self-regulation. At the present time, this pattern, called the "Mediterranean diet", has been broken and many people living by the Mediterranean now consume a high quantity of calories for their needs, mainly from saturated fats and a high proportion of n-6. On the other hand, the relative intake (not necessarily absolute) of MUFA has decreased. Simultaneously, physical activity has decreased and the pattern of stress has changed towards what is called a western or industrialized countries lifestyle. In this new context, if people have a favorable, genetically conditioned SCD1 activity that will let them confront the new situation or else have some other compensatory mechanism, such as being keen on sport, etc, then they can prevent the appearance of some of the complications associated with the metabolic syndrome. If, on the other hand, the SCD1 pattern is genetically unfavorable for this new situation (*e.g.*, the pattern that has emerged with evolution around the Mediterranean) and they have a new cultural context, which is likely, then they do not have the alternative compensatory mechanisms and the probability of developing the metabolic syndrome is high.

Different experimental studies suggest that SCD1 activity and expression increase with the increase in dietary saturated fat, but they undergo few changes with the changes in the dietary MUFA. The increase in n-6, however, induces a decrease in SCD1 activity and expression, whereas a deficit or reduction in n-6 leads to an increase. What is the explanation for this apparent paradox between what is expected and what really happens?

During the course of evolution, the SCD1 activity of the Mediterranean populations may have been different to that of other populations that have evolved in an environment where the intake was mainly of n-3, n-6 or saturated fatty acids. An increased intake of saturated fatty acids, as is the case of the diet in the industrialized countries, could increase SCD1 activity after uptake by the tissues. The situation concerning n-6, however, is apparently paradoxical. A deficit of essential fatty acids produces an increase in saturated fatty acids and delta-9 desaturase activity, as seen by the final increase of MUFA in the tissues. But an n-6 deficit is exceptional and should be considered a disease, not within the context of population nutritional changes. Together with the increase in saturated fatty acids, what has occurred in Mediterranean countries is the replacement of the traditional intake of MUFA by n-6 PUFA. An increase in dietary n-6 fatty acids would compete with the n-9 fatty acids, reducing the proportion, at least the relative proportion, of MUFA, and thus increasing SCD1 activity as well. The final result, both the increase in saturated fats and the reduction in MUFA, would be an increase in SCD1 activity in a group of humans who would theoretically have SCD1 with a lower capacity.

The relative decrease in dietary MUFA and above all the increase in the n-6:n-9 ratio over recent years, would act on a system that is unprepared for this new situation. The relative increase in n-6 would lead to a decrease in the SCD1 activity noted in experimental studies, maintaining a disproportionably high SCD1 activity. The finding of a different polymorphic frequency for the *SCD1* gene in the inhabitants of Mediterranean countries and the possible association of these genotypes with structural and functional changes in SCD1 would satisfy the hypothesis proposed (Fig. 2).

The biological effects of the increased activity of SCD1 are now starting to be known and have been reviewed above. The consequences of this inappropriate increase in the expression and activity of SCD1 in the Mediterranean population would be the increase in obesity and the metabolic syndrome already found in all Mediterranean countries parallel to the changes in life style and traditional nutritional habits.

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