Chapter 6

The Mediterranean Diet in the Prevention of Degenerative Chronic Diseases

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Abstract

Degenerative chronic diseases are a problem related to the aging phenomenon of industrialized countries due to the increase of risk factors and related comorbidity such as overweight, obesity, metabolic syndrome, diabetes, hypertension and hyperlipidemia with a consequent increased risk of cardiovascular disease (CVD) and cancer. Moreover, the significant reduction of physical activity in daily life and the huge growth in food availability have considerably increased the risk of such diseases. Particular attention should be paid to primary prevention by means of health strategies based on improvement in lifestyle intervention such as implementation of Mediterranean diet and promotion of physical activity programs. In this chapter, the protective effect of Mediterranean diet and the role of certain foods and/or their constituents are analyzed; the possible mechanisms by which Mediterranean diet is effective in the prevention of cardiovascular and other chronic diseases are presented, in particular the effects exerted by antioxidants, polyphenols, fibers, unsaturated fatty acids, and alcohol. The genetic revolution in the past decades has produced new fields of study where the interaction between foods, nutrients, and our genetic makeup is investigated. The relationship between nutrigenetics and nutrigenomics and the Mediterranean diet are the future area that research should discover.

Keywords: functional foods, Mediterranean diet, cardiovascular diseases, chronic diseases, prevention

1. Introduction

The progressive improvement of socioeconomic conditions, which occurred in the second half of the last century in industrialized countries, has produced a major change in lifestyle with a significant reduction of physical activity, due to the mechanization of work activities and transport systems, and thus of total energy expenditure, and a contemporary huge increase in food availability. Eating habits have changed substantially and have acquired two characteristics: excess and inadequacy. The biggest change is the adoption of a high-calorie diet, rich in animal fats, cholesterol, refined sugars, salt, and alcohol, with a low ratio of nutrients to calories. These aspects of modern life have favored an increase in overweight and obesity and consequently also the frequency of diabetes, hypertension, and hyperlipidemia. The genetic constitution, meanwhile, has remained the same as that of primitive man as the human genome has not had the time to adapt to the new environment that instead has changed rapidly. The natural selection has favored the appropriate mechanisms to address the deficiency of food rather than those to limit weight gain; consequently, most of the current diseases are the result of a precarious genetic adaptation to the new environment created by man [1]. In addition, improved sanitary conditions, together with the introduction of antibiotic therapy and vaccination, have led to an increase in lifespan: humanity in general has aged and presents all the issues related to aging. There has been a gradual, steady increase of chronic degenerative diseases and in some countries there has been a real epidemic of these diseases and in particular of cardiovascular diseases (CVDs). The social impact of these diseases is considerable, especially for costs, both direct and indirect. The first type of cost is related to medical interventions necessary to the care (hospitalization, drugs, and rehabilitation), while the indirect costs are related to the loss of productivity and the need to replace the person affected by the disease in a period of his/her life characterized by a high professional qualification in its business work. CVDs are still the leading cause of death and disability in many industrialized countries. Recently, also in developing countries or economies in transition, we are observing a continuous and rapid increase in CVD. Smoking is considerably widespread, especially among women, and among the youngest which has further increased the risk of CVD.

These are already the first cause of death worldwide with the exception of Sub-Saharan Africa [2]. They represent a crucial issue in public health and, consequently, their prevention, especially at primary level, is an essential point in the choice of health strategies developed by the governments of several countries.

The importance of environmental factors in the pathogenesis of CVD is recognized as certain and among the most important environmental factors is lifestyle, defined as eating habits and physical activity.

The genetic revolution in the past decades has produced new fields of study focused on the interaction between foods, nutrients, and human genetic make-up to investigate our predisposition and ability to prevent or treat CVD, cancer, diabetes, obesity, cognitive decline and dementia, and inflammatory bowel disease [3–5]. Experimental data demonstrated that environment and foods could regulate gene expression and structure [6]. Food constituents and nutrients may induce the change of structure and function of genes and may be able to prevent

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or cause specific diseases; these new areas of study are called nutrigenomics and nutrigenetics [7]. Nutrigenomics aims at relating in the population the effects of certain foods on human health on the basis of genetic predisposition. It will therefore be possible, in the next few years, to identify the best strategy for the prevention of many chronic degenerative diseases, and with specific tests, it will be possible to understand which foods are the most suitable and which ones need to be avoided. Nutrigenetics specifically investigates the modifying effects of inheritance in nutrition-related genes on micronutrient uptake and metabolism as well as dietary effects on health. In this way, it is possible to hypothesize a diet tailored to the patient, based on his/her genotype, the quality, and quantity of the daily required nutrients to his/her body, with determination of minimum and maximum amounts needed to obtain the most benefits. These two branches of science can combine genetics with nutrition trying to play an active preventive role in defense of the organism; this is the new pathway for genetics applied to nutrition. A new frontier has been opened and has created a new scientific approach to prevention based on genetics. Proper and targeted feeding combined with the genotypic diversity of each individual will allow us to clarify the guidelines for the prevention of a large number of diseases and will allow the development of new experimental therapies, aimed at the treatment of complex pathologies such as metabolic diseases. A proper and balanced diet is essential for a long and healthy life, but it is not the same for everyone; modern genetic testing allows us to determine the best suited diet to each individual. This systemic approach, based on genetics, once fully operational, will provide results that can be functional to the improvement of human well-being. The typing of biomolecules with enhanced nutritional properties will be reflected on the dietary recommendation with a more accurate and effective action of prevention and population health protection.

Actually, nutrigenomics and nutrigenetics are still in a beginning phase, without definite scientific evidence that the effects observed in experimental and small clinical studies have real clinical implications. We have to rely on existing scientific evidence, suggesting nutritional models known to be effective on the health of individuals and communities. One of the most widespread diets is the "*Mediterranean diet (MD)*."

2. Mediterranean diet

The term Mediterranean diet has become a synonymous of a healthful and tasteful pattern of eating. The MD is a way to "enjoy food" while ensuring a long and healthy life. The increasing interest is the consequence of numerous studies conducted around the world in the last 50 years, when the famous nutritionist Ancel Keys launched and organized the Seven Countries Study, an epidemiological study that analyzed the role of diet and other cardiovascular risk factors on cardiovascular disease and death [8–10]. The study originated from the observations that in nations such as Greece, Italy, and Japan the cases of myocardial infarction (at least those in the hospitals) were much lower than those he had observed in Minnesota, in Netherlands, and in Finland.

The observation was conducted in 16 cohorts enrolled in Finland, Greece, Italy, Japan, the Netherlands, USA, and former Yugoslavia. The Seven Countries Study was one of the first examples of international collaboration in medical research and has represented, over the years, the groundbreaking evidence on the effect of diet on health and in cardiovascular and chronic disease epidemiology. The main findings of the study were the demonstration of a significant association between coronary heart disease (CHD) and diet, particularly positive correlation between the consumption of saturated fatty acids and CHD and relevant inverse relationship between the consumption of monounsaturated fat and CHD. The 15-year mortality follow-up demonstrated an inverse association between coronary deaths and the ratio of the dietary monounsaturated/saturated fats [8–10]. Olive oil has been considered one of the principal components of the MD. Wine, garlic, fish, vegetables, legumes, almonds, and other nuts, other constituents of this dietary pattern, have also been identified to have beneficial effects on health [11, 12]. The data of 15-year follow-up of the Seven Countries Study have been followed up by numerous evidences showing important inverse relationships between the MD, and/or its elements, and either CVD or its risk factors [13–16].

More recent studies have demonstrated that MD and its components may be a powerful aid against certain conditions, such as diabetes, stroke, dementia, colorectal cancer (CRC), and mortality. The greater part of the findings up to now comes from epidemiological studies, even if the cause-effect relationship is not so clear. A recent clinical trial study, based on randomized population, showed the positive outcomes of the MD in the prevention of CVD in individual at a high risk for this disease [17]. A recent study aimed to evaluate the effects of adherence to MD on survival on a large sample of 71,333 Swedish men and women, followed up for 14 years, demonstrated a linear dose-response association between the MD score average and the length of life with the higher score associated with longer survival. The difference in the average length of life between subjects with extremes scores (0 vs. 8) of MD was up to 2 years [18]. The PREDIMED trial was performed using an energy-unrestricted MD, enriched with nuts or extra-virgin oil; the relative risk of cardiovascular events was the reduction of approximately 30% in people who were free of CVD at the beginning of the study, reinforcing the evidence of the MD in the primary prevention of CVD with relevant risk reduction [17]. MD is also effective in reducing the rate of cardiovascular complications after myocardial infarction in the secondary prevention as demonstrated in the Lyon Diet Heart Study where a large reduction in rates of coronary heart disease events was observed with a modified MD enriched with alpha-linolenic acid (a key constituent of walnuts) [19]. More recently, the ATTICA study carried out between 2001 and 2002 on 3024 prevalently male individuals between 20 and 89 years living in the province of Attica (Greece) demonstrated on individuals free of CVD or chronic viral infections that higher the level of adherence to the traditional MD pattern lower the risk of left ventricular systolic dysfunction in patients affected by acute coronary syndrome [20, 21].

3. Effective components contained in the Mediterranean diet

The apparent ability of the traditional MD to reduce the risk of CVD, cancer, and degenerative diseases development and progression has been attributed, at least in part, to the content of micronutrients and compounds with antithrombotic and antioxidant capacity.

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3.1. Antioxidants

It is conceivable that the protective effect of the MD, which guarantees a regular intake of substances with antioxidant activity (ascorbic acid, α-tocopherol, retinol, and β-carotene), estimated that 10–100 mg per day is to be ascribed essentially to its ability to maintain constantly high antioxidant capacity in the blood [22, 23]. The abundance of fruits and vegetables, along with extra-virgin olive oil, red wine, aromatic herbs (oregano, parsley, and rosemary), garlic, onion, and pepper (ingredients generously used in Mediterranean cuisine), offers a number of phenolic compounds with a strong antioxidant action that is hardly possible to achieve with other types of diet. Examples are allyl sulfides, which are present in garlic and raw onions, give cardiovascular benefits, improve cognitive ability, and have chemopreventive activity; it was shown that certain isothiocyanates (degradation products of glucosinolates, compounds present in caper berries) can affect the cell cycle and induce apoptosis in HT-29 human colon cancer cells and other isothiocyanates, present in high concentration in cruciferous vegetables (cabbage and broccoli) [24, 25], have the capacity to modulate the metabolism of carcinogens; kaemferolo and flavonoids quercetin and hydrocinnamic acids from capers have well-known anti-inflammatory and antioxidant effects and chives also rich in phenolic compounds with diuretic, antihypertensive, anti-inflammatory, and antioxidant substances [26–28]; catechins fruit (e.g., apple skin and grape) antioxidant molecules prevent the production of reactive oxygen species generated by oxidative stress; the anthocyanins, plant pigments, give the red or blue color to fruits and vegetables (berries, eggplant, black grapes, and red beet), are antioxidants, photoprotective, and are able to inhibit angiogenesis. One other major constituent of MD is vitamin E, which contains a group of eight isomers: four tocopherols (α, β, γ, δ-tocopherol) and four tocotrienols (α, β, γ, δ-tocotrienol). There are several studies demonstrating healthful effects of α-tocopherol, while little is known on γ-tocopherol, the main form of vitamin E in food. In the last 20 years, much of the supposed beneficial effects of antioxidant vitamins were not confirmed in controlled clinical trials [29–31]. However, it is hard to believe that such vitamins may adverse the development of CVD events when administered in patients with advanced stages of the disease, while a protective effect could be supposed in population in which this nutrient is present throughout the life.

Lycopene, a carotenoid present in tomatoes and tomato products, is a dietary antioxidant that has received great consideration. Epidemiological studies have demonstrated a lower incidence of CVD in those with higher consumption of tomatoes and lycopene, confirmed also by lycopene levels in serum and adipose tissue [32–34]. A protective effect on acute myocardial infarction (AMI) with an odds ratio of 0.75 was found in one of the earlier studies that investigated the serum antioxidant status and lycopene [35]. The most remarkable population-based evidence from a multicenter case-control study (EURAMIC) [36] indicated lycopene levels, and not β-carotene, to be protective against myocardial infarction with an odds ratio of 0.52 comparing the 10th to the 90th percentiles. In the Malaga region, the component of EURAMIC study adipose tissue lycopene levels showed an odds ratio of 0.39 [37]. In Atherosclerosis Risk in Communities (ARIC) case-control study, fasting serum antioxidant levels were inversely related to the intima-media thickness with an odds ratio of 0.81 [38]. Although these epidemiological studies provide convincing evidence for the role of lycopene in CVD prevention, they can only suggest but not prove a causal relationship between lycopene intake and the risk of CVD. Such a proof can be obtained only by performing controlled clinical dietary intervention studies where both the biomarkers of the status of oxidative stress and the disease are measured.

3.2. Polyphenols

Polyphenols are the most abundant antioxidants in the diet, present in fruits and plant-derived beverages such as fruit juices, tea, coffee, red wine, cereals, chocolates, and dry legumes. The total dietary intake could be as high as 1 g/d; this is 10 times higher than the intake of vitamin C and 100 times higher than the intakes of vitamin E and carotenoids [39].

Despite the wide distribution in plants, the effects of polyphenols on health have come to the consideration of nutritionists only in recent times. Polyphenols and other antioxidants were considered to protect cell constituents against oxidative damage, through scavenging of free radicals for many years. Nowadays, this theory is drastically changed; polyphenols give signals principally through the receptors or enzymes related to signal transduction and the signal may lead to modification of the redox status of the cell, and may activate a series of redox-dependent responses [40]. Many evidences on the prevention of diseases exerted by polyphenols derives from in vitro or animal experiments, which are often done with higher doses than those humans exposed with a regular diet [41, 42].

Epidemiological studies are necessary to establish the effects of polyphenol consumption on CVD [43]. Moreover, it was shown that short- and long-term black tea consumption increases plasma flavonoids and reverses endothelial dysfunction in CVD patients [44].

All these observations suggest that polyphenols can protect vascular damage via antioxidant effects and nitric oxide restoration. However, clinical trials using different antioxidants have failed to demonstrate preventive effects on major CVD events. One imaginable explanation for this discrepancy is that experimental studies are not comparable to real life in humans, although very useful to understand pathophysiological mechanisms [45]. Moreover, antioxidants quantity used in studies conducted in humans may not have been appropriate, and/or the state of disease too severe to evaluate the protective effect that could probably be existent in a preclinical state.

3.3. Dietary fiber

Dietary fiber (DF) has been widely studied and numerous evidences support the health benefits of its consumption. Several prospective studies have demonstrated the inverse association between DF intake and cardiovascular risk. An important pooled analysis of 10 cohort studies demonstrated that DF consumption was inversely related to coronary heart disease. Thence, the introduction of functional foods enriched in DF—alone or in combination with other bioactive compounds—in the diet may represent a useful strategy to improve the cardio-metabolic profile in high-risk subjects preventing cardio-metabolic diseases. The promotion in use of both natural and functional foods might facilitate adherence to a healthy diet with a higher fiber intake compared with the common nutritional conducts of western populations.

Cohort studies have found a consistent protective effect of dietary fibers on glucose control and serum lipoproteins in diabetic patients [46] and in turn on CVD [47].

However, the biologic mechanisms of fibers on the cardiovascular system have yet to be fully elucidated. In the Nurses Health Study, women in the highest quintile of fiber intake had an age-adjusted relative risk for major coronary events that was 47% lower than women in the lowest quintile [48].

Practical recommendations for CVD prevention include food-based approach favoring an increased intake of whole-grain and dietary fiber (especially soluble fiber), fruits, and vegetables providing a mixture of different types of fibers [49].

3.4. Unsaturated fatty acids

Dietary sources of n-3 polyunsaturated fatty acids (PUFAs) include fish oils, rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), along with plants rich in a-linolenic acid. Regular consumption of fish, characteristic of the MD, allows satisfying the need for omega-3 fatty acids. PUFAs contained in fish regulate effectively hemostatic factors, cancer, and hypertension, and play a crucial role in the maintenance of neural functions in humans and in the prevention of certain psychiatric disorders; evidence from epidemiological and clinical secondary prevention trials suggests a significant role of fish consumption on long-term (20-year) mortality from coronary heart disease and n-3 PUFA in the prevention of CHD and arrhythmias [50, 51]. Prospective randomized trials show a favorable impact on CV health of both fish and plant sources of n-3 PUFAs. The omega-6 is present mainly in vegetable oils (sunflower and corn oils which, however, should not be cooked since these oils are thermolabile). Among them, the linoleic acid content in nuts, grains, legumes, corn and sunflower oil, synthesized, comes from the gammalinoleic acid (or GLA) [52]. Randomized secondary prevention clinical trials with fish oils and a-linolenic acid have demonstrated a reduction in risk that compare favorably to those seen in landmark secondary prevention trials with lipid-lowering drugs. A meta-analysis of randomized trials involving patients with cardiac disease showed that supplementation with the marine n-3 fatty acids EPA and DHA reduced the rate of death from coronary heart disease by 20% [53].

The beneficial effects of olive oil on cardiovascular disease risk factors are now recognized and often attributed only to the high levels of monounsaturated fatty acids (MUFAs). The olive oil is a functional food. Secondary components of olive oil, which constitute only 1–2% of the total virgin olive oil content, are classified into two types: the unsaponifiable fraction, defined as the fraction of the oil extracted after saponification through the use of solvents, and the soluble fraction which includes the phenolic residual. The unsaponifiable fractions of the components are hydrocarbons (squalene), tocopherols, fatty alcohols, triterpene alcohol, 4-methylsterols, sterols, terpene, and other polar compound pigments (chlorophyll and pheophytins). The accumulation of scientific evidence suggests that flavoring and seasoning foods with olive oil bring great health benefits including reducing the risk of coronary heart disease and preventing various cancers (by inhibiting proliferation, inducing apoptosis, and minimizing DNA damage). Also, it appears to have a role in bone mineralization reducing the risk of osteopenia and osteoporosis [54].

3.5. Alcohol

Although the excessive consumption of alcohol must be discouraged due to the significant health damage to individuals and societies [55, 56], increasing evidence shows that moderate consumption of alcoholic beverages may decrease CVD [57]. A dose-response relation between wine intake and vascular risk resulted in a J-shaped curve, with a significant risk reduction at moderate (one to two drinks) consumption (trend analysis $p = 0.032$) [58].

Data derived from PREDIMED demonstrated that moderate red-wine consumption is associated with a lower prevalence of the metabolic syndrome in an elderly Mediterranean population at a high cardiovascular risk [59].

The protective effects of alcohol have been primarily explained by an action on blood lipids (increase in high-density lipoprotein (HDL) levels) and platelets (decreased aggregation) resulting in a reduced rate of coronary artery obstruction [58]. Moderate drinking may improve the early outcomes after AMI and prevent sudden cardiac death, suggesting a direct effect of ethanol on the ischemic myocardium that has been referred to as "ethanol preconditioning" [60].

Moreover, a protective effect of moderate alcohol intake is demonstrated by the Italian Longitudinal Study on Aging (ILSA). In this study, participants with moderate cognitive alterations who consumed approximately 15 g of alcohol a day (moderate drinkers) experienced a decreased rate of progression toward dementia compared to non-drinkers. In the same study, alcohol consumption in older age is associated with healthier hematological values of fibrinogen, HDL cholesterol, Apo A-I lipoprotein, and insulin [61].

4. Effects of the Mediterranean diet on health

4.1. Effects of the Mediterranean diet on cancer and other degenerative diseases

As life expectancy increases, there are an increased number of elderly individuals suffering from cardiovascular disease, dementia, and cancer.

In sedentary people eating Western-type diets, aging is associated with several chronic diseases, including type 2 diabetes mellitus, cancer, and cardiovascular diseases. About 80% of elderly (over 65 years of age) have at least one chronic disease, and 50% have at least two chronic diseases, with an increase in disability related to comorbidity [62]. Data from epidemiological studies and clinical trials indicate that many age-associated chronic diseases can be prevented, and even reversed, by the implementation of healthy lifestyle interventions [63]. Recent data demonstrate that higher Mediterranean-type diet adherence and higher physical activity were independently associated with a reduced risk for Alzheimer disease [64].

Epidemiological burden of cancer in Mediterranean countries is lower when compared to other states, such as the UK and the USA. There is increasing evidence that Mediterranean dietary adherence reduces the risk of several cancer types and cancer mortality. Particularly, high consumption of fruits and vegetables, whole grains, and little assumption of processed meat, characteristic aspects of the Mediterranean diet, is inversely related to the risk of tumor pathogenesis at different cancer sites. Observational studies provide new evidence suggesting that high adherence to a MD is associated with a reduced risk of overall cancer mortality as well as a reduced risk of incidence of cancers of the colorectum, aerodigestive tract, breast, stomach, pancreas, prostate, liver, and head and neck [65]. A recent review and meta-analysis of 23 observational studies with an overall population of 1,784,404 demonstrated that the highest adherence to MD was significantly associated with a 13% lower risk of all-cause cancer mortality, 17% colorectal cancer, 7% breast cancer, 27% gastric cancer, 4% prostate cancer, 42% liver cancer, 60% head and neck cancer, 52% pancreatic cancer, and 90% respiratory cancer. The meta-analyses confirm a prominent and consistent inverse association provided by adherence to MD in relation to cancer mortality and the risk of several cancer types [66].

The Healthy Ageing: a Longitudinal Study in Europe (HALE) Study, which evaluated 3496 participants in 10 European countries, reported that individuals between 70 and 90 years who follow up an MD experienced more than 50% reduction in all-cause mortality [67]. The EPIC study designed to clarify the relationship between diet, environmental factors, lifestyles, and the incidence of cancer and other chronic diseases demonstrated in the Spanish cohort that a lower incidence of cancer (12% reduction) is observed in those with a greater adherence to MD after an 8-year follow-up. The EPIC study has also shown that the contemporary consumption of more components of the diet has a greater effect than the single-component assumption [68].

In an epidemiological study investigating the role of both Dietary Inflammatory Index (DII) and Mediterranean Diet Score (MDS), the DII was positively associated with a risk of lung cancer in current smokers while the MDS was inversely associated with lung cancer risk overall (hazard ratio (HR) = 0.64) and for current smokers (HR = 0.38), demonstrating a protective effect even more evident in high-risk patients [69].

The Women's Health Initiative Observational Study assessed the association between diet quality index scores on Healthy Eating Index 2010 (HEI-2010), Alternative HEI-2010, alternative Mediterranean Diet Index, and the Dietary Approaches to Stop Hypertension (DASH and colorectal cancer (1993–2012)), a US study of postmenopausal women. During an average of 12.4 years of follow-up, there were 938 cases of CRC and 238 CRC-specific deaths. Closer adherence to HEI-2010 and DASH dietary recommendations was inversely associated with a risk of CRC in this large cohort of postmenopausal women [70].

Data from PREDIMED find an effect of a long-term dietary intervention on breast cancer incidence, suggesting a beneficial effect of an MD supplemented with extra-virgin olive oil in the primary prevention of breast cancer. The multivariate-adjusted hazard ratios were 0.32 for the MD with extra-virgin olive oil group and 0.59 for the MD with nuts group. In analyses with yearly cumulative updated dietary exposures, the hazard ratio for each additional 5% of calories from extra-virgin olive oil was 0.72 [71]. Mediterranean diet appeared to exert a protective effect also on hip fracture in two Swedish cohort studies consisting of 37,903 men and 33,403 women (total $n = 71{,}333$, mean age 60 years) free of previous cardiovascular disease and cancer who answered a medical and a food-frequency questionnaire in 1997. One unit increase in modified Mediterranean diet score (mMED; range 0–8 points) was associated with 6% lower hip fracture. Comparing the highest quintile of adherence to the mMED (6–8 points) with the lowest (0–2 points) conferred an adjusted HR of hip fracture of 0.78 [72].

4.2. Reduction in caloric intake in lowering incidence of degenerative disease

A more drastic nutritional interventions and implementation of physical activity programs may have additional beneficial effects on several metabolic and hormonal factors, implicated in the etiology of degenerative diseases and aging [73–75].

The traditional MD means also a diet with a reduced caloric intake, at least referred to the past century; caloric restriction (CR) can be defined as the reduction of all dietary nutrients, except vitamins and minerals (to avoid malnutrition), and has recently emerged as the most promising pro-longevity/anti-aging candidate measure); in fact, it is a highly robust phenomenon capable of slowing aging [76]. Moderate CR can prevent or reverse the damaging effects of visceral obesity, insulin resistance, type 2 diabetes, high blood pressure, dyslipidemia, and inflammation. Energy deficits induced by CR and physical activity in overweight and obese subjects are accompanied by similar improvements in glucose tolerance and insulin action, and similar reductions in several major CHD risk factors, with a loss after 2 years of intervention of 14 kg [77].

CR improves metabolic status also in normal-weight individuals. Data from a series of studies conducted in a group of self-imposed CR (approximately 30% reduction in daily calories) show that a prolonged CR determines sustained beneficial effects on lipid profile, blood pressure, and carotid artery intima-media thickness [78].

Finally, weight loss obtained with an energy deficit of 500–750 kcal per day from their daily energy requirement and exercise was effective in improving the score of physical functioning in obese elderly with frailty, improving, body composition, bone mineral density, physical functions, and quality of life [79].

4.3. Dietary supplements

Dietary supplementation has increased significantly in the last years because of the perception that antioxidant vitamins and minerals may reduce the risk of CVD, cancer, and other chronic diseases. However, no clear evidence in chronic disease prevention is demonstrated for dietary supplements, at least among healthy individuals in the general population [80]. Nevertheless, from a public health perspective, it is extremely important to understand the effects of nutrients on health. At the moment, the use of selenium as supplement in the diet to prevent cardio-metabolic disease is not justified and thus not to be encouraged.

Longitudinal epidemiological studies have led to the identification of recognized functional foods and dietary patterns as beneficial in the primary prevention of cardio-metabolic diseases. The mechanisms by which these foods exert their protective effects are complex and probably related to the macro- and micronutrient contents of the food [81]. The benefits may depend on the clinical status due to risk factors, and state of diseases, may be dose dependent, and may be affected by the food preparation. The benefits of functional food have been reproduced using isolated components of foods as supplements. At the moment, randomized, double-blind, placebo-controlled trials of clinical end points are necessary to establish the efficacy in modifying cardiovascular risk profile in humans.

5. Future directions of nutrigenetics and nutrigenomics in the Mediterranean diet

Increasing evidence enhances the idea that functional foods may improve health status by means of physiologically active components [81]. This area of research is now developing and additional studies are necessary to demonstrate the potential benefit of those foods for which the diet-health relationships are not yet scientifically validated.

A personalized diet based on specific nutrition strategies exerts a pivotal role in the treatment of phenylketonuria, galactosemia, and fructose intolerance, diseases known as “single-gene autosomal recessive disorders.” More than 6000 human monogenic disorders have been identified, including over hundreds of protein-based metabolic disorders. Some are rare and complex dietary diseases, namely fatty-acid oxidation disorders, organic acid metabolism disorders, urea cycle defects, and glycogen storage disease. Patients may reduce their intake of the dietary substrates or metabolites that accumulate in these conditions and nutrigenetics will improve prevention and treatment by identifying specific mutations or haplotype combinations that modulate the dietary response in affected patients [81]. In multifactorial pathologies such as CVD, obesity, type 2 diabetes mellitus, cancer, and so on, nutrigenomic studies have shown that dietary intervention may modulate the onset and progression of the disease.

Recently, there has been notable progress in gene-environment interaction evaluation; this field is now accessible to patients to help them to improve their health. Therefore, the current challenge for nutritional genomics is to clarify the role of food and the human microbiota in human health, to better understand the relationship between them and to use this knowledge to promote and preserve a healthy status [82, 83].

6. Conclusions

Scientific research and the wider dissemination of its results made aware the industrialized countries population of the strong connection between nutrition and health, and the role of certain foods and/or their constituents in maintaining this balance. This helps to clarify the role of diet in the prevention and control of morbidity and premature mortality caused by non-communicable diseases. Adaptations to the diet can not only influence today’s health but also act in determining whether a person will develop or not, in the course of his/her life, diseases such as cancer, cardiovascular diseases, or diabetes. A healthy diet based on the balance between nutrients represents the first preventive intervention to protect the health and physical harmony. As a result, today, nutrition has new meanings. The concept of food has undergone a radical modification to the point of attributing to each food, in addition to its intrinsic nutritional and sensory properties, an important role in maintaining health and the psycho-physical well-being. Improving eating habits and increasing physical activity levels will reduce the risk of death and disability related to chronic diseases. The practical implications of these recommendations should lead to increased consumption of fruits, vegetables, and fish, and to change the quality of fats and oils, as well as the amount of sugar and starch, by acting as much as possible to match the Mediterranean diet dictates that is found in the Hippocrates famous quote “Let food be thy medicine and let thy medicine be food,” the needed action for the twenty-first century population.

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