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Prevention of Coronary Artery Disease through Diet

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Abstract

Our understanding of the potential role of diet in the prevention and risk reduction of coronary artery disease (CAD) has evolved in the past 100 years. Data on trends in food consumption and ecological studies are the early evidences that showed associations between prevalence and fat intake across and within countries. The last 50 years of epidemiology and clinical trials have focused on the efficiency of nutritional interventions in the prevention of CAD.

The original diet-heart hypothesis was very simple: Cholesterol is a constituent of atherosclerotic plaque. This hypothesis was based on the differences in average population serum cholesterol levels and population rates of CAD mortality. The Seven Country study was the first to show that the intake of saturated fat varied considerably by region and populations, with the greatest intake of saturated fat were found to have the highest serum cholesterol levels. Follow-up studies confirmed that these study groups also had the highest incidence of CAD. Thus, it was thought that there was a direct relation between cholesterol in diet, cholesterol in blood, and cholesterol in the plaque and its clinical complications such as myocardial infarction (MI). These findings stimulated further inquiry to determine whether altering the diet could decrease serum cholesterol levels and, thereby, decrease the incidence of CAD. Nearly all clinical trials in the 1960s, 1970s, and 1980s compared usual diets with those characterized by low total fat, low saturated fat, low dietary cholesterol, and increased polyunsaturated fats. Actually, these diets did reduce cholesterol levels. However, they did not reduce the incidence of MI and CAD mortality. With accumulating evidence, we have now moved away from a focus on total fat and cholesterol to the importance of considering the content of fat and total calories in the diet. In other words, the type of fat, rather than the total or the ratio or balance between the saturated and certain unsaturated fats may be the determinant. Recent meta-analyses of intervention studies confirm the beneficial effects of replacing saturated with polyunsaturated fatty acid on CAD risk. Additionally, recent studies indicate that dietary patterns consistent with the traditional Mediterranean-style diets (MedD) with a strong focus on veggies, fruits, fish, whole grain, and olive oil are effective in preventing CAD to a degree greater than low-fat diets and equal to or greater than the benefit observed in statin trials. Recent secondary prevention studies have convincingly demonstrated the

benefit of diets that closely followed the MedD in reducing re-infarction and clinical manifestations of CAD.

In conclusion, CAD is still a significant problem and a growing health concern worldwide. Although mortality rates from CAD have decreased due to advances in pharmacological treatments, the prevalence of cardiovascular risk factors continue to increase. The importance of diet as a key modifiable risk factor in CAD is undisputable. Nutritional interventions have proven that a complicated set of many nutrients interact to influence CAD risk. Therefore, recent guidelines consider diet as a whole and combine nutrient and energy recommendations into a healthy pattern that is nutrient dense and energy balanced.

Keywords: CAD prevention, reducing cholesterol, low-fat diets, Mediterranean diet

1. Introduction

Unfortunately, coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide despite costly aggressive drug and surgical interventions as a *first line* strategy [1]. However, these therapies fail to address the origin of the problem, that is, the most proximal risk factors for progression of atherosclerotic CAD, including poor-quality diet patterns, physical inactivity, obesity, and cigarette smoking [1, 2]. Consistent evidence from landmark epidemiological studies supports the concept that these risk factors contribute nearly 80% of population-attributable risk of cardiovascular diseases (CVD) [3-4]. Accordingly, a healthy lifestyle modification may afford close to 80% protection from CAD [5]. Therefore, lifestyle managements to reduce cardiovascular risk are of superior importance as stated in population-based strategies for cardiovascular prevention such as 2012 European guidelines [6] and the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [7].

Research on the origin of CAD has been ongoing for approximately a century [8]. From the beginning, diet played a paramount role in research on the cause of CAD. At the same time, one of the great interests was explaining differences in the incidence of CAD among populations. In the early 1900s, evidence from cross-cultural studies indicated some associations between diet and cholesterol. However, systemic associations between diet, cholesterol, and CAD were made almost after half a century. In the 1950s, cross-cultural studies indicated that endemic diets had important impact on the variation of CAD across populations [9]. Thus, it was thought that there was a direct relation between cholesterol in diet, cholesterol in blood, and cholesterol in the plaque, and its clinical complications such as myocardial infarction (MI). The findings of cross-cultural studies stimulated further inquiry to determine whether altering the diet could decrease serum cholesterol levels and, thereby, decrease the incidence of CAD. Nearly all clinical trials in the 1960s, 1970s, and 1980s compared usual diets with those characterized by low total fat, low saturated fat, low dietary cholesterol, and increased polyunsaturated fats. Actually, these diets did reduce cholesterol levels. However, they did not reduce the incidence of MI and CAD mortality. Secondary prevention trials in the 1990s,

together with primary prevention approaches in the 2000s, indicate that dietary patterns consistent with the traditional Mediterranean-style diets (MedD) with a strong focus on veggies, fruits, fish, whole grain, and olive oil are effective in preventing CAD to a degree greater than low-fat diets and equal to or greater than the benefit observed in statin trials. With accumulating evidence, we have now moved away from a focus on total fat and cholesterol to the importance of considering the content of fat and total calories in the diet. In other words, the type of fat, rather than the total or the ratio or balance between the saturated and certain unsaturated fats may be the determinant. Recent meta-analyses of intervention studies confirm the beneficial effects of replacing saturated with polyunsaturated fatty acid on CAD risk. Nutritional interventions have proven that a complicated set of many nutrients interact to influence CAD risk. Therefore, recent guidelines consider diet as a whole and combine nutrient and energy recommendations into a healthy pattern that is nutrient dense and energy balanced.

This chapter begins with early studies and interventions for prevention of CAD through diet, and it continues with recent clinical trials. In the next section, we will focus on the newer "whole diet" approach, consistent with the traditional MedD, which has proven to be successful in preventing CAD. Finally, we will summarize the current state of knowledge on dietary fats and prevention of CAD by foods.

2. Diets to prevent CAD: From early studies to recent trials

2.1. Early clues that diet may prevent CAD

In 1908, A.I. Ignatowski was first to observe that cholesterol-rich food promoted atherosclerosis in rabbits [10]. Then, as reported by Finking and Hanke, Nikolai N. Anichkov showed in 1913 that cholesterol-enriched diet led to atheromatous changes such as fatty streaks and advanced atheromatous plaques in the vascular wall of rabbits that are similar to the lesions in humans with coronary atherosclerosis [11]. During the ensuing decades, atherosclerosis moved from a laboratory curiosity to a major public health concern.

Starting in the 1950s, research on atherosclerosis gained more credibility and support, as a multidisciplinary community of clinical investigators accomplished new research programs dedicated to unraveling the puzzle about pathophysiological origins and treatment of CAD. In 1952, Kinsell reported that intake of vegetable oil instead of animal fats resulted in a striking decrease in serum cholesterol and phospholipid levels [12]. Groen et al. found out that intake of vegetarian diets decreased serum cholesterol levels [13].

The first study on the variation in the occurrence of CAD across populations was published in 1916 by the Dutch physician De Langen, who observed that cholesterol levels of Dutch immigrants in the former Dutch Indies were approximately twice as high as those of native Javanese [14]. He hypothesized for the first time that differences in diet patterns could be associated difference in average population cholesterol levels. However, the first systemic association between diet, cholesterol, and CAD waited until the 1950s.

2.2. The first systemic association between diet, cholesterol, and CAD: The diet-heart hypothesis

In 1957, Angel Keys cited extensive epidemiological evidence that indicate a sequence of etiologic relations existed between the saturated fat content of the diet, serum cholesterol concentrations, and the development of CAD [9]. These observations, based on the differences in average population serum cholesterol levels and population rates of CAD mortality, played a pivotal role for the development of diet-heart hypothesis: Dietary saturated fat, and in some versions, dietary cholesterol, raise blood cholesterol, which in turn leads to coronary atherosclerosis [9]. In 1957, Keys et al. began the Seven Countries Study by surveying 12,763 men aged 40 to 59 years formed 16 cohorts in seven countries (Italy, Greece, the former Yugoslavia, the Netherlands, Finland, Japan, and the United States). Study communities were chosen for the relative uniformity of their rural laboring populations and their contrasting dietary patterns. Information on biological risk factors (e.g., serum cholesterol, blood pressure, and anthropometric measurements) were collected and ECG was taken in addition to a physical examination. Information on diet was collected by use of 7-day food records in small samples of each cohort. The risk factor surveys were repeated after five and ten years. Through central chemical analysis of the foods consumed by randomly selected families as well as diet-recall measures, Keys and his colleagues were able to determine that both the blood cholesterol levels and the heart-attack death rates were highest in societies where fat was a major component of every meal (i.e., the US and Finland). Conversely, blood cholesterol was low and heart attacks were rare in cultures where diets were based on fresh fruit and vegetables, bread, pasta, and plenty of olive oil (i.e., the Mediterranean region). The findings of the seven countries study published in 1970 had a significant impact on CAD prevention, as it described one of the first studies to clearly show that dietary saturated fat leads to CAD, and that the relationship is mediated by serum cholesterol [15].

2.3. Dietary recommendations and clinical trials

2.3.1. Low fat/low saturated fat/increased polyunsaturated diets

Even though the three major preventable risk factors for CAD (elevated serum cholesterol levels, high blood pressure, and smoking) had been identified as early as 1956, the link between cholesterol and CAD required the results of large epidemiology studies before gaining widespread acceptance [16-18].

AHA was one of the first organizations to recommend dietary changes to decrease atherosclerosis [19]. Together with the Society for the Study of Atherosclerosis, the AHA Nutrition committee published their recommendations in 1957 [20]. In brief, it was concluded that diet might play a crucial role in the pathogenesis of atherosclerosis, and the most essential factors in the diet were the fat content and the total calories. It was also thought that the type of the fat, rather than the total or the ratio or balance between the saturated and certain unsaturated fats, might be the determinant. The same year, the AHA Nutrition Committee suggested for the first time that CAD might be prevented by treating obesity with low-fat diet [20]. The recommendations of the committee requested obese individuals to confine caloric consump-

tion by reducing dietary fat consumption. The following year, in 1958, Brown and Page published a paper entitled "Lowering blood lipid levels by changing food patterns" and they offered two dietary ways to treat serum cholesterol, namely, a diet containing minimum animal fat together with an increase in vegetable oil and a strict low fat diet [21]. Afterwards, by 1961, AHA's Ad Hoc Committee on Dietary Fat and Atherosclerosis recommended the reduction or control of fat consumption under medical supervision. Additionally, substitution of polyunsaturated for saturated fats to prevent atherosclerosis and decrease the risks of heart attacks and strokes were also recommended [22]. Thereafter, the importance of substitution of polyunsaturated vegetable oil for saturated fat, instead of a low-fat diet, gained widespread acceptance.

2.3.2. Dietary cholesterol reduction

In 1972, the American Medical Association (AMA) Council on Foods and Nutrition in cooperation with the Food and Nutrition Board of National Academy of Sciences-National Research Council published a joint statement that the blood cholesterol level was linked to the risk of CAD [23]. Similar with AHA guidelines, these two representative councils stressed that reasonable means should be followed to modify the nutritional conditions that contribute to elevated plasma cholesterol and triglyceride levels. The primary goals suggested were reduction in foods rich in cholesterol and partial replacement of saturated with polyunsaturated fats.

2.3.3. Clinical trials for secondary prevention of CHD

The US National Diet-Heart Study was a large, double-blind, two-year study on the effects of diet on blood cholesterol levels in both free-living and closed populations [24]. The results of the study indicated that the average change in blood cholesterol with low saturated fat, low dietary cholesterol diets was 25 and 28 mg/dl or -11 and -12% in a free-living population, while it was 36 mg/dl or -17% in the closed-institutional centers.

2.3.4. Lifestyle intervention studies for reversal of CAD

To date, a number of lifestyle intervention studies have been performed. Obtaining substantial differences in lifestyle and diet between the experimental and control groups is complicated. Moreover, it is almost impossible to avoid an aftereffect of a healthy lifestyle and diet advice from the experimental group to the control group. Therefore, comprehensive controlled trials investigating the combined effects of diet and a healthy lifestyle on disease end points in individuals are difficult to perform and expensive.

In 1948, the Framingham Heart Study—under the direction of the National Heart Institute (now known as the National Heart, Lung, and Blood Institute or NHLBI)—embarked on an ambitious project in health research [25]. The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CAD by following its development over a long period of time in men and women free of these conditions at the

outset. The first person was examined in September 1948 and four years later 5,209 persons had received their first examination. The group has now been followed in the study for 24 subsequent biennial examinations. As changes in early detection and treatment of CVD advance, prospective epidemiology is needed to document the value and impact of these changes in an organized fashion. The availability of prospective data on two generations adds to the uniqueness of the Framingham Study among ongoing studies of CAD epidemiology [26].

As a result of corroborative evidence from prospective population studies such as the Framingham study, the scientific community focused on systemic intervention studies to test whether reducing risk factors would reduce disease incidence. Nearly all clinical trials in the 1960s, 1970s, and 1980s compared usual diets with those characterized by low total fat, low saturated fat, low dietary cholesterol, and increased polyunsaturated fats. Unsurprisingly, the reduction in cardiovascular mortality and total mortality was greater in the secondary prevention trials and appeared to be dependent on the baseline cholesterol levels; that is, the higher the baseline risk the greater the obtained benefit.

In 1970, the Oslo Study dealt with 412 men, aged 30 to 64 years, randomized one to two years after a first MI [27]. A diet low in saturated fats and cholesterol, and high in polyunsaturated fats was recommended for the experimental group. After 11 years, a significantly reduced MI mortality in the original diet group was found (32 versus 57, $P = 0.004$). The total number of coronary deaths (fatal MI and sudden death) was 79 in the diet group and 94 in the control group ($P = 0.097$). The CAD mortality was correlated with age, serum cholesterol level, blood pressure, body weight, smoking habits, and a combination of these risk factors.

An early example of a primary prevention trial that used an intervention with regard to more than 1 factor is the first Oslo trial [28]. In this trial, intervention was focused on both diet and smoking. A total of 16,202 men, aged 40 to 49 years, were screened for coronary risk factors. Of these, 1,232 healthy, normotensive men at high risk of CAD were selected for a five-year randomized trial to show whether the lowering of serum lipids and cessation of smoking could reduce the incidence of CAD. These men had high serum cholesterol levels (7.5 to 9.8 mmol/L), were mostly smokers (80%), had systolic blood pressures below 150 mm Hg, and were at very high risk for CAD. They were randomized into two groups; the patients in the intervention group were recommended to lower their blood lipids by change of diet and to stop smoking, and the control group did not receive any advice. The advised diet was low in saturated fat and high in fiber. Saturated fat intake decreased from 18% to 8% of the total energy intake, and saturated fat was partly replaced by n-6 polyunsaturated fatty acids. During the trial, mean serum cholesterol concentrations were approximately 13% lower in the intervention group than in the control group. This difference was in agreement with the difference in fatty acid composition of the diet between the two groups. Besides the difference in diet, 25% of smokers in the experimental group stopped smoking compared with 17% in the control group. At the end of the observation period, the incidence of MI (fatal and non-fatal) and sudden death was 47% lower in the intervention group than in the controls. When the incidence of strokes was added, the difference between the groups was still significant. The reduction in

incidence in the intervention group was correlated with the reduction in total cholesterol, and to a lesser extent, with smoking reduction. It was concluded that, in healthy middle-aged men at high risk of CAD, advice to change eating habits and to stop smoking significantly reduced the incidence of the first event of MI and sudden death.

A large prospective cohort study is the Chicago Heart Association Detection Project in Industry (CHA), which screened blood pressure, cholesterol level, and smoking [28]. Risk factor data were available for 6,766 middle-aged men and women, aged 36 to 64 years. The age-adjusted relative risks of coronary heart disease mortality for low-risk persons compared with those who smoked and had elevated cholesterol and blood pressure levels varied between 0.08 in CHA men aged 18 to 39 years and 0.23 in CHA men aged 40 to 59 years. The life expectancy of persons at low risk was 9.5 years longer in CHA men aged 18 to 39 years and 5.8 years longer in CHA women aged 40 to 59 years compared with persons at elevated risk. These results illustrate the great impact of low risk factor levels on coronary heart disease risk and health in general.

However, the Multiple Risk Factor Intervention Trial (MRFIT), a US multicenter clinical trial, was an unsuccessful large prospective cohort study [29]. The risk factor data were available for more than 360,000 men aged 35 to 57 years. The participants were screened for blood pressure, cholesterol levels, and smoking for 16 years. In the special intervention group, hypertension was treated with standard medications, and smoking cessation was promoted. The dietary goals, reducing saturated fat to less than 8% caloric intake and cholesterol to less than 250 mg/d, with increased polyunsaturated fat (>10%), were nearly accomplished. However, despite the significant reduction in dietary fat, the changes in total cholesterol and low-density lipoprotein cholesterol after seven years of intervention were modest. Total cholesterol decreased by 2.9% in those receiving community care and 5% in those receiving special care. The end points of reduction in total mortality and coronary death were not achieved. This lack of efficacy was striking given that hypertension was better controlled and cigarette cessation was more successful in the special intervention group.

In 1990, Ornish et al. reported a prospective, randomized, controlled trial of 48 patients with angiographically documented CAD [30]. Twenty-eight patients were assigned to an experimental group (low-fat vegetarian diet, stopping smoking, stress management training, and moderate exercise). Follow-up quantitative coronary angiography was performed after intervention and compared with angiograms in 20 usual-care control patients with documented CAD. Overall, 82% of experimental-group patients had an average change towards regression. Additionally, there was angiographic evidence of progression in 53% in the control group. Coronary arteriography was repeated five years later. Additional regression was noted in 20 patients who maintained their lifestyle changes, with further progression in the 15 control patients. These patients followed a very low-fat (10%) vegetarian diet. It was noted that comprehensive lifestyle changes might be able to bring about regression of even severe coronary atherosclerosis after only one year, without use of lipid-lowering drugs.

2.4. Dietary trials for secondary prevention of CAD

2.4.1. Early trials

In 1989, Burr et al. reported the results of the Diet Reinfarction Trial, a randomized controlled trial that investigated the effect of diet on the secondary prevention of MI, involving 2,033 men [31]. The trial had a factorial design, subjects being randomized independently to receive advice or no advice regarding three dietary factors: (1) total fat intake and the ratio of polyunsaturated to saturated fat; (2) fatty fish consumption; and (3) cereal fiber intake. The results suggested that compliance with the advice was reasonably good. There was a slight (3.6%) reduction in cholesterol in those advised to decrease fat. There was no decrease in cholesterol in patients advised to increase fatty fish or cereal fiber intake. None of these three factors influenced the two-year incidence of reinfarction or cardiac death. However, patients counseled to eat fatty fish had a 29% reduction in the two-year all-cause mortality. It was suggested that the difference attributable to advice on fat was somewhat less than anticipated, partly because of failure to comply with the advice and partly because of spontaneous changes in the diets of control subjects.

The Indian Experiment of Infarct Survival Study (1989-1992), a randomized, single-blind, controlled trial, aimed to test whether a fat-reduced diet rich in soluble dietary fiber, antioxidant vitamins, and minerals reduces complications and mortality after acute MI [32]. For this aim, 406 patients with suspected acute MI were randomized to one of two low-fat diets. The experimental group was counseled on a “whole diet approach” that included increased intake of fruits, vegetables, nuts, and fish. Main outcome measures were mortality from cardiac disease and other causes, and serum lipid concentrations and compliance with diet. Total fat was reduced to 24% of daily calories in the experimental group and 28% in control group. Saturated fat was significantly reduced in the experimental group. Dietary cholesterol was 147 mg/d in the experimental group compared with 287 mg/d in the control diet. The experimental group lowered total cholesterol by 13% compared with 5% in the control diet. There was a significant reduction in the combination of nonfatal MI, fatal MI, and sudden death from 82 patients assigned to the control diet to 50 patients on the experimental diet. It was concluded that comprehensive dietary changes in conjunction with weight loss immediately after acute MI might modulate blood lipoproteins and significantly reduced complications and mortality after one year.

In the Lyon Diet Heart Study (1988-1997), a randomized, controlled trial with free-living subjects, 605 survivors of a first MI were randomized to an Mediterranean-type diet (consistent with the new AHA Dietary Guidelines) or a “prudent” low-fat diet on composite measures of the coronary recurrence rate [33]. The Mediterranean-type diet is a whole diet approach that is low in animal products and saturated fat, with an emphasis on the use of olive oil. It is rich in legumes, fruit, vegetables, and fish. Butter and cream were replaced with a canola-based margarine. The saturated fatty acid and oleic acid contents in the margarine were comparable to those in olive oil, with the exception that the margarine was higher in linoleic acid and α -

linolenic acid. Subjects in the experimental group participated in a one-hour counseling session. In contrast, control subjects received no specific dietary advice apart from that generally provided by attending physicians and hospital dietitians. The end points of the Lyon Diet Heart Study were cardiovascular death or nonfatal MI. At the end of the trial, the percentage of daily calories from fat was 30.4% in the Mediterranean diet group and 33.6% in the low-fat/low cholesterol control group. The calories derived from saturated fat were significantly lower in the Mediterranean diet group (8% vs. 11.7%), as was the daily cholesterol intake (203 vs. 312 mg/day). In addition, omega-3 consumption (from vegetables, fish, and margarine) was considerably higher and omega-6 consumption was lower for those on the Mediterranean diet. At the end of the trial, there was no significant difference between the total serum cholesterol or low-density lipoprotein cholesterol levels in those on the two diets. The trial was stopped after 27 months when an intermediate analysis showed that those on the Mediterranean diet had a 73% reduction in CVD deaths and nonfatal MI. After 46 months, despite a similar coronary risk factor profile (plasma lipids and lipoproteins, systolic and diastolic blood pressure, body mass index, and smoking status), subjects following the Mediterranean-style diet had a 50% to 70% lower risk of recurrent heart disease, as measured by three different combinations of outcome measures including (1) cardiac death and nonfatal heart attacks; (2) the preceding plus unstable angina, stroke, heart failure, and pulmonary or peripheral embolism; and (3) all of these measures plus events that required hospitalization.

2.4.2. Contemporary approach for primary prevention of CAD: Mediterranean diet

The Mediterranean diet is considered as one of the most favorable diet for cardiovascular health. It is an evidence-based diet to prevent not only CVD but also some other chronic diseases such as breast cancer, depression, colorectal cancer, diabetes, obesity, asthma, erectile dysfunction, and cognitive decline [34].

The most important feature of the Mediterranean diet seems to be a synergy between the various cardioprotective nutrients and foods [35]. In general, the Mediterranean diet is characterized by a high intake of monounsaturated fats from olive oil, fruits, vegetables, whole grains, legumes, nuts; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets [34, 36, 37].

The high concentration of unsaturated fats, such as olive oil, is the most prominent aspect of the Mediterranean diet. Research on the impact of olive oil consumption for CVD prevention has showed that the cardioprotective effects of olive oil are thought to be attributed to the presence of its phenolic compounds, which are potent antioxidants, free radical scavengers, and enzyme modulators [38].

Numerous observational data show a reduction in CVD by increased consumption of fruits and vegetables. The potential benefit of fruits and vegetables could lie in reduced total caloric burden, or in large amount of micronutrients that they provide. The exact evidence establishes the antioxidant properties of fruit and vegetables [39] and the health benefits of increased flavonol intake [40]. The effects of nitric oxide (NO) species, or concomitant weight loss associated with diets high in fruits and vegetables could be alternative mechanisms [34].

An extensive amount of data suggests a beneficial effect of increased whole grains on CVD morbidity and mortality. AHA guidelines indicate that diets high in fiber such as whole grains, oats and barley reduce cardiovascular disease morbidity and mortality through lipid lowering, and recommend a total dietary fiber intake of 25-30 g per day from whole foods [41].

The data about the beneficial effect of moderate nut consumption are positive. Evaluation of observational studies showed that substituting walnuts, peanuts, almonds, or other nuts for a serving of carbohydrates or saturated fats reduced blood lipids, as well as the risk for cardiovascular disease by 30% and 45%, respectively [42].

Estruch et al. designed a randomized trial, the PREvención con DIeta MEDiterránea (PRE-DIMED) Study, to test the efficacy of two Mediterranean diets (one supplemented with extra-virgin olive oil and another with mixed nuts), as compared with a control diet (advice on a low-fat diet), on primary cardiovascular prevention [37]. A total of 7,447 men and women (age ranged from 55 to 80 years) in Spain who were at high cardiovascular risk at enrollment, but without evidence of cardiovascular disease, were randomized to one of three diets stated above. Participants received quarterly individual and group educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. Total fat intake was not restricted in patients on the Mediterranean diet, but the source of fat was predominantly from fatty fish and plants. The low fat diet group was counseled to reduce all types of fat, including olive oil and nuts. The primary end point was the rate of major cardiovascular events (MI, stroke, or death from cardiovascular causes). The trial was stopped after a median follow-up of 4.8 years on the basis of the results of an interim analysis. Total dietary fat was higher in the Mediterranean diet groups. Both groups were similar with regard to saturated fat and dietary cholesterol intake. The primary end point, namely MI, stroke, or death from cardiovascular causes, was reduced by 30% in the Mediterranean diet supplemented with extra virgin olive oil and 28% lower in the Mediterranean diet group supplemented with mixed nuts compared with controls.

Conclusively, Estruch et al. suggested that dietary patterns consistent with the traditional Mediterranean-style diet were particularly cardioprotective [37]. Mediterranean-style diets are widely accepted to be effective in preventing CHD even though they do not decrease total serum cholesterol or low-density lipoprotein cholesterol [43].

3. Dietary fats and cardiovascular/coronary heart disease

3.1. Total fat

Since the beginning of the concern about diet and CVD risk assessment, dietary fat, especially the total fat, is the main point of interest. Till the beginning of the 1990s, the recommendations for the public health was focused on limiting the total fat intake, especially to reduce CVD. As part of the Dietary Approaches to Stop Hypertension (DASH) diet, low-fat dairy intake has been shown to lower blood pressure [44]. However, lowering total cholesterol by replacing dietary total fat with carbohydrate may contrarily increase serum triglyceride concentration

[45]. Moreover, in a meta-analysis of prospective cohort studies, intake of total fat was not found significantly associated with CHD mortality or CHD events [46]. One of the key studies about total fat intake was the Women's Health Initiative Dietary Modification Trial. In this study, dietary intervention that reduced total fat intake did not significantly reduce the risk of CHD or CVD in postmenopausal women and only modest effects on CVD risk factors were achieved [47]. According to the 2006 AHA Diet and Lifestyle recommendations, for decreasing the CVD risk, the recommendations are much about limitations of intake of each type of fat, instead of reducing the total fat intake. Specifically, the AHA recommends to supply 7% of energy from saturated fat and 1% of energy from trans fat [48]. And also, according to the Dietary Guidelines for Americans 2010, lowering the percentage of calories from dietary saturated fatty acids to 7% of calories and replacing them with monounsaturated and/or polyunsaturated fatty acids can further reduce the risk of CVD [49].

3.2. Saturated Fatty Acids (SFA)

The primary SFA sources are animal fat such as meat, milk, and dairy products, some plant oils such as palm and coconut oils, and the industrially-prepared food (cookies, cakes, and pies). Several meta-analyses showed that SFA intake was not significantly associated with risk of CAD or CVD [50-52]. Recent data from meta-analyses of cohort studies and randomized control trials suggest that SFA consumption on CVD risk depends on the replacement nutrient. The latest epidemiologic studies and clinical trials suggest that differing effects depending on the replacement nutrient scenario such as replacing saturated fat with polyunsaturated fat in the diet is more beneficial for CAD risk than with carbohydrates [53]. In a pooled analysis of 11 prospective cohort studies, Jakobsen et al. revealed that consumption of polyunsaturated fatty acid (PUFA) in place of SFA was associated with reduced CAD risk [54]. In another study, Mozaffarian et al. indicated as the result of 8 randomised clinical trials that changing the energy intake from SFA to PUFA by 5% reduced the CAD risk by 10% [55]. Additionally, in the Cochrane Collaboration meta-analysis of 48 RCTs, Hooper et al. revealed that reducing saturated fat by reducing and/or modifying dietary fat reduced the risk of cardiovascular events by 14% [13]. And this study also suggested that the beneficial effects occurred in the case of fat modification rather than reduction of fat intake and in a two-year period. Also, males and population who have moderate or high risk of CVD are more prone to have benefits from dietary fat modification. However, dietary fat modification was not found to be beneficial on CVD mortality [56]. Based on recent evidence, both the AHA and the European Society of Cardiology advise to limit saturated fat intake to <10% and <7% of total daily calories, respectively [6, 57]. According to the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk, for adults to benefit from LDL cholesterol lowering, only 5%-6% of calories should come from saturated fat (through replacement of PUFA > monounsaturated fat (MUFA) > whole grains > refined carbohydrates). [58]

3.3. Monounsaturated Fatty Acids (MUFA)

The main dietary MUFA is oleic acid, which is abundant in nuts, sunflower oil, olive oil, canola oil, high oleic safflower oil, and avocado. Because olive oil is the essential part of the Mediter-

anean diet, the role of MUFA in the prevention of CAD has a close interest, especially after Mattson and Grundy showed that high SFA diets increase the LDL cholesterol/HDL cholesterol ratio and changing SFA with MUFA reduces LDL cholesterol levels but not HDL cholesterol [59]. Replacing MUFA with carbohydrates in the diet causes several alterations in the lipid profile, such as TG and VLDL cholesterol decrease and HDL cholesterol and apoA1 increase [60, 61]. However, the epidemiologic data about oleic acid and CAD prevention is controversial. While the Nurses' Health Study (NHS) found remarkable protection, in the Zutphen and Puerto Rico Heart Health Program studies there were no beneficial effects reported between controls and CAD cases [62-64]. In a recent study, Schwingshackl and Hoffmann recapped the most available data about MUFA and CVD risk in which they found no accepted rationale for MUFA recommendation, although there are no significant side effects of diets with rich MUFA up to date [65]. Also, according to the Cochrane meta-analysis by Hooper et al., reduction of SFA intake and replacement with unsaturated fat is advised for the population under risk of CVD [66].

3.4. Trans Fatty Acids (TFA)

Trans fatty acids (TFA) are a type of unsaturated fat that became commonly produced industrially from vegetable fats for use in margarine, snack food, packaged baked goods, and frying fast food. TFA has at least one carbon-carbon double bond in the trans, rather than the typical cis configuration. Early in the 20th century, TFA was invented for increasing the shelf life of oils and consumption of these fats, as margarine increased all over the world. Recently, it has been recognized that it causes elevated cholesterol levels and has a major role in the risk of CAD [67]. Beyond their energy value, TFA does not have any known health benefits and there is an apparent association between TFA consumption and the risk of heart disease. In a meta-analysis of 28 cohort studies, there has been found a highly significant positive association between TFA intake and CAD morbidity and mortality [68]. Energy replacement of TFA with SFA, MUFA, or PUFA 1% resulted in the decrease of the TC: HDL ratio in controlled trials and each 2% replacement would lower CAD risk in prospective cohort studies [69]. Because of this CVD risk increase, the Food and Drug Administration (FDA) and the other Health Regulatory Agencies required food manufacturers to list TFA on the Nutrition Facts and some Supplement Facts sections on the package of food, although TFA levels of less than 0.5 g per serving can be listed as 0 g [70].

3.5. N-3 fatty acids

Because of the low rates of ischemic heart disease in Greenland Eskimos, there was close attention to their diet. This protection was thought to be caused by long-chained PUFA's anti-thrombotic effects, which is an important part of their diet [71]. Prospective cohorts revealed the protective effects of intake of n-3 fatty acids on CAD, and since then evidence suggests that n-3 fatty acid intake may be effective for secondary prevention. The possible effects were thought to be prevention of arrhythmias, as well as lowering of heart rate and blood pressure, decreasing platelet aggregation, and lowering triglyceride concentration [72]. The n-3 fatty acids also decrease hepatic TG secretion and increase clearance from plasma. In diabetic

patients, n-3 PUFA are found to reduce TG levels by 25% and VLDL levels by 36%; however, LDL concentrations increased slightly by 5.7% [73]. Since then, several meta-analysis and RCTs have been published about the role of seafood n-3 fatty acids on CVD and CVD mortality. Some of them suggested that n-3 fatty acid intake lowers the CVD risk, but some of them found no significant effect on CVD risk and/or mortality. In the last US guidelines on patients with CAD, fish and/or fish oil supplement is indicated only in the control of a patient's lipid profile (class IIB, level of evidence B) [74]. But in the latest European Society of Cardiology (ESC) guidelines, the protective effects of fish on CVD is associated with n-3 PUFA. Moreover, it is suggested that eating fish at least once a week reduces the CAD risk by 15% [6]. There are controversies between epidemiologic studies and clinical trials, probably due to the different study groups. Epidemiologic observational studies usually evaluate the disease-free population, but clinical trials are often conducted in a population at risk of CVD.

3.6. Plant-based fatty acids

α -linolenic acid (ALA) is a short chain n-3 PUFA found in plant sources such as soybeans, walnuts, rapeseed oil, and flaxseed. It could be an alternative to fish n-3 PUFA because it can be converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are n-3 PUFAs that are found in fish. But this conversion is limited and the evidence for ALA in CVD protection is limited. In a systematic review of 14 human studies, at least four weeks of supplementation of ALA has no significant effect on the lipid profile [75]. However, since no current specific recommendations for ALA for CAD risk reduction is present, epidemiologic studies suggest a protective role, the diet including ALA (2 to 3 g per day) has been recommended for both primary and secondary prevention of CAD [76]. Further studies need to strengthen the evidence for the effects of ALA on CVD.

3.7. B Vitamins

The main role of B vitamins is principally for energy production, cell metabolism, and nerve function. Beside these, vitamins B12, B6, and folic acid are known to have homocysteine lowering effect. Several studies suggested that high homocysteine levels are associated with increased risk of MI and/or stroke. Because folic acid, B12, and B6 decreased the blood homocysteine level in 20%-40%, from baseline, it has been assumed that these supplements can subsequently reduce CVD risk [77]. The studies about the effects of folic acid and B vitamin supplementation failed to prove that reducing homocysteine level by folic acid and vitamin B supplements decreases CVD incidence. Most of the epidemiologic studies suggested protective effects of B vitamins on CAD but the randomized clinical trials did not show the same beneficial effects. A meta-analysis of 12 randomized trials that has 16,958 participants with pre-existing vascular disease revealed that folic acid supplementation had no effect on CAD risk [78]. After 1996, the US FDA made a regulation for the fortification of grain products (flour, breads, rice, pasta, cornmeal, etc.) with folic acid. Since then, the prevalence of low plasma folate concentrations has decreased [79]. The role of B vitamins and folate are plausible in the prevention of CVD and more studies are needed.

4. Foods and cardiovascular/coronary heart disease

4.1. Fruit and vegetables

Epidemiological studies have suggested that fruits and vegetables reduce CAD risk. A meta-analysis of nine cohort studies (including 129,701 women, 91,379 men, and 5,007 CAD events) showed that each additional fruit serving a day lowered the CHD risk by 7% (RR 0.93, 95% CI: 0.89-0.96; $P < 0.001$) [80]. Increasing fruit and vegetable consumption to 600 g/day, could reduce the incidence of ischaemic heart disease and ischemic stroke by 31% and 19%, respectively [81]. In the CARDIO2000 study, daily consumption of more fruit was associated with 72% lower risk of CAD (95% CI: 0.11-0.54, $P < 0.001$) and of more vegetables was associated with 70% lower risk for CAD (95% CI: 0.22-0.40, $P < 0.001$) [82]. However, the results of the WHI Dietary Modification Trial suggest that an additional portion of vegetables and fruit daily does not influence the risk of CAD [4]. Fruit and vegetable intake are part of the nutritional recommendations in the interventional studies where fruit and vegetable consumption was associated with lower blood pressure only [83] but the association with other CAD risk factors is not apparent. As the intervention studies did not exist, AHA recommends intake of at least eight vegetables and fruits a day [47]. With all these data, vegetables and fruits that are deeply colored (e.g., carrots, peaches, spinach, and berries) are recommended for consumption and preparation techniques that preserve nutrient and fiber content is important. The mechanism of action of their healthy effects is not known, but it can be attributed to their high dietary fiber and antioxidants content.

4.2. Fish

A meta-analysis of 11 cohort studies of 222,364 individuals showed that individuals who consumed fish 2-4 times/week had 23% lower risk of CAD mortality. Moreover, the individuals with higher frequency of fish consumption, i.e., ≥ 5 times/week, had greater reduction of risk. It is estimated that a daily fish intake of 20 g was associated with 7% lower risk of CAD mortality [84]. The benefit of fish intake for reducing the risk for CAD is due to n-3 PUFA according to the studies showing that fatty fish is associated with protection but lean fish is not. Fatty fish is the primary source of n-3 fatty acids. A prospective cohort study (including 1,373 men) suggested that fatty fish consumption reduces the risk of sudden coronary death risk compared to lean fish consumption [85]. Besides the type and amount of fish consumed, the cooking method of fish is also important. According to the Cardiovascular Health Study, only modest consumption of tuna or other broiled or baked fish was associated with a lower risk of heart failure, but fried fish was not [86]. The most recent Diet and Lifestyle recommendations of AHA for CVD risk reduction include consuming fatty fish at least twice a week [48]. The AHA also recommends eating fish within the recommendations established by the FDA and Environmental Protection Agency to prevent the possible adverse effects due to environmental pollutants such as mercury [87].

4.3. Whole grains

There are many definitions for whole grain present but according to The American Association of Cereal Chemists, a whole-grain ingredient is "...the intact, ground, cracked, or flaked caryopsis, whose principal anatomical components, the starchy endosperm, germ, and bran, are present in substantially the same relative proportions as they exist in the intact caryopsis" [88]. The alternative definition is used by studies that explicitly describe or define whole grain, but do not meet the classical definition of whole grains, by including bran and germ, and studies that do not explicitly use the term "whole grains" but were in fact conducted with individual whole grains such as oats or barley [89]. Whole-grain foods contain fiber, vitamins, minerals, phenolic compounds, phytoestrogens, and other unmeasured constituents. Whole-grain foods may have favorable effects on health by lowering blood pressure and serum lipids, and by also improving glucose and insulin metabolism and endothelial function [90]. They have also beneficial effects by reducing oxidative stress and inflammation.

Recently, many epidemiologic studies have searched the relation between whole grain intake and CVD risk. A meta-analysis of seven large-prospective cohort studies showed that whole grain intake was related with 21% lower risk of CVD for both genders [91]. In the NHS study, among women with type 2 diabetes with 26 years of follow-up, whole grain intake was found to be associated with lower risk of CVD-specific mortality and also bran intake was significantly associated with 35% lower risk of mortality [92]. As recent evidence about the protective role of whole grains in prevention of CVD was strong, FDA declared in Health Claim Notification for Whole Grain Foods that "Diets high in plant foods—i.e., fruits, vegetables, legumes, and whole-grain cereals—are associated with a lower occurrence of coronary heart disease and cancers of the lung, colon, esophagus, and stomach" [93].

Recently, a meta-analysis of 14 studies indicated that the highest whole grain intake amount compared with the lowest amount was significantly associated with reduced risk for CAD. The association was significant in cohort studies but not in case-control studies [94].

4.4. Alcohol

The data on the association between alcohol and CVD come either from short-term interventional studies or from the effects of alcohol on risk factors, as well as long-term observational mortality studies. Many studies suggested that moderate alcohol consumption, compared to no or heavy alcohol consumption, decreased CVD risk in many populations. The evidence suggests a J- or U-shaped relationship between alcohol consumption and risk of CAD [95]. Moderate intake of alcoholic beverages (1 to 2 drinks per day) is associated with a reduced risk of CAD in healthy populations in both men and women [96] and there is no difference between the types of beverages [97]. Different mechanisms have been suggested about the benefit of light-to-moderate alcohol intake on CVD such as an increase in HDL-C, reduction in plasma increase in fibrinolysis, decrease in platelet aggregation, improvement in endothelial function, reduction in inflammation, and promotion of antioxidant effects [98, 99]. However, these are still not enough to prove causality. Despite the evidence from cohort studies about moderate alcohol drinking and CVD, current guidelines do not recommend to begin consuming alcohol for preventing CVD. The recommendations of AHA on alcoholic drinks are that they should

limited to no more than two drinks per day for men and one drink per day for women, ideally with meals [48].

5. Conclusions

CHD remains one of the leading causes of morbidity and mortality worldwide, in spite of the advances in pharmacological treatments and better control of risk factors. Diet is a centrally important modifiable risk factor in the prevention and risk reduction of CAD. Progress in understanding the importance of diet on CAD has evolved in the past 100 years. Data on trends in food consumption and ecological studies are the early evidences that showed associations between prevalence and fat intake across and within countries. The last 50 years of clinical trials and nutritional interventions have established a clear link among diet, atherosclerosis, and CAD. Numerous meta-analyses of intervention studies confirm the beneficial effects of replacing saturated with polyunsaturated fatty acid on CAD risk. Moreover, the type of fat, rather than the total or the ratio or balance between the saturated and certain unsaturated fats is determinant. Recent guidelines consider diet as a whole and combine nutrient and energy recommendations into a healthy pattern that is nutrient dense and energy balanced. A “whole diet” approach with equal attention to what is consumed and what is excluded is proven to be more effective in preventing CAD than low-fat, low-cholesterol diets. Dietary patterns consistent with the traditional Mediterranean-style diets with a strong focus on veggies, fruits, fish, wholegrain, olive oil are effective in preventing CAD even though they do not decrease total serum cholesterol.

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