Association of dietary patterns and components with atherosclerosis risk biomarkers in familial hypercholesterolemia

Luiza Antoniazi[a], *Raquel Arroyo-Olivares*[b], *Pedro Mata*[b] *and Raul D. Santos*[a,c]

Purpose of review
Familial hypercholesterolemia (FH) is a relatively common genetic disorder associated with elevated atherosclerotic risk. Dietary interventions can modulate processes associated with cardiovascular risk and potentiate the impact of pharmacological lipid-lowering therapies. This review evaluates recent findings of dietary patterns and their components on risk biomarkers in people with FH.

Recent findings
Diets lower in saturated fatty acids (SFA) may reduce low-density lipoprotein-cholesterol (LDL-C); however, their effects seem to be modest. A Mediterranean style diet apparently exerts more robust effects on plasma LDL-C, apolipoprotein B and C reactive protein concentrations than one restricted in SFA. Supplementation of plant sterols and stanols reduces LDL-C especially in children with FH. Caloric restricted diets may reduce weight and improve triglyceride levels in individuals with FH and excess body weight.

Summary
Despite the strong impact of genetic variants, dietary patterns mostly low in SFA and especially the Mediterranean diet may influence risk biomarkers in FH. However, most available studies are limited by cross-sectional design, small number of study subjects and short-term follow-ups. Robust interventional studies are necessary to test the impact of dietary patterns in people with FH.

Keywords
atherosclerosis, cholesterol, diet, familial hypercholesterolemia, genetics, inflammation

INTRODUCTION

Familial hypercholesterolemia (FH) is an inherited metabolic disease associated with substantially elevated low-density lipoprotein-cholesterol (LDL-C) and early onset of atherosclerotic cardiovascular disease (ASCVD) [1]. FH is caused by variants in the LDL receptor gene (*LDLR*) and, less frequently, in the apolipoprotein B gene (*APOB*) and pro-protein convertase subtilisin/kexin type 9 genes (*PCSK9*). FH is not a rare disease. The current prevalence is estimated in 1 in 200–250 individuals in the general population [1].

Although FH highly increases cardiovascular risk, ASCVD prevalence varies substantially by cohort and country, even across cases with the same genetic pathogenic variant. In addition to higher LDL-C concentrations and the presence of other risk biomarkers like smoking, low high-density Lipoprotein-cholesterol (HDL-C) and higher lipoprotein(a) concentrations, environmental factors, including lifestyle behaviors, may partially explain the heterogeneity in ASCVD risk. In fact, in addition to pharmacological therapy, prevention guidelines recommend that individuals with FH should be encouraged to be physically active, not smoke, maintain an adequate weight, and consume a healthy diet [2].

Recent studies suggest focusing qualitatively on patterns of healthy eating, in particular patterns of food intake rather than on individual nutrients, for ASCVD prevention [3]. Overall, the recommended

[a]Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil, [b]Fundación Hipercolesterolemia Familiar, Madrid, Spain and [c]Hospital Israelita Albert Einstein, Sao Paulo, Brazil

Correspondence to Raul D. Santos, MD, PhD, MSc, Av. Dr Eneas C. Aguiar 44, 05403-000 São Paulo, Brazil. E-mail: raul.santos@Incor.usp.br

Curr Opin Lipidol 2021, 31:000–000
DOI:10.1097/MOL.0000000000000813

KEY POINTS

- Diet may modulate different atherosclerotic mechanisms in familial hypercholesterolemia (FH).
- Low in saturated fat acid (SFA) diets are recommended for FH.
- Reduction in SFA brings apparently modest reductions in LDL-cholesterol.
- Mediterranean diets may be superior to ones restricted in SFA.
- More studies are needed to test the impact of diets in FH.

cardioprotective diet for individuals with FH is essentially one low in saturated fats with a reciprocal increase in polyunsaturated fats particularly within the context of diets focused on heart health, such as a Mediterranean diet [2]. Nevertheless, there is scant literature evidence on diet management and its impact in risk biomarkers and ASCVD events in people with FH and consensus has yet to be reached on the most appropriate dietary recommendations [4].

This article will review the relevant previous and recent literature evaluating the association of dietary patterns and components and their impact on ASCVD risk biomarkers in people with FH.

WHERE DO THE NUTRITIONAL RECOMMENDATIONS FOR INDIVIDUALS WITH FAMILIAL HYPERCHOLESTEROLEMIA COME FROM?

Several international consensus statements emphasize the need for dietary treatment additive to pharmacological therapy for individuals with FH [2,5].

Adequacy of dietary habits, which can help reduce LDL-C concentration in people with FH [4], is also important to treat and prevent additional cardiovascular risk factors or mediators like hypertension, obesity, diabetes mellitus, oxidative stress, inflammation and endothelial dysfunction, involved in the complex and known multifactorial pathophysiological mechanisms of atherosclerosis [2,4,6,7▪▪].

One recent study including 42,167 adults with FH from 56 countries, found a prevalence of 19.2%, 50% and 5% respectively for hypertension, excess body weight (body mass index $> 25\,kg/m^2$) and diabetes [7▪▪]. Nutritional treatment is of great importance, as it helps to control classic and nontraditional factors, with special attention to the population at high risk for developing ASCVD, such as individuals with FH [4,8].

Individuals with genetic diseases may benefit even more from the impact of an LDL-C lowering diet than individuals without genetic variations because of the higher risk of ASCVD attributed to elevations in cholesterol since birth [4]. Despite this, most evidence supporting dietary recommendations for lowering LDL-C in FH comes from studies done in the general population. Therefore, according to the Cochrane Database [9] review on nutritional therapy in people with FH, further studies are needed to reach a consensus on the appropriate diet with the aim of preventing ASCVD.

Prevention guidelines recommend that nutritional treatment for people with FH should include a low intake of saturated fatty acids (SFA) and trans fatty acids (TFA), adequacy of consumption of unsaturated fatty acids, through a diet rich in fruits, vegetables, whole grains, lean meats, and low-fat dairy products. In addition, dietary intervention should be combined with adherence to a healthy lifestyle, physical activity and smoking cessation [2,6,10].

These recommendations involve the main dietary aspects, such as the amount and type of dietary fat and content of cholesterol, applied in the treatment of dyslipidemias in general, without genetic origin. The quality of fatty acids plays an important role in the pathophysiology of atherosclerosis by modulating the lipid profile, postprandial vascular reactivity, coagulation, and inflammation [11].

THE MECHANISMS BEHIND NUTRIENTS AND LOW-DENSITY LIPOPROTEIN-CHOLESTEROL

Intakes of elevated amounts of SFA and TFA are positively associated with increased total and LDL-C fractions [12]. On the other hand, it has been shown that reductions in saturated fats in the diet produce a reduction in total cholesterol and LDL-C fraction and possibly decrease the risk of coronary artery disease. Reduction in SFA produces reductions in LDL-C by increase in LDL receptor mRNA or its activity, reduced activity of hepatic acyl cholesterol acyltransferase (ACAT) causing a decrease in the content of cholesterol esters in lipoproteins rich in ApoB and, inhibition of hepatic secretion of lipoproteins containing ApoB with a consequent decrease in plasma triglyceride levels [13].

TFAs elevate LDL-C similarly to SFA, with an additional adverse effect of lowering HDL-C probably by inducing increased Apolipoprotein AI (Apo AI) catabolism and increased cholesteryl ester transfer protein activity [14,15].

The actions of polyunsaturated fatty acids (PUFA) in modulating pathways that could

influence cholesterolemia to involve decreased hepatic production of very-low density lipoproteins (VLDL), increased fluidity of hepatocyte membranes with improved LDL receptor activity and change in the spatial structure of LDL. Since the polyunsaturated molecules of phospholipids present a cis configuration and occupy more space in the lipoprotein, there is a restriction in the available volume of the LDL particle to transport cholesterol. In addition, PUFA stimulate the degradation of ApoB via presecretory proteolysis, which reduces its secretion and thus its availability for the production of VLDL [16,17].

Consumption of oleic acid reduces plasma LDL-C concentration and does not cause LDL oxidation compared to SFA [18], possibly because it is a better substrate for ACAT in the liver. Moreover, the substitution of SFA for monounsaturated fatty acids (MUFA) derived mainly from olive oil not only reduces LDL-C but also protects against LDL oxidation and may prevent cardiovascular mortality [19]. Therefore, excess cholesterol in its free form is rapidly esterified, not inducing LDL receptor suppression [20]. Furthermore, oleic acid induces less endogenous cholesterol synthesis when compared to PUFA [21].

Total fiber, insoluble fiber and especially soluble fiber reduce plasma cholesterol fractions, especially LDL-C. Soluble fibers form a gel that binds to bile acids in the intestinal lumen, increasing their fecal excretion and decreasing their reabsorption during the enterohepatic cycle. This induces de novo synthesis of bile acids, decreasing the cholesterol available for incorporation into lipoproteins. Furthermore, the fermentation of soluble fibers by bacteria present in the large intestine produces short-chain fatty acids, which help to reduce cholesterol levels [22].

WHAT STUDIES WITH INDIVIDUALS WITH MOLECULARLY DEFINED FAMILIAL HYPERCHOLESTEROLEMIA SHOW?

One dietary component that has been studied in subjects with FH is the supplementation of plant sterols that have shown favorable effects in reducing total cholesterol (TC) and LDL-C with most of the evidence coming from studies in children [11,23–26]. Furthermore, a six-month low-calorie diet had positive impact on weight, plasma non-HDL-cholesterol and triglyceride concentrations in adults with both FH and overweight [27].

Pimstone *et al.* [28] many years ago had suggested that lifestyle and diet could influence the phenotype of people with FH. In a small sample of Chinese individuals with FH living in China and Canada, they observed differences in the phenotype, mainly lower LDL-C concentrations, less tendinous xanthomas, and absence of previous ASCVD in those in China despite similar FH causing genetic variants with those in Canada. Those in China followed a traditional Chinese diet, whereas in Canada a western type of diet higher in SFA predominated. This finding prompted further investigations in this regard.

A 39-month follow-up of 26 men diagnosed with FH participating in the St. Thomas' Atherosclerosis Regression Study, showed that those who followed a prudent diet and received a cholesterol binding resin treatment had 35% lower LDL-C concentrations and less progression and even regression of angiographic coronary atherosclerosis [29]. The prudent diet included all food groups and contemplated 27% of the total caloric value from total fats, between 8 and 10% of the total caloric value from SFA, and 100 mg of cholesterol for every 1,000 Kcal, in addition to a high consumption of soluble fiber, preference for lean meats and encouraging the consumption of vegetables and healthy foods. The study suggested that reduction of LDL-C without the use of statin therapy would influence the evolution of atherosclerosis in FH.

More recently, a sub-study of Spanish Familial Hypercholesterolemia Cohort Study comprising adults with genetic diagnosis of FH ($n = 2736$) and their nonaffected relatives ($n = 978$), showed that compared to unaffected individuals, those with FH consumed less energy, total fats, saturated fats, and sugar [30▪]. On the other hand, consumption of vegetables, fish and low-fat dairy products was higher in affected individuals, who also showed greater adherence to the Mediterranean diet. Other lifestyle aspects were also better in individuals with FH, such as a lower rate of smoking and a higher rate of moderate physical activity

A healthier lifestyle and different dietary pattern may in part explain a more favorable lipid and inflammatory profile presented by individuals with FH in Spain, in comparison with their counterparts from the Hipercol Brasil genetic cascade screening program [31▪]. Brazilian individuals had significantly higher LDL-C (179.0 vs. 161 mg/dL), ApoB (141 vs. 103 mg/dL), and high-sensitivity C reactive protein (hs-CRP) (1.6 vs. 0.8 mg/L) concentrations than Spaniards. Dietary components were associated with these outcomes regardless of variables that may influence the lipid profile such as *LDL receptor*-null vs. receptor-defective variants, differences in the use of lipid-lowering therapies and body mass index. An inverse association of LDL-C with fiber, fiber/1,000 Kcal, percentages of MUFA, PUFA, MUFA/SFA, PUFA/SFA, and (MUFA + PUFA)/ SFA was encountered (all P values < 0.001). On the other

hand, dietary cholesterol, protein, and TFA intakes were positively associated with LDL-C (all $P < 0.001$).

The findings suggest that components of the Mediterranean diet may have a greater benefit in relation to the lipid and inflammatory profile for individuals with FH. This was explored in a subsequent study, which considered adherence to the Mediterranean diet. With the same sample of Brazilian ($n = 92$) and Spanish ($n = 98$) individuals with FH, Antoniazzi *et al.* [32▪▪] have observed that most Brazilians had low adherence (83.7%), whereas most of the Spanish presented moderate (35.7%) and strong adherence to the Mediterranean diet (37.8%) pattern ($P < 0.001$). There was a significant inverse association of adherence to the Mediterranean diet score with higher LDL-C, ApoB, and hs-CRP after adjusting for socio economic parameters, caloric and fatty acid intakes as well as pharmacological lipid-lowering therapies.

The scarce available evidence of impact of dietary treatment in individuals with FH has led to proposals such as the one of low carbohydrate diet, based on the insulin resistance phenotype to reduce ASCVD risk in FH. However, the impact of proposals like these must be tested in controlled studies with FH populations and not extrapolated from the general population to prove the best dietary treatment for FH [33].

Roy *et al.* [34▪], conducted a systemic review on the impact of diet on the lipid profile of people with FH and concluded that the apparent lack of effectiveness of diet manipulation in modulating LDL-C levels and other plasma lipids is likely due to biases in study designs, rather than a true lack of effects. This finding highlights the need to conduct randomized clinical trials assessing the impact of dietary patterns on cardiovascular health in individuals with FH.

Kinnear *et al.* [35▪] evaluated the feasibility of a study on the impact of an intervention aimed to improve diet and lifestyle in 21 families (22 children and 17 adults) with FH. In a 12-week randomized trial, individuals received usual care or a behavioral intervention aimed at reducing dietary intakes of total and saturated fat and cholesterol whereas increasing intakes of unsaturated fats, fiber, fruits, vegetables and plant stanol or sterol-fortified foods. Intervention also aimed at reducing sedentary behavior and increasing physical activity. Almost all families completed the intervention (97%). It was possible to observe improvements in body composition, LDL-C concentrations (8–10% reduction respectively in children and adults), and a positive impact on nutritional intake [35▪]. Effects on physical activity were less pronounced. The study opened the possibility of a robust trial to test the impact of diet and lifestyle intervention on ASCVD risk factors in FH.

CAN DIET BE EVEN MORE IMPORTANT AT SOME STAGES OF LIFE IN PEOPLE WITH FAMILIAL HYPERCHOLESTEROLEMIA?

Given the controversy about the risks and benefits of using lipid-lowering drug therapy in specific stages of life such as childhood [23–26] and pregnancy [36], these can be considered even more important stages for diet as an intervention to reduce ASCVD risk in people with FH. Despite this, studies are also limited [23–26]. Barkas *et al.* [37▪▪] conducted a meta-analysis of 17 trials with only 376 participants to investigate the impact of cholesterol-lowering diet and other dietary interventions on plasma lipids of children and adults with FH. Of importance, omega-3 fatty acids reduced plasma triglycerides in comparison with placebo. There were nonsignificant trends to reduction in TC and LDL-C with dietary interventions. On the other hand, the addition of plant sterols or stanols reduced cholesterol especially in children. There was no heterogeneity among the studies included in the analysis, but the small number of individuals and short follow-ups (3–13 weeks) are a limitation.

Rodríguez-Borjabad *et al.* evaluated in a cross-sectional study the association of components of Mediterranean and Nordic diets with lipids in children (4–18 years old), with FH from Norway ($n = 114$) and from Spain ($n = 145$) [38▪]. The Spanish FH group had a higher intake of fiber, and total fats, mainly MUFA and dietary cholesterol, but a lower intake of PUFA compared to the Norwegian FH group. The Norwegian children consumed more rapeseed oil, low-fat margarine and whole grains and less olive oil, eggs, fatty fish, meat, legumes, and nuts. In this study, monounsaturated fats, differently from studies in adults [30▪,31▪,32▪▪], were positively associated with LDL-C in Norwegian children. In Spanish children, the intake of fats (mainly MUFAs) was directly associated with HDL-C and Apo A1. Of interest despite differences in diet components, LDL-C concentrations were similar between the FH groups. The authors suggested that recommendations should focus more on dietary patterns rather than on individual dietary components.

ARE THERE ASSOCIATIONS OF MOLECULAR DEFECTS THAT CAUSE THE FAMILIAL HYPERCHOLESTEROLEMIA PHENOTYPE WITH RESPONSE TO DIETARY PATTERNS?

Classically the heterozygous FH phenotype is caused by loss of function variants in *LDLR* and *APOB* and by gain of function variants in *PCSK9* [1]. However, in many individuals with the phenotype variants on the three canonical genes are not encountered even

with use of next generation sequencing. In some of these individuals, severe hypercholesterolemia may occur due to the impact of small effect genes that can be aggregated in polygenic scores and those at the highest values of the latter are classified as having polygenic hypercholesterolemia [40▪▪]. Will dietary patterns or its components influence differently on plasma LDL-C according to the genotype? Usually, those with variants on *APOB* have lower LDL-C levels than those where FH is caused by variants on the *LDLR* [39]. But will that influence on response to diet? What about those with the FH phenotype due to polygenic hypercholesterolemia? There are no specific studies on these issues in people with FH. However, one study in Korean individuals suggests that some single nucleotide variations in *LDLR (rs1433099 and rs11557092)*, *ApoB* (rs13306194) and *PCSK9* (rs11583723) when aggregated in a polygenic score were associated higher cholesterol and triglyceride plasma levels in comparison with individuals with low genetic scores (those with minor alleles) [40▪▪]. Furthermore, those with a high score (those with greater numbers of major alleles in the four variations) had higher LDL-C concentrations when consumed a Westernized diet rich in carbohydrates than those with a low genetic score. This was not seen in people who consumed a more balanced Korean style and rice-style diet. The data suggest gene-diet interactions; however, it is important to emphasize that those were not individuals with FH and that this was a cross-sectional study. With the advances of genomics, it will be possible in the future to perform randomized studies to test the impact of dietary patterns on atherosclerosis risk biomarkers in people with FH with well-characterized molecular defects and in those with polygenic hypercholesterolemia.

CONCLUSION

The association of dietary components with lipid profile and other risk biomarkers in individuals with FH needs to be better studied to generate robust recommendations for each stage of life of individuals with this genetic alteration.

However, despite methodological limitations with the evidence available so far, there is possibility of benefit from adopting a dietary pattern with controlled content of saturated fat, and a greater supply of unsaturated fats, especially monounsaturated, suggesting the superiority of the Mediterranean dietary pattern. Additionally, diets with higher content of fruits, vegetables, and consequently higher fiber and plant stanol intake seem to be beneficial. It is noteworthy that the adoption of this dietary pattern must be accompanied by the adoption of a healthy lifestyle, physical activity, body weight adequacy, smoking avoidance, and maintenance of optimized pharmacological lipid-lowering therapy. Nonetheless, robust studies need to be performed to better understand the role of dietary interventions on ASCVD risk biomarkers in people with FH.

Acknowledgements

R.D.S. is recipient of a scholarship from Conselho Nacional de Pesquisa e Desenvolvimento Tecnológico, Brazil, (CNPq) #303734/2018-3.

Financial support and sponsorship

None.

Conflicts of interest

R.D.S. has received honoraria related to consulting, research and or speaker activities from: Abbott, Amgen, Aché, Astra Zeneca, Esperion, EMS, GETZ Pharma, Kowa, Libbs, Merck, MSD, Novo-Nordisk, Novartis, PTC Therapeutics, Pfizer, Roche and Sanofi. Other authors: none to declare.

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