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EDITORIAL COMMENT

Healthy Lifestyles and Cardiovascular Disease in Familial Hypercholesterolemia

Can We Change the Impact of Genes?*

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Certainly genes influence our health and destiny. Familial hypercholesterolemia (FH) is a codominant autosomal genetic disease characterized by elevation of plasma low-density lipoprotein (LDL)-cholesterol (LDL-C) from birth and early onset of atherosclerotic cardiovascular disease (ASCVD) in comparison with unaffected people.[1] In FH, high LDL-C plays a pivotal, but not the sole, role in development of early atherosclerosis and its consequences. Observational studies indicate association of biomarkers like male, smoking, low-plasma high-density lipoprotein-cholesterol, hypertension, obesity, diabetes, and elevation of plasma lipoprotein(a) with greater ASCVD risk in FH.[2,3] Moreover, heterogeneity in risk has been related to non-FH-causing genes[4] and presence of coronary artery calcification,[5,6] a surrogate of atherosclerotic plaque burden.

Robust pharmacologic LDL-C–lowering therapies with statins, ezetimibe, and inhibitors of PCSK9 are recommended to mitigate the elevated ASCVD risk in people with FH.[2] Guidelines also emphasize control of other risk factors like smoking, hypertension, diabetes, sedentarism, obesity, and avoidance of inadequate diets to reduce ASCVD risk in people with FH.[7]

Epidemiologic studies have associated some behaviors and lifestyles with a reduced burden of ASCVD.[8] Indeed, when public health is concerned, lifestyles that have been considered as "healthy" are publicized and recommended as a primordial way to prevent ASCVD for the population overall.[8] A healthy diet pattern, physical activity, smoking avoidance, and adequate adiposity (ie, body weight) may favorably modulate many other proatherogenic mechanisms like inflammation, thrombosis, blood pressure, insulin resistance, and glucose homeostasis as well as endothelial function and, therefore, reduce ASCVD risk.[9,10]

There is evidence that people affected by FH, when aware of the implications of their disease, follow a healthier lifestyle than their unaffected counterparts as shown in the Spanish Familial Hypercholesterolemia Study-SAFEHEART.[11] Indeed, the question that ensues is how much this healthy lifestyle could mitigate the impact of an autosomal-dominant disease exposing people to proatherogenic high LDL-C since birth? In the current issue of *JACC: Asia*, Tada et al[12] try to answer this question. The authors tested the association of a score measuring a healthy lifestyle with the occurrence of ASCVD in 951 patients with the heterozygous FH phenotype (mean age: 52 ± 16 years, 46.7% males, median baseline and on treatment LDL-C, respectively, of 234 [IQR: 206-279] mg/dL and 110 [IQR: 93-131] mg/dL and, 30.6% with previous cardiovascular disease). Molecular defects on canonic FH-causing genes were encountered in 699 individuals (73.1%). Participants answered a questionnaire on admission at the lipid clinic evaluating diet, exercise, smoking, and obesity attributing 1 point to each favorable parameter. Overall, a healthy diet pattern, regular exercise, not smoking, and absence of obesity were encountered in 77%, 46.9%, 68.7%, and 89.9% of participants, respectively. A favorable lifestyle score (4 points), however, was encountered in only 1 in 4 subjects, whereas roughly 1 in 3 had an unfavorable one (0-2 points) and the rest had an intermediate score.

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Those presenting FH molecular defects were younger (50 ± 16 years vs 56 ± 15 years), had higher LDL-C concentrations (251 [IQR: 216-292] mg/dL vs 209 [IQR: 196-229] mg/dL), and had a greater frequency of prior history of cardiovascular disease (34% vs 21%). Lifestyle scores, however, were similar between the 2 groups. After a median follow-up of 12.6 years, 179 patients (18.8%) had major atherosclerotic cardiovascular events (MACE). As previously shown, older age, male, hypertension, diabetes, the cholesterol-year score, previous ASCVD,[2] and FH variants[13,14] were associated with MACE. Of importance, each point on the healthy lifestyle score was associated with a 31% lower risk of MACE during follow-up (95% CI: 0.40-0.98). All components of the healthy lifestyle score except for absence of obesity were associated with lower risk of MACE. The greatest impact was seen with smoking avoidance, adjusted HR = 0.38 [95% CI: 0.27-0.49]. Positive impacts of healthier lifestyle were seen in both variants carriers and in those whose genetic tests were negative. The authors tested an interaction between presence of FH genetic variants and lifestyle and encountered a risk of MACE gradient by the age of 75 years from 21% for those with negative genetic tests and favorable lifestyle to 32% for those with negative tests and unfavorable lifestyle and from 29% to 55.4% for those with genetic variants with favorable and unfavorable lifestyles, respectively. Main study conclusions were that a healthy lifestyle was associated with reduced risk of MACE in those with the FH phenotype independent of the genetic diagnosis. Results are indeed encouraging and reinforce recommendations not to smoke, to eat adequately, to be active, and to lose weight and suggest that one can modify ASCVD risk in people affected by a strong genetic disease acting in mechanisms other than cholesterol.[2,7]

The study is limited by its retrospective design, lack of long-term ascertainment of participants adherence to a healthier lifestyle or to cholesterol-lowering therapies, relatively small number of study subjects and events, and by being performed in a single center in Japan. Results, however, are quite like the ones encountered in the study by Fahed et al[15] that was performed in the United Kingdom and suggest that the study from Tada et al[12] may be applied to other populations.

According to Tada et al,[12] not smoking was the strongest protective factor against MACE and the higher the healthy lifestyle score the lower was the risk, clearly reinforcing the role of smoking cessation for prevention of ASCVD in this high-risk population. Moreover, physical activity[16] and diet[17,18] may be of extreme importance in modulating proatherogenic mechanisms and reducing ASCVD burden in FH. In the past Pitsavos et al[16] had encountered a direct association between low exercise capacity and MACE occurrence in ASCVD-free FH individuals. Recently Antoniazzi et al[17,18] compared a Mediterranean diet pattern with the classic cholesterol-restricted and saturated fat–restricted diet in molecularly proven individuals with FH from Brazil and Spain. The components of the Mediterranean diet and also adherence to the diet were associated with lower concentrations of proatherogenic lipids and less low-grade inflammation.

The lack of association between absence of obesity and reduced risk of MACE in the study by Tada et al[12] should be seen with caution considering that body mass index instead of more specific markers of ectopic adiposity like waist or waist hip ratios[19] were used in the current study.

Finally, the authors should be congratulated on their work. Our inheritance is important, but our fates depend on much more than our genes, even in an autosomal-dominant disease like FH.

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