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Editorial

Diabetes and familial hypercholesterolemia: an unhealthy marriage

Diabetes e hipercolesterolemia familiar: un matrimonio peligroso

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Both familial hypercholesterolemia (FH) and type 2 diabetes (T2D) are considered high-risk conditions for cardiovascular disease.[1,2] While FH is primarily associated with elevated low-density lipoprotein cholesterol (LDL-C), atherosclerotic heart disease and, to a lesser extent, aortic stenosis, T2D is associated with a wider range of morbidities, beyond atherosclerotic heart disease, including heart failure and the complications of peripheral vascular/small vessel disease.

Historically, and before the onset of the global obesity epidemic and the availability of statin treatment to prevent atherosclerotic heart disease, the potential for overlap in these conditions in the same individual was less likely. Morbidity related to FH typically occurred prematurely, in persons younger than 60 years.[1] Onset of T2D developed in middle to late middle age with cardiovascular complications developing over decades, and incident events typically occurring after middle age.[3] In the current era, statins delay the onset of heart disease in persons with FH treated at a young age, T2D occurs earlier in life and is more prevalent secondary to the obesity epidemic, and statin treatment has been associated with the incidence of T2D, at least in susceptible individuals. These epidemiologic trends now make the presence of FH and T2D in the same person more likely.

Two further scientific observations suggest an important overlap between the conditions. First is the finding that, in a northern European population, the likelihood of developing T2D in persons with genetically confirmed FH is about half that of the general population.[4] As yet, no prospective studies have looked at persons with FH to determine rates of onset of T2D and the relationship with statin treatment. There are no confirmatory studies in ethnic groups with a higher likelihood of developing T2D than Caucasians, such as those of African or southeast Asian descent. Second is the fact that overproduction of very low-density lipoprotein is a hallmark of obesity-related conditions and insulin resistance.[5] Ultimately, this excess production will yield higher levels of low-density lipoprotein, which must be cleared by the liver. The presence of FH in a person with T2D, or predisposing factors to T2D, could thus lead to much higher levels of LDL-C than typically seen because of the combination of overproduction and delayed clearance. This phenomenon has also not been prospectively studied.

In a recent article published in *Revista Española de Cardiología*, Climent et al.[6] provide important new retrospective observations from the dyslipidemia registry of the Spanish Arteriosclerosis Society. The investigators compare persons with and without T2D among registry participants diagnosed with FH according to genetic and Dutch Lipid Clinic Network criteria. The principal finding is that the combination of FH and T2D doubles the risk of cardiovascular disease in persons with FH.

The prevalence of T2D in the cohort was 5%.[6] This is lower than the reported prevalence of T2D in Spain as a whole (estimates of 13% of the adult population with about half unrecognized are published) indirectly confirming that the likelihood of T2D in FH may be lower than that in the general population.[7] Nonetheless, persons with T2D were older, were more likely to have hypertension and to be overweight.[6] These characteristics are typical of T2D and suggest that the presence of FH does not preclude the development of T2D in susceptible individuals. Furthermore, persons with T2D had higher baseline LDL-C levels, consistent with the hypothesis that clearance of LDL particles is likely impaired in individuals with both FH and T2D.

Both persons with and without T2D had a similar prevalence of genetically-diagnosed FH. [6] This is of interest as features of T2D and aging could increase the likelihood of a phenotypic Dutch Lipid Clinic Network diagnosis (premature heart disease, positive family history of heart disease, LDL-C level). The equal prevalence of a genetic diagnosis in persons with and without FH suggests that the clinical characteristics of T2D did not bias the reported results.

Because of the retrospective design of the study, important questions regarding the interface of FH and T2D cannot be answered. Most important is the risk of developing T2D with long-term treatment for FH with statins. While it seems unlikely that this risk would be higher than that in the general population, it remains unknown whether or not the risk is the same or is in fact lower. The FH/T2D relationship with regard to incidence must be confirmed in other racial and ethnic groups beyond those of European descent.

As more is written about the interface between FH and T2D, the terminology surrounding the consequences of individuals with both of these conditions must be used more precisely. One term often used is "protection" when referring to the lower prevalence of T2D in persons with FH. Certainly, there is no protection from heart disease in persons with both conditions and we know that those with FH can acquire T2D. Given the prolonged exposure to elevated LDL-C in individuals with FH who develop T2D, it is likely that the converse of the message in this article might also be true: persons with T2D and FH may be much more likely to develop

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atherosclerotic heart disease at an earlier age than those with T2D and without FH. Furthermore, individuals with prediabetic states, such as insulin resistance or polycystic ovary syndrome, who have FH might have higher levels of LDL-C due to the interaction with excess production of very low-density lipoprotein. Until prospective studies clarify remaining natural history connections between these conditions, the use of the term "protection" is misleading.

A second term used ambiguously is "risk stratification".[8] For me, risk stratification implies that the presence or absence of a specific factor could either lower or raise a person's risk. For example, the absence of coronary calcification in someone older than 70 years might suggest that statin treatment may be discontinued as the likelihood of an event in the next 15 years is very low, regardless of cholesterol level. FH is high risk because of lifelong elevated levels of LDL-C and the higher the LDL-C, the higher the risk. Acquired risk factors such as T2D, smoking, and hypertension increase risk but the absence of these factors does not suggest the need for less intense treatment of LDL-C. For persons with several established risk factors, the critical question remains: should LDL-C lowering therapy be intensified or is control of additional risk (normalization of hemoglobin A1c, control of blood pressure, smoking cessation) sufficient? Most important, the role of atherosclerosis imaging in high risk individuals and its relationship with treatment intensification needs to be clarified. Until we understand more about vascular factors that protect individuals from atherosclerosis, I suggest the focus should be on reasons to intensify therapy, rather than stratify therapy.

Perhaps the most important reaffirmation in the work of Climent et al.[6] is the value of early diagnosis and prevention regarding both FH and T2D. Early diagnosis and treatment of FH mitigate risk substantially, as does a healthy lifestyle and maintaining normal body weight regarding T2D.[9] The median age of registry participants in this study was well into the sixth decade of life, and efforts to mitigate risk must begin much earlier in life to be effective.

CONFLICTS OF INTEREST

S.S. Gidding was Medical Director of the FH Foundation from May 2018 until December 2019.

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