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EDITORIAL

Gut microbiota: An indispensable tool in the fight against cardiovascular disease[☆]

La microbiota intestinal: una herramienta indispensable en la lucha contra la enfermedad cardiovascular

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In recent years, the role of the intestinal microbiota in various mechanisms related to cardiovascular health has been highlighted, with special emphasis being placed on aspects related to atherosclerosis, stressing the importance of the intestine-heart axis.¹ As in most diseases, the mechanisms that have been discussed include dysfunction of the intestinal barrier, with ensuing endotoxemia due to lipopolysaccharide (LPS) levels, together with decreased amounts of short-chain fatty acids (SCFAs). However, these mechanisms are not exclusive to cardiovascular disease.² Expectations were changed by the discovery that the metabolite trimethylamine-*N*-oxidase (TMAO), of microbial origin and formed from dietary components with L-carnitine or phosphatidylcholine, could be not only a marker of cardiovascular disease, but also a predictor of it.³ However,

thus far, its involvement in more specific mechanisms beyond those related to diet has yet to be ascertained.

However, within this system, the intestinal microbiota has emerged as a powerful weapon in the search for new preventive strategies, mainly in stratifying patients based on their microbiota profiles.⁴ Therefore, of particular relevance within this stratification strategy would be that of identifying patients who, despite not being at high risk or not having developed a serious cardiovascular disease a priori, have clinical features that might be related to cardiovascular disease.

With this premise, in this issue of *Clínica e investigación en aterosclerosis*, Ortega-Madueño et al. have linked the commonly accepted tool of coronary calcium quantification (CCC) from computed axial tomography (CAT), a technique widely used to select individuals with coronary atherosclerosis, with the composition of the intestinal microbiota.⁵ Thus, in a pilot study with 20 participants without prior cardiovascular disease, we studied how the microbiota profiles differed when the CCC levels were above or below 100 on the Agatston score. While this is a pilot study that should be properly validated with a larger population size, the results indicate that even in the absence of cardiovascular disease,

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the microbiota is able to discriminate between two types of CCC levels, corresponding to different risks of atherosclerosis. In particular, the authors observed that individuals with higher BCC values had higher levels of the Proteobacteria phylum, classically proinflammatory bacteria; this was observed even independently of age. In fact, they were able to correlate the abundance of these bacteria with plasma levels of TNF- α and IL-1 β . Going one step further, the authors measured the metabolite TMAO, observing that the levels were also higher in those subjects with a CCC value of >100. Finally, by inferring the metabolism of these bacteria, they saw that certain pathways, such as those related to the synthesis of lipopolysaccharide (LPS), were also increased in these subjects, which could be involved in their inflammatory state. In this way, the authors have been able to observe most of the characteristics associated with cardiovascular disease in these subjects, who apparently do not have cardiovascular disease, with respect to the intestinal microbiota.

The translational importance of this approach goes beyond the mere description of the bacteria that are increased or decreased, but one of the great stakes in terms of developing the science of microbiota study and its translation to clinical practice is the real possibility of varying the intestinal microbiota. In other words, if the intestinal microbiota plays a role in the pathophysiology of atherosclerosis and the intestinal microbiota can be altered by means of different strategies, this opens a significant window of opportunity to create treatments based on knowledge of the microbiota that will enable us to anticipate the progression of the disease towards more serious conditions.

Among the more widely studied real possibilities with higher yields are: dietary strategies, the use of probiotics, prebiotics, and synbiotics, the use of antimicrobial agents, or fecal microbiota transplants (FMT).

Thus, we know that the relationship between atherosclerosis and diet is highly dependent, and even more so in the relationship with TMAO through choline,⁶ so that a timely change in a person's lifestyle, including changes to a healthier diet with low levels of choline, such as diets high in vegetable products, as is the case of the Mediterranean diet,⁷ will produce healthy changes in the microbiota that will help to mitigate the progression of the disease.

On the other hand, different probiotic strains have been tested, principally those belonging to the *Lactobacillus* genus, which have been associated with reductions in cholesterol and triglycerides.⁸ Moreover, prebiotic substances such as inulin, which is known to be capable of changing the microbial population, are being tested to improve variables related to atherosclerosis, although the results are not as satisfactory as expected⁹ and we need to search for new prebiotics specifically targeting those bacteria that are particularly beneficial. In this context, we may also focus on selectively deleting certain bacteria with the use of antimicrobials, a subject that was addressed at the time,¹⁰ but which has yet to prove successful.

Finally, we come to FMTs. Following the tremendous success in treating recurrent *Clostridioides difficile* infection using FMT,¹¹ many other diseases have been treated with this approach. In the case of atherosclerosis, animal models have demonstrated that the disease can be alleviated by this route.¹² In addition, different strategies have been tried,

albeit not directly in atherosclerosis, such as transplanting microbiota from subjects who follow a vegan diet with a scant or zero capacity to produce TMAO in patients with metabolic syndrome in an attempt to lower the production of this microbial metabolite that is so closely related to cardiovascular disease.¹³

In short, the interesting work published in this issue of Clinics and Research in Atherosclerosis contributes to progress in translating knowledge about this very new science of microbiota into routine clinical practice in atherosclerosis.

References

1. Forkosh E, Ilan Y. The heart-gut axis: new target for atherosclerosis and congestive heart failure therapy. *Open Hear*. 2019;6:e000993. Available from: <http://openheart.bmj.com/content/6/1/e000993.abstract>
2. Trøseid M, Andersen GØ, Broch K, Hov JR. The gut microbiome in coronary artery disease and heart failure: current knowledge and future directions. *eBioMedicine*. 2020;52, <http://dx.doi.org/10.1016/j.ebiom.2020.102649>. Available from:..
3. Tang WHW, Li XS, Wu Y, Wang Z, Khaw K-T, Wareham NJ, et al. Plasma trimethylamine N-oxide (TMAO) levels predict future risk of coronary artery disease in apparently healthy individuals in the EPIC-Norfolk prospective population study. *Am Heart J*. 2021;236:80–6.
4. Jie Z, Xia H, Zhong S-L, Feng Q, Li S, Liang S, et al. The gut microbiome in atherosclerotic cardiovascular disease. *Nat Commun*. 2017;8:845, <http://dx.doi.org/10.1038/s41467-017-00900-1>. Available from:..
5. Ortega-Madueño I, Modrego J, Gómez-Gordo R, Ortega-Hernández A, de Isla LP, Carlos Muñoz J, Luisa Nieto M, et al. Relación entre la cuantificación de calcio coronario y la composición de la microbiota intestinal en sujetos sin enfermedad cardiovascular previa: estudio piloto. *Clin Invest Arteriosc*. 2022, <http://dx.doi.org/10.1016/j.arteri.2021.11.008>.
6. Lindskog Jonsson A, Caesar R, Akrami R, Reinhardt C, Fåh Hållénus F, Borén J, et al. Impact of gut microbiota and diet on the development of atherosclerosis in apoe^{-/-} mice. *Arterioscler Thromb Vasc Biol*. 2018;38:2318–26, <http://dx.doi.org/10.1161/ATVBAHA.118.311233>. Available from:..
7. Meslier V, Laiola M, Roager HM, De Filippis F, Roume H, Quinquis B, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut*. 2020;69, 1258 LP–1268. Available from: <http://gut.bmj.com/content/69/7/1258.abstract>
8. O'Morain VL, Ramji DP. The potential of probiotics in the prevention and treatment of atherosclerosis. *Mol Nutr Food Res*. 2020;64:e1900797.
9. Hoving LR, De Vries MR, De Jong RCM, Katiraei S, Pronk A, Quax PHA, et al. The prebiotic inulin aggravates accelerated atherosclerosis in hypercholesterolemic APOE*3-leiden mice. *Nutrients*. 2018;10.
10. Muhlestein JB. Antibiotic treatment of atherosclerosis. *Curr Opin Lipidol*. 2003;14:605–14.
11. Baunwall SMD, Lee MM, Eriksen MK, Mullish BH, Marchesi JR, Dahlerup JF, et al. Faecal microbiota transplantation for recurrent *Clostridioides difficile* infection: an updated systematic review and meta-analysis. *eClinicalMedicine*. 2020;29, <http://dx.doi.org/10.1016/j.eclinm.2020.100642>. Available from:..

12. Kim ES, Yoon BH, Lee SM, Choi M, Kim EH, Lee B-W, et al. Fecal microbiota transplantation ameliorates atherosclerosis in mice with C1q/TNF-related protein 9 genetic deficiency. *Exp Mol Med*. 2022;54:103–14, <http://dx.doi.org/10.1038/s12276-022-00728-w>. Available from:.
13. Smits LP, Kootte RS, Levin E, Prodan A, Fuentes S, Zoetendal EG, et al. Effect of vegan fecal microbiota transplantation on carnitine- and choline-derived trimethylamine-N-oxide production and vascular inflammation in patients with metabolic syndrome. *J Am Heart Assoc*. 2018;7.