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Commentary

Gut microbiota in diabetes and HIV: Inflammation is the link

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Type-2 diabetes mellitus (T2D) is a common disease characterized by hyperglycemia, insulin resistance and relative reduction in insulin secretion. Its prevalence has markedly increased in parallel to the obesity epidemic associated with a sedentary lifestyle in the Western world. The etiology of T2D is exceptionally complex and includes a combination of varying degrees of insulin resistance and insulin deficiency, with multiple genetic and environmental factors involved. A chronic state of low- grade inflammation is postulated as the mediator that links obesity with insulin resistance, but its cause is not well-known. The relationship between microbiota, obesity, and T2D has been extensively studied. In a seminal work of Turnbaugh et al. [1] it was shown that microbiota transplantation from genetically obese mice to germ-free mice induced a significant weight gain, in comparison to those mice that received microbiota transplantation from thin mice. Obese mice show alteration in the diversity or structure of the intestinal microbiota, a situation known as dysbiosis, with a relative abundance of Firmicutes with a corresponding decrease in the amount of Bacteroidetes. This relative abundance of the genus Firmicutes could be responsible for an increase in the capacity to digest some indigestible polysaccharides, giving rise to monosaccharides and short-chain fatty acids (SCFA) capable of being absorbed by the host, thus obtaining more energy from caloric intake [2]. In T2D there is a reduction in the proportion of butyrate-producing bacteria with the ability to protect the intestinal mucosa [3]. This increase in intestinal permeability coupled with dysbiosis with a preponderance of bacteria capable of inducing inflammation could be the link between DM2, chronic inflammation, and microbiota. The reduced production of butyrate and other short-chain fatty acids (SCFA) may affect the production of specific intestinal peptides that influence body weight, glucose metabolism, gut barrier function, and.energy hemostasis. Also, the gut microbiota of T2D patients, mainly by the action of bacteria of the genus Firmicutes, can alter the metabolism of bile salts involved in insulin and GLP-1 production [4].

HIV infection is associated with a significant inflammatory response and immune activation which does not entirely fade with antiretroviral therapy. Reduced diversity in gut microbiome composition has been shown in some studies, and there is an independent association between alpha-diversity of the microbiome and peripheral levels of CD4 lymphocyte in naıve HIV-infected patients. Given the close interaction between the intestinal microbiota and gut immunity, it is suggestive to assume that the HIV patient's microbiota is partly responsible for these alterations. A direct effect of HIV on the gut mucosal barrier has been hypothesized as a cause of dysbiosis; this may induce a leak in gut mucosa resulting in increased translocation of bacterial products from the gut producing systemic inflammation [5]. A direct correlation has been found between levels of microbial translocation and representation of the Proteobacteria phylum in feces, suggesting that microbiome composition affects gut mucosa permeability. The proinflammatory state induced by HIV is also associated to derangements of tryptophan metabolism through an induction human indoleamine-2, 3-dioxygenase-1 (IDO-1), which results in the production of immunosuppressive kynurenine derivatives which impair mucosal immunity, resulting in bacterial translocation [6].

Therefore, T2D and HIV infection have in common some gut microbiome alterations associated with a proinflammatory state. In the study published in *EBioMedicine*, JY Moon et al. [7] study the association between T2M or HIV infection and the differences in gut microbiota and plasma metabolomics. The authors examine the intestinal microbiota and a broad spectrum of metabolite profile of a population of women with diabetes with HIV. The selection of women avoids the bias of the influence of sexual orientation on the composition of the microbiota since men who have sex with men (MSM) show a significantly richer and more diverse fecal microbiota than non-MSM regardless of HIV infection [8]. The control group includes women at risk of HIV, making them fully comparable to the experimental group. The main findings are that in patients with T2D, regardless of HIV, there is a reduction in the relative proportion of several bacterial genera (Finegoldia, Anaerococcus, Sneathia, and Adlercreutzia). These bacteria are known to produce butyrate, which is associated to anti-inflammation and insulin sensitivity improvement; also, the presence of these bacteria is inversely related with kynurenine/tryptophan ratio, an indicator of tryptophan catabolism and involved in inflammation and bacterial translocation. The authors observed higher plasma levels of several metabolites of tryptophan catabolism and branched-chain amino acid and proline metabolism pathways, also associated with inflammatory pathways in T2D.

These findings allow them to speculate with the possibility that these variations of the microbiota could be related to the development of T2D through a proinflammatory state, partly mediated by the alterations of the tryptophan metabolism.

No recognized therapy can change this scenario of proinflammatory gut microbiota, but there are preliminary experiences that could

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suggest that modifying the microbiota could have a positive effect on the development of T2D. The Mediterranean diet reduces the risk of cardiovascular disease, improves glycemic control, partly through the modification of the intestinal microbiota [9]. The use of probiotics could induce changes in the composition of the intestinal microbiota, but the experience so far has been scarce with inconclusive studies [10]. The potential usefulness of these therapies is still to be confirmed and is an area in which results are expected in the coming years. It would be an exciting strategy modifying the microbiota through diet or with probiotics; in this way, the inflammatory state of the intestine could be reduced by acting on specific bacterial populations that are overrepresented in patients with T2D. Finally, fecal microbiota transplantation could be an alternative for some patients, although the experience published so far is very preliminary, and the potential adverse effects of this type of treatment are unknown.

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