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Intestinal microbiota and its host: harmony or discord?

Acting on gut microbiota in cardiometabolic disorders: who, what, when and how

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CARDIOMETABOLIC NUTRITIONAL DISEASES: AN ALARMING PROBLEM OF PUBLIC HEALTH

According to WHO, the increased prevalence of chronic diseases – or noncommunicable diseases – is closely related to phenomena such as rapid and unplanned urbanization, globalization of unhealthy lifestyles, and aging populations.[1] At the individual level, inadequate diet and sedentariness that result from changes in lifestyle are reflected by an increase in blood pressure, glycemia and lipidemia, which, in connection with the development of obesity, contribute to pathological changes in metabolism that become chronic over time. These combined risk factors are major contributors to the development of cardiovascular diseases, the leading cause of premature death responsible for 17.9 million deaths annually.[2]

Cardiovascular and metabolic diseases, together with some non-alcoholic liver diseases, as a whole referred to as cardiometabolic diseases, are closely linked disorders that constitute a global public health problem. They represent a significant burden of disease irrespective of the income level of the population. Being overweight or obese is the second and hyperglycemia is the third most important metabolic factor responsible for increased morbidity attributable to cardiometabolic diseases, with high blood pressure being the first.[1] In terms of health economics, the high prevalence of metabolic disorders entails considerable costs.[3]

Because some of them are modifiable, cardiometabolic risk factors are targeted by national prevention plans, especially in industrialized countries where, to various degrees, increased efforts have resulted in a reduction of cardiometabolic mortality.[4] Lifestyle modifications provide the basis for the clinical management of these disorders, which are at the same time closely linked and very heterogeneous,[5] and which evolve during the individual's life. It is now accepted that obesity is a disease.[6] Some obese or non-obese patients with metabolic disorders will progress rapidly to complications, while others will progress more slowly. Factors capable of predicting rapid progression or slow progression to complications are not known today. Some patients, despite significant obesity, may show a relatively normal metabolic risk profile – at least for a while – while others who are only overweight may present or progress rapidly to metabolic complications such as diabetes or a cardiovascular disease.[7]

The intestinal microbiota, considered today as the second brain of the human body, is currently recognized as a key player at the interface between environmental modifications and host biology.[8]

THE INTESTINAL MICROBIOTA AND DIET-RELATED CARDIOMETABOLIC DISEASES

Chronic metabolic diseases induce organic alterations and impairment of the signals involved in the communication between affected organs. Changes in both inflammation and the immune system are associated with major metabolic abnormalities. Interactions exist between the gut microbiota and these multiple and diverse

abnormalities[9] that do not occur at the same time in all patients and, therefore, have different clinical courses. Changes occur in the composition of the microbiota, both in terms of richness and in terms of bacterial groups that become enriched or depleted. The mechanisms by which the gut microbiota affects metabolic diseases (cardiovascular disease, type 2 diabetes) involve several pathways, the biological activity of which regulates the host's functions, such as:

1. Microbiota-derived bacterial metabolites such as short chain fatty acids, trimethylamine (TMAO) or, more recently, imidazole propionate, are to various degrees involved in metabolic (lipid metabolism, carbohydrate metabolism, insulin resistance) as well as inflammatory processes. Liver-derived TMAO is associated in some populations with an increased risk of chronic disease (cardiovascular events or kidney diseases).
2. The innate immune response to the structural components of bacteria such as lipopolysaccharide causes inflammation and insulin resistance, and contributes to the metabolic syndrome. Other membrane components may also lead to inflammatory and immune changes.[10,11]

The oral microbiota also has a role in diabetes and cardiovascular diseases, but this role needs to be clarified.[12,13]

ACTING ON THE MICROBIOTA: COULD THE MICROBIOME BE A TREATMENT FOR COMPLEX HUMAN METABOLIC DISEASES?

Numerous questions arose after the spectacular initial results of studies of the gut microbiota, especially with regard to the many actions proposed to modulate it.

What? What kinds of interventions can be used: diet, pre- and probiotics, bacterial metabolites, fecal transfer, or possibly combinations of these factors.

Who? Who is likely to be targeted by this type of approach and what kind of patient could benefit from an intervention directed at the microbiota? The main problem is the clinical heterogeneity of patients because 1) there are individual differences in the disease and stages of progression: "diabetes" or "obesity" differ from one patient to another; 2) organ alterations and impairment of inter-organ signals occur at different stages of the disease progression.

Why, when and on which target? In some diseases, the rationale for using interventions directed at the microbiota may be questioned. For example, in type 2 diabetes, a disease for which a large therapeutic arsenal is available, what would be the effectiveness of such an intervention? Should we intervene early, before the onset of the disease? In obesity, a pathology for which we lack effective treatment, could modulation of the microbiota directly affect weight or should it rather be directed at the complications, for example, by affecting inflammation?

Should we act directly on the microbiota or on the intestinal barrier with impaired permeability? Can we act on molecules produced by the microbiota such as the metabolites? Which host targets should be selected, especially with in combined strategies? At which point of the individual trajectory, i.e., at which stage of the disease should we consider action on the microbiota as type of treatment?

These are some of the numerous questions that scientists will have to answer.

BACTERIAL RICHNESS AND CLINICAL PHENOTYPES IN OBESITY

In many pathological fields including metabolic diseases, microbiota sequencing shows that a part of the population exhibits decreased microbial diversity. In a population with weight problems, decreased diversity may be observed in non-obese individuals (around 15%) or, conversely, microbial diversity may remain unchanged in obese individuals.[14] Phenotypic characterization of overweight or obese patients shows that these problems are not necessarily associated with metabolic complications and that normal BMI may be associated with complications.[15,16] Decreased richness of the microbiota is one of the characteristics of dysbiosis which is also associated with changes in bacterial groups. These may undergo loss or enrichment.

Thus, in patients with dysbiosis, a decrease in bacterial groups has been associated with metabolic benefit and anti-inflammatory effects, and an enrichment in bacteria associated with pro-inflammatory effects, have been described.[15,16] Patients with dysbiosis have more cardiometabolic risk factors (significant dyslipidemia, increased body fat, abdominal fat, and insulin resistance, and low-grade inflammation).[15,16]

Given the continuum and progression of obesity towards more severe forms, the evolution of bacterial richness raises some questions. In a recent French study (the Microbaria study), microbiota collapse and low gene abundance was observed in 75% of patients with severe obesity who had been referred for bariatric surgery.[17] This finding suggests a close relationship between complicated obesity and the collapse of bacterial richness.[17] Clinical changes also appeared to be associated with these phenomena. Compared with patients with high bacterial richness, patients with the same BMI, but with depleted gene count, had an increased truncal mass and more complications related to obesity: hypertension, diabetes, dyslipidemia, and even sleep apnea syndrome.[17] The relationship between gene richness and stool characteristics was also examined in this study. The results of this analysis confirm the inflammatory nature of the decrease in bacterial richness, particularly in bacteria that produce butyrate, a short-chain fatty acid with a role in metabolic processes.[17]

It is also possible to identify people with a collapse of bacterial richness using metabolomic techniques, which are simpler than sequencing. There is a positive relationship between bacterial richness and circulating hippurate. By studying bacterial metabolites, it is possible to relate metagenomic species changes to certain metabolites known to be produced by bacteria.

The MetaCardis study[18] is a research project conducted in six European countries, which aims to study the role of gut microbiota in cardiometabolic diseases. The study protocol uses a metagenomic approach to evaluate long-term relationships between diet and these diseases. Data collected at different stages of cardiometabolic disease progression were examined for potential bacterial signatures. The resulting database, containing dietary characteristics, clinical information and molecular, metagenomic and metabolomic phenotypes from a cohort of more than 2000 French, German and Danish subjects, was described in a recent publication reporting this study.[19] The results confirm the relationship between collapse of bacterial richness and worsening of obesity, indicating a metabolic signature of severe obesity. Similarly, it was observed that non-obese patients with type 2 diabetes also had a collapse in bacterial richness and diversity. Thus, in severely obese individuals, the ability to identify diabetes is lost and the occurrence of dysbiosis indicates the probable evolution of the disease.

In a Belgian study, carried out in patients with Crohn's disease, a relationship between some enterotypes and the microbial load was described.[20] This study identified the microbial burden as a key factor in microbiota alterations observed in patients with Crohn's disease, associated with an enterotype (so called enterotype 2) with low *Bacteroides* count.[20]

A MATTER OF INDIVIDUAL COURSE

Which moment of the individual course and progression of disease (aggravation, acute phase, or relapse) may be deemed a reversible stage at which an intervention directed at the microbiota can be considered? Is it possible to reverse the phenotype of microbial alteration and loss of bacterial richness? Nutrition, bariatric surgery, future probiotics including Akkermansia are considered from this perspective.[12,16,21-27]

Interactions between food, microbial functions and host metabolism

Dietary metabolites derived from intestinal microbiota, as well as those derived from protein consumption, could play a key role in regulating host metabolism.[28] Various studies have evaluated these interactions, including production of short-chain fatty acids in the colon (via bacterial fermentation of dietary fiber) that is beneficial in terms of insulin sensitivity[29-31], regulation by bile acids of blood glucose and metabolism[32-34], production of branched-chain amino acids by microbiota of low bacterial richness[35,36], and production of TMAO (a choline and L-carnitine bacterial metabolite) that is correlated with the risk of a cardiovascular events.[37-39]

Koh et al[40] report that histidine, an essential amino acid provided by the diet, can be converted into imidazole propionate by the gut microbiota. This process is likely to be increased in type 2 diabetes. This observation suggests that dietary protein uptake by patients with type 2 diabetes induces an adjustment of bacterial metabolism towards imidazole propionate production. In addition, it was observed that the mouse exposed to this metabolite develops glucose intolerance and insulin resistance.[40]

These results suggest a possible need to reconsider protein intake in cardiometabolic diseases, especially in type 2 diabetes. In fact, various observational and case-control studies report an increased risk of type 2 diabetes mellitus associated with increased protein consumption.[41-44] However, nutritional intervention studies report extremely heterogeneous results related to the issue of weight loss induced by the hypocaloric diet. Metabolic responses differ depending on the bacterial profile and food consumption.
Nevertheless, some arguments are available today in favor of:

1. The existence of an interaction between nutrients and cardiometabolic phenotypes.
2. The relationship between insulin resistance and animal protein intake.
3. The association between animal protein intake and insulin resistance markers in individuals with low bacterial richness and a *Bacteroides* enterotype.

INTERVENTION: CAN DYSBIOSIS BE REVERSED?

Bariatric surgery is an important factor in resolution of type 2 diabetes. Nevertheless, it is a transient solution because several years of experience in the field have shown that despite the potential for delaying disease progression, type 2 diabetes is probably not reversible.

The evolution of the microbiota in patients who have undergone bariatric surgery shows that, despite some increase over time, both bacterial richness and diversity remain low. There is, therefore, no method for full restoration of the microbial profile. This observation raises the clinical question of the possibility of restoring this diversity and saving metabolic improvement by more invasive techniques, such as microbiota transfer.

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