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Review Article

Arterial Hypertension, Type 2 Diabetes Mellitus, Microbiota Transplantation and its Generics

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Abstract

Through an extensive review of the World Literature we have formed a criterion, which has to do with the incidence of the Intestinal Microbiota in two Diseases that are present in millions of human beings (Hypertension and Type 2 Diabetes Mellitus) and that produce a series of added Pathologies, which enhance them as an enormous cause of complications in the concert of pathologies. The arterial hypertension that appears in more than 50% of the cases of type 2 Diabetes Mellitus and that together generate a number of vascular diseases, both micro and macrocirculation, ending with death due to cardiovascular complications in around 60 to 80% of diabetics. While 75% of hypertensive patients die from the same cause. This can be reduced by using treatments that modulate the Microbiota. We conclude with the perspective of the rational use of the Microbiome, as well as its different units, such as: probiotics, prebiotics, symbiotic, postbiotics: (FIFs: Fermented Infant Formulas and Inactive Bacterial Cells), Paraprobiotics, Phage Therapy and Microbiota Transplantation.

Keywords: *Arterial Hypertension (AH); Type 2 Diabetes Mellitus (T2DM); Virus (Vs); Intestinal Microbiota (IM); Fecal Microbiota Transplant (FMT); Intestinal Microbiota Transplant (IMT)*

Introduction

We carried out an extensive review of the world literature in relation to the possibility that patients who co-occur with AH and Type 2 Diabetes Mellitus (T2DM) have of being treated with Fecal Microbiota Transplantation (FMT), also known as Intestinal Microbiota (IMT), as well as its generics. We found interesting reports that refer to the positive effect that these procedures have, by modulating the Microbiome. Likewise, changes in lifestyle, including dietary modifications, increased physical activity, stress management and avoiding tobacco smoke, are effective in preventing sequelae such as cardiovascular diseases, the main cause of death in United States of America.

Gut microbiota

Bacteria, Viruses (Vs), intestinal and pseudolysogenic Bacteriophages; Archaeal Viruses, Eukaryotic Viruses (Metazoa, Fungi and Protozoa), are unique in each individual and are the components of the Intestinal Microbiota (IM), the Queen of the Microbiota. The IM is a complex endocrine system capable of consolidating the correct functioning of the organism, although it is responsible for numerous pathologies: T2DM, coronary syndromes, cancer, neurodevelopmental disorders and many others. The diet [1], is considered one of the main

drivers of IM configuration throughout genetics, lifestyle, sex, age, stress, childbirth and lactation, environment, hygiene, physical activity also influence; antibiotics and other medications. The microbiome is composed of a complex system that includes all microorganisms, cells, luminous compounds, antimicrobial peptides and the interactions between them. Bacterial (indole, tryptamine and indolic acid) and endogenous (serotonin, melatonin, and kynurenine) metabolites impact microbial metabolism, the immune system, and the composition of the microbiota. Indoxyl can impact the functions of the circulatory system by decreasing the production of NO (nitric oxide), increasing the production of reactive oxygen species and favoring cardiac interstitial fibrosis. *E. coli, Paracolobactrum coliform, Proteus vulgaris, Bacteroides* Spp and *Achromobacter liquefaciens* can generate indole. And this, improve the secretion of peptide 1 similar to glucagon, an incretin with an intense impact on the metabolism of the host.

Intestinal dysbiosis (Dysbacteriosis)

We cannot ignore this concept, since the imbalances that occur in IM, caused by various etiologies, directly affect the conditions that we analyze (AH and T2DM). IM dysbiosis can be prevented through the consumption of butyrate. This dysfunction generates alteration of the host mechanisms and through it, a significant number of diseases, including AH, T2DM, obesity and metabolic syndrome. Therefore, dysbiosis can be treated with new therapies such as Fecal Microbiota Transplantation (FMT). When dysbiosis of the blood microbiota occurs, cardiovascular events and T2DM appear.

Brain-gut axis

The most significant incidence in patients with AH and T2DM occurs in the gut-brain axis [2]. In this axis, a series of widely demonstrated activities are directly manifested, which have to do with both intestinal and neurological immune systems, within which both components located in both systems stand out, as well as the production of a series of substances that impact on the genesis or not of arterial hypertension, such as bacterial metabolites, the immune system, endocrine effects and the vagal afferent pathway. Neuroinflammation can generate an autonomic nervous system without regulation, which translates into exacerbated neurogenic arterial hypertension [3]. Likewise, the hyperactive peripheral immune system can affect the central immune system and modulate neuronal action in cardioregulatory brain regions, collaborating with arterial hypertension. Short Chain Fatty Acids (SCFA) from MI have many beneficial effects on the host and as they are present in the brain they can affect both systems, vasodilating and reducing blood pressure [4]. The intake of dietary fiber as a source of SCFA has positive effects on blood pressure. Butyrate and lactate regulate metabolism and have a direct effect on the Central Nervous System. Finally, the role of the Vagus Nerve, GABA (gamma-aminobutyric acid), Glutamate and Dopamine also stand out in intestinal dysbiosis.

Arterial hypertension

Progressive cardiovascular syndrome with genetic predisposition in response to interrelated and complex etiologies. The Gut Microbiota, the super-organ, is microbial and endocrine and lives symbiotically within the gut. It produces substances that through circulation affect the circulatory system. It generates many vital substrates for human homeostasis, such as vitamins B and K and contributes to the transformation and degradation of bile acids and steroids. SCFAs, indole, and intestinal metabolites have effects on homeostasis of the circulatory system and humoral and nervous controls [5]. SCFAs are made from carbohydrates through bacterial fermentation, and contribute to daily energy needs. Within the SCFA, especially propionate and butyrate play a transcendent role in cell differentiation. Bioactive metabolites of IM affect blood pressure homeostasis. Trimethylamine is oxidized in the liver to trimethylamine N-oxide, which is associated with an increased risk of atherosclerosis and significant adverse cardiovascular events. Hypertension and systolic pressure are related to bacterial diversity. In severe hypertension, intense intestinal dysbiosis is observed, with a significant reduction in bacterial diversity.

Type 2 diabetes mellitus

T2DM affects more than 400 million people in our world [6]. In them, the balance of IM is essential to maintain energy harmony and their metabolism. Lipopolysaccharides as bacterial products of IM could cross the impaired intestinal barrier and reach the peripheral circulation, contributing to a low-grade chronic inflammatory state, favoring T2DM. Inflammation and oxidative stress play an important role in the underlying mechanisms of cardiovascular diseases and other complications of T2DM. IM adjusts host metabolism, since many complex carbohydrates cannot be degraded by their enzymes. Reduced carbohydrate metabolism has been found after *Trichuris* infection. Demonstrating, that in part, the malnutrition caused by helminths is due to negative effects on fermentative microorganisms. Fact that must be taken into account. The relative proportion of SCFA induces the host response, and there is, at the same time, hepatic clearance, which induces lipogenesis and other transformations.

Insulin resistance

Altered body response to insulin, resulting in elevated blood glucose levels (a key component of T2DM and metabolic syndrome). It usually shows an increase in *Firmicutis*-butyrate producers- and a decrease in *Bacteroidetes* in the distal colonic area. They are usually accompanied by increased glycoside hydrolase, butyrate and acetate. In T2DM and heart failure there is insulin resistance, accompanied by an increase in aldosterone, angiotensin II, neprilysin and norepinephrine. The increases in monosaccharides and hepatic triglyceride level facilitated by IM show a strong association between it and host metabolism in glucose homeostasis and lipogenesis [7]. It has been shown that the depletion of lipoprotein lipase inhibitors is mediated by IM [8]. Metabolic entoxemia (elevated plasma levels of lipopolysaccharides) and metabolic processes associated with obesity generate insulinemia, insulin resistance and increased liver fat. Le Chatelier., *et al*. and Cotillard., *et al*. [9] showed that low diversity in IM is associated with obesity and a higher prevalence of insulin resistance, non-alcoholic fatty liver disease and low-grade inflammation. Low-grade inflammation in visceral adipose tissue leads to the link between insulin resistance and obesity. Indicating strong role of the innate immune system in insulin resistance.

Treatments

Ketogenic diet, probiotics, prebiotics, synbiotics, postbiotics, paraprobiotics, bacteriophages, intestinal microbiota transplantation (Fecal).

Ketogenic diet

Today the ketogenic diet has gained immense popularity, even though it has been in use since 1921 [10]. Russel Wilder first used it to treat epilepsy [11]. It is currently used as a rapid weight loss formula and has been shown to be quite effective, at least in the short term. It is contraindicated in carnitine palmitoyltransferase deficiency, carnitine translocase deficiency, pyruvate kinase deficiency, primary carnitine deficiency, liver failure, pancreatitis, porphyrias and fat metabolism disorders. Unfortunately many of these conditions occur in diabetics, obese and hypertensive, diseases where it has been indicated. The ketogenic diet is low in carbohydrates, regular in protein and high in fat, another aspect to take care of. This diet has health benefits and is 75% fat, 20% protein, and 5% carbohydrate.

Probiotics, prebiotics, synbiotics, postbiotics and paraprobiotics

Modulation of IM with the use of probiotics, prebiotics, synbiotics, postbiotics and paraprobiotics can benefit both glucose metabolism, insulin resistance and AH [12]. There are probiotics that have been beneficial in metabolic diseases, such as T2DM and we believe that at the same time they can directly or indirectly help in the processes of insulin resistance and AH. On the other hand, there are several publications that confirm the beneficial effect of probiotics in T2DM, arterial hypertension, metabolic syndrome and insulin resistance, where it is mentioned that *Lactobacillus* species have been shown to be effective in managing T2DM. *Firmicutes* species was positively correlated with decreased insulin resistance, however, causality has yet to be proven [13]. *L. gasseri* and *L. plantarum* have been considered to

decrease weight in both animal and human studies [14]. A significant incidence of probiotics was shown in the reduction of triglycerides and total cholesterol. Probiotics decrease cardiovascular risk by controlling hypertension and dyslipidemia in people with T2DM. *Bifidobacterium, Lactobacillus, Lactococcus, Propionibacterium* and *Acetobacter* genera for eight weeks improved insulin resistance in T2DM patients. Lastly, probiotics improve the immune response, lactose tolerance; they have anti-inflammatory effect and regulate intestinal disorders caused by obesity.

Prebiotics

Fructooligosaccharides (FOS) and galactooligosaccharides (GOS) could have an adverse effect on glucose metabolism by reducing butyrate-producing microbes [13].

Synbiotics

L. acidophilus, L. casei, L. rhamnosus, L. bulgaricus, B. breve, B. longum and *Streptococcus thermophilus* combined with fructooligosaccharides for 8 weeks significantly reduced fasting serum glucose level [14]. Synbiotics are favorable to IM and consequently to the processes we are studying. They can be consumed through the intake of raw fruits and vegetables. They are used to stimulate the growth of bacterial strains in the digestive tract. Bacteria of the genus *Bifidobacterium* or *Lactobacillus* with fructooligosaccharides are the most popular synbiotics. The administration of *Lactobacillus casei, Lactobacillus rhamnosus*, *Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum* and *Lactobacillus bulgariccharides adultccharides*, together with a prebiotic, reduced the generation of TNF-α [15]. *Lactobacillus rhamnosus*, together with *Bifidobacterium lactis*, with inulin and oligofructose increased IgA. The administration of a synbiotic resulted in a significant increase in HDL and a decrease in blood glucose.

Postbiotics

Are functional bioactive compounds, generated in matrix during fermentation, can be used to promote health [16]. Both FIF (Fermented Infant Formulas) and inactive bacterial cells are considered postbiotic [17]. In addition to teichoic acid, short-chain fatty acids, pili-like structures, microbial cell fractions, cell lysates, metabolites, peptidoglycan-derived muropeptides, extracellular polysaccharides and functional proteins. They can generate direct and clinically relevant immunomodulatory effects. They are promising alternatives as antibiotics.

Paraprobiotics

Non-viable microorganisms that may produce health benefits similar to those produced by live probiotics. They can be used in immunocompromised patients, in whom live microorganisms could cause severe health problems. They have long shelf life, safety and beneficial effect such as modulation of immunity, lowering of cholesterol, and modification of biological responses. Its way of acting has not yet been determined.

Bacteriophage therapy

Bacteriophages (phages) have made a comeback, just as they did before the start of the antibiotic era [18]. And they resurface due to the enormous difficulty due to the serious resistance that antibiotics have. Six bacteriophage-based probiotics against *Listeria monocytogenes* have been approved by FDA, revealing the importance of this old therapy [19]. His interest focuses on three families: Myoviridae, Siphoviridae and Podoviridae. In addition to filamentous and cuboidal phages. However, there is still a long way to go in the West for bacteriophages to become a reality.

Intestinal microbiota transplantation

Fecal transplantation can reduce the risk of obesity, T2DM, insulin resistance, and increased BMI [20]. The modulation of IM through IMT has been demonstrated numerous times. And transplantation can reduce the cardiovascular complications of diabetes. FMT in men with metabolic syndrome produced improved insulin sensitivity, with intestinal microbial diversity, including increased butyrate-producing bacterial strains. Butyrate has beneficial metabolic effects by increasing mitochondrial activity. There is sufficient evidence of the success of IMT in different conditions, including cardiovascular conditions. As well as its minimal complications, this procedure should not be feared. What we do have to carry out are the different suggestions of the FDA.

Future

Newly identified bacterial strains will be used in the near future, so their efficacy will need to be evaluated. There will be intervention with microbiota metabolites and SCFA butyrate, evaluating their effects on energy expenditure and food intake. The metabolic syndrome-producing effects on IM mean that its manipulation continues to be a promising therapeutic approach.

Conclusion

- Analysis and mapping of individual microbial composition at the metagenomic level will provide more information on specific targets in therapeutic interventions.
- Researchers will continue to use next generation sequencing technology and there will be many discoveries related mostly to viruses and their virome.
- There will be new discoveries about the Microbiome through large-scale longitudinal studies.
- Knowledge about the role of bacteriophages will be developed.
- Probiotics, prebiotics, synbiotics, transbiotics and paraprobiotics will be consolidated.
- There will be greater determination in the use of different treatments, according to the stage of the disease.
- Knowledge of the factors that affect the composition of the Microbiome will be expanded.
- Research protocols will be standardized so that there is an effective comparison between the findings.
- The use of Intestinal Microbiota Transplantation (IMT) and the components of the microbiota, especially the intestinal microbiota, will continue to be very promising.
- The possible effects of the transfer of antibiotic resistance genes or virulent genes will be minimized by deepening the specific tests.
- Research related to the interactions of the Microbiome and inflammatory processes, the immune response and intestinal parasitic diseases will be deepened.
- The IMT procedures (faecal) will need to be standardized to generate quality and safety in the various institutions.

Conflicts of Interest

The authors declare that do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

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