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Editorial

Blood Microbiome Role in Diabetes, Obesity, and Cardiovascular Diseases

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"Blood is an exceptional juice," said Johann Wolfgang von Goethe, the German writer and statesman. For more than three hundred years, blood was considered a sterile and immensely immunologically protected environment, and that any presence of microbes in the blood is only associated with an infectious disease. However, this concept was negated over the past decade by several lines of evidence reporting the presence of the blood microbiota and their cellular components and product. In fact, in the mid-20th century, some bacterial species were detected using traditional culturing techniques in healthy individuals' blood. Subsequently, bacterial, viral, bacteriophages, archaea, and some fungal (Basidiomycota and Ascomycota) DNA molecules were detected using both Sanger and next-generation sequencing techniques in the blood of both healthy and diseased individuals. However, the presence of living microbes and their cellular components in blood emphasized their influence on host immune and on their possible role in inducing chronic systemic inflammation associated with obesity, diabetes, and cardiovascular diseases (CVD). Thus, numerous microbial taxa can reside in host blood, but few can turn invasive and establish pathogenic diseases. Microbes can reach the host's blood through several suggested entry points such as maternal source, i.e. placenta, amniotic fluid, injuries, infections, obliteration of cellular tight junctions, and permeability of barriers. Moreover, the oral cavity can also be an essential entry point to oral microbiome components into the bloodstream during periodontitis. Furthermore, surgical and non-surgical medical procedures can allow bacterial cells' infiltration and their metabolites into the bloodstream. The blood microbiota is dominated by Proteobacteria and genera *Achromobacter*, *Pseudomonas*, *Serratia*, *Sphingomonas*, *Staphylococcus*, *Corynebacterium,* and *Acinetobacter*, along with some Viruses, archaea, and fungi. Most blood microbiota is from the skin and oral origins, suggesting that they are the biological source pool in healthy situations. Although healthy blood microbiota does not exhibit any pathological interactions, they may be involved in the healthy host physiology and immune modulation. However, blood microbiota and their cellular components (i.e. lipopolysaccharide, LPS) and metabolites are associated with several diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). If they are not eliminated from the bloodstream by the reticuloendothelial system (RES), they induce chronic inflammatory associated with diabetes, obesity, and CVD. Furthermore, antimicrobial therapy was suggested for the treatment of disease-associated chronic inflammation. Several blood bacterial taxa and their cellular components have been associated with T2DM, namely, *Staphylococcus* spp., Proteobacteria, *Klebsiella* spp., *Ralstonia* spp., *Sediminibacterium* spp., *Actinotalea* spp., *Alishewanella* spp., *Pseudoclavibacter* spp., *Atopobium* cluster, and *Clostridium coccoides*. Besides, Gram-negative bacteria and their cellular components, such as LPS, can access the host's bloodstream causing metabolic endotoxemia, low-grade inflammation, and other systemic implications. This associated low-grade chronic inflammation has significant cumulative effects on host adiposity and insulin resistance. LPS induced metabolic endotoxemia disrupts the inflammatory tone and initiates body weight gain and diabetes. It was found that LPS interaction with CD14/TLR4 receptors system sets the tone of insulin sensitivity and the onset of diabetes and obesity. Thus, reducing plasma LPS concentration might be a powerful approach for controlling metabolic ailments. Furthermore, it was suggested that free LPS transfer initially to the high-density lipoprotein (HDL) and then to very-low-density lipoprotein (VLDL), whereas the LPS-bound low-density lipoprotein (LDL) portion is mainly resultant from VLDL catabolism; the latter may hence denote an LPS catabolic pathway. T2DM patients show lower LDL-LPS secondary to reduced VLDL catabolism, which may represent an impaired catabolic pathway. Consequently, T2DM patients showed impairment in LPS degradation; thus, the disease per se promotes endotoxemia. Additionally, several early life viral infections have been linked to type 1 diabetes (T1DM) by destroying pancreatic β cells. These include hepatitis C virus, herpes simplex virus, and Coxsackieviruses. It is well accepted that blood circulating microbiota serves as the leading cause of microbial colonization of atherosclerotic plaques and subsequent inflammation and CVD development. Furthermore, elevated levels of bacterial taxa were detected in

patients with ischemic heart disease (IHD), congenital heart disease (CHD), and valvular heart disease (VHD). Similarly, elevated blood circulation levels of *Lactobacillus* spp., *Bacteroides* spp., and *Streptococcus* spp. were observed amongst ST-segment elevation myocardial infarction (STEMI) patients. Additionally, a significant reduction of cholesterol-metabolizing bacterial taxa was observed amongst patients with heart failure and myocardial infarction (MI). However, the pathophysiological mechanisms connecting the blood microbiota and varying CVD are not precise and require further investigation. Similarly, elevated levels of bacteriophages were detected in the circulating blood virome of CVD patients, while eukaryotic viruses were dominant amongst healthy individuals. Additionally, human microbiota manufactures a wide range of metabolites, including short-chain fatty acids (SCFAs), vitamins, anti-inflammatory compounds, hormones, amino acid derivatives, carbohydrate fermentation derivatives, and antioxidants. A healthy microbiota creates a robust partnership with the host's intestines in a symbiotic relationship and performs vital functions such as carbohydrate fermentation and energy balance homeostasis. These important fermentation processes produce gas and numerous metabolites, including short-chain fatty acids (SCFA), butyrate, propionate, and acetate, which function as a fuel for the gut's intestinal cells and also as signaling molecules in both gut and extraintestinal tissues. Butyrate plays an important role in decreasing gut permeability, modulating the gut-brain axis interactions via the vagus nerve, in addition to numerous metabolic processes. Moreover, both propionate and butyrate enhance the intestinal gluconeogenesis process and an important role in energy and glucose homeostasis mechanisms. While acetate plays a crucial role in reducing appetite through interacting with hypothalamic receptors. When a small section of nutriment (dietary fibers/microbiota accessible carbohydrates (MAC)) is not digested in the small intestine, it is fermented by microbiota in the colon to produce the SCFAs. Furthermore, a diet high in fiber led to changes in the gut microbiota that played a protective role in developing cardiovascular disease. The favorable effects of fiber may be explained by the generation and distribution of one of the gut microbiota's main metabolites, the short-chain fatty acid acetate. Acetate affected several molecular changes associated with improved cardiovascular health and function. Moreover, protein and amino acid microbial metabolites are found to affect several metabolic disorders. Phosphatidylcholine-derived microbiota metabolites, i.e., choline, Trimethylamine (TMA), and betaine, are associated with increased CVD risk. Long-term adherence to the Paleolithic diet (PD) is associated with different gut microbiota and increased serum trimethylamine-N-oxide (TMAO) associated with CVD and atherosclerotic plaque. Thus, an assortment of fiber component sources is vital to sustaining gut microbiota and cardiovascular health. Besides, the administration of antibiotics can overturn TMAO blood level and consequent cardiovascular events. Augmented TMAO plasma levels are associated with an increased risk of T2DM, cardiovascular and cerebrovascular diseases, STEMI, and heart failure. Further investigations are still required to elucidate TMAO's role in cardiovascular complications. Besides, increased levels of branched-chain amino acids (BCAAs) were detected in individuals with insulin resistance. This increase correlated with *Prevotella copri* and *Bacteroides vulgatus*, the potential producers, and *Butyrivibrio crossotus* and *Eubacterium sireum*, the potential BCAAs transporters. These results suggest the microbiota as targets to lessen insulin resistance and decrease metabolic and cardiovascular disease incidence. Additionally, high levels of Hydrogen sulfide (H_2S) are the major byproduct of protein fermentation and are linked to islet cell damage, glucose dyshomeostasis, inflammation, and cardiovascular failure. Several other microbiota metabolism derivatives and or chemicals have been suggested to be involved in the progression or the suppression of metabolic diseases such as Polyphenols, 5-(3,5-Dihydroxyphenyl)-gamma-valerolactone, dioxins, non-caloric artificial sweeteners (NAS), and endocrine-disrupting chemicals; however, extensive investigations are still required to elucidates their effect on the alternations of circulating microbial metabolites levels. No doubt, targeting the microbiota and derivative compounds can provide excellent metabolic disorders treatment that can enhance the outcomes of current therapies such as dietary modifications, lifestyle interventions, bariatric surgeries, and pharmacological treatment. There are five ways to restore microbiota's equilibrium to correct their imbalance (dysbiosis), namely, probiotics, prebiotics, synbiotics treatments, dietary intervention, and Fecal microbiota transplant (FMT). Besides, removing blood microbiota and its metabolites from the bloodstream can target many innovative solutions and therapeutics. Moreover, such as TMAO, the most promising target for therapeutic target for CVD, metabolomics aided discovery of other microbiota metabolites linked to other metabolic diseases can also provide additional diagnostic and therapeutic targets.

Thus, both the medical and scientific community must recognize that blood is not a sterile environment and that microbes and their metabolites can leak into the bloodstream and cause numerous physiopathological effects. Moreover, human microbiome dysbiosis, spe-

cifically blood microbiome dysbiosis, is associated with diabetes, obesity, metabolic disorders, and CVD. More importantly, this research arena is still wide open for further extensive investigations to establish and elucidate the microbiome's causality of these ailments.

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