Endothelial Dysfunction in Mexican Obese Children, is there A Role of the Gut Microbiota?

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Abstract

Endothelial dysfunction is a predisposing factor for atherosclerosis and other cardiovascular diseases; and at the same time, endothelial dysfunction is associated to obesity. The prevalence of endothelial dysfunction, atherosclerosis and obesity is quite high among Mexican children; on the other hand, gut microbiota has been associated to obesity in the same population. Atherosclerosis is associated to gut microbiota in humans, and this association raise the possibility that endothelial dysfunction is also related with the gut microbiota in obese population. This review addresses the current knowledge of association of endothelial dysfunction, with obesity and atherosclerosis; however, there are no reports of association of endothelial dysfunction with gut microbiota through the measurement of adhesion molecules like ICAM-1, VCAM-1, and selectins.

Keywords: Microbiota; Obesity; Endothelial Dysfunction; Children; SCFA

Endothelial Dysfunction

Endothelium is the thin layer of simple squamous cells that lines the interior surface of blood vessels and lymphatic vessels, forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall. Endothelial Dysfunction (EDF) is a state of imbalance of vasodilatation or vasoconstriction, or diminished availability of (NO) Nitric oxide [Figure 1]. Here NO works as a vasodilator. This imbalance leads down-regulation of endothelial NO Synthase (eNOS), up-regulation of Reactive Oxygen Species (ROS) [1], C - Reactive Protein (CRP) [2], Vascular Cell Adhesion Molecule-1 (VCAM-1) [3] and it further causes loss of endothelial dependent dilation, blood thickening and formation of small plates. In addition, this imbalance causes impairment of endothelium- dependent vasodilatation and it

may cause further atherosclerosis and other cardiovascular diseases [4]. Endothelial dysfunction can be diagnosed by the gold standard method - angiography with acetylcholine injection, with Flow Mediated Dilation (FMD) method, or by measurement of endothelial dysfunction markers – VCAM-1, Intercellular Adhesion Molecule-1 (ICAM-1), E-selection and CRP in blood [5,6].

Endothelial Dysfunction and Atherosclerosis

Atherosclerosis is a hardening process of the arteries, in which plaque builds up inside the arteries. Plaque is made of cholesterol, fatty substances, cellular waste products, calcium and fibrin. It can block the blood's flow through an artery in the heart and that may lead a heart attack or stroke (American Heart Association, 2014). Endothelial dysfunction is an early marker for atherosclerosis. In Mexico, around 29.8% children are suffering with endothelial dysfunction [7]. It has been reported that atherosclerosis was observed in 53% in Mexico during 2005-2007.

Obesity

Obesity is a metabolic disease and a worldwide health issue. In 2014, more than 600 million adults were obese and 41 million
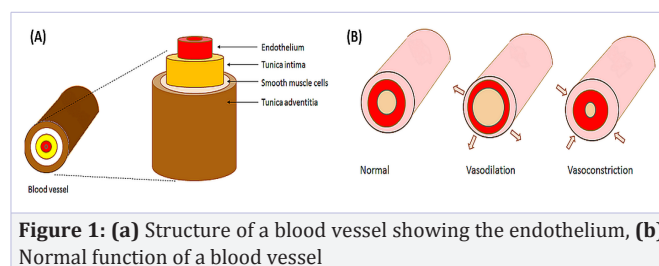
Figure 1: (a) Structure of a blood vessel showing the endothelium, **(b)** Normal function of a blood vessel

children under the age of 5 were overweight or obese in 2014 [8]. Initially, obesity was restricted to some developed country but now it has become a global health problem and the prevalence of obesity has also increased from few decades [9]. Obesity and overweight are the fifth death cause with more than 3 million deaths worldwide [10]. In Mexico, more than 70% adults are overweight [11], 13.3% of children between the age of 5-11 years old are obese [12], and 1 out of 3 children are overweight [13].

Gut Microbiota

The development of obesity has influence of human gut microbiome [14]. A human gut is occupied by up to – 100 trillion of microorganisms [15], these gut microorganisms help us to balance the digestive system. Alterations in gut microbiome are associated with obesity and with weight loss [16]. Human gut microbial population is dominated by five bacterial phyla; Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Verrucomicrobia. On the other hand, obesity is associated with changes in the relative abundance of phylum Firmicutes and Bacteroidetes [15]. Recent studies showed that the relative abundance of phylum Firmicutes was higher than Bacteroidetes in a sample of United States obese population [17]. In addition, it was reported that bacterial genera like *Roseburia* spp., *Blautia* spp., *Coprococcus* spp., *Faecalibacterium* spp. and families like Lachnospiraceae, Enterobacteriaceae relative abundance are significantly higher in Mexican overweight and obese children than normal children [18]. These bacteria are associated with high capacity of energy harvest in obese population [19]. Anaerobic intestinal gut microbiota ferments the dietary fiber, and produces Short-Chain Fatty Acids (SCFAs) such as acetic acids, propionic acids and butyric acid [20] and regulates the host energy metabolisms [21, 22]. In animal models, it has been found that genetically obese *ob/ ob* mice shows high amount of SCFAs in their caecum and less in their feces as comparative to their lean littermates [19]. These SCFAs have many positively effect on intestinal health such as, an energy source for the colonic epithelium (butyrate), and for peripheral tissues (acetate and propionate), an inflammation modulator, helps in the gut motility and in wound healing, nurture the blood flow by vasodilating the colonic vessels as well. In addition, propionate augments the muscular activity, epithelial cell proliferation, and butyrate as a main energy source for colonocytes [21].

Diet Alters the Gut Microbiota

Diet plays an important role in human health by modulating the gut microbial composition. High fat diet is associated with obesity whereas dietary fiber-rich diet can reduce the risk of obesity. It was suggested that obese microbiota might produce more SCFAs and extract more energy from provided diet than lean microbiota [18]. A dietary fiber containing food enriches the gut microbiota and protects the colonic mucus barrier and it reduces the risk of colitis. Whereas, dietary fiber-free diet increases the mucus-eroding microbiota which degrades the colonic mucus barrier and allow mucosal pathogens like *Citrobacter rodentium* bacteria to epithelial layer which can cause colitis [23]. A recent study showed that dietary fiber-free diet and captivity increases the intestinal colonization of bacteria *Bacteroides* spp. and *Prevotella* spp. in Non Human Primates (NHPs), which reflects in parallel the converge of NHPs microbiota towards the modern human microbiota, and suggests the recent loss of core microbiota in humans [24]. These bacterial genera *Bacteroides* spp., *Prevotella* spp. or *Ruminococcus* spp. are dominant in each enterotype and are associated with the consumption of a diet and not affected by gender, age or nationality [25].

Overview of a Molecular Mechanism Associating Endothelial Dysfunction, Atherosclerosis and Obesity

Atherosclerosis can cause by any stress to the endothelium like aging, systemic arterial high blood pressure, hypercholesterolemia, Diabetes, smoking, hypertension and with obesity as well. Any of these factors can damage the endothelium and stimulate the secretion of primary proinflammatory cytokines, such as Interleukin-1 (IL-1) and the Tumor Necrosis Factor-α (TNF-α). These cytokines enhance the expression of adhesion molecules such ICAM-1, VCAM-1 and P-, E-, and L-selectins [Figure 2].

Obese children between the ages 5 to 17 years have more risk of cardiovascular disease. Obesity is associated of high levels of cholesterol, triglycerides in adipose tissues which induces many proinflammatory molecules such as TNF-α, IL-6, leptin, Plasminogen Activator Inhibitor-1 (PAI-1), angiotensin-II, resistin and CRP, Monocytes Chemoattractant Protein-1 (MCP-1). These molecules can cause vascular inflammations. Obese also associated with high levels plasma-CRP which directly reflects the high body fat [26]. Angiotensin-II can stimulate the production of ROS which can oxidize the Low-Density Lipoprotein (LDL). These high-levels of CRP, ROS and oxidized Low-Density Lipoprotein (oxLDL) reduce the availability of intracellular nitric oxide [1,2]. In addition, they increase the expression of adhesion molecules as well. These adhesion molecules - VCAM-1, ICAM-1 and E-selectins helps the adhesion of blood leukocytes such as monocytes, T-cells, dendritic cells and mast cells to the endothelium layer. Furthermore, leukocytes trans-migrate into inner layer of endothelium called tunica intima where monocytes convert into macrophages; along with remaining leukocytes participates in inflammatory immune reactions that's make plaques. These reactions lead impairment of endothelial function, which later can appear as atherosclerosis [27].
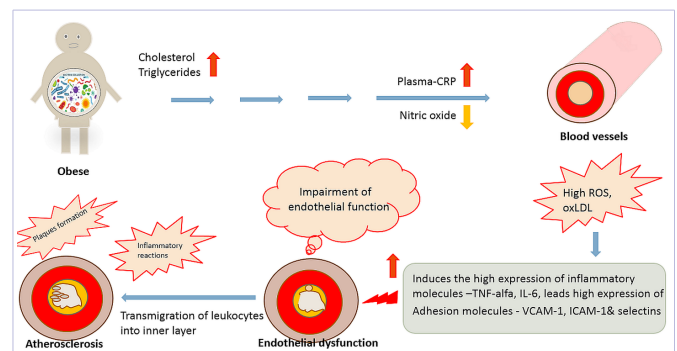
Figure 2: Overview of a molecular mechanism associating with endothelial dysfunction, atherosclerosis and obesity

Endothelial Dysfunction, Obesity and Gut Microbiota

Atherosclerosis and obesity are associated with endothelial dysfunction and obesity with gut microbiota [17]. Recent studies suggested that the gut metagenome is associated with the symptomatic atherosclerosis [28]. As we know atherosclerosis is a deposition of lipid molecules and the gut microbiota causes inflammation by Lipopolysaccharide (LPS) and peptidoglycan that can lead metabolic disease. Pyrosequencing showed that atherosclerotic plaque contains bacterial DNA [29]. Shotgun sequencing of the gut metagenome revealed that the genus *Collinsella* spp. was dominated in patients with symptomatic atherosclerosis whereas *Roseburia* spp. and *Eubacterium* spp. were observed more in healthy controls [28].

Obese children between the ages 5 to 17 years have more risk of cardiovascular disease. Recently, our group has reported the microbial diversity in Mexican obese children [18]. We found that the relative abundance of the phylum Firmicutes was more than the Bacteroidetes in obese children with high-level triglycerides and cholesterol. We also observed the SCFAs concentration in feces was lower in obese children feces than normal weight; it was attributed to an increase in the mucosal absorption of SCFAs. EDF and atherosclerosis prevalence is slightly higher in Mexican population. Although, there is no report up to our knowledge about association between EDF and gut Microbiota, even in the Mexican population. However, we believe SCFAs and gut microbiota play a role in endothelial dysfunction by inflammatory molecules in overweight and obese Mexican children population [Figure 3].

Conclusion

Endothelial dysfunction is a predisposing factor for atherosclerosis and for other cardiovascular diseases, and although there is a solid association of the gut microbiota with obesity in Mexican children, it is necessary to investigate the association between EDF and the gut microbial diversity or function. Further studies are necessary to establish whether a consequence of EDF is to alter the gut microbiota composition or its function. A more appealing hypothesis is that a primary gradual change occurs in the microbiota attributes before the appearance of EDF in children. An altered gut microbiota could contribute significantly to endothelial function by the production of currently undescribed bioactive metabolites.
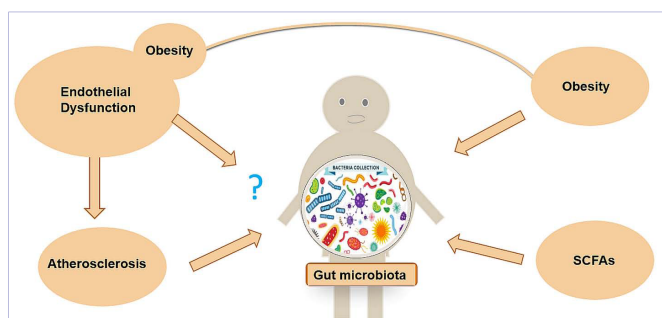

Figure 3: Association of gut microbiota with different factors (see text)

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