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SM Journal of Public Health and Epidemiology

Special Article- Malnutrition and Public Health

Malnutrition: Role of the Diet on the Microbiota and In the Functioning of the Gut Immune System

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Article Information

Received date: Feb 29, 2016
Accepted date: Apr 06, 2016
Published date: Apr 11, 2016

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Keywords Obesity, Probiotics, Mucosal immune system, Gut microbiota

Abbreviations HFD: High Fat Diet; Fiaf: Fasting-Induced Adipose Factor; LPL: Lipoprotein Lipase; L: Lactobacillus; FM: Fermented Milk; FTO: Fat Mass And Obesity-Associated Protein; VSG: Vertical Sleeve Gastrectomy; NFLD: Nonalcoholic Fatty Liver Disease; (UCP)-2: Uncoupling Protein; TG: Triglycerides; TC: Total Cholesterol; HDL-C: High Density Lipoprotein; LDL-C: Low Density Lipoprotein; IBD: Inflammatory Bowel Disease; LPS: Lipopolysaccharide; NFLD: Nonalcoholic Fatty Liver Disease; FOS: Fructooligosaccharides; TNFα: Tumor Necrosis Factor Alpha; IFNγ: Interferon Gamma; MCP-1: Macrophage Chemoattractant Protein 1; IL: Interleukin; NKT: Natural Killer T Cells

Abstract

The intestinal microbiota in health is characterized by stability and diversity; any changes under different metabolic or inflammatory diseases cause an imbalance, changes in the composition and consequently modification in the intestinal homeostasis.

The intestinal microbiota is influenced by the microorganisms that enter with the diet. Malnutrition processes, both obesity and malnourishment, induces changes in the intestinal microbiota composition, affecting mainly lactobacillus, bifidobacteria and bacteroides populations. These changes are accompanied by alterations in the intestinal villi architecture and in the intestinal barrier function.

The intestinal ecosystem is a complex microenvironment where, multiple cells type (prokaryote and eukaryote) interacting constantly. The microbiota modifications induced by changes in the eating habits have repercussion on intestinal immunity.

Probiotic microorganisms contained in different foods constitute an alternative to induce a positive balance in the microbiota. On the other hand several studies demonstrate their ability to stimulate the immune system at the intestinal level.

We summarize here the results published specifically on the relationship between microbiota, obesity and intestinal immune system.

Introduction

The obesity is a chronic inflammatory disease with a multifactorial origin that has reached epidemic proportions in worldwide [1]. This pathology is characterized by abnormal or excessive fat accumulation, which increases the mortality [2]. The obesity is a significant risk factor for type 2 diabetes, cardiovascular disease, obesity-related fatty liver disease, and certain cancers [2-4]. Recent works has suggested an important role of the gut microbiota in obesity [5,6]. DiBaise, et al. showed in animal and humans models that the gut microbiota composition differs in lean versus obese hosts [5]. Also, Backhed et al., (2004, 2005 and 2007) demonstrated that germ-free mice are protected from High Fat Diet (HFD)-induced obesity and metabolic dysfunction, including glucose intolerance, which is due to depression of Fasting-Induced Adipose Factor (Fiaf), an inhibitor of Lipoprotein Lipase (LPL) [7-9]. The colonization of germ-free animals with gut microbiota isolated from conventionally raised obese donors led to a significant increase in body fat content, and insulin resistance in receptors mice [10,11].

These studies suggest that the gut microbiota could have an important role in the development of obesity; the changes in the same could be a tool for future treatments.

On the other hand, there are many evidences showing that the Probiotic supplementation in the diet has a beneficial effect to combating the obesity and its related disorders, especially due to the anti-inflammatory effects of these microorganisms [12].

In our experience we demonstrated in a mice model, that oral administration of *Lactobacillus (L) casei* CRL 431 suspension or it's Fermented Milk (FM) for long period of time (60 days) maintained or diminished the body weight of non-obese animals receiving conventional balanced diet [13]. These observations led us to study the association to this loss body weight with biochemical parameters, microbiota and immune system, comparatively between obese and non-obese mice.

Obesity, Causes, Consequences and Treatments

Among the numerous causes of obesity, one of the most recognized is the energy imbalance, when the calories consumed are greater than that utilized by the different physiological body processes [14].

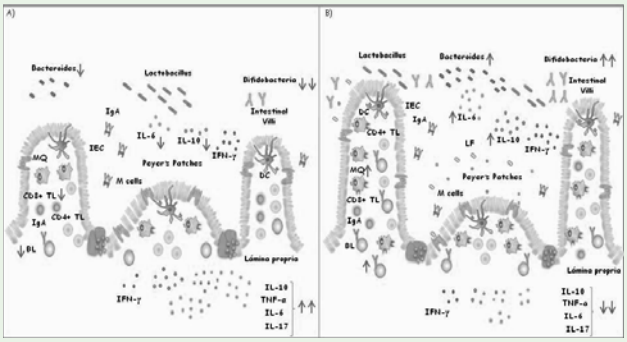

Figure 1: Changes in the gut microenvironment in obese host.
A) Obesity exert an important influence in the gut microbiota with diminution in the bacteroides, bifidobacteria and lactobacillus population. It was observed major production of inflammatory cytokine in lamina propria and changes in the length of intestinal microvilli.
B)-The probiotic administration to obese mice was able to restore the normal intestinal architecture, decreasing the proinfammatory cytokine and improve the microbiota balance.

Is important to consider there are many factors influencing simultaneously the energy balance. These factors are related with the sedentary life style, accompanied by the offering of the food market, with fast foods high in fat. Furthermore there are certain factors called "obesogenic factors" e.g. changes in the circadian rhythm, where the light/day cycles can be altered by the different activities. The desynchronization induced by shift work or chronic jet lag are frequently associated with metabolic dysfunctions (chronobesity), being the light, an important stimulus that can maintain the internal clock [15]. Furthermore there are genetic factors associated with obesity [16]. It is genetically demonstrated that, social behavior and environmental factors are capable of influence the obese phenotype [17].

Metabolic pathway can regulate the obesity, fat deposits and insulin resistance, latter being one of the consequences of the obesity [18].

Other important consequences of obesity are the cardiovascular disorders. Recent studies in animal's model showed that obesity mediates alterations in myocardial lipid metabolism, and this condition is in association with the type 2 diabetes. The alterations in either myocardial fatty acid uptake or fatty acid β-oxidation results in the accumulation of various lipid intermediates, triacylglycerol, diacylglycerol, ceramide, long-chain acyl CoA, acylcarnitine, and many others that are linked to the progression of ventricular dysfunction [19].

Shahid et al reports the correlation between Fat Mass and Obesity-Associated Protein (FTO) gene polymorphism rs9939609, with coronary heart diseases in obese patients of Pakistan. The variant showed influence in the glucose levels, however the lipid parameter did not appear to be affected [20].

Obesity could influence the mood and self esteem, because in many societies the thinness is considered a beauty attribute [21]. Thus the obesity is a source of clinically significant distress or depression, thereby reducing the quality of life.

Actually has been converted in one of the major problem around the world, where the prevalence is increasing rapidly, with characteristics of a pandemic. One of the major effects induced by obesity is the immunodeficiency state of the host, being more susceptible to infections [22].

Current treatments for obesity are focused on combination of therapies, which includes aerobic and resistance exercise; nutrition therapy, with energy deficient diets; pharmacological treatment of cardiovascular co-morbidities or weight loss medications; in these sense there are many drugs used, such us phentermine or the combination of phentermine-fenfluramine, that have a stimulant effect, decreasing appetite by increasing metabolism. However it was reported that the patients that used these medicaments developed heart disease or pulmonary hypertension, and several deaths were also reported [23].

Actually others medicaments are used e.g. Pancreatic lipase inhibitor as ORLISTAT or list at, but this medicament is not well-accepted for the patients due to the side-effects. There are patients who reported gastrointestinal side effects, including fatty/oily stool, increased defecation frequency, liquid stools, fecal urgency, flatulence, flatulence with discharge, or oily evacuation [24].

The combination bupropion/naltrexone is an antidepressant that besides has effect on body weight. This is contraindicated in patients with hypertension, eating disorders, benzodiazepine or opioid dependence [24].

Is important taking into account that all the drugs can have side effects, including increased blood pressure, headache, nervousness, palpitations, sleeping travels, nausea, constipation, and dry mouth.

Gastric bypass and Vertical Sleeve Gastrectomy (VSG) are others strategies used to mitigate the metabolic consequences of obesity. A multidisciplinary team is responsible for the evaluation and selection of metabolic surgery patients. This examination includes a full medical assessment with risk stratification, nutritional counseling, and behavioral health evaluation and support [25].

Current research efforts have focused in the improving of the treatments for obese patients and raising awareness in society on the importance of good nutritionals habits, which are accompanied by changes in lifestyle.

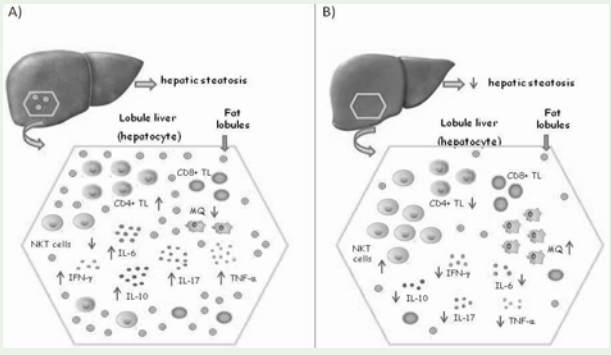

Figure 2: Probiotic effect on obesity mice liver.
A)-The HFD ingested conducted to hepatic steatosis, evidenced by a increases in the number of fat lobules in the liver. The CD4+ T cells are in greater number with the proinflammatory cytokines release. At the same time it was observed a NKT cells diminution. B)- After probiotic consumption the obesity mice showed a regulation in the inflammatory markers (IL-6, IFNγ, TNFα). The number of macrophages and the NKT cell population increases with reduction of CD4+T cells.

Manipulation of gut microbiota is a novel strategy for obesity treatment. In these sense, the incorporation of Probiotics or fermented food containing these microorganisms, as part of regular diet, could be an alternative to contribute to the health of gut microbiota and the improvement in the functioning of the Immune System. Nevertheless many reports show that Probiotics diminished food intake and appetite, body weight and metabolic functions through gastrointestinal pathways and modulation of the gut bacterial community [26].

Obesity and their Intestinal Microbiota Relation

At the time of birth the gut is sterile but it is gradually colonized by different microorganisms until the child reaches the age of three years, [27] when the microbiota is stable. The gene pool of the microbial habitants is diverse and comprises 10^{14} microorganisms, which is major than our total somatic and germ cells. These microorganisms constitute the "gut microbiota" [7].

The gut microbiota plays an important role in the regulation of the host's metabolism and in the extraction of energy from ingested food. It is important to note that the development and functions of the gut immunity depends of the microbiota establishment [28,29].

An imbalance in the gut microbiota is associated with obesity; metabolic syndrome and others related pathology (diabetes, cardiovascular disease, obesity-related fatty liver disease and certain cancers) [30].

The principal bacterial species in the mouse and human gut belong to the phyla Bacteroidetes and Firmicutes. There are evidences demonstrating that in lean leptin-deficient ob/ob mice were a decrease in Bacteroides and some gram-positive bacteria, such as Bifidobacterium species, accompanied of an increase in Firmicutes [31].

Similar observations were reported in a human trial in which obese host had fewer Bacteroides and after weight loss, the relative proportion of Bacteroides was increased [32].

Some recently reports suggest a direct correlation between gut microbiota and the appetite-regulating hormones. Authors demonstrated that the increases of serum leptin levels were related negatively with the Bacteroides, Clostridium and Prevotella quantity [33]. Also, other study demonstrated that a Prevotella genus was identified in obese and diabetic db/db mice [34].

Recently Probiotics consumption is being used as a strategy for treating obesity. Probably, it is due to these microorganism are able to induce a positive balance in the intestinal microbiota [35,36].

The Probiotic microorganisms most commonly used as dietary supplement in the obesity and metabolic disorders belonging to the genera Bifidobacteria and Lactobacilli [37].

Probiotics are defined as live microorganisms that, when administered in adequate amounts, provide a health benefit to the host [38].

In a previous work we evaluated, in an obese mouse model, the effect of the continuous administration of a probiotic bacterium *Lactobacillus casei* CRL 431 or the Fermented Milk (FM) by *L. casei*, on different parameters altered in obese host. In this study we demonstrated that the first beneficial effect obtained with the FM administration was a significant decrease of the body weight in mice given high fat diet [39]. These results are in concordance with others authors; Million et al., showed that the administration of *L. plantarum* and *Lactobacillus gasseri* is associated with weight loss in obese humans and animals models [40]. Karlsson, et al. also, showed that *L. plantarum* administration diminished the body weight in rats with a high-energy-dense diet [41]. Kang et al. demonstrated that the *Lactobacillus gasseri* BNR17 administration decreased significantly the body weight in diet-induced overweight rats [42].

As a consequence of the results obtained related to the body weight in obese animals fed with FM, we evaluated the lipid profile as an indicator of coronary heart disease, and also a sign of metabolic syndrome in combination with high blood sugar. The increased Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein (HDL-C) and Low Density Lipoprotein (LDL-C) concentrations observed in obese mice were significantly decreased in obese mice that received Probiotics (FM and Lc), whereas the obese animals given FM had values similar to the normal control [39].

Other authors demonstrated similar results with the probiotics and prebiotics administration. Yoo et al. showed that *Lactobacillus plantarum* KY1032 and *Lactobacillus curvatus* HY7601 reduced cholesterol in plasma and liver in mice fed with a high-fat high-cholesterol diet [43]. Wu et al. demonstrated that *L. plantarum* K21 administration reduced the cholesterol and triglyceride plasma levels and ameliorated the leptin levels in mice fed with HFD [44].

Other study showed that *Bifidobacterium* CECT 7765 reduced the cholesterol, triglyceride, and glucose serum levels, also, decreased insulin resistance and improved glucose tolerance in obese mice [45]. Hu et al. also demonstrated that *Lactobacillus plantarum* NS5 and *Lactobacillus delbrueckii* subsp. *bulgaricus* NS12 diminished the serum total cholesterol, LDL-C, apolipoprotein B and free fatty acids levels and increased the apolipoprotein A-I levels in rats fed with a high cholesterol diet [46].

As was mentioned, the intestinal microbiota plays an important role in the regulation of the gut immunity, metabolism, and the histological structure of the gut, which has been well demonstrated [47,48].

There are several evidences suggesting that obese and lean people have different gut microbiota, as it was demonstrated in previous studies [49].

The probiotic supplementation to obese mice prevented the diminution of Bacteroides in the large intestine, population [39,50,51]. The Bifidobacteria population showed significant increases in the large intestine of mice that received FM or *L. casei* CRL 431 suspension, independent of the conventional or high-fat diet administration [39]. This effect was observed previously with another strain of *Lactobacillus*, *L. paracasei* CNM I-1518 (formerly called L. casei DN-114001) [52]. These results are similar to those observed by others authors. Turnbaugh et al., showed a decrease in Bacteroides and a corresponding increase in Firmicutes in leptin-deficient ob/ob mice [53].

Recent works related the reduction in beneficial bacteria (such as Bifidobacterium or butyrate-producing bacteria) and the increases in pro-inflammatory/pathogenic bacteria (such as, Desulfovibrionaceae) with the obesity development, the systemic inflammation and the metabolic disorders in both humans and rodents [54,55,56].

In another work, it was demonstrated that two Lactobacillus and one Bifidobacterium strains, individually administrated attenuated the inflammation and the metabolic syndrome in HFD-induced obesity mice. In this study the Lactobacillus and Bifidobacterium strains affected host inflammation, gut microbial fermentation and microbiota composition, so the authors suggest that the probiotic intervention strategies could be play an important role in the diet to prevent or attenuate the obesity and the related metabolic disorders [57].

In addition to those improvements induced by probiotics consumption in body weight and in the gut microbiota in obese mice, it was showed a reduction of hepatic steatosis [58,59]. In our obesity mouse model we observed a restoration of the intestinal villi length which, was altered by the high fat diet. Renz et al. demonstrated that the microbiota composition promoted changes in the gut morphology such as the villi length, crypts depth and in the maturation of mucosa-associated lymphoid tissues. These studies were performed in germ-free mice, where the microvilli are longer and thinner than in the wild type mice [60].

Several recent studies demonstrated that the HFD in obese animals induced not only gut histological changes but also increased gut permeability and reduced the expression of tight junction protein in the intestinal epithelial cells of mice [61].

The modulation of the gut microbiota composition by probiotics improve gut permeability and increase the IgA+ cells production in the lamina propria of the small intestine [62], which it is a beneficial effect due to IgA is an important components of the gut barrier.

Studies performed in obese mice given probiotics *L. casei* CRL 431 as a FM or suspension, showed an improvement in IgA+ B cell populations [39]. These results demonstrated the importance of the FM administration to reinforce the gut barrier that was impaired by the high fat diet intake, as a consequence of the endotoxemia caused by LPS.

Probiotics in Intestinal Immunity in Obese Host

Obesity is considered an inflammatory process in which the adipose tissue plays an important role [63]. The obesity is associated with a chronic inflammation state, due to the production of pro-inflammatory cytokines by the adipose tissue. Adipose tissue contains fibroblasts, pre-adipocytes, adipocytes and macrophages, which contribute to the inflammatory process [64].

The imbalance in the cellular homeostasis and the chronic inflammation state could development certain diseases such as cancer, Inflammatory Bowel Disease (IBD) and metabolic syndrome [65,66,67].

Cani et al., suggests that increases in the pro-inflammatory cytokines in obese host is a consequence of the endototoxemia produced by Lipopolysaccharide (LPS), which is derived from Gram (-) bacteria residents of gut microbiota. The LPS binds to CD14 receptor present on the surface of innate immune cells and triggers the expression of pro-inflammatory cytokines (such as TNF-α, IL-1, IL-6). The activation of this system CD14 / LPS regulates the onset of obesity and associated disorders (sensitivity to insulin and diabetes) [68,69].

Some reports suggest that the probiotic administration in obese host induce a decrease of the inflammatory condition, resulting in a gut immune system modulation [70,71].

In this sense, the analysis of the different cytokines at the intestinal level in mice given HFD, showed increases in the production of pro-inflammatory cytokines TNF-α, IL-6, IL-17; as well as the regulatory cytokine IL-10 [72]. Others authors reported similar results where demonstrated increases TNF-α and IL-6 serum levels of obese individuals compared with lean individuals [73]. The IL-6 and principally TNF-α increases produced by multiple immune cell types in the gut, could be an early response to HFD, promoting the development of obesity and insulin resistance [74,75].

It was also demonstrated that obesity promotes the selective expansion of Th17 cells with progressively production of IL-17 in an IL-6–dependent process [76]. Regarding to the increases of IL-10-positive cells in the small intestine from obese mice could be due to a normal response of the obese host with the aim of reduce inflammatory state. Reporters showed that dendritic cells in obese individuals produced a significant increase of IL-10 compared with lean patients [77].

Nonalcoholic Fatty Liver Disease (NFLD) is currently the most common liver disease in both adults and in children, associated with obesity and is considered to be the hepatic manifestation of the metabolic syndrome. In the liver is induced an inflammatory microenvironment with pro-inflammatory cytokines increase, due to injury induced by LPS [78].

In our obese mouse model induced by a HFD, we evaluated cytokine-positive cells in the hepatic tissues. The results obtained showed increases in the number of pro-inflammatory cytokines with higher amounts of IL-10-positive cells, similar to those observed in the small intestine. When the obese animals received probiotic supplementation the pro-inflammatory cytokines decrease at the expense of IL-10-positive cells increases. It is also important to note that the inflammatory markers in obese mice were higher in the liver than in the small intestine, reaching to duplicate the number of cytokine positive cells [72].

There are evidences showing similar results, where mice treated with VSL#3 improves the hepatic insulin resistance and also has effect on fatty acid oxidation and uncoupling protein (UCP)-2 expressions [78].

The first evidences that the probiotics administration could improve the liver damage induced by NAFLD were provided by Loguercio et al. The study was performed in patients with different types of chronic liver diseases, which were given a mixture of different species of bacteria belonging to Lactobacillus and Bifidobacterium genera associated with Fructooligosaccharides (FOS), vitamins and minerals. After this treatment, the patients showed a reduction in the serum levels of the aminotransferases, markers of oxidative stress (malondialdehyde and 4 hydroxynonenal) and TNF-α [79].

In another work, it was demonstrated the beneficial effect of probiotics in the steatosis and insulin resistance improvements in liver in obese mice. Xiong et al. suggest that this effect is due to increases hepatic NKT cell numbers and to the reduction of inflammatory signaling [80].

The NKT cells are immune cells, whose function is to balance the pro- and anti-inflammatory cytokines production. We reported that these cells are decreases in obese mice and after the probiotics or fermented milk supplementation, the number of these cells increase significantly in the liver [72].

The anti-inflammatory effect induced by probiotic in the liver was also associated with improvement in the liver histology. This fact was reported in HFD induced obese mice model treated with the probiotic bacterium *L. casei* CRL 431 or with fermented milk containing these bacteria [72].

Malaguarnera et al. using histological evaluation, provided evidences that *Bifidobacterium longum* with FOS administration, in combination with lifestyle modifications, are able to reduce the hepatic steatosis, TNF-α, C-reactive protein and aspartate transaminase serum levels [81]. The visceral adipose tissue in obese host, are infiltrated by macrophages, which are attracted to the TNF production and the CCL2 secreted by hypertrophic adipocytes [82,83].

The study of the cytokine production by the adipocytes isolated from visceral fat of obese mice reveled increases of pro-inflammatory cytokines and the MCP-1. These pro-inflammatory cytokines increases have been accompanied by immune-infiltrating cells and an increase in secretion of MCP-1 by adipocytes. All these alterations were reverted after probiotic administration [72].

Recent support demonstrated that the probiotics administration in obese mice produced changes in adipose tissue and in liver, down-regulating the expression of pro-inflammatory genes (TNF-α, IL6, IL1b and MCP1) and up-regulating fatty acid oxidation-related genes [84]. Miyoshi et al. performed studies where showed that the consumption of *Lactobacillus gasseri* SBT2055 in obese mice prevented the fat accumulation and pro-inflammatory gene expression in adipose tissue and also in the liver [85].

The same group of researchers conducted a double-blind, randomized, placebo-controlled intervention trial with 87 obese patients to those given a FM containing *Lactobacillus gasseri* SBT2055. They showed a significant reduction in abdominal visceral and subcutaneous fat areas with the probiotic LG2055 administration, suggesting its beneficial influence on metabolic disorders [86,87].

All of these evidences show that the Probiotics supplementation to obese host is effective to improve the health and it represents a good alternative to include during the obese treatment.

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