Influence of *Lactobacillus casei* Shirota Strain on Body Composition: A Review

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A review of the literature is made about the most relevant aspects of the effects of the administration of prebiotics and probiotics on body composition, mainly on fat mass and on the Body Mass Index, as well as the effect they have on the inflammation that causes obesity in humans and that results in unfavorable health outcomes. There is evidence that suggests that the administration of prebiotics and probiotics, support the fight against obesity.

**Keywords:** Inflammation; Obesity; Prebiotics.

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**Obesity**

Obesity is defined as “an abnormal or excessive accumulation of fat that poses a health risk”, which can be determined through the calculation of the Body Mass Index (BMI), and must be $e^30$ kg / m².

Because obesity represents an imbalance between intake and energy expenditure, this is therefore a consequence of the combination of diets with high caloric density, as well as zero or low physical activity², leading to an increase in adipose tissue, which in turn generates a state of mild chronic inflammation³.

Afshin *et al*⁴, indicate that obesity represents a public health problem, as it is considered a chronic disease [3], with a prevalence that is constantly increasing; according to Ng *et al*⁵, of 857 million people with obesity and overweight to 2.1 billion. It should also be noted that this is associated with other diseases such as insulin resistance, type 2 diabetes mellitus, heart disease and cancer⁶,⁷.

According to data from the National Survey of Health and Nutrition (ENSANUT) 2016, in Mexico, the prevalence of overweight and obesity in adults 20 years of age or older, went from 71.2% in 2012 to 72.5% in 2016. However, this increase in 1.3 percentage points was not statistically significant. Meanwhile, the prevalence of overweight, obesity and morbid obesity were higher in the female sex. Similarly, although the combined prevalence of overweight
and obesity does not differ much in urban areas (72.9%) than in rural areas (71.6%), the prevalence of overweight was 4.5 percentage points higher in rural areas, while the prevalence of obesity it was 5.8 percentage points higher in urban areas.

**The inflammatory process in obesity**

Adipose tissue, in addition to having thermoregulatory function, giving mechanical protection to organs and storing triglycerides during caloric excesses, or, releasing them under fasting conditions, also acts as an endocrine organ because it secretes peptides called adipokines, which are cytokines that when synthesized by this type of tissue receive that name. In addition, they can be pro-inflammatory in nature such as leptin, monocyte chemoattractant protein 1 (MCP-1), tumour necrosis factor alpha (TNF-α) and interleukin (IL) -6, causing in the organism a low-grade inflammatory state that favors the progression of obesity; while on the other, that same tissue, inhibits the secretion of anti-inflammatory adipokines, such as adiponectin, whose function is to protect from the complications caused by such disease.

In contrast, the considerable increase in adipose tissue that results from obesity, leads to deterioration of its function, since the adipose hypertrophy coming from, generates an increase in the levels of pro-inflammatory adipokines, while adiponectin and other anti-inflammatory adipokines, such as interleukin (IL) -10, are reduced.

It should also be mentioned that adipokines also intervene in other specific processes, such as leptin, which regulates appetite and satiety, glucose metabolism, insulin sensitivity and atherogenesis. However, because in obesity serum concentrations of proinflammatory factors increase, (IL) -6 and (TNF-α) decrease insulin sensitivity; while in the case of leptin, although at the level of the hypothalamus it increases the synthesis of anorexigenic peptides and decreases that of orexigenic peptides, this serum increase prevents food intake and hyperglycaemia from being reduced, so that these changes explain the link between obesity and other metabolic and cardiovascular comorbidities in addition to inflammation.

Regarding adiponectin, beyond having anti-inflammatory action, they also have anti-apoptotic and insulin sensitization action. However, several studies indicate that in people with obesity their plasma levels are low, since it has been seen that in fat cells in vitro, some hormones associated with insulin resistance, such as TNF-α and IL-6, regulate their expression and secretion, so, with based on Ryo et al., have a negative relationship with the accumulation of visceral fat.

Thus, the fact of having a reduction in the body weight of people with obesity, has been associated with an increase in plasma levels of adiponectin, as well as a plasma reduction in markers of inflammation such as IL-6.

**Signalling mechanisms associated with obesity inflammation**

The mechanism of inflammatory signalling may arise due to the presence of extracellular mediators such as adipokines associated with inflammation and excess lipids, or they may be the product of some intracellular mediators such as endoplasmic reticulum stress or the abundant production of Species Oxygen Reagents (ERO). Meanwhile, regardless of the type, in the end both mediators lead to two paths, because on the one hand they activate inflammatory mediators through transcriptional regulations, and on the other they directly inhibit insulin signalling.

Although, at the level of the endoplasmic reticulum, obesity overload the ability of cells to perform protein folding, generating a stress mechanism that involves the activation of the N-terminal c-Jun kinase 1 (JNK1) and the inhibitor of kappa kinase â (IKK2). In turn, Koop et al. mention that IKK2 is activated and phosphorylates the inhibitor of NF-êB (IêB), leading to its degradation and the inhibition of nuclear factor Kapa B (NF-êB) in basal conditions. However, the latter, when released into the cell nucleus, stimulates the transcription of some inflammation mediators, such as TNF-á and IL-6, which, according to Ferrer et al., are also known as immunological mediators. Also, in addition to intervening in the inflammatory response, the transcription factor NF-êB also participates in the immune response, while suppressing adiponectins and type 4 glucose transporter proteins (GLUT-4).

On the other hand, there are several experiments with mice in which it has been
seen that, at the level of the hypothalamus, the activation of JNK1 in Agouti-related Peptides (AgRP) produces neuronal and systemic conditions in leptin, as well as induces weight gain and adiposity after hyperphagia. In contrast, the activation of IKK2 reduces insulin signaling in AgRP neuropeptides, leading to an alteration in glucose homeostasis, which is why both kinases play an important role in the cellular and systemic resistance of insulin (IKK2) and leptin (JNK1) associated with obesity.

Another mechanism that initially leads to the activation of inflammatory pathways is oxidative stress49, which, at the mitochondrial level, generates an increase in the production of reactive oxygen species, therefore, in people with obesity, the obtaining of ERO is elevated as a result of the increase in glucose metabolism41,42, since the endothelial cells of adipose tissue introduce large amounts of glucose through their respective glucose transporters, GLUT 449.

Thus, in these hyperglycaemic conditions, excessive production of ROS causes oxidative damage in endothelial cells that activates inflammatory signalling44, allowing adipose tissue to attract other inflammatory cells such as macrophages41, which are also part of it43, and whose function under normal conditions is to participate in the innate immune response43, and express certain adipocyte genetic products such as the receptor Nuclear Peroxisome-Proliferator-Activated Gamma (PPARγ) and Fatty Acid Conveyor Protein (FABP), especially those of the aP2 type (FABP-aP2)44,45, said proteins regulating the accumulation of cholesterol in macrophages and the accumulation of lipids in adipocytes, which modulates therefore, atherosclerosis and insulin resistance42. However, the consequent inflammation of adipose tissue associated with obesity causes macrophages to absorb and store lipids to become atherosclerotic foam cells as well as contribute, by themselves or in conjunction with adipocytes, to the production of inflammation mediators42.

Finally, other pathways that are also associated with insulin inhibition as a consequence of inflammation, are those regulated by the iNOS proteins (nitric oxide synthetase) and those that belong to the family known as Cytosine Signaling Suppressor (SOCS)42, which means that expression is mediated by cytosines46). So that, in the case of iNOS, this is induced in skeletal muscle and fat after the action of pro-inflammatory cytokines, so that excess nitric oxide impairs the function of the cells of the pancreas and the action of insulin in muscle cells47,48.

In contrast, SOCS, including SOCS1, SOCS3 and SOCS6, inhibit insulin signaling through proteosomal degradation of insulin receptors (IR) such as IRS-1 and IRS-246,49, or else, inhibit it by hindering tyrosine phosphorylation in such receptors. However, the increase in SOCS is not only linked to obesity, but also due to endotoxemia induced by a compound called lipopolysaccharide (LPS)50, thus being an endotoxin that It constitutes the cell membrane of most Gram-negative bacteria7.

In this regard, it is known that LPS activates Toll-like receptors (TLR), which participate in the innate immune response. As a result of the union between LPS and TLR-4, an intense inflammatory response is obtained that leads the organism to a state of inflammation51,52,53, because, based on the provisions of Muzio, et al54, this activation leads to the translocation of NF-êB in the cell nucleus, thus initiating the transcription of IL-6 and TNF-ê, since TLRs also induce degradation of ðêB once they trigger NF-êB55.

Similarly, TLR-4 receptors can also be activated by saturated fatty acids that are ingested through the diet, thereby inducing inflammation signalling after allowing the synthesis of the same pro-inflammatory adipokines (IL-6 and TNF-ê) associated with insulin resistance and increased adiposity, both in macrophages and in fat cells56.

In summary, it could be said that the intestinal microbiota has the ability to promote a low-grade inflammatory state, favour insulin resistance and increase cardiovascular risk through the mechanisms described above, including its exposure to LPS51.

The role of lipids in the regulation of inflammatory signalling pathways

Although the consequent obesity-associated hyperlipidaemia leads to the production of fatty acid metabolites that activate the inflammatory response and inhibit insulin signalling56, some intracellular lipids such as liver X receptor (LXR) and PPAR nuclear receptor families counteract inflammatory processes, since
they inhibit the expression of genes associated with inflammation in macrophages and adipocytes through the suppression of NF-κB that occurs in the nucleus. In addition, both transcription factors are responsible for promoting metabolism, nutrient transport and cholesterol and lipid flow stored in macrophages and adipocytes, respectively.

Despite the above, once the inflammatory pathways are underway, the activity of LXR and PPAR is influenced by the aP2 fatty acid transporter protein (FABP-aP2) found in the adipocyte cytoplasm, which means that, far from exerting its beneficial action, this type of sequestration protein is probably linked to said transcription factors to favour the state of inflammation.

**Intestinal microbiota and its relationship with obesity**

Although they seem indistinct terms, there is a difference between the definition of microbiota and the microbiome. Although, the first refers to a community made up of several types of organisms that are present in an environmental habitat, and may be of the Archaea, Bacteria or Eukarya domain, as well as viruses. Meanwhile, the microbiome constitutes the total of microorganisms that are found in an environmental habitat, including their functions, genes and metabolites, therefore, the composition of the microbiome depends on the region of the body in which it is present.

Thus, the intestinal microbiota is the result of a symbiosis between microbial species of any domain. Meanwhile, the intestinal microbiome is made up of more than 100 billion bacteria that colonize the human intestine, predominantly the **Firmicutes** and **Bacteroidetes**, which represent those anaerobic bacteria whose purpose is to ferment non-digestible carbohydrates.

Among the benefits provided by the intestinal microbiota to the host is to regulate its immune function, as it provides protection against pathogenic bacteria and chronic inflammation.

On the other hand, the intestinal microbiota also regulates energy homeostasis, as it is involved in the extraction of energy from food, obtaining compounds that can cross the intestinal barrier and the production of vitamins and hormones. However, both the function and the microbial composition can be impaired (dysbiosis) by intrinsic factors, such as intestinal motility, pH, antibacterial proteins and mucus, as well as by extrinsic factors, some of these being the genetic determinants of host, medications, such as antibiotics, and diet.

Meanwhile, when energy homeostasis is affected, the development of obesity is encouraged, which is why Parséus et al. point to the intestinal microbiota as another environmental factor that triggers this disease, since there are several studies that have shown that, when people with obesity, microbial diversity is reduced, which leads them to suffer metabolic complications that depend on both genetic effects and dietary patterns. However, eating a high-fat diet not only modulates the intestinal microbiota, but also the plasma concentration of LPS, since following a diet with these characteristics increases the amount of bacterial LPS, modifying in turn the composition of the microbiota.

Regarding the fermentation metabolites produced by Firmicutes and Bacteroidetes in the lumen of the colon, it should be noted that these are known as short chain fatty acids (SCFA) and include acetate, propionate and butyrate, absorbing the first two directly to the portal circulation; while the third is used by the colonocytes as a source of energy. In fact, it is estimated that 10% of the energy used by the body comes from said fermentation, meanwhile, how these metabolites are involved in the release of ghrelin, a molecule that acts at the brain level in the regulation of appetite and insulin action, the reduction in bacterial taxa that produce SCFA is associated with the development of obesity.

On the other hand, with regard to the microbial composition of the intestine, it is known that it differs between healthy individuals and those with excess adipose tissue, insulin resistance and dyslipidemia, and there may even be a decrease in its richness. In this regard, scientific evidence indicates that the prevalence of the Bacteroidetes edge is lower in people with obesity. However, this proportion may increase as weight is lost after following a hypocaloric diet. Meanwhile, the Firmicutes edge increases proportionally, which is associated with a greater presence of enzymes for the fermentation of non-digestible carbohydrates, relating the above with higher levels of energy collection through diet.
After all of the above, it is likely that the low-grade inflammatory state attributed to obesity is due to changes in the microbial constitution, increased intestinal permeability and metabolic endotoxemia, which is why which scientific evidence has revealed that probiotics could be the organic component that helps regulate the intestinal microbiota, because through them it is possible to increase the amount of bacteria that produce short chain fatty acids, adiposity is reduced and the production of some metabolites such as lipopolysaccharides decreases, as well as the inflammation that the latter cause in the body.

The use of probiotics and prebiotics as a modulating therapy of the intestinal microbiota in the treatment of obesity

So far we know that, because the diet is a factor that determines the composition of the intestinal microbiota, ingest large amounts of fats, in addition to increasing the edge Firmicutes and decrease Bacteroidetes, increases the permeability of the intestine, resulting in a bacterial translocation and an increase in LPS, which affects weight gain, morphological alterations of adipose tissue, insulin resistance and inflammation, all of which is characteristic of obesity. After the above, it has been shown that after colonizing the intestine of germ-free mice with intestinal microbiota of conventionally raised mice, their body fat increases by up to 60% compared to germ-free control mice, which implies greater absorption of monosaccharides that induce de novo lipogenesis in the liver.

In this regard, it could be said that, in addition to following a diet high in fats and sugars, colonizing the intestine with conventional microbiota promotes obesity, since a study in mice deduced that those that were free of germs were protected against the development of said disease despite following a diet with such characteristics. This could be due to elevated levels of Fasting Induced Adipose Factor (FIAF), also known as angiopoietin type 4 protein, which is produced in the liver, intestine, white fat and brown fat, and inhibits lipoprotein lipase (LPS), whose function is to regulate the release of fatty acids belonging to lipoproteins rich in triglycerides of muscle, heart and fat. However, Bergö, et al., mention that, because LPS is inhibited, this translates into a greater absorption of fatty acids, as well as a greater accumulation of adipocyte triglycerides. However, it should be noted that everything described above is only carried out in the intestinal epithelium and not in the liver or in both types of fat.

Thus, there are several studies that have shown that, in contrast to the control groups, those who have received probiotic supplementation have presented significant reductions in anthropometric measurements, such as body weight, BMI, waist circumference, Fat mass and fat percentage, so these could be used both in the prevention and treatment of obesity, because the intestinal microbiota is an environmental factor that promotes fat storage.

In particular, those bacteria that have a beneficial effect on health are known as probiotics, provided they are administered in adequate amounts. In fact, according to O’Toole, et al., among the most frequently used species are the genus Lactobacillus, Bifidobacterium and Saccharomyces, although other genera such as Bacillus, Propionibacterium, Streptococcus and Escherichia, are used.

On the other hand, it has been established that prebiotics are a type of non-digestible dietary fiber that includes oligosaccharides or short polysaccharides with inulin, oligofructose, galactofructose, galacto-oligosaccharides and xylo-oligosaccharide, which after fermentation generate an increase in the amount of beneficial bacteria in the liver. In this regard, it is believed that especially inulin-type fructans, could contribute to the treatment of obesity after fermentation and promote the growth of beneficial bacteria, resulting in a change in the composition and/or activity of the intestinal microbiota in favor of health, such as weight reduction and improvement in lipid and glucose levels after studies in rats.

As a result, inulin-type fructans containing short chain oligosaccharides increase the levels of proglucagon mRNA and glucagon-1-like peptide (GLP-1) in the proximal colon, allowing such prebiotics to ferment and reduce intake of food, fat mass, body weight and homeostasis of inulin, as long as there is a functional GLP-1 receptor (GLP-1R), which in turn also depends on the type of bacteria that colonize the intestine. In this regard, the increase in the amount and release of GLP-1 is mediated by intestinal L cells through the factor NGN-3 and NeuroD. These cells...
allow the expression of the proglucagon gene, which could occur due to the action of SCFA, especially butyrate\textsuperscript{91}, thus synthesizing the active form of GLP-1, as well as PYY, another peptide that is also secreted by L cells and that is involved in the regulation of food intake by being an anorexigenic hormone that reduces weight gain after inhibiting such intake\textsuperscript{58,91}. In fact, in a study with experimental animals, it was confirmed that after administering high-fat diets with oligofructose, a kind of inulin fructane, proglucagon expression increased in the proximal colon, favoring the beneficial effect that the prebiotic has on glycemia, the development of fat mass and weight gain\textsuperscript{91,94}. On the other hand, it was observed that, after following an oligofructose treatment, the number of Kupffer cells increased, thereby increasing the ability to eliminate proinflammatory agents such as LPS\textsuperscript{95}. Likewise, it was also shown that the PYY portal increased, while serum ghrelin levels decreased, which could be related to the satiating effect of the prebiotic\textsuperscript{96}, remember that ghrelin, when synthesized mainly in the stomach, increases appetite and stimulates food intake, favoring weight gain and adiposity (Santos-Marcos, Perez-Jimenez, & Camargo, 2019).

In addition to the above, prebiotics are also related to the increase of glucagon-2-like peptide (GLP-2), allowing the intestinal barrier to be restored, which translates into improvements in its permeability, which is also associated with a decrease in proinflammatory cytokine levels, such as IL-6 and MCP-1\textsuperscript{58}.

Finally, it should be mentioned that in another study conducted with rats, where in addition to administering the same type of diet and prebiotic, Bifidobacterium strains were added, a positive correlation was obtained with the improvement in glucose tolerance and the normalization of inflammatory tone, which included both reductions in endotoxemia and in proinflammatory cytokines of adipose tissue and plasma\textsuperscript{98}, although ultimately, both Lactobacilli and Bifidobacteria can have the same beneficial effects on the metabolism of glucose and endotoxemia after these increase after following a prebiotic treatment\textsuperscript{99}.

**CONCLUSION**

With the results detected in this review, it is concluded that the field of probiotics and prebiotics is promising for the management of body composition and obesity.

Now, the way is to carry out multiple clinical studies in different populations to show if they have clinical efficacy in reducing body composition and decreasing the percentage of obesity in the population.

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