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REVIEW

Adipose tissue inflammation and metabolic syndrome. The proactive role of probiotics

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Abstract

Purpose The first part of this review focuses on the role of cells and molecules of adipose tissue involved in metabolic syndrome-induced inflammation and in the maintenance of this pathology. In the second part of the review, the potential role of probiotics-modulating metabolic syndrome-related inflammatory components is summarized and discussed.

Methods The search for the current scientific literature was carried out using ScienceDirect, PubMed, and Google Scholar search engines. The keywords used were: metabolic syndrome, obesity, insulin resistant, adipose tissue, adipose tissue inflammation, chronic low-grade inflammation, immune cells, adipokines, cytokines, probiotics, and gut microbiota.

Results and Conclusions Chronic low-grade inflammation that characterized metabolic syndrome can contribute to the development of the metabolic dysfunctions involved in the pathogenesis of its comorbidities. Adipose tissue is a complex organ that performs metabolic and immune functions. During metabolic syndrome, an imbalance in the inflammatory components of adipose tissue (immune cells, cytokines, and adipocytokines), which shift from an anti-inflammatory to a pro-inflammatory profile, can provoke metabolic syndrome linked complications. Further knowledge concerning the immune function of adipose tissue may contribute to finding better alternatives for the treatment or prevention of such disorders. The control of inflammation could result in the management of many of the pathologies related to metabolic syndrome. Due to the strong evidence that gut microbiota composition plays a role modulating the body weight, adipose tissue, and the prevalence of a low-grade inflammatory status, probiotics emerge as valuable tools for the prevention of metabolic syndrome and health recovery.

Keywords Metabolic syndrome · Obesity · Chronic low-grade inflammation · Adipose tissue · Adipokines · Probiotics

Abbreviations

ASP	Acylation stimulating protein
BMI	Body mass index
C3	Complement component 3
CCL4	C–C motif chemokine ligand-4
CNS	Central nervous system
CRP	C-reactive protein
CTRPs	C1qTNF-related proteins
HDL	High-density lipoprotein
IFN	InterFeroN
ICAM-1	Intercellular adhesion molecule 1
IL	InterLeukin
IRS-1	Insulin receptor substrate-1
KLF	Krüppel-like factor proteins
LDL	Low-density lipoprotein
LPS	Lipopolysaccharides
MIP-1	Macrophage inflammatory protein 1
MCP-1	Monocyte chemoattractant protein 1
MIF	Macrophage migration inhibitory factor
NF-κB	Nuclear factor Kappa-light-chain-enhancer of activated B cells
PAI-1	Plasminogen activator inhibitor-1
PBEF	Pre-B-cell enhancing factor
RANTES	Regulated on activation, normal T cell expressed and secreted
TGF	Tumor growth factor
TLR	Toll-like receptor

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TNF Tumor necrosis factor
VCAM-1 Vascular cell adhesion molecule 1

Introduction

The metabolic syndrome is a clinical condition associated with at least three of the following metabolic risk factors: excess visceral adiposity (abdominal obesity), insulin resistance, hyperglycemia, hypertension and dyslipidemia [high triglycerides and low high-density lipoprotein (HDL) cholesterol]. Particularly, a strong association between obesity and metabolic syndrome was found in prior studies [1]. The perpetuation of these metabolic dysfunctions affect negatively on life expectancy and can eventually lead to the development of type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, some types of cancer or autoimmune disorders. Recently, scientific evidence has demonstrated that the progress in these metabolic dysfunctions is closely related to the chronic low-grade inflammation state, characteristic of obesity and metabolic syndrome [1–3].

Chronic low-grade inflammation probably occurs as result of the imbalance between pro-inflammatory stimuli and decreased anti-inflammatory mechanisms. Table 1 summarizes the evidence of the immune and metabolic role of adipose tissue during the prevalence of health or metabolic syndrome. Inflammation in general, comprise the cascade of reactions that occur to reestablish body homeostasis and involves both molecular effectors and immune response. Although the inflammatory response is beneficial, if it becomes uncontrolled or chronic, it can turn harmful. The chronic low-grade inflammation that accompanies obesity and metabolic syndrome is associated with the expansion of adipose tissue. This differs from classical inflammation in terms of its signs, but the same mediators are involved in its development. Adipose tissue is not only a reserve organ that stores energy, but it is also an endocrine and immune organ capable of secreting a variety of hormones and bioactive peptides, known as adipokines, with implications in both energetic homeostasis and immune function (Table 1) [4]. The extension of this tissue, particularly in the abdominal region, emphasized its role as immunological tissue affecting systemic inflammation.

Scientific evidence suggests that intestinal microbiota is a key player in the development of a chronic low-grade inflammatory state associated with metabolic syndrome [5]. In 2007, Cani et al. described the link between gut microbiota and the onset of metabolic inflammation related to obesity, insulin resistance and type 2 diabetes mellitus [6, 7]. Among the events that lead to the establishment of these conditions, metabolic endotoxemia, caused mainly by Gram-negative bacterial membrane component known as lipopolysaccharide (LPS), plays a crucial role. In addition, the intestine

Table 1 Prevailing of adipose tissue immune cells phenotype and adipokines with immune and metabolic functions during health or metabolic syndrome

Anti-inflammatory state (health)	Pro-inflammatory state (metabolic syndrome)
Adipose tissue immune cells	
M2-like macrophages	M1-like macrophages
Regulatory T-cells (CD4+)	Memory T cells
T helper type 2 cells (CD4+)	Cytotoxic T cells (CD8+)
Eosinophils	T helper type 1 cells (CD4+)
	T helper type 17 cells (CD4+)
	B cells
	Dendritic cells
	Mast cells
Adipose tissue adipokines	
Adiponectin	TNF-α (tumor necrosis factor alpha)
IL-10	IL-1β
IL-4	IL-6
C1qTNF-related proteins (CTRP)	Adipsin (complement factor D)
CTRP-3 (Cartonectin)	C3 (complement component 3)
CTRP-9	ASP (acylation stimulating protein or C3adesArg)
CTRP-12 (Adipolin)	Leptin
Omentin (Intelectin-1)	P-selectin
Vaspin	MCP-1 (monocyte chemoattractant protein-1)
	PAI-1 (plasminogen activator inhibitor-1)
	Resistin
	Visfatin

can establish a metabolic crosstalk with metabolically active tissues such as adipose tissue, through molecules (e.g., short chain fatty acids, bile acids, peptides) produced by the intestinal microbiota [3].

The impact of diet on the composition of the gut microbiota open a new field of research. Within the new approaches in nutritional interventions, the manipulation of intestinal ecology or specific microbial species, are currently suggested. In this field, specific probiotics can, in addition to their immunomodulatory and metabolic effects, modulate the gut microbiota [8, 9]. Probiotics for these reasons could play a proactive role in the immunomodulation to prevent chronic low-grade inflammation linked to metabolic syndrome.

The first part of this review summarizes the evidence for the role of cells and molecules of adipose tissue involved in metabolic syndrome-induced inflammation and in the maintenance of this pathology and the initiation and progress of its comorbidities. In the second part of the review, the potential role of probiotics modulating metabolic syndrome-related inflammatory components is discussed.

First part: adipose tissue and chronic inflammation

Adipose tissue is a heterogeneous and very plastic tissue composed of mature adipocytes, and other cells such as preadipocytes, fibroblasts, immune cells and vascular endothelial cells, usually named as the stromal vascular fraction [2, 10, 11]. In addition, immune structures such as lymph nodes, fat associated lymphoid clusters, and milky spots (which are clusters of leukocytes embedded in the omental tissue) are found in adipose tissue [12]. These last structures act like secondary lymphoid organs and provide places for the development of the adaptive immune response. In obesity, immune cells within lymph nodes can sustain low chronic inflammation, recruiting and activating immune cells to defend adipose tissue against damage, toxicity or impaired function [11, 13]. Recently, Magnuson et al. demonstrated that the lymphatic system could also act like an immune link that enables the crosstalk between visceral adipose tissue and gut [14].

The cellular composition of adipose tissue, particularly its composition of immune cells, is regulated by stimuli such as diet, body weight, and caloric excess ingest capable of causing metabolic distress. In response to these stimuli, immune cells of stromal vascular fraction switch from anti-inflammatory subtypes towards more pro-inflammatory subtypes. This lead to a pro-inflammatory and pro-oxidative microenvironment, which favors the recruitment of immune cells for the establishment of a chronic low-grade inflammation state. Thus, in metabolic syndrome or obesity, the imbalance among these immune cells induce systemic inflammation and peripheral insulin resistance [12].

Adipose tissue and immune cells

Immune cells of the adipose tissue are cells of innate immunity (e.g., macrophages, mast cells, dendritic cells, eosinophils) and cells of adaptive immunity (B and T cells) [15–18]. The existing information about the percentage of each cell type depends on the methodology used in each case under study. Macrophages are the largest immune cell population of adipose tissue. In lean mice and human adipose tissue, they comprise about 4–15% of all cells of the stromal cell count [19, 20]. These values can increase over 40% in both mice and human adipose tissue in obesity [19]. The second largest subpopulation of immune cells in adipose tissue of lean mice and humans are lymphocytes, which represent about 10% of the stromal fraction. Approximately the half of these cells belong to T cells (CD3C) (3:1 between CD4+ T-cells and CD8+ T-cells) [21]. In obesity, along with the increment in the total number of lymphocytes, also a change in the proportions of the different cell subsets was observed.

The changes in immune cells composition during metabolic syndrome drive adipose tissue inflammation and affect the ability of adipocytes to store lipid, their insulin sensitivity, systemic glucose metabolism, and metabolic homeostasis [12].

Macrophages

Macrophages are considered the key cells accountable for the inflammatory mechanisms that occur in adipose tissue. The number of macrophages in adipose tissue correlates with body mass index, adipocyte size and total body fat [2]. In normal or lean individuals, the macrophages are found as M2-like macrophages, which are the anti-inflammatory phenotype that secretes anti-inflammatory cytokines such as IL-10 [12]. In metabolic syndrome, obesity or against stimuli known as “danger associated molecular patterns”, such as hyperglycemia, free fatty acids or cholesterol, macrophages change from M2-like phenotype to the pro-inflammatory M1-like phenotype that secretes pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12 and monocyte chemoattractant protein-1 [MCP-1]) and phagocyte and present antigens inducing CD4+ T cells proliferation (adaptive immune response) [2, 12]. However, the mechanisms that induce macrophages phenotypic polarization remain unclear. Current investigations showed that obesity triggers the polarization to M1-like phenotype in adipose tissue macrophages through the induction of Notch1 signaling, associated with cell differentiation [22]. Obesity downregulates MicroRNA miR-30 family inducing Notch1 gene expression [22].

Recent research has demonstrated the relation between macrophage infiltration into adipose tissue that amplifies inflammatory responses, with the increase of circulating inflammatory molecules, ectopic lipid accumulation

and insulin resistance development [2, 23]. Inflammatory cytokines produced by adipose tissue macrophages provoke adipocytes hypertrophy by inhibition of cell differentiation. Hypertrophic adipocytes may produce themselves pro-inflammatory mediators (cytokines and chemokines, such as IL-1β, IL-6, TNF-α, and MCP-1) and are responsible for adipose tissue hypoxia [24]. Both events induce recruitment of macrophages and overproduction of pro-inflammatory cytokines, increasing inflammation in adipose tissue, and even causing adipocytes necrosis that triggers localized inflammation in adipose tissue and dissemination of systemic inflammation [23, 25]. This dysfunction in inflammatory response with the misregulation in adipocytokines production is thought to be the cause of the development of related comorbidities such as insulin resistance and type 2 diabetes [2].

T cells

In adipose tissue, after macrophages, T cells CD3+ constitute the second most abundant immune cells. In lean individuals, regulatory T cells CD4+ (Treg) prevail in adipose tissue. Together with T helper type 2 CD4+ lymphocytes promote in the adipose tissue a M2-like macrophage polarization, which sustain an anti-inflammatory state [25]. The Treg are known to produce the anti-inflammatory cytokine IL-10 and TGF β that reduces the proliferation and activation of T cells [12]. Several studies reveal the relationship between the reduction in regulatory T cells and the development of metabolic disorders and chronic diseases [26, 27]. During obesity or metabolic syndrome, an overall increase in total T cells occur, but regulatory T cells are replaced by memory T cells and cytotoxic CD8+, T helper type 1 CD4+ and T helper type 17 CD4+ lymphocytes, that stimulate M1-like macrophage polarization [25]. Moreover, in obesity the pro-inflammatory phenotype is related with high leptin levels, a hormone secreted by adipose cells [26]. Leptin levels correlate with adipose mass. A high adipose mass results in high leptin levels in blood and adipose tissue. Also, pro-inflammatory stimuli such as TNF-α increases leptin secretion, and at the same time, leptin stimulates the production of TNF-α and pro-inflammatory IL-6 in monocytes [28]. Additionally, leptin acts as a negative signal for regulatory T cells proliferation and promotes T helper type 1 CD4+, typically associated with insulin resistance and type 2 diabetes [26].

B cells

In obesity or metabolic syndrome, B cells infiltration in adipose tissue occur. B cells have the ability to present antigens to CD4+ T lymphocytes contributing to adipose tissue inflammation and systemic insulin resistance, presumably mediated by IgG and suppression of IL-10 secretion [29–31]. Through LTB4/LTB4R1 signaling, that is increased in the visceral adipose tissue of obese mice, B-cells boost leukocyte infiltration into adipose tissue tissues [31]. Indeed, *in vivo* studies in mice fed a high-fat diet showed that B-cells promote macrophage recruitment, TNF-α production and accumulation of IFN-γ-producing CD4+ and CD8+ T-cells in visceral adipose tissue [31, 32].

Eosinophils

Eosinophils are versatile granulocytic leukocytes able to produce a set of cytokines that confers immunomodulatory competence [33]. These cells are found in peripheral blood and infiltrating tissues including adipose tissue where it can migrate from the blood through an integrin-dependent process [34]. These leukocytes are usually associated with helminth immunity and allergy, but they perform other diverse functions, such as wound healing, tissue damage regulation, and immune cells regulation [26, 27, 33, 34]. However, in 2011, Wu et al. described an unexpected role of adipose tissue eosinophils in metabolic homeostasis. These cells, which are increased in adipose tissue of lean individuals, are able to secrete IL-4 promoting M2-like macrophage polarization in adipose tissue [34, 35]. Previous studies showed in high-fat diet fed mice, that the reduction in eosinophils numbers was related to an increase in body weight and insulin resistance [26, 27, 34]. Furthermore, helminth-induced adipose eosinophilia enhanced glucose tolerance in high-fat diet fed mice [34]. However, new results disagree with these observations. Recently, Reid Bolus et al. have shown that restoring adipose tissue eosinophils in obese mice to physiologically normal levels is not sufficient to restore the metabolic dysregulation in obesity [33]. These results suggested that eosinophils participate in the regulation of adipose tissue function, but their implication appears to be intricate and further studies are required.

Dendritic cells

Dendritic cells (plasmacytoid CD11b–CD11c + B220+ and conventional CD11b + CD11c+) are antigen-presenting cells that link innate and adaptive immunity. These cells can secrete IL-6, tumor growth factor (TGF-β) and IL-23, and stimulate the generation of T helper type 17 CD4+ lymphocytes, favoring adipose tissue inflammation [20]. Studies conducted in mice models of obesity and obese humans showed an increment of both dendritic cell subtypes in adipose tissue in correlation with adipose tissue inflammation and insulin resistance [20]. Along this line, the adipokine chemerin (chemoattractant for plasmacytoid dendritic cells) was increased in serum of obese individuals and may intervene in the dendritic cells recruitment into the adipose tissue

in obesity [35]. In addition, it was demonstrated that dendritic cells within lymphoid structures in adipose tissue can increase in response to dietary lipids [20]. Thereby dietary lipids may trigger a metabolic response through the dendritic cells.

Mast cells

Mast cells are increased and highly activated in obese adipose tissue [26]. Indeed, accumulation of mast cells in visceral adipose tissue and elevated levels of serum mast cell tryptase were observed in animal models of obesity [20]. Mast cells secrete TNF-α and IL-8 inducing leukocyte infiltration [20, 26]. Moreover, mast cells activation may promote obesity driving adipose tissue expansion, adipocyte protease expression, and stimulating microvessel growth [20]. In fact, a reduction in the weight of obese mice was reported after mast cell inactivation [26]. Moreover, studies in obese humans inhibiting mast cells degranulation further supported their contribution to the development of metabolic diseases [20]. In those investigations, pharmacological stabilization of mast cells in obese and type 2 diabetic patients reduced diet-induced metabolic alterations [20, 36].

Adipose tissue and pro-inflammatory proteins

TNF-α Tumor Necrosis Factor-alpha is a key cytokine that intervenes in acute and chronic phase inflammation inducing inflammation, apoptosis, tumor necrosis and cachexia. TNF-α is mainly produced by M1-macrophages, but also by many other immune cells, as well adipocytes which also express TNF-α receptors [37]. Besides its role in inflammation, TNF-α has now been implicated in energy homeostasis and the development of obesity-induced metabolic syndrome and type 2 diabetes mellitus [2, 28]. TNF-α increase secretion in adipose tissue of pro-inflammatory molecules such as IL-6, MCP-1, leptin, and plasminogen activator inhibitor-1 (PAI-1), thus contributing to inflammatory conditions linked to obesity [2, 37]. In obese individuals, an increase in the production of TNF-α by adipocytes was observed, that positively correlates with insulin resistance and type 2 diabetes mellitus [25, 38]. In adipose tissue and liver, TNF-α suppresses the expression of genes involved in the storage of free fatty acids and increases the expression of genes involved in the *de novo* synthesis of cholesterol and fatty acids. The increase of serum fatty acids has been shown to induce insulin resistance in multiple tissues [37]. Furthermore, TNF-α also impairs insulin signaling by decreasing the expression of the insulin-sensitive glucose transporter 4 and insulin receptor substrate-1 (IRS-1), suppresses tyrosine phosphorylation of IRS-1, and enhances serine phosphorylation of IRS-1 (increasing degradation of insulin receptors) [1, 39]. New therapies to counteract the deleterious effects of chronic inflammation were developed and some of these novel drugs have also shown effects on metabolism (e.g., IL-1 and TNF-α blockers molecules) [40–42]. Recent studies have demonstrated in patients with rheumatoid arthritis (a disease with a high prevalence of insulin resistance and metabolic syndrome) the success of anti-TNF long therapy (12 weeks of treatment) in the improvement of insulin sensitivity [43]. The anti-TNF agents used in these trials were infliximab, adalimumab or etanercept. In addition, other study showed the efficacy of 6-month therapy with etanercept to improve fasting glucose in obese subjects [42]. Nevertheless, further studies are necessary to determine whether TNF-α is a viable goal for the treatment of insulin resistance in obesity or metabolic syndrome.

IL-1β Interleukin 1β is a major pro-inflammatory cytokine produced by macrophages [44]. In adipose tissue, macrophages produced IL-1β via activated NLRP3 inflammasome. IL-1β is also released by nonfat cells from adipose tissue and this secretion is enhanced in obesity. This cytokine is a promoter of adipose tissue inflammation in obesity. IL-1β induces hypertrophic adipocyte cell death that launches the inflammatory cascade, leukocyte and macrophage recruitment, and macrophage lipid accumulation [45]. Scientific evidence suggests that IL-1β is key linking obesity-associated inflammation to insulin resistance and pathogenesis of type 2 diabetes [44, 45]. Recently, it was demonstrated in rodent models the implication of IL-1β in pancreatic beta-cell demise that precedes diabetes development [45]. Also, various works showed the role of IL-1β in the macrophage–adipocyte crosstalk which blocks insulin action in human adipose tissue (inhibition of insulin signaling and glucose metabolism in human adipocytes) [44]. Furthermore, studies have suggested the potential role of IL-1β promoting ectopic fat accumulation (and decreasing subcutaneous fat storage), and thus favoring liver steatosis and obesity-associated morbidity [45].

IL-6 Interleukin 6 is a cytokine involved in the regulation of the hematopoiesis, immune response, and acute and chronic phase inflammation [2]. This cytokine secreted by T cells, macrophages and adipocytes, plays together with TNF-α a key role in the development of insulin resistance and atherosclerosis, pathologies related to obesity and metabolic syndrome [2, 37]. Up 35% of circulating IL-6 is produced by adipose tissue and increase with the expansion of adipose tissue, particularly visceral adipose tissue [23, 37]. IL-6 promotes the production by macrophages and T cells of pro-inflammatory C-reactive protein (CRP), associated with increased risk of diabetes, hypertension and cardiovascular disease [23]. However, the role of IL-6 in insulin resistance is controversial. Some studies suggest a positive role of IL-6 on metabolism since it was showed that deficient IL-6 (IL-

$6^{-/-}$) mice develop obesity and metabolic disorders such as increased insulin resistance, decreased glucose tolerance, as well as increased inflammation in the liver. In line with this, during acute exercise skeletal muscle secretes peptides involved in muscle hypertrophy, which are included in the secretory peptides called myokines [46]. Among this myokines, IL-6 is the first detectable cytokine released into the circulation and its secretion its associated with anti-inflammatory effects and improved insulin sensitivity and glucose metabolism [46, 47]. These effects of IL-6 are attributed to the inhibition of TNF-α and the stimulation of IL-1 receptor antagonist (IL-1ra) inhibiting IL-1β signaling, and IL-10 production by blood mononuclear cells [47].

MCP-1 Monocyte chemoattractant protein-1 is a cytokine produced in adipose tissue that recruits monocytes, macrophages, T cells and dendritic cells to the sites of inflammation [2, 37, 48]. In obesity, it has been suggested that MCP-1 is responsible for the beginning of the macrophages infiltration into adipose tissue, in addition to contributing to the development of insulin resistance and increment in adiposity [48, 49]. The increment in MCP-1 level was associated with other visceral obesity-related complications, such as neointimal formation with the development of atherosclerosis [2]. However, emerging evidence now position MCP-1 as a necessary inflammatory mediator required for adipose tissue protection (Cranford). Cranford et al. observed that MCP-1 deficiency in high-fat-diet feed mice exacerbated inflammatory processes and metabolic dysfunction, resulting in a further increase in adiposity and inflammatory cell infiltration in adipose tissue [48]. These authors suggested that MCP-1 might be necessary for the maintenance of a healthy adipose tissue in response to high-fat-diet feedings.

PAI-1 Plasminogen activator inhibitor-1 is serine protease inhibitor that arrests fibrinolysis via inhibition of the tissue-type plasminogen activator. PAI-1 is secreted by several tissues, including adipocytes and other cells of adipose tissue. Serum levels of PAI-1 are increased in metabolic syndrome (obesity, visceral adiposity, and insulin resistance) and in response to TNF-α. Scientific evidence suggested that high levels of PAI-1 are necessary to the development of obesity and its comorbidities [23, 37]. This protein is implicated in angiogenesis and atherogenesis, and therefore, in the development of cardiovascular disease related to obesity [37].

Leptin Leptin is a polypeptide secreted by adipose cells that is a mediator of long-term regulation of energy balance through the central nervous system (CNS) [20]. Leptin suppresses food intake, by inhibiting orexigenic neuropeptides and stimulating anorexigenic ones, as well as increases energy expenditure. This peptide has structural homology to helical cytokines, such as IL-2. Its receptors, found both in cells of the CNS and in the periphery, belong to the cytokine receptor class I superfamily, such as the IL-6 receptor [37]. As was already mentioned, leptin secretion increases with the expansion of adipose tissue, particularly visceral adipose tissue, and was found high in metabolic syndrome and obesity [50]. Leptin correlates with many parameters of metabolic syndrome including, waist circumference, glucose level, insulin level, insulin resistance and triglyceride level [51]. This peptide acts promoting proliferation of pro-inflammatory cells and cytokines, as well endothelial cell growth and angiogenesis [37]. In monocytes, leptin promotes the production of pro-inflammatory TNF-α and IL-6. In macrophages, leptin stimulates the production of chemoattractant molecules MIP-1α (macrophage inflammatory protein), MIP-1β and RANTES, that promotes the recruitment and activation of multiple immune cells [52].

Other pro-inflammatory proteins Adipsin (complement factor D) is a serine protease synthesized by adipocytes implicated in the enzymatic production of C3adesArg or acylation stimulating protein (ASP), a complement protein that intervenes in systemic energy balance regulation (lipid and glucose metabolism). Studies in humans show that adipsin is associated with insulin resistance, dyslipidemia, metabolic syndrome and cardiovascular disease [37, 50]. Complement component 3 (C3) is an immune protein produced mainly by the liver, but also by adipose tissue [53]. C3 is cleaved by spontaneous hydrolysis or by C3 convertase enzyme complex in catalytic C3b and C3a. C3a is a potent chemoattractant and plays a large role in the immune response. C3a induces the production of pro-inflammatory IL-6 and TNF-α, leading to attract and activate T cells, mast cell degranulation, and macrophage activation, amplifying obesity-induced inflammation. C3a is cleaved to remove its carboxy-terminal arginine to generate C3adesArg (or ASP), a molecule with lowered inflammatory function but, a metabolic effector [53]. Numerous investigations reported up to a threefold increased risk of the metabolic syndrome, and its associated metabolic perturbations, in subjects with high C3 levels [54].

P-selectin is a protein produced by activated platelets and endothelial cells, that functions as a cell adhesion molecule [1]. Increased levels of this protein have been associated with metabolic syndrome. Indeed, P-selectin expression and secretion have also been associated with increased visceral adipose tissue, low HDL cholesterol, high oxidized LDL and elevated fasting glucose [1].

Resistin is a peptide secreted by adipocytes, immune and epithelial cells. High levels of resistin were found in metabolic syndrome [50]. This pro-inflammatory cytokine causes the resistance of peripheral tissues to insulin and is considered by many researchers as a possible link between

obesity and Type 2 diabetes mellitus [55]. Resistin promotes the secretion of TNF-α and IL-6 by mononuclear cells.

Visfatin is an adipokine mainly produced by visceral fat increased in individuals with obesity [56]. This protein is a pro-inflammatory mediator, recognized as a pre-B-cell enhancing factor [PBEF] that also interferes with insulin-receptor signaling [15, 57]. Visfatin enacts recruiting immune cells and producing chronic inflammation in adipocytes [56]. Some studies have shown higher plasma visfatin levels associated with metabolic syndrome [57].

Adipose tissue and anti-inflammatory proteins

Adiponectin Adiponectin is an anti-inflammatory adipokine exclusively produced in differentiated adipocytes of white adipose tissue and secreted at high levels into the circulating bloodstream [2, 4]. This protein shares strong homology in its primary sequence with complement factor C1q. Adiponectin expression is higher in subcutaneous than in visceral fat. Its multiple metabolic functions include decrease of intracellular triglyceride content in liver and skeletal muscle (through the increase in fatty acid oxidation), decrease of gluconeogenesis in liver, increase of glucose uptake in skeletal muscle, increment in insulin sensitivity, anti-inflammatory and anti-atherogenic effects [2, 28, 58]. Antiatherogenic properties of adiponectin are due to the inhibition of endothelial expression of adhesion molecules (VCAM-1 and ICAM-1), the attenuation of smooth muscle cell proliferation, suppression of the transformation of macrophages into foam cells, plus vasodilatation via increase of nitric oxide production in endothelial cells, and stimulation of angiogenesis [37, 51, 59]. Adiponectin also diminishes the infiltration of CD4+ T cells into atherosclerotic lesions via the suppression of chemoattractants in macrophages [59]. Anti-inflammatory effects of adiponectin are also modulated via switch of macrophages from the pro-inflammatory M1-like phenotype that secretes pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and MCP-1) to anti-inflammatory M2-like phenotype that produce anti-inflammatory IL-10 [4, 59], further inhibition of Toll-like receptor (TLR)-mediated NF-κB activation in macrophages [4, 52, 59].

Adiponectin exerts its activity through the bind to AdipoR1 and R2 (G-protein-coupled) receptors and T-cadherin (CDH13) receptor (Fang). Upon binding to AdipoR1 and R2 adiponectin induces an increase in AMPK (glucose uptake and fatty acid oxidation) and peroxisome proliferator-activated receptor alpha (PPARα) levels. T-cadherin receptor lacks a transmembrane domain, but facilitates binding of adiponectin to AdipoR1 and R2 playing an essential role in promoting adiponectin dependent AMPK phosphorylation [4]. Recent studies have demonstrated that adiponectin levels are dependent on T-cadherin [60]. Moreover, investigations provide further evidence of the association between CDH13 gene (T-cadherin gene) variants prevalence, adiponectin-resistant status and the deterioration of metabolic syndrome and related diseases [60–62].

Several clinical studies have demonstrated a close association between low plasma adiponectin concentration and visceral adipose tissue with obesity, type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome and its related disorders (low HDL cholesterol and high triglyceride levels) [4, 59, 63]. Indeed, some authors consider this multifunctional protein as a key molecule in the pathogenesis of metabolic syndrome [51]. Adiponectin expression is higher by the functional adipocytes of subcutaneous fat of lean organisms. However, its expression is downregulated in the dysfunctional adipocytes of obese subjects [52]. Studies in rodents and human showed that circulating adiponectin decreased in obesity (negative correlation with the accumulation of body fat, particularly visceral fat) and inflammatory states (TNF-α, IL-1β, and IFN-γ), and is positively correlated with insulin sensitivity [2, 23, 50, 59, 64]. Consistent with these findings, increase in adiponectin level was observed associated with insulin sensitivity improvement and reduction in inflammatory markers, such as C-reactive protein and IL-6, after weight loss in overweight individuals [37, 52, 59]. Furthermore, the absence of adiponectin in adiponectin-deficient mice was associated with vascular alterations and abnormal metabolic profiles, independently of diet or body weight [37].

IL-10 IL-10 is one of the most important anti-inflammatory cytokines that is a produced by activated M2-like macrophages, B cells and T cells [65]. This cytokine acts suppressing M1-macrophage polarization and the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [66]. Exogenous IL-10 administration reduces the levels of inflammatory cytokines and recombinant IL-10 has been successfully tested for the treatment of inflammatory diseases [66]. Consistent with this, several investigations in human and mice demonstrated a positive correlation between circulating IL-10 levels and amelioration of metabolic syndrome or obesity: reduction of body mass index, percentage of fat mass, and improvement of insulin resistance and adipose tissue inflammation [67, 68]. Importantly, mice lacking IL-10 displayed increased IL-10 expression in liver and adipose tissue, suggesting a compensatory mechanism for IL-10 levels in these organs [69]. Despite adipose and serum IL-10 were reduced in obesity and type 2 diabetes, a recent study conducted in obese children showed an interesting result [70, 71]. Adipose and serum IL-10 were only reduced in obese children with hypertriglyceridemia, indicating a possible protective effect of IL-10 on the lipid metabolic disorders [72].

Other anti-inflammatory proteins C1qTNF-related proteins (CTRPs) are adiponectin paralogs produced mainly by adipocytes, that shares structural similarities with C1q complement factor [73, 74]. CTRPs can share up to 43% identity of amino acids to adiponectin [75]. CTRPs are also multifunctional proteins involved in metabolism, cell differentiation and apoptosis, and innate immunity. Similarly, to adiponectin, several CTRPs have hypoglycemic effects and anti-inflammatory functions. CTRP-3 or cartonectin modulates the immune system by suppressing the NF-κB signaling pathway. Cartonectin suppresses TLR stimulation in macrophages and adipocytes. Also, it inhibits monocyte-derived macrophages recruitment via macrophage migration inhibitory factor (MIF), MCP-1, or C–C motif chemokine ligand-4 (CCL4) [15, 59]. Cartonectin promotes the secretion of adiponectin in adipocytes. CTRP-12 or adipolin diminishes inflammatory responses in fat tissues and promotes insulin sensitivity through activation of insulin signaling in the liver and adipose tissue, where suppresses gluconeogenesis and enhances glucose uptake [16]. Adipolin attenuates macrophage infiltration and reduce the expression of pro-inflammatory cytokines (TNFα, IL-1β, and MCP-1) in response to stimulation with LPS or TNF-α. Clinical trials confirmed a negative correlation between adipolin levels and obesity and type 2 diabetes [59]. CTRP9 can form heterotrimers with adiponectin and share adiponectin receptors [59]. CTRP9 protein promotes glucose uptake induced by insulin and fat oxidation in skeletal muscle [59]. CTRP6 can induce the expression of anti-inflammatory cytokine IL-10 in human monocyte-derived macrophages [59]. It also increases fatty acid oxidation in skeletal muscle cells. CTRP1, secreted by adipose tissue in response to infections and cytokines has many metabolic adiponectin-like functions.

Omentin (or intelectin-1) is an adipocytokine that is highly expressed in visceral fat tissue and in omentum (visceral peritoneum) [58, 59]. Circulating omentin levels are reduced in obese individuals or individuals with increased waist circumstance and in obesity-linked metabolic disorders such as insulin resistance, glucose intolerance, dyslipidemia, elevated blood pressure and type 2 diabetes mellitus [58, 59].

Vaspin or visceral adipose tissue-derived serpin is an adipokine expressed mainly in the visceral adipose tissue [76]. Vaspin is a serine-protease inhibitor with insulin-sensitizing properties (improvement of insulin resistance in obese mice) and anti-inflammatory (inhibition of TNF-α and activation of NF-κB) effects. Serum vaspin levels were found higher in patients with metabolic syndrome than control subjects and related to the development of atherosclerosis.

Second part: handling the inflammatory status in metabolic syndrome. The proactive role of probiotics

Specific approaches for the prevention or treatment of metabolic syndrome may include probiotics. The International Scientific Association for Probiotics and Prebiotics maintained in 2014 the FAO/WHO definition for probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [77]. The *Lactobacillus* and *Bifidobacterium* are the most cited genera with positive effects on body weight, fat mass, adipose tissue inflammation, hepatic steatosis or glucose metabolism [78]. These genera belong to the classical probiotics. However, currently, other genera such as *Bacteroides* are proposed as no traditional probiotics with impact on metabolism disorders [79]. The evidence gathered indicates that the effects of these probiotics on the host are strain-specific. This is probably due to different mechanisms of action and the production of different metabolites. At the moment, the trend is the search of single specific-strains able to produce the desired effects, such as *Akkermansia muciniphila*, the so-called "next-generation" probiotics [80].

Probiotics, intestinal dysbiosis and inflammation of adipose tissue

It is well known that probiotics are a valuable tool to modulate gut microbiota and ameliorate host immune status [17, 18]. Probably in these attributes are sustained their usefulness to improve the health condition of metabolic syndrome (Fig. 1). The intestinal microbiota, which includes all microbial life in the intestine, has been associated with the development of various human diseases including metabolic syndrome, obesity and related metabolic dysfunctions [81, 82]. In the gut of healthy individuals, the microbiota is more diverse with the prevalence of bacteria from the phyla Firmicutes and Bacteroidetes and higher presence of Verrucomicrobia (*Akkermansia muciniphila*) [83, 84] (Fig. 1). Furthermore, many studies have associated a healthy gut microbiota to the increase in variety and abundance of Bacteroidetes rather than Firmicutes and a higher *Akkermansia muciniphila* to *Ruminococcus gnavus* ratio [84, 85]. However, these findings are inconclusive and more evidence is needed to support that affirmation [84]. Through its intervention in host energy homeostasis, systemic inflammation, and metabolic functions, the gut microbiota can control the body weight, a role that was demonstrated by means of numerous studies performed in rodent models [81]. These experiments have demonstrated a causal role of the intestinal microbiota in the etiology of obesity and insulin resistance by triggering a low-grade inflammatory response. Even, the potential mechanisms have already been explained in detail in

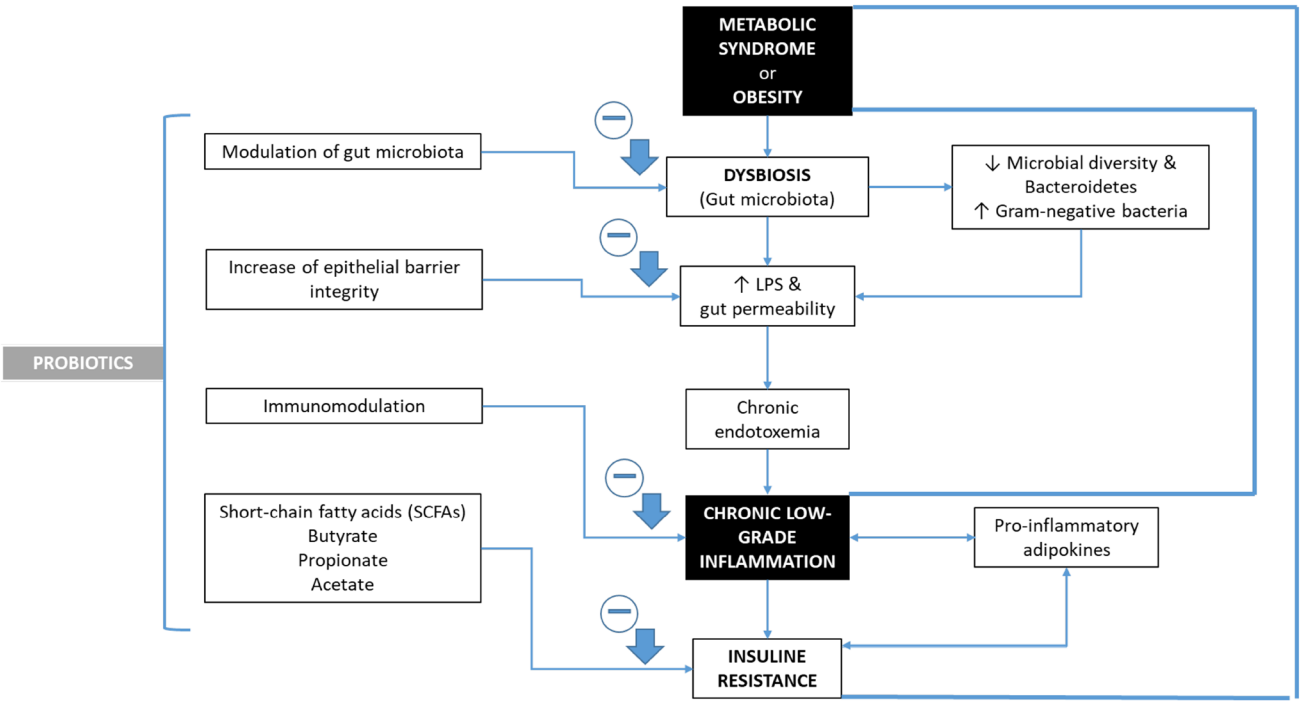

Fig. 1 Probiotic-induced changes in the gut microbiota and immunomodulation as possible mechanisms to improve metabolic syndrome and associated pathologies

previous reviews, however, more evidence is needed to demonstrate such causal relation in humans [81, 83, 85–88]. Probiotics can catabolize complex polysaccharides from diet to short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. These compounds are suspected to ameliorate metabolic disorders during metabolic syndrome and related pathologies [89]. There is evidence supporting the role of SCFAs in improving weight gain (propionate and butyrate) and food intake and glucose homeostasis (acetate) [89–92]. These effects may result from the action of SCFAs on eukaryotic cells receptors. Other studies have shown that acetate can suppress insulin signaling in adipocytes, inhibiting fat accumulation in adipose tissue [93]. Thus, SCFAs acts at different levels decreasing inflammatory state that reduces insulin resistance, increasing the protective Glucagon-like peptide-1 (GLP-1) secretion that stimulates insulin release, and improving β-cell function [89, 93, 94]. In addition to the effect of microbiota-derived metabolites like SCFAs that may show beneficial effects on host metabolism and innate and adaptive immunity, a complex and close relationship between gut microbiota, low-grade chronic inflammatory status, and insulin resistance was proposed [81, 88, 96, 97].

A proper balance in the gut microbiota is essential to support the barrier function of the intestinal epithelium. The gut microbiota maintains intestinal epithelial barrier by restoring tight-junction protein structure and suppressing intestinal inflammation (Fig. 1). Several studies suggest that during dysbiosis that characterized metabolic syndrome or obesity, the impaired gut microbiota let to an increase in the intestinal permeability and lipopolysaccharide (LPS)-related endotoxemia. LPS, a component of the cell wall of gram-negative bacteria, binds through adapter protein MyD88 to toll-like receptor 4 (TLR4) inducing activation of the transcription nuclear factor-kappa B (NF-κB) in intestinal epithelial cells [96, 97]. NF-κB triggers chronic systemic inflammation, including the activation of macrophages with the ability to infiltrate in the visceral adipose tissue, which drives a shift to a pro-inflammatory profile in this tissue (increase in TNF-α, IL-1β and IL-6, leptin and resistin, PAI-1, and C-reactive protein) and induces insulin resistance. That imbalance in gut microbiota sustains a pro-inflammatory microenvironment and metabolic endotoxemia in the liver (Brandi, Borrelli). Numerous investigations showed the role of dysbiosis in the development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), pathologies closely related to metabolic syndrome [82, 99]. In these pathologies, dysbiosis was evinced through the increment in *Enterobacteriaceae* and *Proteobacteria*, and a reduction in *Bacteroidetes* [82].

Thus, the modulation of intestinal microbiota composition by the intake of probiotics could be an approach for the handling of low-grade inflammation in adipose tissue and lead to the attenuation of insulin resistance and the plethora of pathology states associated to this condition that affects

the progression of metabolic syndrome-related diseases. Furthermore, these data suggest that it is necessary to study, when evaluating the effect of probiotics on host inflammation and related metabolic disorders, not only gut microbiota composition, but also TLR signaling and related pathways, increased levels of IgA and IgM against LPS of specific Gram-negative bacteria and other microbiota metabolites and cometabolites that have been implicated in metabolic disease, such as trimethylamine and branched chain amino acids [18, 100].

It has also been established that modulation of immune responses of the host is another mechanism by which probiotics can suppress low-grade chronic inflammation [18]. As it was previously stated, inflammatory responses in the gut can take place through the activation of TLRs pathway. The key in this inflammatory signaling pathway is again NF-κB, which is present in an inactive form in the cytoplasm, bound to the inhibitory IκB molecule. When inflammatory stimuli trigger TLRs pathways, this molecule is broken down and NF-κB is released activating the pro-inflammatory cascade [101, 102]. Several probiotic strains, such as *Lactobacillus rhamnosus* GG or *Lactobacillus casei* DN-114 001, have been effectively proven as inhibitors of IκB degradation, thereby reducing the expression of pro-inflammatory molecules [103, 104]. Probiotics can also show anti-inflammatory effects by means of various mechanisms that include: (a) the regulation of the maturation of dendritic cells in the intestine; (b) changes in the expression of TLR on intestinal epithelial cells and dendritic cells; (c) induction of a shift towards the production of anti-inflammatory cytokines (including IL-10 and TGF-β from Tregs); (d) induction of the differentiation of T-helper cells into Th2 cells [102 108–112]. It has also been proposed that probiotics can suppress chronic inflammation modulating adipokines secretion in the adipose tissue, conducting to the inhibition of macrophage-mediated pro-inflammatory cytokines and/or upregulation of adiponectin in adipocytes [17, 109]. In this regard, *Lactobacillus casei* CRL431 administration decreased inflammatory cytokines, in a diet-induced obese mouse model, including TNF-α, IL-6, and IL-17, and leptin, IL-6, TNF-α and MCP-1, in adipocytes and macrophages cocultured cell lines [17, 109].

Effects of probiotic strains on metabolic syndrome and related diseases: studies in cell lines, animal models and clinical trials

Numerous studies concerning probiotics, metabolic syndrome and related diseases have been recently carried out [Tables 2, 3 and 4]. Both, studies conducted in adipocytes or macrophage cell lines, high-fat fed animal models or in human intervention trials, showed that administration of probiotic bacteria was able to reduce leptin secretion and increase adiponectin levels [17, 79, 110–116, 120.121]. Some of this results were accompanied by a shift to an anti-inflammatory cytokine profile along with the partial restoration of metabolic alterations and/or dysbiosis that characterize obesity and metabolic syndrome [17, 79, 100, 110–112, 117–121]. Furthermore, in vitro and in vivo studies have also provided evidence that anti-inflammatory properties exerted by lactic acid bacteria in adipose tissue are strain-specific, prevailing in particular strains of *Lactobacillus* and *Bifidobacterium* genera (Tables 2, 3) [17, 110, 118–126]. Moreover, strains of these genera were reported to induce changes in gut microbiota composition [18]. The administration of a probiotic mix containing *Lactobacillus rhamnosus* and *Bifidobacterium animalis* subsp. *lactis* to obese mice was able to improve dysbiotic gut microbiota and increase

Table 2 Effects of probiotics on inflammatory status evaluated using cell line models

Probiotic	Inflammatory state	Experimental model	References
L. fermentum CMUL54, *L. gasseri* CMUL57, *L. gasseri* CMUL80, or *L. plantarum* CMUL140	↓ IL-8 and ↑ IL-10 secretion	Caco-2 cell line stimulated with IL-1β	[134]
L. casei CRL431, *L. casei* CRL72, *L. casei* CRL117, *L. fermentum* CRL1446, *L. plantarum CRL*350, *L. plantarum CRL*352, *L. plantarum CRL*353, *L. plantarum CRL*355, LAB strain CRL143, or *L. rhamnosus* CRL576	↓ leptin, IL-6, TNF-α and MCP-1 secretion, ↓ Ob-Rb [leptin receptor] expression	Mouse macrophage cell line	[17]
L. casei CRL431, *L. acidophilus* CRL258, *L. acidophilus* CRL1063, *L. casei* CRL72, *L. casei* CRL117, *L. paracasei* CRL575, or *L. rhamnosus* CRL576	↓ leptin, IL-6, TNF-α and MCP-1 secretion	Mouse adipocyte cell line	[17]
L. acidophilus CRL258, *L. acidophilus* CRL1063, *L. casei* CRL72, *L. fermentum* CRL1446, *L. plantarum* CRL350, or *L. plantarum* CRL353	↓ leptin, IL-6, TNF-α and MCP-1 secretion	Mouse macrophage–adipocyte cell lines coculture	[17]

Table 3 Probiotic strains with positive impact (in body weight, adiposity, glucose or lipid metabolism) on metabolic syndrome and related diseases evaluated in animal models

Probiotic	Inflammatory state	Experimental model/treatment (duration)	References
Mixture of *B. longum, B. infantis*, and *B. Breve, L. acidophilus, L. casei, L. delbrueckii* subsp. *L. bulgaricus, and L. plantarum*, and *Streptococcus salivarius* subsp. *thermophilus* [VSL#3 probiotic; VSL Pharmaceuticals]	↑ IL-10 in Peyer's patches and spleen, ↑ IL-10 expression in pancreas	NOD mice model/8 w	[135]
L. rhamnosus PL60	↓ serum leptin and ↓ TNFα expression in white adipose tissue	HFD mice model/8 w along with diet	[110]
Mixture of *B. longum, B. infantis*, and *B. Breve, L. acidophilus, L. casei, L. delbrueckii* subsp. *L. bulgaricus, and L. plantarum*, and *Streptococcus salivarius* subsp. *thermophilus* [VSL#3 probiotic; VSL Pharmaceuticals]	↑ NKT cells in liver, ↓ TNFα, and ↑ IL-4	HFD mice model/8 w after diet	[111]
L. plantarum 14	↓ serum leptin	HFD mice model/11 w along with diet	[113]
L. casei Shirota	↓ plasma CRP and IL-6	NOD rat model [streptozotocin-induced]/3 w	[136]
B. longum	↓ IL-1β and histological inflammatory activity index [small intestine]	HFD rat model/12 w along with diet	[137]
L. plantarum DSM 15,313	↓ serum leptin	HFD rat model/6 m along with diet	[116]
Mixture of *B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, *B. longum* SPM 1207	↓ serum leptin	HFD mice model/7 w along with diet	[115]
B. uniformis CECT 7771	↓ serum leptin, ↑ function of peritoneal macrophages and T-lymphocyte proliferation	HFD mice model/7 w along with diet	[79]
L. rhamnosus GG	↑ adiponectin production in adipose tissue	HFD mice model/12 w along with diet	[118]
B. pseudocatenulatum CECT 7765	↓ serum leptin, IL-6 and MCP-1, ↑ serum IL-4, ↑ function of peritoneal macrophages and T-lymphocyte proliferation	HFD mice model/7 w along with diet	[117]
L. plantarum OLL2712	↓ inflammation in adipose tissue	HFD mice model/12 w along with diet	[122]
Mixture of *L. plantarum* KY1032 and *L. curvatus* HY7601	↓ plasma leptin ↓ pro-inflammatory genes expression in adipose tissue: TNFα, IL-1β, IL-6, and MCP-1	HFD mice model/8 w along with diet	[119]
L. plantarum strain Nº 14	↓ TNFα, IL-6, and MCP-1 in adipose tissue	Diabetic KK/Ta mice/8 w along with diet	[123]
Mixture of *L. plantarum* KY1032 and *L. curvatus* HY7601	↓ TNFα and IL-1β in liver	HFD mice model/9 w along with diet	[138]
L. reuteri ATCC6475	↓ macrophages in adipose tissue	HFD mice model/12 w along with diet	[124]
L. gasseri SBT2055	↓ mRNA expression of MCP-1, PAI-1and leptin in epididymal adipose tissue	HFD mice model/24 w along with diet	[139]
L. coryniformis CECT5711	↓ TNFα, IL-1β, MCP-1, and JNK in liver	HFD mice model/12 w along with diet	[140]
L. rhamnosus GG	↓ TNF-α, IL-8R and IL-1β expression in the liver	High-fructose diet mice model/6 w along with diet	[141]
Mixture of *L. paracasei* CNCM I-4034, *B. breve* CNCM I-4035 or *L. rhamnosus* CNCM	↓ serum TNF-α	ob/ob mice model/30 d	[142]
B. breve CNCM I-4035 or *L. rhamnosus* CNCM	↓ serum TNF-α	ob/ob mice model/30 d	[142]
L. paracasei CNCM I-4034	↓ serum IL-6	ob/ob mice model/30 d	[142]

Table 3 (continued)

Probiotic	Inflammatory state	Experimental model/treatment (duration)	References
L. paracasei CNCM I-4270, *L. rhamnosus* I-3690, or *B. animalis* subsp. *lactis* I-2494	↓ macrophage infiltration into epididymal adipose tissue and ↓ TNFα in liver	HFD mice model/12 w along with diet	[125]
L. rhamnosus GG	↓ M1-like macrophage activation in white adipose tissues	db/db mice model	[126]
Mixture of *B. lactis* LA 303, *B. lactis* LA 304, *L. acidophilus* LA 201, *L. plantarum* LA 301 and *L. salivarius* LA 302	↓ expression of IL-6 gene and ↑ expression of adiponectin gene in adipose tissue	HFD mice model/14 w along with diet	[121]
Mixture of *B. bifidum* JLAU4, *L. casei* B10, and *L. plantarum* CGMCC NO. 11172	↑ serum leptin, ↓ liver TNF-α	HFD-induced liver injury mice model/6 w along with diet	[143]
L. casei CRL431	↑ IgA + cells and macrophages in small intestine, ↑ phagocytic activity of macrophages ↓ serum IL-6, IL-17, and TNF-α ↓ MCP-1 in adipocytes	HFD mice model/60 d along with diet	[109, 143]
Mixture of *L. rhamnosus, L. acidophilus and B. bifidum*	↓ TLR4 signaling pathway in liver, muscle and hypothalamus ↓ TNF-α and IL-6 mRNA expression in liver, muscle and hypothalamus ↓ serum IL-6 and TNF-α ↑ leptin sensitivity	HFD mice model/5 w along with diet	[145]
Mixture of *L. acidophilus* CBT LA1 (KCTC 11906BP), *L. rhamnosus* CBT LR5 (KCTC 12202BP), *B. bifidum* CBT BF3 (KCTC 12199BP), *B. lactis* CBT BL3 (KCTC 11904BP), *B. longum* CBT BG7 (KCTC 12200BP), and *St. thermophilus* CBT ST3 (KCTC 11870BP). (Duolac Gold probiotic formulation)	↓ serum IL-6, MCP-1, and TNF-α	HFD rat model/8 w along with diet	[146]

NOD not obese diabetic, *HFD* high-fat diet, *d* days, *w* weeks, *m* months

Table 4 Probiotic strains with positive impact (in body weight, adiposity, glucose or lipid metabolism) on metabolic syndrome and related diseases evaluated in clinical trials

Probiotic	Inflammatory state	Pathology/treatment (duration)	References
B. longum + FOS	↓ TNF-α and CRP	SH/24 w	[128]
Mixture of *L. acidophilus, L. bulgaricus, L. bifidum*, and *L. casei*	↓ IL-6	T2D/6 w	[129]
B. lactis HN019	↓ serum IL-6 and TNF-α	MS/45 d	[130]
B. animalis ssp. *lactis* 420	↓ CRP levels [tendency]	OB/6 m	[131]
Mixture of *L. acidophilus, L. plantarum, L. fermentum, and L. gasseri*	↓ serum IL-6 and CRP↑ serum IL-10	PCOS/12 w	[147]
Probiotic yoghurt: *L. acidophilus* La5, *Bifidobacterium* BB12, and *L. casei* DN001	↓ serum CRP and leptin	OB/8 w	[132]
L. rhamnosus CGMCC1.3724	↓ serum leptin	OB/24 w	[148]
L. gasseri SBT2055	↑ serum adiponectin	OB/12 w	[114]

d days, *w* weeks, *m* months, *MS* metabolic syndrome, *SH* nonalcoholic steatohepatitis, *T2D* type 2 diabetes, *OB* obesity, *PCOS* polycystic ovary syndrome, pathology closely related to MS, which shares clinical and metabolic components with MS (insulin resistance, low-grade chronic inflammation and central obesity)

the levels of *Akkermansia muciniphila*, related to the amelioration of metabolic health in obesity [18, 127] (Table 3). However, other genera of unconventional probiotics such as *Bacteroides* have also been related to improvements in metabolic and immunological parameters in mice with high-fat-diet induced obesity [79]. Another example is the yeast *Saccharomyces boulardii* that was found to change gut microbiota, reduce body weight and fat mass and attenuate the markers of metabolic inflammation in obese and diabetic mice [97].

There are few clinical trials studying the effects of probiotics on metabolic syndrome and related diseases and even less exploring their effect on the markers of inflammation in these pathologies. These few probiotic interventions in humans also showed beneficial effects on the parameters of metabolic syndrome and inflammatory status (Table 4) [114, 128–131]. Probiotic microorganisms, such as *Bifidobacterium lactis* HN019 or *Lactobacillus gasseri* SBT2055, showed significant improvement in abdominal visceral fat areas, body weight or lipid profile associated with an attenuation of low-grade inflammation, with reduction of pro-inflammatory markers, such as TNF-α and IL-6, and increment of anti-inflammatory ones, such as adipose-derived adiponectin [114, 130]. Probiotic yogurt containing *Lactobacillus acidophilus* La5, *Bifidobacterium. animalis* subsp. *lactis* BB-12, and *Lactobacillus casei* DN001 administered to obese individuals under low-calorie diet showed synergistic effects on T-cells subset-specific gene expression in peripheral blood mononuclear cells, and decreasing leptin levels and C-reactive protein, associated to a decrease in fat percentage, and body weight [132]. Despite these promising results obtained in humans, further clinical trials are necessary to confirm these positive effects and to unveil how probiotics might ameliorate the metabolic syndrome. Especially after some human trials suggested a species-specific effect of *Lactobacillus* on body weight, causing in certain cases weight gain [133].

Conclusion

Imbalance of inflammatory components of adipose tissue contributes to the development of metabolic syndrome-linked pathologies such as insulin resistance, type 2 diabetes or cardiovascular disease. Thereby, the control of inflammation in metabolic syndrome, as well as obesity, may outcome in the control of many of the pathologies related to these. In this regard, further knowledge concerning the immune function of adipose tissue may contribute to finding better alternatives for treatment or prevention of metabolic syndrome-related disorders. Furthermore, due to the strong evidence that gut microbiota composition plays a role modulating the body weight, adipose tissue and the prevalence of a low-grade inflammatory status, probiotics emerge as valuable tools for the prevention of metabolic syndrome and health recovery.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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