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Review

Development of a lactic acid bacteria strain that suppresses chronic inflammation and improves glucose and lipid metabolism

Takayuki TOSHIMITSU[1]

[1]*Applied Microbiology Research Department, Food Microbiology Research Laboratories, Division of Research and Development, Meiji Co., Ltd., 1-29-1 Nanakuni, Hachioji, Tokyo 192-0919, Japan*

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Chronic inflammation caused by aging, obesity, and lifestyle disturbances can lead to the production of inflammatory cytokines and insulin resistance, reducing glucose and lipid metabolism. Lactic acid bacteria (LAB) have various bioactivities, and certain types of LAB have been reported to exhibit anti-inflammatory effects. We hypothesized that LAB strains, which can strongly induce the production of anti-inflammatory cytokines by immune cells in the intestinal tract, may improve glucose and lipid metabolism by suppressing chronic inflammation. We selected *Lactiplantibacillus plantarum* OLL2712 (OLL2712) from the LAB library owned by Meiji Co., Ltd. based on its ability to induce the production of interleukin-10 (IL-10), optimized the culture conditions of OLL2712 for industrial applications, and verified the efficacy of the strain in animal and clinical studies. The results showed that OLL2712 bacterial cells in the exponential phase had notably higher anti-inflammatory properties than the cells in the stationary phase and led to the inhibition of chronic inflammation and improvement of glucose and lipid metabolism in animal studies. Two randomized controlled trials consisting of healthy adults with elevated blood glucose levels or body mass indices (BMIs) also showed that the intake of OLL2712 suppressed the aggravation of chronic inflammation and improved glucose and lipid metabolism. This review identified a novel LAB strain that may contribute to diabetes and obesity prevention and demonstrated its clinical efficacy. In addition, the mechanism of action of this LAB strain through the intestinal immune system was partially elucidated, and the importance of optimizing the culture conditions of LAB was clarified.

Key words: chronic inflammation, culture condition, diabetes mellitus, insulin resistance, interleukin 10, lactic acid bacteria, metabolic syndrome

INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia caused by insufficient insulin action and is accompanied by various characteristic metabolic abnormalities [1]. Metabolic syndrome is a condition in which people are prone to diabetes and other lifestyle-related diseases and have a high incidence of arteriosclerotic diseases, such as myocardial infarction and cerebral infarction. The increase in the number of patients with diabetes and metabolic syndrome has become a major public health problem worldwide, as it leads to the deterioration of national health standards and an increase in medical and nursing care costs [2]. Globally, the number of patients with diabetes is rapidly increasing, especially in Asia and the Middle East region, with more than 400 million people diagnosed with it. In addition, more than 2 billion people worldwide are overweight or obese, with body mass indices (BMIs) of 25 or higher. Therefore, the prevention and improvement of these diseases through daily food intake is an extremely important public health issue.

Lactic acid bacteria (LAB) have a wide variety of physiological effects, including intestinal regulation; however, their immunostimulatory activity against immune cells is particularly noteworthy. It has been reported that LAB exhibit immunostimulatory activity by affecting immune cells such as dendritic cells, macrophages, and T cells in the intestinal tract, thereby improving immunity [3]. Previous studies have reported that oral administration of LAB improves obesity and insulin resistance [4, 5]. The LAB strains used in those studies had been confirmed to have high immunostimulatory activity, such as an ameliorating effect on allergies, suggesting that certain LAB can prevent or improve metabolic disorders by stimulating immune cells in the intestinal tract, thereby affecting visceral

Corresponding author. Takayuki Toshimitsu (E-mail: takayuki.toshimitsu@meiji.com)

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adipose tissue and metabolism-related organs throughout the body. However, the relevance of immunostimulatory activity in the improvement of obesity and insulin resistance is unclear, and there has been no clear understanding of its mechanism of action. No studies have been performed to select *Lactobacillus* strains showing immunostimulatory activity that may be optimal for improving metabolic disorders and to verify their efficacy *in vivo*.

In this study, the selection of an optimal LAB strain for the prevention and improvement of diabetes and metabolic syndrome and the optimization of culture conditions of the LAB strain in actual production were highlighted. In addition, we performed basic experiments to verify the efficacy of the strain in animal models of diabetes and obesity and in clinical trials and to elucidate its mechanism of action.

PATHOGENIC BASIS OF DIABETES AND METABOLIC SYNDROME AND APPROACHES TO PREVENT THESE DISEASES

The underlying causes of diabetes and metabolic syndrome are thought to be chronic inflammation caused by aging, unhealthy lifestyle habits, and obesity [6]. When chronic inflammation causes visceral adipose tissue to secrete large amounts of pro-inflammatory cytokines, it inhibits the functions of insulin, a hormone that lowers blood glucose levels in adipose tissue, skeletal muscle, and the liver, resulting in insulin resistance [7, 8]. As a result, the consumption of sugar and lipids decreases, and the synthesis of lipids is accelerated by insulin, leading to hyperglycemia, abnormal lipid metabolism, and body fat accumulation. Furthermore, increased obesity associated with body fat accumulation exacerbates hyperglycemia by inducing chronic inflammation and insulin resistance and induces hyperlipidemia, which leads to stroke and cardiovascular disease [9]. Chronic inflammation with the production of inflammatory cytokines forms a vicious cycle that leads to the development of various lifestyle-related diseases.

Inflammatory cytokines are proteins that play a role in signal transduction for the elimination of foreign substances *in vivo* but are known to cause inflammation when produced in excess, resulting in various adverse effects, as described above [6]. Furthermore, inflammatory cytokines promote the production of free fatty acids from adipose tissue, and free fatty acids transferred to the blood inhibit glucose uptake and consumption in the skeletal muscle and liver. Systemic chronic inflammation associated with increased blood levels of inflammatory cytokines inhibits insulin secretion from the pancreas and increases blood glucose levels [10].

An important cause of chronic inflammation in visceral adipose tissue is the infiltration of macrophages present in the intestinal tract and abdominal cavity into visceral adipose tissue [11]. Macrophage infiltration increases the production of inflammatory cytokines and exacerbates insulin resistance [12]. Interactions between macrophages and adipocytes are thought to be a major cause of chronic inflammation in the visceral adipose tissue. Macrophages produce inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), which in turn make adipocytes produce IL-6 and monocyte chemotactic protein 1 (MCP-1), forming a cycle that exacerbates chronic inflammation. Therefore, it is possible to alleviate chronic inflammation and normalize glucose and lipid metabolism by inhibiting the excessive activation of macrophages and their infiltration into visceral adipose tissue.

On the other hand, adiponectin, a hormone secreted in large amounts by visceral adipocytes, has been reported to improve insulin resistance and enhance glucose and lipid metabolism [13]. Anti-inflammatory cytokines secreted by immune cells in the intestinal tract and visceral adipose tissue are also thought to inhibit the progression of chronic inflammation by inhibiting the function of inflammatory cytokines and promoting adiponectin production [14].

INTERLEUKIN 10

We focused on interleukin 10 (IL-10), an anti-inflammatory cytokine secreted by dendritic cells, macrophages, and T cells. IL-10 inhibits the production of inflammatory cytokines such as IL-6, TNF-α, and MCP-1, which induce chronic inflammation in visceral adipose tissue [14]. It has long been known that the immune cells described above produce IL-10 in the intestinal tract. Recently, it has been reported that immune cells infiltrating visceral adipose tissue produce IL-10 and suppress chronic inflammation [15]. Regulatory T cells and anti-inflammatory M2-type macrophages are known to be IL-10-producing cells in visceral adipose tissue [15]. These immune cells can infiltrate visceral adipose tissue from the intestinal tract or abdominal cavity in response to signals from the gut immune system induced by stimuli from food components or gut bacteria. The predominance of IL-10 also suppresses the production of inflammatory cytokines such as MCP-1 in visceral adipose tissue and inhibits the infiltration of inflammatory M1-type macrophages [15]. In other words, inducing the production of IL-10 may interrupt the vicious cycle of chronic inflammation in visceral adipose tissue and maintain a normal, insulin-sensitive state.

Epidemiological studies have reported a 2.7-fold increased risk of developing type 2 diabetes in individuals with low IL-10 production capacity compared with those with high IL-10 production capacity [16]. Inhibition of IL-10 has been reported to increase inflammation and worsen glucose and lipid metabolism in animal models [17]. *In vitro* studies have also reported that supplementation of 3T3-L1 adipocytes with IL-10 suppresses the increase in insulin resistance induced by TNF-α and promotes glucose uptake [15]. These findings suggest that IL-10 plays an important role in alleviating chronic inflammation and that modulation of IL-10 production may prevent metabolic disorders, such as obesity, lipid abnormalities, and diabetes.

However, because it is difficult to efficiently supply IL-10 to the body, the intake of food components that have high IL-10-inducing activity is considered an effective and safe method of promoting its production in the body so that immune cells control the deterioration of glucose and lipid metabolism.

LACTIPLANTIBACILLUS PLANTARUM OLL2712

We focused on LAB as a food ingredient with the abovementioned effects and selected a strain with a high ability to induce IL-10 production by immune cells from the LAB library owned by Meiji Co. Ltd. in Japan. Dendritic cells derived from the bone marrow of mice (BMDCs) and macrophages derived from the abdominal cavity of mice were used as models of immune cells in the intestinal tract. Heat-treated cells of various

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LAB strains were added to these immune cells *in vitro*, and their IL-10-inducing activities were evaluated by enzyme-linked immunosorbent assay (ELISA). In the study, *L. plantarum* OLL2712 (OLL2712) showed the highest IL-10-inducing activity for each of the immune cells [18].

OLL2712 is a strain isolated from the feces of healthy Japanese adults, and it has a variety of aspects that make it highly suitable as a probiotic, such as gastric acid and bile acid tolerance and adherence to the digestive tract [18]. However, the IL-10-inducing activity was significantly higher in heated bacteria than in live bacteria; therefore, we decided to use heated bacteria. Subsequently, when heat-treated OLL2712 cells were applied to dendritic cells derived from the Peyer's patch and mesenteric lymph nodes of mice, IL-10 was remarkably produced [19]. Oral administration of heat-treated OLL2712 cells to mice for 6 days increased the expression of IL-10 in dendritic cells of mesenteric lymph nodes. Therefore, orally consumed OLL2712 may reach the intestinal immune system and induce the production of IL-10 by immune cells *in vivo*, suppressing chronic inflammation in the intestine and adipose tissues (Fig. 1).

OPTIMIZATION OF LAB CULTURE CONDITIONS AND EVALUATION OF EFFICACY USING DIABETES AND OBESITY MODEL ANIMALS

KKAy mice, a model of diabetes and obesity, were orally administered heat-treated LAB cells daily for 3 weeks, and the effects on chronic inflammation and glucose and lipid metabolism were investigated. The results showed that administration of OLL2712 decreased the levels of inflammatory cytokines such as IL-6 and MCP-1 in the blood and adipose tissue and improved the indices of glucose and lipid metabolism in the blood [18]. Further, macrophage infiltration into adipose tissue, which causes chronic inflammation, was suppressed.

However, it has been suggested that the immunomodulatory activity of LAB varies greatly depending on the culture conditions. For industrial applications, it is important to confirm that the functionality of LAB is maintained or improved when cultured at high concentrations. Although many efforts have been made to select strains of LAB using immunomodulatory activity as an indicator and to develop health functions based on immunomodulatory activity, the effects of culture conditions on the immunomodulatory activity and health functions of the selected strains have not been investigated sufficiently. If the immunomodulatory activity of LAB can be enhanced by optimizing their culture conditions, LAB with higher health benefits can be provided to the general public (Fig. 2). Therefore, we investigated the relationships between LAB culture conditions and their immunomodulatory activities and functions in improving glucose and lipid metabolism.

In the study, OLL2712 was cultured at a constant pH by adding a neutralizer to a medium containing mainly milk components, assuming actual production, and the effects of different culture phases, medium components, neutralizing pH, and culture temperature on the IL-10-inducing activity of the strain on immune cells were examined. The results showed that the effect of the culture phase was the most prominent, and the activity was significantly higher in the exponential phase (8 hr) than that in the stationary phase (14 hr) [20]. The addition of oleate to the culture medium was also found to increase the IL-10-inducing activity during the exponential phase. The immunomodulatory activity was also determined for heat-treated OLL2712 cells cultured statically in MRS broth until the stationary phase and lipopolysaccharide (LPS) for comparison. The results revealed that the OLL2712 cells cultured to the exponential phase in a medium containing mainly milk components and oleate showed equal or higher IL-10-inducing activity, significantly lower IL-12-inducing activity, and a significantly higher IL-10/IL-12 ratio, suggesting that the bacterial cells had excellent anti-inflammatory properties. Subsequently, the OLL2712 cells in the exponential phase or stationary phase were orally administered daily to KKAy mice for 3 weeks to examine their effects on chronic inflammation and glucose and lipid metabolism. The results showed that the OLL2712 cells in the exponential phase suppressed chronic inflammation and improved glucose and lipid metabolism in adipose tissue, whereas the OLL2712 cells in the stationary phase showed no significant effects on the indicators related to chronic inflammation or glucose and lipid metabolism.

These results indicated that the anti-inflammatory effects of LAB are enhanced by optimizing the culture conditions. In addition, it was shown that bacterial cells cultured under conditions showing high IL-10-inducing activity have a strong effect on improving glucose and lipid metabolism.

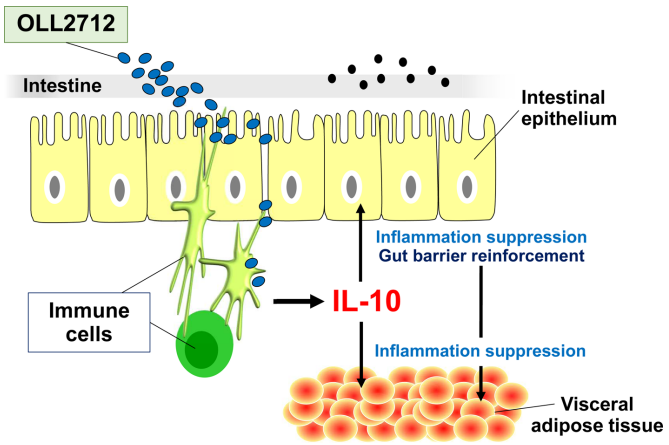

Fig. 1. Putative mechanism of action for the effects of OLL2712 on intestinal immunity.

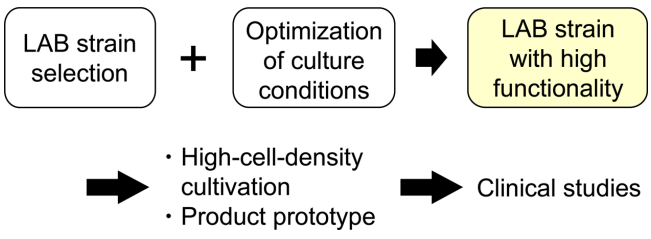

Fig. 2. Development strategy for novel lactic acid bacteria. LAB: lactic acid bacteria.

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EFFECTS OF OLL2712 ON IMPROVING GLUCOSE AND LIPID METABOLISM IN CLINICAL TRIALS

Preliminary trial

An exploratory clinical trial was conducted using a single-arm, open design to evaluate the effects of OLL2712 on the suppression of chronic inflammation and improvement of glucose and lipid metabolism in humans. Thirty healthy adults with fasting blood glucose levels from 105 to 130 mg/dL consumed a zero-calorie beverage containing heat-treated OLL2712 for 12 weeks. The primary endpoints were glucose metabolism indices, and the secondary endpoints were lipid metabolism indices and chronic inflammation markers.

The results showed that fasting blood glucose, blood glycoalbumin, and the insulin resistance index (HOMA-IR) were significantly lower after ingestion than at baseline [21]. As chronic inflammation markers, blood MCP-1 and IL-6 were significantly lower after ingestion than at baseline, and a stratified analysis confirmed that OLL2712 intake prominently reduced fasting blood glucose and HOMA-IR in subjects who had higher levels of these markers than the averages for all the subjects at baseline. Furthermore, among the lipid metabolism indices, a significant reduction in the body fat percentage was observed. Thus, the intake of OLL2712 can improve glucose and lipid metabolism by suppressing chronic inflammation.

Based on the results of the preliminary trial described above, the number of cases and other conditions were established, and two confirmatory trials were designed and conducted.

Confirmatory trial for prediabetic subjects

For the first trial, a randomized, double-blind, placebo-controlled, parallel-group study was conducted in healthy adults with blood hemoglobin A1c (HbA1c) levels ranging from 5.6 to 6.4% and fasting blood glucose levels ranging from 100 to 125 mg/dL (n=130; age range: 20–64 years). The test food and placebo consisted of 112 g yogurt containing at least 5×10^9 heat-treated OLL2712 cells and yogurt without OLL2712, respectively, which were consumed daily for 12 weeks. The primary endpoints were blood HbA1c and fasting blood glucose levels, and the secondary endpoints were insulin resistance indices and chronic inflammation indices in the blood.

The results showed that the reduction in HbA1c was significantly greater in the OLL2712 group after 12 weeks of intake than that in the placebo group [22]. In addition, HOMA-IR, an indicator of insulin resistance, and blood IL-6 and high-sensitivity C-reactive protein (CRP), indicators of chronic inflammation, significantly worsened compared with the baseline values in the placebo group but did not change and remained normal in the OLL2712 group. It was inferred that OLL2712 intake normalizes glucose metabolism by suppressing insulin resistance and preventing the exacerbation of chronic inflammation. In this study, yogurt was used as the test food. The yogurt itself has been suggested to be effective in preventing diabetes, obesity, metabolic syndrome, and chronic inflammation [23–25]. The inclusion of LAB as probiotics in yogurt would make the food more suitable for blood glucose management. In fact, the results of this study showed that HbA1c level decreased significantly in the placebo group compared with the baseline level. Considering that the intake period of the test foods was from August to November, when HbA1c generally increases easily, the yogurt itself may have contributed to this decrease.

Confirmatory trial for obese subjects

For the second trial, a randomized, double-blind, placebo-controlled, parallel-group study was conducted in healthy adults with BMIs between 25–30 (n=100; age range: 20–64 years). The test foods and intake period were the same as those used in the study described in the confirmatory trial for prediabetic subjects above. The primary endpoint was the abdominal fat area measured by CT scan, and the secondary endpoints were glucose and lipid metabolism indices and chronic inflammation indices.

The results showed that the changes in abdominal fat area and fasting blood glucose levels after 12 weeks were significantly lower in the OLL2712 group than those in the placebo group [26]. In addition, the blood IL-6 levels in the OLL2712 group were significantly lower than at baseline, and the changes were significantly lower than those in the placebo group. Thus, the results indicated that OLL2712 intake can inhibit body fat accumulation in obese healthy adults, as well as blood glucose elevation and aggravation of chronic inflammation. Certain LAB may prevent obesity by normalizing glucose and lipid metabolism via the control of chronic inflammation. In this study, the same yogurt as in the confirmatory trial for prediabetic subjects above was used as the test food. In the placebo group, body weight and BMI increased significantly compared with the baseline values, whereas these increases were not observed in the OLL2712 group [26]. As mentioned in the previous section, yogurt itself has been suggested to have an anti-obesity effect; therefore, the increase in body weight in the placebo group was likely due to seasonal variation caused by the fact that the test food was consumed from September to December. Furthermore, the results suggested that body fat accumulation was suppressed because insulin sensitivity was maintained in a normal state by OLL2712 intake.

CONCLUSION

In this review, LAB with high IL-10-inducing activity in immune cells were shown to improve glucose and lipid metabolism in diabetic and obese model mice and prediabetic and obese subjects. The induction of IL-10 production suppressed chronic inflammation in adipose tissue, which may have contributed to the suppression of insulin resistance and improvement of glucose and lipid metabolism (Fig. 3).

In contrast, other LAB strains with low IL-10-inducing activity in immune cells, or OLL2712 prepared under culture conditions that reduced the activity, showed no anti-inflammatory action or improvement of glucose and lipid metabolism in diabetic and obese mouse models. Based on these results, we speculate that the high inducibility of IL-10 production may play an important role in the functional expression of the OLL2712 strain. Further clinical and basic studies are needed to elucidate the mechanism of action of OLL2712 *in vivo* and the role of IL-10 production in improving glucose and lipid metabolism in the intestinal immune system.

The test food for the clinical trials in the study was in yogurt form and contained OLL2712 produced under culture conditions expected to have the highest efficacy. Various health functions of yogurt have been reported, and the preventive effects of yogurt against diabetes and obesity and its inhibitory effect on chronic inflammation have been attracting attention. Yogurt is a suitable food for continuous intake of OLL2712 in the daily diet. Yogurt

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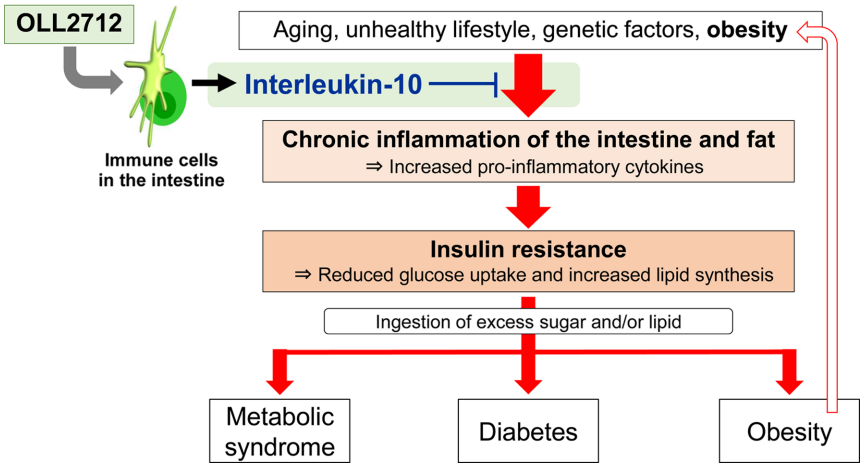

Fig. 3. Putative mechanism of action for the effects of OLL2712 on glucose and lipid metabolism.

containing OLL2712 is expected to improve blood glucose control and improve public health.

CONFERENCE PRESENTATION

The contents of this article received a 2021 Research Encouragement Award and were presented at the Annual Meeting of Intestinal Microbiology held on July 7, 2022.

REFERENCES

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. 2017. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 128: 40–50. [Medline] [CrossRef]
2. Oggioni C, Lara J, Wells JCK, Soroka K, Siervo M. 2014. Shifts in population dietary patterns and physical inactivity as determinants of global trends in the prevalence of diabetes: an ecological analysis. Nutr Metab Cardiovasc Dis 24: 1105–1111. [Medline] [CrossRef]
3. Parvez S, Malik KA, Ah Kang S, Kim HY. 2006. Probiotics and their fermented food products are beneficial for health. J Appl Microbiol 100: 1171–1185. [Medline] [CrossRef]
4. Naito E, Yoshida Y, Makino K, Kounoshi Y, Kunihiro S, Takahashi R, Matsuzaki T, Miyazaki K, Ishikawa F. 2011. Beneficial effect of oral administration of *Lactobacillus casei* strain Shirota on insulin resistance in diet-induced obesity mice. J Appl Microbiol 110: 650–657. [Medline] [CrossRef]
5. Takemura N, Okubo T, Sonoyama K. 2010. *Lactobacillus plantarum* strain No. 14 reduces adipocyte size in mice fed high-fat diet. Exp Biol Med (Maywood) 235: 849–856. [Medline] [CrossRef]
6. Shoelson SE, Herrero L, Naaz A. 2007. Obesity, inflammation, and insulin resistance. Gastroenterology 132: 2169–2180. [Medline] [CrossRef]
7. Fantuzzi G. 2005. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 115: 911–919, quiz 920. [Medline] [CrossRef]
8. Lumeng CN, Saltiel AR. 2011. Inflammatory links between obesity and metabolic disease. J Clin Invest 121: 2111–2117. [Medline] [CrossRef]
9. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. 2005. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 111: 1448–1454. [Medline] [CrossRef]
10. Ehses JA, Perren A, Eppler E, Ribaux P, Pospisilik JA, Maor-Cahn R, Gueripel X, Ellingsgaard H, Schneider MK, Biollaz G, Fontana A, Reinecke M, Homo-Delarche F, Donath MY. 2007. Increased number of islet-associated macrophages in type 2 diabetes. Diabetes 56: 2356–2370. [Medline] [CrossRef]
11. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. 2003. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112: 1796–1808. [Medline] [CrossRef]
12. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. 2003. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112: 1821–1830. [Medline] [CrossRef]
13. Iwabu M, Yamauchi T, Okada-Iwabu M, Sato K, Nakagawa T, Funata M, Yamaguchi M, Namiki S, Nakayama R, Tabata M, Ogata H, Kubota N, Takamoto I, Hayashi YK, Yamauchi N, Waki H, Fukayama M, Nishino I, Tokuyama K, Ueki K, Oike Y, Ishii S, Hirose K, Shimizu T, Touhara K, Kadowaki T. 2010. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. Nature 464: 1313–1319. [Medline] [CrossRef]
14. Winer S, Chan Y, Paltser G, Truong D, Tsui H, Bahrami J, Dorfman R, Wang Y, Zielenski J, Mastronardi F, Maezawa Y, Drucker DJ, Engleman E, Winer D, Dosch HM. 2009. Normalization of obesity-associated insulin resistance through immunotherapy. Nat Med 15: 921–929. [Medline] [CrossRef]
15. Lumeng CN, Bodzin JL, Saltiel AR. 2007. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 117: 175–184. [Medline] [CrossRef]
16. van Exel E, Gussekloo J, de Craen AJ, Frölich M, Bootsma-Van Der Wiel A, Westendorp RG, Leiden 85 Plus Study. 2002. Low production capacity of interleukin-10 associates with the metabolic syndrome and type 2 diabetes: the Leiden 85-Plus Study. Diabetes 51: 1088–1092. [Medline] [CrossRef]
17. Cintra DE, Pauli JR, Araújo EP, Moraes JC, de Souza CT, Milanski M, Morari J, Gambero A, Saad MJ, Velloso LA. 2008. Interleukin-10 is a protective factor against diet-induced insulin resistance in liver. J Hepatol 48: 628–637. [Medline] [CrossRef]
18. Toshimitsu T, Mochizuki J, Ikegami S, Itou H. 2016. Identification of a *Lactobacillus plantarum* strain that ameliorates chronic inflammation and metabolic disorders in obese and type 2 diabetic mice. J Dairy Sci 99: 933–946. [Medline] [CrossRef]
19. Takano T, Endo R, Wang Y, Nakajima-Adachi H, Hachimura S. 2020. *Lactobacillus plantarum* OLL2712 induces IL-10 production by intestinal dendritic cells. Biosci Microbiota Food Health 39: 39–44. [Medline] [CrossRef]
20. Toshimitsu T, Ozaki S, Mochizuki J, Furuichi K, Asami Y. 2017. Effects of *Lactobacillus plantarum* strain OLL2712 culture conditions on the anti-inflammatory activities for murine immune cells and obese and type 2 diabetic mice. Appl Environ Microbiol 83: e03001–e03016. [Medline] [CrossRef]
21. Toshimitsu T, Gotou A, Furuichi K, Hachimura S, Asami Y. 2019. Effects of 12-wk *Lactobacillus plantarum* OLL2712 treatment on glucose metabolism and chronic inflammation in prediabetic individuals: a single-arm pilot study. Nutrition 58: 175–180. [Medline] [CrossRef]
22. Toshimitsu T, Gotou A, Sashihara T, Hachimura S, Shioya N, Suzuki S, Asami Y. 2020. Effects of 12-week ingestion of yogurt containing *Lactobacillus plantarum* OLL2712 on glucose metabolism and chronic inflammation in prediabetic adults: a randomized placebo-controlled trial. Nutrients 12: E374. [Medline] [CrossRef]
23. Gijsbers L, Ding EL, Malik VS, de Goede J, Geleijnse JM, Soedamah-Muthu SS. 2016. Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. Am J Clin Nutr 103: 1111–1124. [Medline] [CrossRef]
24. Sayon-Orea C, Martínez-González MA, Ruiz-Canela M, Bes-Rastrollo M. 2017. Associations between yogurt consumption and weight gain and risk of obesity and metabolic syndrome: a systematic review. Adv Nutr 8: 146S–154S. [Medline] [CrossRef]
25. Dumas AA, Lapointe A, Dugrenier M, Provencher V, Lamarche B, Desroches S. 2017. A systematic review of the effect of yogurt consumption on chronic diseases risk markers in adults. Eur J Nutr 56: 1375–1392. [Medline] [CrossRef]
26. Toshimitsu T, Gotou A, Sashihara T, Furuichi K, Hachimura S, Shioya N, Suzuki S, Asami Y. 2021. Ingesting yogurt containing *Lactobacillus plantarum* OLL2712 reduces abdominal fat accumulation and chronic inflammation in overweight adults in a randomized placebo-controlled trial. Curr Dev Nutr 5: nzab006. [Medline] [CrossRef]

