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Pilot study

Effects of 12-wk *Lactobacillus plantarum* OLL2712 treatment on glucose metabolism and chronic inflammation in prediabetic individuals: A single-arm pilot study

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ABSTRACT

Objective: Previously, we demonstrated that the administration of heat-killed OLL2712 cells suppressed chronic inflammation and improved hyperglycemia in a mouse model of obesity and diabetes. The aim of this study was to preliminarily examine the effect of OLL2712 supplementation on glucose metabolism and chronic inflammation in prediabetic subjects.
Methods: This study was a prospective, 12-wk, single-arm, open trial, followed by a 4-wk posttreatment period. Inclusion criteria were fasting plasma glucose levels of 105 to 130 mg/dL in an age range of 35 to 65 y. Thirty individuals consumed a dairy beverage containing $\sim 1 \times 10^{10}$ heat-killed OLL2712 cells for 12 wk.
Results: The ingestion of the OLL2712 beverage significantly improved fasting plasma glucose levels, serum glycoalbumin levels, and insulin resistance indexes compared with baseline levels. The intervention also suppressed serum monocyte chemotactic protein-1 and interleukin-6 levels, which are proinflammatory cytokines involved in the development of insulin resistance and hyperglycemia. Furthermore, stratified analysis by these proinflammatory cytokine levels revealed that the beneficial effects of OLL2712 beverage were observed particularly in individuals with chronic inflammation at baseline.
Conclusion: The results of this study suggested that heat-killed OLL2712 cells have the potential to improve insulin resistance and glucose metabolism by suppressing chronic inflammation.

Introduction

The prevalence of metabolic disorders, including type 2 diabetes mellitus, has dramatically increased worldwide and has become a global public health problem [1]. Among the investigations of various foods for their ability to prevent and/or treat metabolic disorders, recently, certain lactic acid bacteria (LAB) have shown promising results. In particular, it was previously confirmed that certain LAB strains improved lipid metabolism and reduced body fat in both animal studies [2] and clinical trials [3]. On the other hand, a few reports have shown that LAB improves glucose metabolism for animals [4], and only two studies have been reported for humans [5,6]. Conversely, some clinical trials demonstrated that the ingestion of LAB did not lower blood glucose levels [7,8], and thus the effect of LAB in improving glucose metabolism is controversial. Although such conflicting results may be caused by strain differences, few studies have been performed to clarify the types of LAB that are effective against metabolic disorders.

Suppression of chronic inflammation is one of the deduced mechanisms involved with the LAB function in metabolic disorders [8,9]. Chronic inflammation causes insulin resistance (IR) and impairs glucose and lipid metabolism in the adipose, muscle, and liver tissues [10]. Increased production of proinflammatory cytokines, such as monocyte chemotactic protein (MCP)-1 or interleukin (IL)-6, has been reported to induce chronic inflammation in these tissues [11,12]. Thus, the alleviation of chronic inflammation by suppressing MCP-1 and IL-6 might ameliorate or prevent metabolic disorders.

In a previous study, we selected *Lactobacillus plantarum* OLL2712 (OLL2712) for its high ability to induce IL-10 production in murine immune cells [13]. IL-10 is known to suppress the production of proinflammatory cytokines, including MCP-1 and IL-6 [14,15]. Accordingly, the induction of IL-10 was shown to prevent

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IR and improve glucose metabolism in obese mice [16,17]. Additionally, the administration of heat-killed OLL2712 cells alleviated chronic inflammation and improved hyperglycemia in KKAy mice, which is a model of obesity and diabetes [13]. In another animal study, we demonstrated that the administration of heat-killed OLL2712 cells significantly reduced blood glucose concentrations after insulin treatment in a diet-induced obesity model, suggesting the improvement of IR [18]. We therefore considered that the administration of OLL2712 cells suppressed chronic inflammation by inducing IL-10 production, consequently improving IR and glucose metabolism.

In the present study, we conducted a pilot study to examine whether 12-wk ingestion of a test beverage containing heat-killed OLL2712 cells is effective in improving IR and glucose metabolism in prediabetic subjects. Additionally, we attempted to investigate the association of inflammation suppression for these antidiabetic effects.

Methods

Study design and participants

A prospective, 12-wk, single-group, open trial study, followed by a 4-wk post-treatment period, was conducted by a contract research organization, TES Holdings Co., Ltd. (Tokyo, Japan) from June to October 2015 at the Oriental Ueno Medical Examination Center in Tokyo, Japan. Participant inclusion criteria were fasting plasma glucose levels of 105 to 130 mg/dL during the screening period and an age of 35 to 65 y. Subjects were excluded from the study if they had any diseases; had taken any medication; regularly ingested yogurt, LAB beverages, or probiotic supplements more than twice a week; consumed excessive alcohol within the previous 3 mo; or had a food allergy.

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Oriental Ueno Medical Examination Center Ethical Committee for Human Participants and Meiji Institutional Review Board. Participants provided written informed consent before study initiation.

Test food

The test food was a 100-g beverage containing heat-killed OLL2712 ($\sim 1 \times 10^{10}$ cells/100 g of beverage). It was delivered under refrigeration to each participant weekly and then refrigerated until consumption. The beverage consisted of sweeteners, an acidulant, a stabilizer, grapefruit juice, and a small amount of flavoring; it was virtually free of energy, protein, fat, carbohydrates, and calcium. Heat-killed OLL2712 cells were prepared as previously described [19]. Briefly, the cells were grown to late log-phase in a culture medium mainly composed of skim milk concentrate with mono-oleic acid esters at pH 5.8 and 33°C in a pH-controlled culture.

Participants were instructed to consume the 100-g test beverage every day for 12 wk. For the duration of the study, they were asked to maintain their normal diet and lifestyle habits including the quality and quantity of exercises. A life diary was provided to the participants to confirm compliance and report any problems, such as side effects. They also described the type and amount of exercises every day in their life diaries. A physician monitored participant compliance as based on interviews and the diaries at each clinic visit.

Measurements

After overnight fasting, blood samples were drawn from the antecubital vein of each participant. The samples were prepared into plasma or serum and analyzed at the Health Sciences Institute (Tokyo, Japan). An automatic biochemical analyzer (JEOL, Tokyo, Japan) was used with each dedicated reagent (Serotec, Sapporo, Japan; Kyowa Medex and Kanto Chemical, Tokyo, Japan) to analyze the following, using the enzyme method: whole blood glycosylated hemoglobin (HbA1c), plasma glucose, serum glycoalbumin (GA), serum total cholesterol (TC), serum low-density lipoprotein cholesterol (LDL-C), serum high-density lipoprotein cholesterol (HDL-C), serum triacylglycerols (TGs), and serum non-esterified fatty acids (NEFAs). Serum insulin levels were analyzed using the chemiluminescence immunoassay (CLIA) method with an automatic CLIA system (Siemens Healthineers, Tokyo, Japan). Body fat percentages were measured using a DC-320 body analyzer (Tanita, Tokyo, Japan). Blood pressures were measured using the IistminiBP-10 (Fukuda Colin, Tokyo, Japan). Serum proinflammatory cytokines levels were measured using a multiplex human cytokine bead array system (Bio-Rad, Hercules, CA, USA).

The homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated according to the formula:

HOMA-IR = fasting glucose (mg/dL) × fasting insulin (μU/mL) / 405 [20] and QUICKI = 1 / [{log(fasting glucose (mg/dL)} + log{fasting insulin (μU/mL)}] [21].

Diet records

Participants recorded the details of meal contents in questionnaires to calculate the nutrition intake for 3 d before each clinical examination. They also received detailed written and verbal instructions on how to complete these records. These records were then used for the assessment of habitual energy intake and diet composition. Diet records were analyzed using the Healthy Maker Pro 501 R8 (Mushroomsoft, Okayama, Japan).

Statistical analysis

The primary outcome measurements were fasting plasma glucose levels, GA, HOMA-IR, and QUICKI. Secondary outcome measurements were serum proinflammatory cytokine levels, fasting serum fat levels, body mass index, and body fat percentage. Data analysis was performed by one-way repeated measures analysis of variance (ANOVA), followed by the paired *t* test or the Wilcoxon signed rank test with Bonferroni correction using SPSS Statistics 19 for Windows (IBM Japan, Tokyo, Japan). Measurements are presented as mean ± SE. Statistical significance was considered at $P < 0.05$.

Results

Participant characteristics

The screening and inclusion of the study participants are shown in Figure 1. In all, 221 healthy participants from the volunteer bank attended the clinic within 3 wk of study initiation for a screening test. Thirty-four participants (23 men, 11 women) were selected and consumed the test food. Four individuals were excluded because of compliance violations, and 30 (22 men, 8 women) were analyzed. The mean age of the participants was 51.9 ± 8.7 y for men and 54.3 ± 6.3 y for women. The intake compliance rate of the test food was >95% for all participants, and no adverse events were recorded for any participants with regard to safety parameters, including blood and urine tests (data not shown). Daily nutrition intakes are shown in Table 1. Habitual energy intake and diet composition as well as lifestyle habits were similar for each participant throughout the test period.

Effects of OLL2712 on glucose metabolism and IR

Table 2 shows the changes in parameters that are related to glucose metabolism and IR, including fasting plasma glucose, GA, HbA1c, insulin, HOMA-IR, and QUICKI. Compared with those at baseline, fasting plasma glucose and GA levels were significantly reduced at 4- and 8-wk treatment time points, respectively. Fasting serum insulin levels, HOMA-IR, and QUICKI were significantly improved at the 12-wk treatment time point. These improvements were not observed at post-treatment time point. On the other hand, HbA1c did not change significantly compared with baseline, and was significantly reduced at the 12-wk treatment time point compared with the 4-wk treatment time point, probably because this parameter reflects average blood glucose levels over the previous 1 or 2 mo.

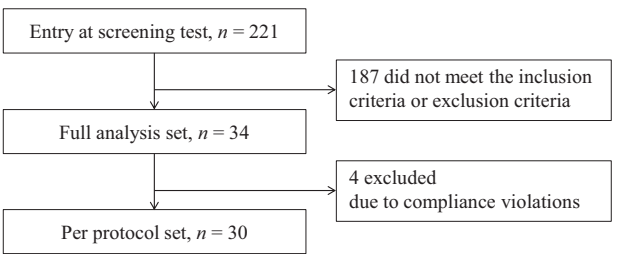

Fig. 1. Participant screening and inclusion.

Table 1
Daily nutrition intakes*

		Treatment			Post-treatment	ANOVA
	0-wk	4-wk	8-wk	12-wk	4-wk	
Energy (kcal/d)	1818 ± 74	1839 ± 73	1784 ± 70	1882 ± 78	1834 ± 90	NS
Fat (g/d)	57.9 ± 3.3	60.7 ± 3.5	56.2 ± 3	63.6 ± 3.8	61.8 ± 4.1	NS
Carbohydrates (g/d)	238 ± 9	237 ± 10	231 ± 11	239 ± 11	230 ± 12	NS
Protein (g/d)	67.1 ± 3.3	68.1 ± 3.1	67.2 ± 2.8	69.4 ± 3.1	67.7 ± 3.3	NS
Dietary fiber (g/d)	12.8 ± 1	12.5 ± 0.6	12.7 ± 0.9	12.6 ± 1	12.9 ± 0.9	NS

ANOVA, analysis of variance; NS, not significant.
*Values are expressed as mean ± SE (n = 30). Significant differences compared with measurements at 0 wk were determined by one-way repeated measures ANOVA from 0 to 12 wk, followed by the paired t test.

Table 2
Parameters related to glucose metabolism and insulin resistance

		Treatment			Post-treatment	ANOVA
	0-wk	4-wk	8-wk	12-wk	4-wk	
FPG (mg/dL)	116 ± 1	111 ± 2*	111 ± 2*	112 ± 2	115 ± 2	P-value <0.05
GA (%)	16.2 ± 0.4	15.9 ± 0.4*	15.8 ± 0.4†	16.1 ± 0.4	15.9 ± 0.5*	P-value <0.01
HbA1c (%)	5.90 ± 0.09	6.00 ± 0.09	5.92 ± 0.11	5.87 ± 0.10	5.98 ± 0.09	P-value <0.05
Insulin (μU/mL)	10.4 ± 1.8	7.7 ± 1.2	8.0 ± 1.2	6.9 ± 1.0*	13.7 ± 4.1	P-value < 0.05
HOMA-IR	2.95 ± 0.51	2.16 ± 0.35	2.18 ± 0.31	1.91 ± 0.28*	3.90 ± 1.18	P-value <0.05
QUICKI	0.345 ± 0.007	0.358 ± 0.007	0.359 ± 0.008	0.362 ± 0.007*	0.342 ± 0.007	P-value <0.05

ANOVA, analysis of variance; FPG, fasting plasma glucose; GA, glycoalbumin, HbA1c, whole blood glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.
Values are expressed as mean ± SE (N = 30). Significant differences compared with measurements at 0 wk were determined by one-way repeated measures ANOVA from 0 to 12 wk, followed by the paired t test or the Wilcoxon signed rank test with Bonferroni correction (*$P < 0.05$; †$P < 0.01$).

Effects of OLL2712 on chronic inflammation

Table 3 shows the changes in serum proinflammatory cytokine levels. Serum MCP-1 levels were significantly reduced at the 4-, 8-, 12-wk, and post-treatment time points. Serum IL-6 levels were significantly reduced at the 8-wk treatment time point and tended to be lower at the 4-wk treatment time points. Other cytokine levels did not change significantly throughout the study. MCP-1 and IL-6 are proinflammatory cytokines secreted abundantly from the adipose tissue with chronic inflammation [14,15]. These results suggested that OLL2712 ingestion might suppress chronic inflammation in the adipose tissue.

Characteristics of participants with decreased blood glucose levels after OLL2712 ingestion

We performed a stratified analysis by serum proinflammatory cytokine levels at baseline to investigate the association between decrease of blood glucose levels and suppression of chronic inflammation. Because there are no criteria for defining the extent of chronic inflammation based on serum proinflammatory cytokine levels, we divided the participants into two groups: those with serum proinflammatory cytokine levels above or below the mean value of all participants. The reduction in fasting plasma glucose levels was prominent in participants with serum MCP-1 or IL-6 levels higher than the average of all participants at baseline. Significantly decreased fasting plasma glucose levels, HOMA-IR, and proinflammatory cytokine levels were observed in these individuals but not in those with low inflammation (Fig. 2). Many of those with high inflammation also had IR (HOMA-IR ≥2) at baseline (Fig. 2), which supports the validity of this stratification method.

Effects of OLL2712 on other parameters related to metabolic disorders

Other parameters related to metabolic disorders are shown in Table 4. Body fat percentage was significantly reduced at the

Table 3
Serum proinflammatory cytokine levels

		Treatment			Post-treatment	ANOVA
(pg/mL)	0-wk	4-wk	8-wk	12-wk	4-wk	
MCP-1	15.2 ± 5.4	1.5 ± 0.8†	3.6 ± 1.7*	1.2 ± 1.2†	1.1 ± 0.9*	P-value <0.05
IL-6	1.89 ± 0.42	1.27 ± 0.23	1.21 ± 0.21*	1.37 ± 0.26	1.23 ± 0.22	P-value <0.05
IL-8	4.99 ± 0.52	5.22 ± 0.52	5.08 ± 0.40	4.51 ± 0.36	4.25 ± 0.32	NS
TNF-α	2.30 ± 0.57	2.24 ± 0.54	2.03 ± 0.47	1.75 ± 0.41	1.51 ± 0.48	NS
IL-1β	0.30 ± 0.05	0.29 ± 0.04	0.31 ± 0.04	0.28 ± 0.03	0.22 ± 0.03	NS
IL-17	8.56 ± 1.70	9.25 ± 4.02	12.31 ± 3.34	9.24 ± 2.32	10.85 ± 4.43	NS

ANOVA, analysis of variance; IL, interleukin; MCP, monocyte chemotactic protein; NS, not significant; TNF, tumor necrosis factor.
Values are expressed as mean ± SE (n = 30). Significant differences compared with values at 0 wk were determined by performing one-way repeated measures ANOVA from 0 to 12 wk, followed by the paired t test or the Wilcoxon signed rank test with Bonferroni correction (*$P < 0.05$; †$P < 0.01$).

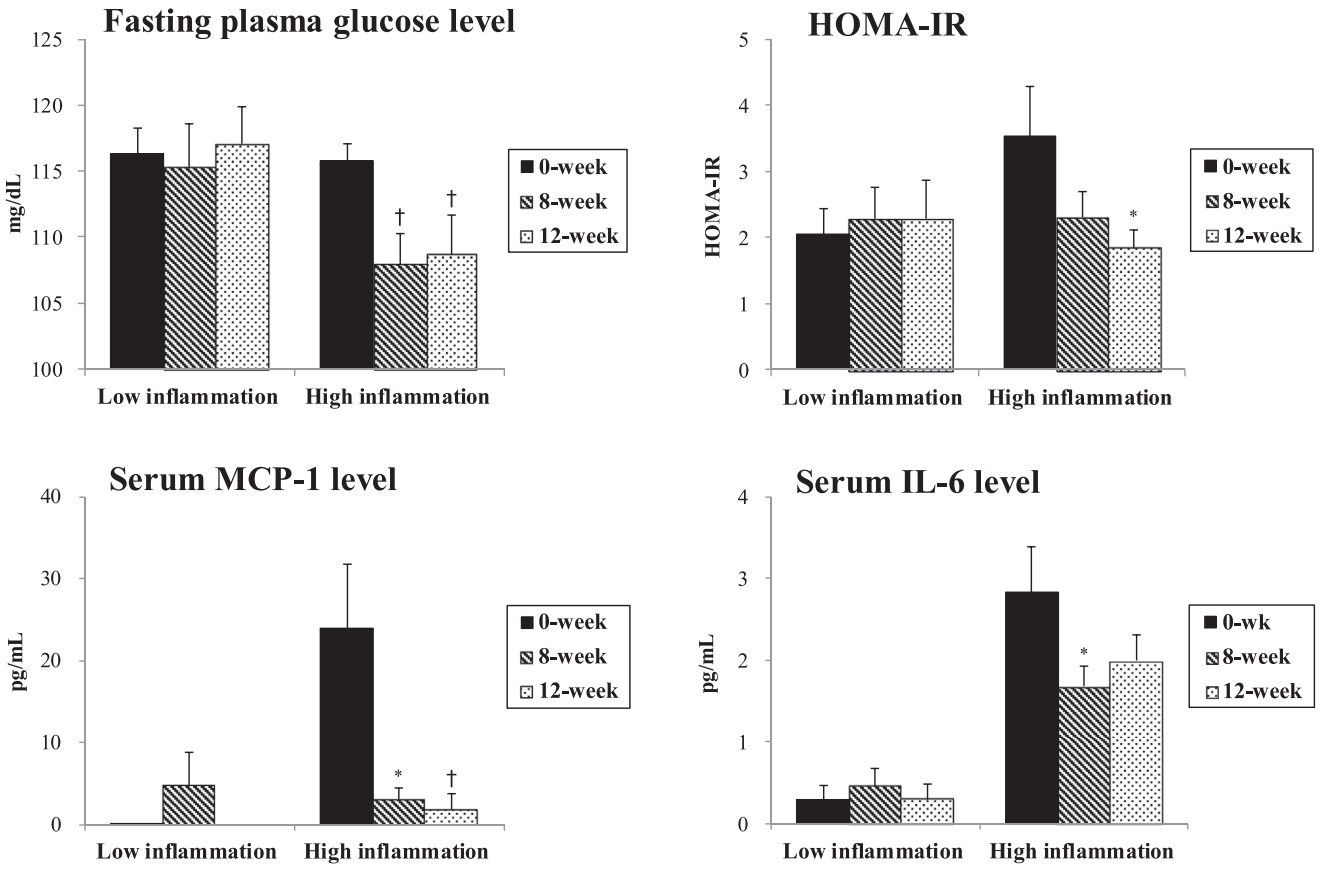

Fig. 2. Stratified analysis by serum proinflammatory cytokine levels in prediabetic individuals treated with OLL2712 beverage. Low inflammation: Individuals with serum MCP-1 and IL-6 levels lower than the average of all participants at baseline (n = 11; 8 men, 3 women). High inflammation: Individuals with serum MCP-1 or IL-6 levels higher than the average of all participants at baseline (n = 19; 14 men, 5 women). Significant differences compared with values at 0 wk were determined by the paired *t* test or the Wilcoxon signed rank test with Bonferroni correction (*$P < 0.05$; †$P < 0.01$). HOMA-IR, homeostasis model assessment-insulin resistance; IL, interleukin; MCP, monocyte chemotactic protein.

8- and 12-wk treatment time points but not at the post-treatment time point. Serum TC levels were significantly reduced at the 8-wk treatment points. The others did not change significantly from 0 to 12 wk by ANOVA.

Discussion

In the present study, we demonstrated that the 12-wk ingestion of a beverage containing heat-killed OLL2712 cells improved fasting plasma glucose levels, GA, HOMA-IR, and QUICKI in individuals who are prediabetic compared with baseline levels (Table 2). These beneficial effects were prominent in participants with high baseline serum proinflammatory cytokine levels, and these cytokine levels were reduced by ingesting OLL2712 cells (Fig. 2).

Previously, we selected OLL2712 as an optimal anti-inflammatory LAB strain, as it exhibited the highest IL-10-inducing activity for immune cells among our LAB library [13]. The IL-10-inducing activity of heat-killed OLL2712 cells was higher than live cells. We also

Table 4
Parameters of lipid metabolism and blood pressure

		Treatment			Post-treatment	
	0 wk	4-wk	8-wk	12-wk	4-wk	ANOVA
BW (kg)	70.3 ± 2.6	69.9 ± 2.5	70 ± 2.5	70.1 ± 2.5	70.4 ± 2.5	NS
BMI (kg/m^2)	25.3 ± 1	25.1 ± 1	25.1 ± 1	25.2 ± 1	25.3 ± 1	NS
BFP (%)	26.1 ± 1.7	25.5 ± 1.8	25.4 ± 1.8*	25.4 ± 1.7*	25.7 ± 1.9	*P*-value <0.05
TC (mg/dL)	215 ± 7	212 ± 7	204 ± 6*	207 ± 6	212 ± 6	*P*-value <0.05
LDL-C (mg/dL)	131 ± 7	129 ± 7	123 ± 6	130 ± 6	132 ± 6	NS
HDL-C (mg/dL)	60 ± 3.7	59.8 ± 3.5	59.2 ± 3.3	60.6 ± 3.4	60.7 ± 3.5	NS
TG (mg/dL)	124 ± 11	115 ± 11	125 ± 12	118 ± 12	128 ± 14	NS
NEFA (mEq/L)	0.555 ± 0.043	0.512 ± 0.039	0.470 ± 0.031	0.533 ± 0.040	0.541 ± 0.033	NS
SBP (mm Hg)	122 ± 3	117 ± 3	118 ± 3	118 ± 3	122 ± 3	NS
DBP (mm Hg)	75.2 ± 2.1	73.3 ± 2.1	73.6 ± 2	75.6 ± 1.9	77.3 ± 2.1	NS

ANOVA, analysis of variance; BFP, body fat percentage; BMI, body mass index; BW, body weight; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NEFA, non-esterified fatty acids; SBP, systolic blood pressure; NS, not significant; TC, total cholesterol; TG, triacylglycerol.
Values are expressed as mean ± SE (*n* = 30). Significant differences compared to values at 0 wk were determined by one-way repeated measures ANOVA from 0 to 12 wk, followed by the paired *t* to test or the Wilcoxon signed to rank test with Bonferroni correction (*$P < 0.05$; †$P < 0.01$).

succeeded in enhancing this property by optimizing their culture conditions [19]. OLL2712 cells, used in this study, are presumed to possess a particularly high anti-inflammatory activity. Because chronic inflammation is considered to be a primary cause of metabolic disorders, the anti-inflammatory activity is deduced to be an important mechanism of action for LAB in preventing or treating metabolic disorders [8,9]. However, to the best of our knowledge, no previous clinical studies have shown that certain LAB improved glucose metabolism by suppressing inflammation. In this study, we found that many participants who exhibited decreased fasting plasma glucose levels with intervention showed high baseline levels of serum proinflammatory cytokines; in these individuals, inflammation and IR also were improved by OLL2712 ingestion. Although the causal relationship is unclear, the results of the stratified analysis suggested that OLL2712 might exert antidiabetic effects by suppressing proinflammatory cytokine production.

Numerous studies have investigated the correlation between proinflammatory cytokine levels and metabolic disorders. Serum MCP-1 levels increased proportionately with the degree of obesity and were reduced by receiving treatment for type 2 diabetes mellitus [22,23]. It has been reported that serum IL-6 levels are positively correlated with metabolic syndrome [24,25]. These data indicate that high serum levels of these proinflammatory cytokines are involved in the development of human IR and hyperglycemia. In our previous studies, the administration of heat-killed OLL2712 cells significantly suppressed these proinflammatory cytokine levels in both visceral adipose tissue and the serum of KKAy mice [13,19]. The suppression of these proinflammatory cytokines by heat-killed OLL2712 cells were also confirmed in a co-culture system comprising 3-T3-L1 adipocytes and RAW264.7 macrophages [13]. In the present study, we demonstrated that the administration of OLL2712 cells to humans resulted in a significant decrease in serum MCP-1 levels and tended to lower serum IL-6 levels (Table 3).

Recently, Kawano et al. demonstrated that suppressing intestinal MCP-1 expression prevented or improved hyperglycemia through suppression of MCP-1 expression in visceral adipose tissue [26]. Moreover, the addition of an *Lactobacillus plantarum* strain has been reported to suppress excessive MCP-1 expression in an intestinal epithelial cell line [27]. In a previous study, we suggested that the cell wall components of OLL2712 activate toll-like receptor 2 in immune cells, which then induces IL-10 production [19]. IL-10 is known to suppress the production of proinflammatory cytokines including MCP-1 [14,15]. By integrating these results, we deduce that the ingested OLL2712 cells affect the intestinal immune system, induce IL-10 production in immune cells, and then suppress MCP-1 expression in the intestine and in visceral adipose tissue. However, in most of the participants in this study, serum IL-10 levels were below the detection limit (data not shown). Although IL-10 is produced to suppress inflammation, its level is quickly down regulated as inflammation is sufficiently suppressed [16]. Based on results from previous animal studies, we determined that it is necessary to observe reactions in a shorter period of time to confirm the IL-10-inducing activity of OLL2712 [13]. Regarding this, we plan to examine the detailed mechanism of action in further clinical trials, animal studies, and in vitro studies.

Some reports have suggested that the intake of LAB improves IR in rodents [18,28] and humans [9,29]. We reported that the administration of heat-killed OLL2712 cells significantly reduced blood glucose levels after insulin treatment in a diet-induced obesity mice model [18]. Andreasen et al. reported that the ingestion of *L. acidophilus* NCFM for 4 wk preserves insulin sensitivity [9]. In contrast, in a study by Tripolt et al., the ingestion of *L. casei* Shirota for 12 wk failed to improve insulin resistance in individuals with metabolic syndrome [30]. In the present study, we demonstrated that the administration of OLL2712 cells significantly improved HOMA-IR and QUICKI, which are popular IR indexes (Table 2). The improvement of HOMA-IR was prominent in individuals with chronic inflammation at baseline (Fig. 2). Chronic inflammation is known to inhibit insulin signaling and impair GLUT4 translocation to the cell membrane, thereby inducing IR [14,15,31]. Therefore, the ability of OLL2712 supplementation to improve IR was most likely due to the suppression of chronic inflammation.

This was a single-arm, open trial. There is an important limitation owing to the absence of a placebo group; however, we considered that this study could preliminarily evaluate the functionality of OLL2712 cells. The reasons were as follows: First, without any interventions, prediabetic individuals are known to have steadily worsening IR, which leads to an increase in blood glucose levels. Past clinical trials showed that blood glucose levels tended to be worse during the intake period in the placebo group [5–7]. Second, the period of intervention in this study was from June to October. It was reported for Japanese that the HbA1c levels were lowest in July, although they are stable from spring to autumn [32–34].

We confirmed through diet analysis that there were no changes in energy intake throughout the test period (Table 1). Participants described the type and amount of exercises every day in their life diaries. A physician in charge checked the diaries to confirm that there were no overall changes. Moreover, blood glucose levels decreased in accordance with improvement of IR and suppression of inflammation, only in individuals with chronic inflammation at baseline (Fig. 2). These improvements were no longer observed after stopping the ingestion of OLL2712 cells (Table 2). Considering all these, the beneficial effects observed in this study were considered to be the result of ingesting OLL2712 cells. However, we did not measure step counts of participants as a way to quantify their physical activity; this is one of the limitations of this study. Placebo-controlled trials are needed to prove the efficacy of OLL2712 cells. Based on the results of this study, we plan to conduct further studies with a randomized, double-blind, placebo-controlled design.

Conclusion

The ingestion of heat-killed OLL2712 cells has the potential to improve IR and glucose metabolism in prediabetic individuals. The ingestion of OLL2712 cells also suppressed serum MCP-1 and IL-6 levels, which are proinflammatory cytokines involved in the development of IR and hyperglycemia. Additionally, the result of the stratified analysis suggested that OLL2712 cells might exert antidiabetic effects by suppressing chronic inflammation.

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