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PROBIOTICS' EFFECT ON NUTRITIONAL STATUS, APPETITE HORMONES, AND INFLAMMATION IN PRE-OBESE WOMEN

PROBİYOTİKLERİN PRE-OBEZ KADINLARDA BESLENME DURUMU, AÇLIK-TOKLUK HORMONLARI VE İNFLAMASYON DURUMU ÜZERİNE ETKİSİ

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ABSTRACT

Objective: Obesity is one of the most common health problems in the world. The following methods are currently used to treat obesity: medical nutrition therapy, behavioral therapy, medical treatment, and surgical therapy. Discussions are still ongoing regarding whether changing the plasma levels of the hormones that regulate satiety and appetite can be used as a new add-on therapy to pre-existing obesity treatments to decrease food consumption. One possibility for changing the levels of the hormones that control hunger and satiety involves the use of probiotics. This study has been planned and conducted to examine the effects of probiotics on appetite, inflammation, and nutritional status in overweight individuals.

Materials and Methods: The study includes 35 overweight females aged 19-30 years old to who a questionnaire form had been applied prior to the study. Probiotics were given to these individuals for 8 weeks. Food consumption records and anthropometric measurements were taken and a body composition analysis conducted three times during the study. Inflammatory markers such as CRP, TNF-α, and IL-6 and the hormone analyses (i.e., leptin, adiponectin, cholecystokinin, ghrelin, GLP-1, and PYY) were evaluated at the beginning and end of the study using the ELISA method.

Results: The women were asked about their physical activity status, and their appetite hormones and inflammatory markers were analyzed both at the beginning and end of the study. When taken together, the study found the individuals' anthropometric measurements, inflammatory markers, and hunger hormone levels to have decreased significantly and their satiety hormone levels to have increased significantly after the use of probiotics ($p<0.05$). However, no significant changes occurred regarding their energy, macronutrients, fiber intake, or physical activity levels ($p>0.05$).

Conclusion: The study clearly shows an appropriate probiotic strain to be able to significantly affect anthropometric measurements, inflammatory markers, and appetite hormones in overweight individuals without any other intervention.

Keywords: Obesity, probiotics, nutritional status, hormones, inflammatory markers

ÖZ

Amaç: Obezite dünyadaki en yaygın sağlık sorunlarından birisidir. Obezite tedavisinde güncel yöntemler; tıbbi beslenme tedavisi, davranış terapisi, tıbbi tedavi ve cerrahi tedavidir. Mevcut obezite tedavilerine yeni bir ek tedavi olarak açlık tokluk hormonlarının plazma düzeylerinin değiştirilmesinin besin tüketimini azaltıp azaltmayacağı halen tartışılmaktadır. Açlığı ve tokluğu kontrol eden hormonların düzeylerini değiştirme yöntemlerinden birisi probiyotik kullanımıdır. Bu çalışma hafif şişman bireylerde probiyotiklerin iştah, inflamasyon ve beslenme durumu üzerindeki etkilerini incelemek amacıyla planlanmış ve yürütülmüştür.

Gereç ve Yöntem: Bu çalışmaya yaşları 19-30 arasında değişen 35 hafif şişman kadın dahil edilmiştir ve çalışma öncesinde anket formu uygulanmıştır. Probiyotikler katılımcılara 8 hafta boyunca verilmiştir. Çalışma sırasında 3 kez besin tüketim kayıtları, antropometrik ölçümler ve vücut kompozisyonu analizi yapılmıştır. CRP, TNF-α ve IL-6 gibi inflamatuar belirteçler ve hormon analizleri (Leptin, Adiponektin, Kolesistokinin, Ghrelin, GLP-1, PYY) ELISA yöntemiyle çalışmanın başlangıcında ve sonunda değerlendirilmiştir.

Bulgular: Çalışmanın başında ve sonunda fiziksel aktivite durumu sorgulanmış olup, açlık tokluk hormonları ve inflamatuar belirteçler değerlendirilmiştir. Çalışmanın sonunda başlangıç durumuna göre antropometrik ölçümlerde, inflamatuar belirteçlerde ve açlık hormon düzeylerinin önemli ölçüde azaldığını ancak probiyotik kullanımı sonrasında tokluk hormonu düzeylerinin istatistiksel olarak anlamlı arttığını tespit edilmiştir ($p<0,05$). Ancak enerji, makrobesin, lif alımı ve fiziksel aktivite düzeyinde istatistiksel olarak fark olmadığı tespit edilmiştir ($p>0,05$).

Sonuç: Çalışmamız, uygun probiyotik suşunun kilolu bireylerde başka herhangi bir müdahaleye gerek kalmadan antropometrik ölçümleri, inflamatuar belirteçleri ve iştah hormonlarını önemli ölçüde etkileyebileceğini açıkça göstermektedir.

Anahtar Kelimeler: Obezite, probiyotikler, beslenme durumu, hormonlar, inflamatuar belirteçler

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INTRODUCTION

Probiotics are healthy supplements consisting of live bacteria. The morphemes *pro* and *biota* that form the term probiotic mean "for life" (1). Over the past few years, probiotics have experienced tremendous growth. Probiotics are live bacteria that provide health benefits for their hosts (2). Additionally, oral probiotics have the ability to modify the composition of the intestinal microbiome, and this altered microbiome may have an impact on the host's inflammatory pathways as well as how they metabolize glucose and lipids (3). Furthermore, changes in the gut microbiome have been demonstrated in other contexts to influence these host responses (4). As a result, probiotics have been recommended as a treatment approach for obesity due to their ability to effectively lower waist circumference and body mass index (BMI) (5). Based on animal studies, the use of probiotics has been shown to positively impact the hormones that regulate appetite and satiety (6, 7). People need to change their lifestyle habits and adopt new ones to avoid becoming overweight. The most important lifestyle factor is eating habits. One of the main reasons why people gain weight is an imbalance between energy intake and energy expended. This balance requires modifying food consumption when the energy intake exceeds the energy expended (8). Individuals' eating habits are influenced by various factors, with the changes in the hormones regulating appetite and satiety having a particular impact on physical change and body weight. The peripheral control of food intake is managed by cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptides 1 and 2 (GLP-1 and GLP-2), ghrelin, and other hormones that are released by the gastrointestinal system. Among these hormones, ghrelin is the only orexigenic peptide that is known for increasing hunger. Other hormones known as anorexigenic peptides suppress appetite and send repletion signals (9). In fact, by enlarging the number of functional microorganisms in the intestinal microbiota and being involved in the intestinal lumen, probiotics oversee changes in the plasma levels of the hormones that are released from the gastrointestinal system for regulating appetite and satiety. Therefore, probiotics have been argued to play a significant role in controlling appetite and food consumption (10). The following methods are used for treating obesity: medical nutrition therapy, behavioral therapy, medical treatment, and surgical therapy. Behavioral and medical nutrition therapy are indispensable parts of treatment (11). Discussions are still ongoing regarding whether changing the plasma levels of the hormones that regulate satiety and appetite can be used as a new add-on therapy to pre-existing obesity treatments for decreasing food consumption. Of course, one possibility for changing the levels of the hormones that regulate appetite and satiety is the use of probiotics. However, current research in these direction instead involves animal experiments and only a limited number of clinical trials. Therefore, more studies are needed to clearly demonstrate the effects of probiotics on the hormones that regulate satiety and hunger (12). This study has been planned and conducted to observe the effects of probiotics on hunger and satiety hormones, inflammation, and nutritional status in overweight individuals.

MATERIALS and METHODS

Study design

The study is a prospective clinical study.

Participants

The study includes 35 healthy, overweight, female adult participants between 19-30 years of age. The inclusion criteria are that the participants have no chronic illnesses and a BMI between 25.00-30.00 kg/m^2 and to not be dieting for weight loss or any other purpose during the study. The exclusion criteria are being male, being pregnant, lactating, using tobacco or alcohol, chronic illnesses (mild allergies excepted), permanent use of medication, ingestion of antibiotics within three months of the first examination, having used probiotics for at least three months before the first examination, and the regular use of vitamin and mineral supplements. This research was conducted between September 2019-April 2020.

Procedures

The first stage of the study was carried out in the Nutrition and Diet Polyclinic of the Gazi University Faculty of Health Sciences Department of Nutrition and Dietetics. The study has included individuals living in Ankara. All individuals who were found to comply with the inclusion and exclusion criteria were explained the study in detail, and all who then agreed to participate in the study signed a voluntary consent form in accordance with the Declaration of Helsinki (World Medical Association, 1968). The study protocol was approved by the TOBB University of Economics and Technology Faculty of Medicine Clinical Research Ethics Committee (Approval no. 043 dated July 24, 2019).

The study has been planned in three stages. The first stage of the study is the acceptance stage and involves applying a questionnaire to the individuals. After receiving their anthropometric measurements, blood samples, food consumption records, and International Physical Activity Questionnaires taken, the participants started the probiotics usage (13). The researcher explained to them how to use probiotics, and providing the probiotics weekly ensured the follow-ups, which is the second stage involving taking the individuals' food consumption records and anthropometric measurements. The third stage is the final stage of the study, with the last interview also applying a questionnaire to the individuals; their anthropometric measurements, International Physical Activity Questionnaire, and blood samples were taken again, and then the individuals were recorded as having finished the study (13). The subjects were not given any dietary treatment and nutrition training during the study period. The study design is summarized in Figure 1. During the first interview, probiotics with no product label were given to the individuals in seven daily packs. Probiotics were re-delivered to the participants at their individual weekly interviews, during which their usage status was monitored. The study emphasizes the effectiveness of the combined strains on the obesity treatment, the given probiotic strains being *Lactobacillus acidophilus* L1 (NBIMCC-8759; 2.9x10^9 colony forming units [CFUs]), *Lactobacillus rhamnosus liobif* (ATCC-7469; 2.9x10^9 CFUs), *Bifidobacterium longum* LBL-01 (NBIMCC-8329;

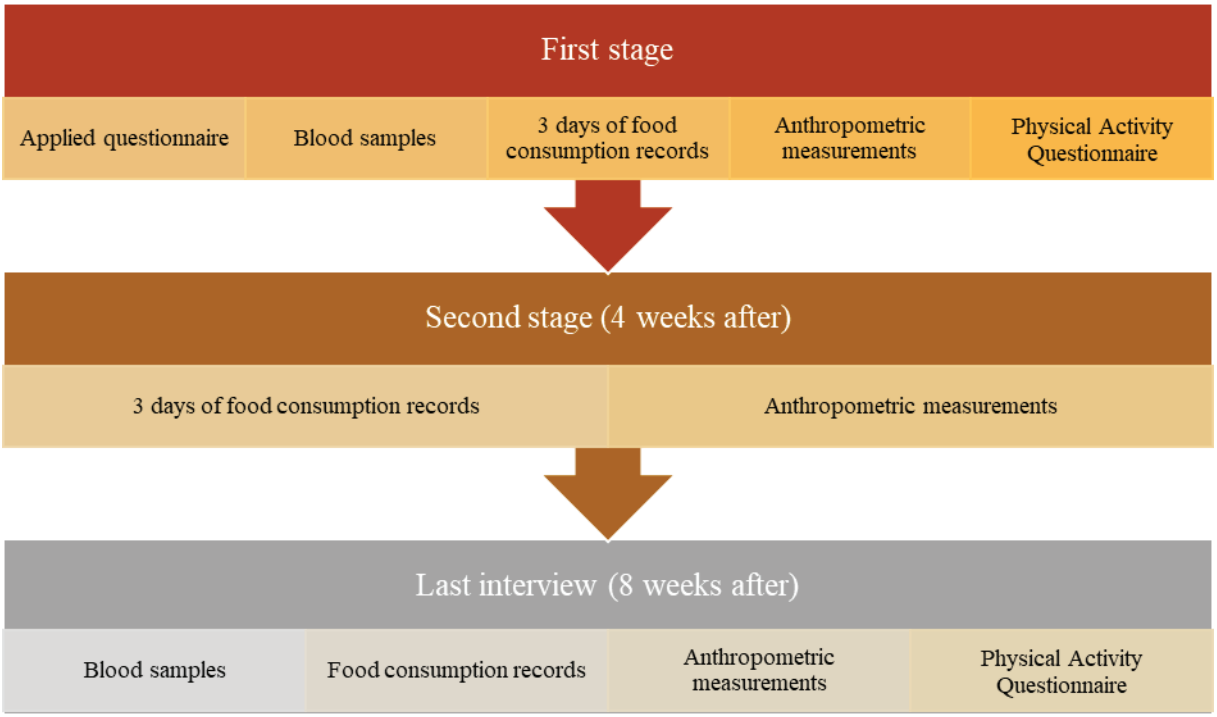

Figure 1: Study design

2 .9x10^{9} CFUs), and *Saccharomyces boulardii* (CNCM I-3799; 1.3x10^{9} CFUs).

The researcher received the anthropometric measurements (i.e., body weight [kg], height [cm], waist circumference [cm], hip circumference [cm], and neck circumference [cm]) of the individuals participating in the study in accordance with techniques of anthropometric measurements.

Body weight measurement was made using the Tanita BC 418 brand bioelectrical impedance analyzer (BIA). The individuals' measurements were made on an empty stomach in the morning with their shoes taken off and while wearing a minimal amount of clothing. The measurement was recorded at a sensitivity of 0.1 kg (14).

All individuals' food consumption records were taken for three consecutive days (two days on weekdays, one day on the weekend) during Week 0 of the study, during Week 4, and during the final week (Week 8) of the study. For cases where not enough information about the number of nutrients in the meals was available, the book titled *Standard Recipes* was used to illustrate the amount of food recommended for one portion of a meal (15). The *Beslenme Bilgi Sistemi* [nutritional information system] (BEBİS) package program was used to evaluate the obtained data (16).

For the biochemical analyses conducted within the scope of the study, two blood vials (approximately 7 mL) were drawn from all individuals, one at the end of the first interview and the second at the end of the study. Blood samples were taken from all individuals after eight hours of fasting. These blood samples were rapidly centrifuged for 10 min at 1000 x g using a YUDA 800D® brand centrifuge. After centrifugation, the supernatant portion was separated out, and the serum portion was transferred to four 1.5 mL Eppendorf tubes with the help of a Pasteur pipette. Serum samples were stored in a deep freezer at -32ºC until the time of analysis.

Blood samples were drawn at baseline and after eight weeks of intervention (final stage of the study) following an overnight fast. Inflammatory markers such as CRP, TNF-α, and IL-6 and hormones assays (i.e., leptin, adiponectin, cholecystokinin, ghrelin, GLP-1, PYY) were carried out using the enzyme-linked immunosorbent array (ELISA). Measurements for all serum parameters were done in duplicate, and mean concentrations were calculated.

Data analysis

The obtained data were evaluated in the package software IBM SPSS Statistics version 21 (IBM SPSS Corp., Armonk, NY, USA). Frequency and percentage distributions were examined for the demographic variables. In addition, descriptive statistics (e.g., means, standard deviations, minima, and maxima) are provided for the analyzed variables. The normality assumptions of the variables were examined using the Kolmogorov-Smirnov test. The independent samples t-test was used for independent variables with two levels, the dependent samples t-test was used for the dependent variables, and the one-way analysis of variance (ANOVA) F test was used for variables with three or more levels. The results were accepted at a 95% confidence interval and a significance level of $p<0.05$ (17).

RESULTS

After screening for the inclusion criteria, a total of 35 subjects were recruited. Their mean age is 22.8±0.48 years (Range=19-30). Table 1 shows the IPAQ-SF (MET-min/week) evaluation for each individual. For Week 0, the average IPAQ-SF (MET-min/week) result for the participants was 1,141.98±547.97, whereas at the end of the study (Week 8), the average was 1,201.07±503.46 (MET-min/week). No statistical difference was found between the first and last IPAQ-SF results (p=0.122).

Information on energy intake, macronutrient intake, and fiber intake are shown in Table 2. The average caloric intake was 1,609.37±310.51 kcal/day at the beginning of the study, 1,552.90±393.32 kcal/day in Week 4, and 1,535.52±364.79 kcal/day in Week 8. During the study, each participant had a similar average caloric intake (p>0.05). The study found no significant differences regarding daily energy intake, macronutrient intake, or fiber intake (p>0.05). Table 3 shows the participants' BMI and anthropometric assessment results. The average weight of all participants was 73.16±5.90 kg before the use of probiotics, 72.48±6.04 kg at Week 4, and 71.36±5.87 kg at the end of the study (p<0.05). The average BMI of all individuals was 27.32±1.30 kg/m^2 at the beginning of the study, 27.01±1.42 kg/m^2 in Week 4, and 26.64±1.37 kg/m^2 in Week 8 (p<0.05). All anthropometric measurements were significantly reduced by using probiotics (p<0.05) except the waist-hip ratio (p>0.05).

Table 4 shows the evaluation for each participant's biochemical parameters. The GLP1 and leptin levels significantly increased after probiotics intake, while the cholecystokinin, ghrelin, peptide YY, and adiponectin levels decreased significantly (p<0.05).

Table 4 also illustrates the evaluations regarding the inflammation markers and glucose and insulin levels. After the use of probiotics, the CRP, IL-6, and TNF-a levels dropped to 0.21 mg/L, 4.09 ng/L, and 40.64 ng/L, respectively. Statistically, the

Table 1: The evaluation of IPAQ-SF (MET-min/week)

	0 WK		8 WK			
	$\bar{X}_{\pm SD}$	Min-Max	$\bar{X}_{\pm SD}$	Min-Max	*t*	p
IPAQ (MET-min/WK)	1,141.98±547.97	330-2,772	1,201.07±503.46	495-2,772	-1.585	0.122

Paired samples t-test, MET: Metabolic unit, IPAQ: International Physical Activity Questionnaire, WK: week, p<0.05

Table 2: Individuals' daily intake of energy and nutrients

Nutritional information	0 WK		4 WK		8 WK		
	$\bar{X}_{\pm SD}$	Min-Max	$\bar{X}_{\pm SD}$	Min-Max	$\bar{X}_{\pm SD}$	Min-Max	p
Energy (kcal/day)	1,609.37±310.51	1,069.03-2,166.13	1,552.90±393.32	874.63-2,427.74	1535.52±364.79	881.94-2,326.92	0.374
Energy (kcal/Weight kg/day)	22.14±4.85	15.25-37.48	21.51±5.49	12.58-31.82	21.68±5.57	11.22-36.02	0.322
Protein (g/day)	63.12±11.50	37.66-84.63	59.43±19.03	25.18-95.57	61.15±13.25	28.61-91.37	0.395
Protein (%)	15.82±1.92	10.90-20.20	15.22±2.62	10.20-20.80	16.20±2.66	9.50-21.90	0.365
Animal proteins (g/day)	38.47±10.46	17.34-61.59	35.46±13.90	10.38-65.11	38.39±10.97	19.89-62.79	0.360
Vegetable protein (g/day)	24.64±6.76	14.18-42.37	23.97±8.23	8.55-40.52	22.75±7.86	8.72-39.80	0.362
Protein (g/Body weight kg/day)	0.83±0.16	0.57-1.25	0.87±0.27	0.38-1.31	0.81±0.18	0.41-1.41	0.586
Fat (g/day)	68.00±13.58	42.52-110.58	68.15±15.62	38.88-103.96	68.11±17.70	29.09-114.67	0.999
Fat (%/day)	38.26±4.61	30.60-47.60	40.33±7.12	30.60-59.70	40.05±6.00	29.10-58.70	0.391
Carbohydrate (g/day)	182.10±47.69	103.19-285.72	171.72±58.85	60.65-315.79	166.01±51.19	74.50-294.14	0.077
Carbohydrate /%)	44.91±5.34	33.10-54.80	43.49±7.36	26.70-56.30	42.81±6.07	29.20-58.70	0.324
Fiber (g/day)	17.44±6.00	7.24-32.22	16.59±6.06	5.26-30.82	16.05±6.20	5.55-30.99	0.315

ANOVA F test: p<0.05, kcal: Kilocalories, WK: Week

Table 3: Individuals' BMI and other anthropometric measurements

	0 WK			4 WK			8 WK				
Characteristic	$\bar{X}\pm SD$	**Min-Max**	**Median**	$\bar{X}\pm SD$	**Min-Max**	**Median**	$\bar{X}\pm SD$	**Min-Max**	**Median**	**F**	**p**
Body weight (kg)	73.16±5.90	57.80-90.90	73.10	72.48±6.04	57.60-91.20	72.90	71.36±5.87	56.50-87.00	71.30	56.33	<0.001*
BMI (kg/m^2)	27.32±1.30	25.29-29.60	27.40	27.01±1.42	24.11-29.56	27.71	26.64±1.37	24.62-29.32	26.67	42.15	<0.001*
Waist circumference (cm)	83.17±6.05	70-98	83	82.95±6.17	70-97	83	82.20±6.13	69-96	82	30.10	<0.001*
Hip circumference (cm)	105.95±5.83	93-121	106	105.37±6.06	93-122	105	104.54±5.85	93-120	104	35.53	<0.001*
Waist/Hip ratio	0.78±0.06	0.63-0.87	0.80	0.78±0.05	0.64-0.87	0.80	0.78±0.05	0.64-0.87	0.80	1.79	0.182
Body fat mass (%)	36.66±3.49	28.60-44.50	36.90	36.48±3.20	29.10-44.30	36.80	36±3.26	28.70-42.60	36.10	4.64	0.020*
Body fat mass (kg)	27±4.38	19.10-40.40	26.30	26.70±4.29	19.30-40.40	25.40	26.06±4.06	19.50-37	25.90	10.38	<0.001*
Body fat Free mass (kg)	45.94±3.44	36.80-54	45.60	45.86±3.02	38.30-52.50	45.80	45.38±3.10	38.70-52.90	45.20	2.5	0.110
Total body water (kg)	33.82±2.23	28.40-39.50	33.50	33.64±2.21	28-38.40	33.50	33.45±2.18	28.30-38.70	33.50	4.63	0.013*

ANOVA F test: p<0.05*, WK: Week

Table 4: Evaluation of individuals' biochemical parameters

	0 WK	8 WK	Difference (0 WK-8 WK)	p
	$\bar{X}\pm SD$	$\bar{X}\pm SD$		
Cholecystokinin (ng/L)	53.81±30.42	52.52±29.10	-1.31	<0.001*
GLP 1 (pmol/L)	79.32±43.88	80.16±43.15	0.86	<0.001*
Ghrelin (ng/ml)	4.92±2.84	4.80±2.65	-0.12	<0.001*
Leptin (ng/ml)	25.36±15.96	25.87±15.37	0.49	<0.001*
Peptit YY (pg/mg)	340.90±203.17	332.19±195.82	-8.71	<0.001*
Adiponectin (mg/L)	25.40±15.46	21.61±13.55	-3.78	<0.001*
Fasting Blood Glucose (mg/ dl)	92.57±10.87	92.37±8.57	-0.30	0.170
Insulin (mIU/L)	29.98±19.94	28.14±16.94	-1.83	<0.001*
CRP (mg/L)	2.36±1.47	2.15±1.50	-0.21	<0.001*
IL-6 (ng/L)	228.70±142.81	224.61±130.08	-4.09	<0.001*
TNF-α (ng/L)	369.29±241.98	328.64±195.56	-40.64	<0.001*

Dependent samples t test *p<0.05, GLP-1: Glucagon-like peptide-1, TNF-α: Tumor necrosis factor alpha, IL 6: interleukin 6, pmol: Picomole, ng: Nanogram, dL: Decilitre, mlU: Milliunit, WK: Week

reduction in the inflammation markers is significant (p<0.05). Furthermore, observations regarding the changes in glucose and insulin levels reveal a significant positive development for insulin (p<0.05), whereas blood glucose levels after fasting exhibited no significant results (p=0.870).

DISCUSSION

Gut microbiota are effective in the development and treatment of obesity. Eating habits are the most important reason for changes in microbiota. One effective way for increasing the

number of healthy microorganisms in microbiota is the use of probiotics (18). New methods have been developed for treating obesity in addition to pre-existing methods, and one recently discussed possible treatment method involves the use of probiotics. Studies have shown that manipulating the gut microbiota can be an alternative treatment model for obesity and that the use of probiotics can provide this effect (19). Food consumption and the levels of hunger-satiety hormones have been reported to only change through a change in gut microbiota using probiotics. Probiotic supplements have also been shown to improve individuals' anthropometric measurements (20).

Jung et al. researched the effects of probiotics on the adiposity of obese individuals. *Lactobacillus curvatus* HY7601 and *Lactobacillusplantarum* KY103 were used as the probiotic strains. Compared to the values at the beginning of their study, significant changes were observed in terms of weight, waist-hip ratio, and BMI through the use of probiotics without even changing physical activities or the amount of food consumed (21). Kadooka et al.'s study intended to evaluate the effects of the *Lactobacillus gasseri* SBT2055 strain on the adipocytes of obese individuals, comparing the anthropometric measurements from the beginning and end of the study over both the test and control groups. The reduction in body weight, BMI, and waist-hip ratios was considered significant in both groups (22). Minami et al.'s study further aimed to evaluate the effects of the *Bifidobacterium breve* strain on the body fat values of 80 overweight people and also identified their body fat, BMI, and waist-hip ratio values to have been reduced (23). Minami et al. as well as the other studies identified a reduction in body weight, BMI, and waist-hip ratio without even changing physical activity habits or the amount of food consumed. Only the reduction in anthropometric measurements for the waist-hip ratio was not statistically significant ($p>0.05$). The present study chose to use *Lactobacillus acidophilus* L1 (NBIMCC-8759; $2.9x10^9$ CFUs), *Lactobacillus rhamnosus liobif* (ATCC-7469; $2.9x10^9$ CFUs), *Bifidobacterium longum* LBL-01 (NBIMCC-8329; $2.9x10^9$ CFUs), and *Saccharomyces boulardii* (CNCM I-3799; $1.3x10^9$ CFUs) based on previous studies (20, 21, 23). As shown in the literature, this study found body weight and BMI to reduce significantly ($p<0.05$). The study also found the waist-hip ratio to show no significant change, similar to the previous literature (23). These results show the use of probiotics even without changing physical activities or the amount of daily caloric intake to be able to clearly improve anthropometric measurements. Yet, this study considers that study duration and the strains used as probiotics may vary the effects on anthropometric measurements and body composition.

An individual's food consumption is affected by many factors, with change in hunger and satiety hormones in particular being among the most important physiological factors affecting food consumption and body weight (9). The use of probiotics can lead to a change in hormone levels. Of course, the leptin, ghrelin, adiponectin, GLP-1, Peptide-YY and cholecystokinin hormone levels are known to be able to change by consuming probiotics (18).

Zarrati et al.'s study on overweight and obese individuals aimed to observe the extent to which the *Lactobacillus acidophilus* LA5, *Lactobacillus casei* DN001, and *Bifidobacterium lactis* BB12 strains affect inflammation markers and hormone levels by consuming yogurt with probiotics. The study found leptin levels to have reduced by the end of the research (24). Behrouz et al. conducted a study on overweight individuals with nonalcoholic high-fat livers in order to evaluate the effects of probiotics and prebiotics on leptin and adiponectin glycemic parameters. They gave the *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Bifidobacterium breve* strains to the probiotic group and 8 gr maltodextrin to the prebiotic group during the 12-week-long weekly follow-ups. At the end of the research, they showed the use of probiotics to have led to significant increases in leptin and adiponectin (25). Another study found obese individuals who'd used the *Pediococcus pentosaceus* LP28 strain over a period of 12 weeks to have shown no significant effects regarding their leptin and adiponectin levels (26). The current study also evaluated the effects of probiotics on cholecystokinin, GLP-1, ghrelin, leptin, PYY, and adiponectin levels. The comparison of the beginning and end of the study has shown the leptin and GLP-1 levels to have increased and the levels of cholecystokinin, ghrelin, peptide PYY, and adiponectin to have decreased. The changes in all hormone levels were statistically significant in the current study ($p<0.05$). The study has shown that taking probiotics without even changing eating habits or physical activities can change the levels of hormones regulating satiety and appetite. Therefore, the study can clearly speculate the use of probiotics to be able to have a positive impact on managing hormones; however, the results do not sufficiently indicate at which specific duration of probiotics intake this impact actually occurs.

Obesity is associated with changes in immunity, chronic low-grade inflammation, and high circulating proinflammatory cytokines. However, how obesity precisely triggers inflammation remains unclear. Several hypotheses have been proposed, one being that an overload of nutrients in adipocytes triggers intracellular stress, leading to the activation of inflammatory cascades. A second hypothesis suggests that overloading adipocytes with fat overwhelmingly increases the infiltration of macrophages. These processes can result in the subsequent differentiation and activation of cytotoxic T cells that initiate and proliferate inflammatory cascades. A third hypothesis suggests that, as adipose tissue grows, the tissues become relatively hypoxic. Hypoxia within adipose tissue can activate inflammatory pathways. A final hypothesis is that overloaded adipocytes can directly activate the immune pathogen sensors that cause chronic inflammation (27). Probiotics have a significant effect on the gut barrier by stimulating β cells to produce IgA (28). Probiotics influence the production of cytokine (29), and the inflammation period depends on pro-inflammation and anti-inflammation cytokines. In fact, a lower-level chronic inflammation period, which is typical for obesity, can be improved (30). Furthermore, the use of probiotics can diminish the levels of such cytokines as CRP, TNF-α, and IL-627. To evaluate inflammation markers with regard to the *L. Reuteri* strain, Hansen

et al. divided participants into two random groups, providing one group with the *L. Reuteri* strain and the other group with a placebo. They observed the effects for 12 weeks, and after comparing against the control group at the end of the study, they found no significant results regarding IL-1β, IL-6, IL-8, and IL-10 levels (31). Kullisaar et al.'s study exhibited the use of the *L. Fermentum* strain to lead to changes in lipid profiles and inflammation markers. Their research analyzed the inflammation marker IL-6, and when comparing the test results against the control group, they found a significant difference in the IL-6 levels (32). Kobyliak analyzed the extent to which probiotics affected the levels of diabetic individuals' resistance to insulin by providing them with the *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, and *Propionibacterium* strains for eight weeks. At the end of the research, Kobyliak found no significant differences in IL-6 and TNF-α appetite levels between the control (placebo) and test (probiotics) groups (33). Bernini et al.'s study aimed to evaluate the effects of the *Bifidobacterium lactis* strain on inflammation markers and on the lipid profile (34). Meanwhile, the current study's comparison between Week 0 and Week 8 found the levels for the pro-inflammatory factors CRP, IL-6, and TNF-α to have reduced significantly. Therefore, this study can state that, due to probiotics ability to improve inflammation markers, they can be used effectively as an alternative therapy.

Limitations

The study has several limitations. The first was not having a control group due to the emergence of COVID-19 as the study was being conducted. The second is the use of various different bacteria strains in the content of the probiotics may have had varying impacts on the study, as discussed above. Finally, the number of participants and duration of the study are also considered another limiting factor.

CONCLUSION

Studies investigating the effects of probiotics on health are increasing these days. One such research area involves investigating the effectiveness of probiotic usage in the treatment of obesity. According to this study's results, the use of probiotics with appropriate strainscan increase the success rate when treating obesity, in addition to other treatment approaches that are applied. However, more studies are needed in order to rule further on these findings.

Ethics Committee Approval: This study was approved by TOBB University of Economics and Technology Faculty of Medicine Clinical Research Ethics Committee (Date: 24.07.2019; Approval no. 043).

Informed Consent: Informed consent was obtained from each patients.

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