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Effects of Synbiotics Supplement on Body Weight and Fasting Blood Sugar Levels in Obese and Lean Subjects: A Randomized Placebo-Controlled Trial

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Covering Letter

November, 25 2020

Dear Dr. Rafaela Camacho Bejarano
Editor-in-chief
Enfermería Clínica Journal

I am submitting a manuscript for consideration of publication in Enfermería Clínica Journal. The manuscript is entitled "Effects of Synbiotics Supplement on Body Weight and Fasting Blood Sugar Levels in Obese and Lean Subjects: A Randomized Placebo-Controlled Trial ". It has not been published elsewhere and that it has not been submitted simultaneously for publication elsewhere. This study protocol was approved by the Medical Faculty Hasanuddin University Review Board, and all research participants gave informed consent. Authors declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The research was conducted after obtaining approval from the Health Research Ethics Commission of the Faculty of Medicine, Hasanuddin University (Approval number: 719/UN4.6.4.5.31/PP36/ 2019). The clinical trial has been registered at ClinicalTrials.gov (NCT number: 04642482).

The use of synbiotics (a combination of probiotic and prebiotic) to change the gut microbiota composition is a new approach to reduce the risk of obesity and glucose intolerance. But no study has examined whether the supplementation's positive effect is still there after the termination of the supplementation. Hence, this study aims to examine the effect of synbiotics supplementation on body weight and glucose tolerance of obese and lean subjects during and 2 months after cessation of the treatment. Besides, we also want to know whether the synbiotic supplement can affect body weight and fasting blood glucose of underweight lean subjects.

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Thank you very much for your consideration.

Sincerely yours,

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Research Article

Efectos del suplemento de simbióticos sobre el peso corporal y los niveles de azúcar en sangre en ayunas en sujetos obesos y delgados: un ensayo aleatorizado controlado con placebo

Effects of Synbiotics Supplement on Body Weight and Fasting Blood Sugar Levels in Obese and Lean Subjects: A Randomized Placebo-Controlled Trial

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Short Title: Effects of Synbiotic on Body Weight and Fasting Blood Glucose

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What is known

Obesity and type 2 diabetes have a strong correlation. Although many strategies and efforts to overcome obesity have been implemented, the percentage of individuals who lose weight and successfully maintain the loss has been estimated to be as small as 1 to 3 percent. Moreover, it is known that similar food intake and physical activity can lead to different weight gain or loss. This can be due to the human microbiota's different metabolic activities, including the different components of the gut microflora. Alterations of the microbiota's composition and function, termed dysbiosis, are common features of several pathologies, including metabolic diseases such as obesity and T2DM. Incretin hormones GLP-1 and GIP are released from enteroendocrine cells and stimulate insulin secretion. The fermentation action of gut microbiota in the colon could impact the number of enteroendocrine cells. Consuming a high-fat diet can decrease the number of bifidobacteria and lactobacilli, chronic systemic endotoxemia that may lead to metabolic diseases including type 2 DM.

What it contributes

The use of synbiotics (a combination of probiotic and prebiotic) to change the gut microbiota composition is a new approach to reduce the risk of obesity and glucose intolerance. Although results of the studies are still conflicting. Some studies reported synbiotic supplement reduced body weight in obese subjects and improved glucose tolerance, while other studies found no effects of the synbiotic supplements on body weight. Hence this study will contributes to the benefial effects of the synbiotic supplements. In addition, no study has examined whether the supplementation's positive effect is still there after the termination of the supplementation.

Moreover there is no study that evaluate the effect of synbiotic supplement in underweight/lean subjects. Therefore, this study aims to examine the effect of synbiotics supplementation on body weight and glucose tolerance of obese and lean subjects during and 2 months after cessation of the treatment. Besides, we also want to know whether the synbiotic supplement can increase body weight and affect fasting blood glucose of underweight/lean subjects.

Effects of Synbiotics Supplement on Body Weight and Fasting Blood Sugar Levels in Obese and Lean Subjects: A Randomized Placebo-Controlled Trial

Short Title: Effects of Synbiotic on Body Weight and Fasting Blood Glucose

Abstract

Objective: Evaluate the effects of the synbiotic supplement on body weight (BW), BMI, and fasting blood glucose (FBG) in obese and lean subjects.

Method: This study used a Randomized, Double-Blind Placebo-controlled design. Participants were allocated with randomization into 3 groups: Obese group with synbiotic supplementation; the obese group with placebo and underweight lean group, each group consist of 8 participants. BW, BMI, and FBG from vein were measured at baseline, 8 weeks after supplementation, and 4 weeks after the supplement's termination. Analysis of data using One-way Anova and Repeated Anova.

Results: There were no alteration in BW and BMI in obese (1.0 kg, p=0,721;0.434, p=0.662) and lean (0.375 kg, p=0.855;0.152, p=0.736) groups supplemented with synbiotics but there were significant increase in BW (3.38 kg, p<0.003) and BMI (1.37 kg/m^2, p<0.004) in control obese group. FBG significantly decreased by 6.125 mg/dL (p= 0.033) after synbiotic supplementation in obese group but not significantly changed in control obese (-0.016 mg/dL, p=0.066) and in lean group (0.593 mg/dL, p=0.331).

Conclusions: Although Body weight and BMI were unaltered by synbiotic supplement, it may prevent body weight increase over time in obese subjects. Synbiotic supplementation may lower FBG in obese subjects, yet body weight and BMI do not decrease. There were no significant effects of synbiotic supplementation on body weight, BMI, and fasting blood glucose in lean subjects.

Keywords: Synbiotic supplement, obesity, body weight, fasting blood sugar level

Resumen

Objetivo: Evaluar los efectos del suplemento simbiótico sobre el peso corporal (BW), el IMC y la glucemia en ayunas (FBG) en sujetos obesos y delgados.

Método: Este estudio utilizó un diseño aleatorizado, doble ciego controlado por placebo. Los participantes fueron asignados al azar en 3 grupos: Grupo obeso con suplementación simbiótica; el grupo obeso con placebo y el grupo delgado con bajo peso, cada grupo consta de 8 participantes. El peso corporal, el IMC y la FBG de la vena se midieron al inicio del estudio, 8 semanas después de la suplementación y 4 semanas después de la finalización del suplemento. Análisis de datos utilizando One-way Anova y Repeated Anova.

Resultados: No hubo alteración en el peso corporal y el IMC en los grupos obesos (1.0 kg, p = 0,721; 0.434, p = 0.662) y magros (0.375 kg, p = 0.855; 0.152, p = 0.736) suplementados con simbióticos pero hubo aumento del peso corporal (3,38 kg, p <0,003) y del IMC (1,37 kg / m2, p <0,004) en el grupo de control de obesidad. FBG disminuyó significativamente en 6,125 mg / dL (p = 0,033) después de la suplementación con simbióticos en el grupo de obesos, pero no cambió significativamente en el grupo de control con obesidad (-0,016 mg / dL, p = 0,066) y en el grupo magro (0,593 mg / dL, p = 0,331).

Conclusiones: Aunque el peso corporal y el IMC no se vieron alterados por el suplemento simbiótico, puede prevenir el aumento de peso corporal con el tiempo en sujetos obesos. La suplementación con simbióticos puede reducir la FBG en sujetos obesos, pero el peso corporal y el IMC no disminuyen. No hubo efectos significativos de la suplementación simbiótica sobre el peso corporal, el IMC y la glucosa en sangre en ayunas en sujetos delgados.

Palabras clave: Suplemento simbiótico, obesidad, peso corporal, nivel de azúcar en sangre en ayunas.

Introduction

Obesity is a public health problem that affects at least 650 million adults worldwide in 2016 and represents the fifth leading cause of death globally.[1,2] More than 1.9 billion adults aged 18 years and older were overweight. As many as 39% of adults aged 18 years and over were overweight. Overall, about 13% of the world's adult population were obese.[1] Similar to obesity, the prevalence of diabetes has increased immensely worldwide and is becoming a leading cause of death in many countries. The International Diabetes Federation (IDF) highlights that 425 million people around the world, or 8.8% of adults 20–79 years, are estimated to have diabetes.[2]

Reduced energy expenditure plays an important role in developing obesity by decreasing resting energy expenditure, energy activity, diet-induced thermogenesis, or a combination of all of these components. It thus contributes to positive energy balance and subsequent weight gain.[3]

Overweight and obesity are clearly the results of a complex set of genetic, behavioral, and environmental factors. Although many strategies and efforts to overcome obesity have been implemented, the percentage of individuals who lose weight and successfully maintain the loss has been estimated to be as small as 1 to 3 percent.[4] Moreover, it is known that comparable food intake and physical activity can lead to different weight gain or loss.[5] This can be due to the human microbiota's different metabolic activities, including the different components of the gut microflora.[6]

The preservation of normal and healthy gut microbiota plays a critical role in maintaining good health. *Bacteroidetes* and *Firmicutes*, including the *Ruminococcus,* *Lactobacillus*, and *Clostridium* genera species, constitute over 90% of the known phylogenetic categories and dominate the healthy intestinal microbiota.[7] Alterations of the microbiota's composition and function, termed dysbiosis, are common features of several pathologies,

including metabolic diseases such as obesity and T2DM.[2] Incretin hormones, mainly represented by glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), are gut peptides released from enteroendocrine cells. They are secreted into the blood stream and rapidly stimulate insulin secretion from beta cells in response to nutrients to control meal-related glycemic excursions.[8] The fermentation action of gut microbiota in the colon could impact the number of enteroendocrine cells. The addition of non-digestible carbohydrates, such as oligofructose, has been shown to improve glucose tolerance, insulin response and reduce food intake in mice and humans. These beneficial metabolic effects have been linked to higher plasma GLP-1 levels.[9–11]

Consuming a high-fat diet can decrease the number of bifidobacteria and lactobacilli, chronic systemic endotoxemia that may lead to metabolic diseases.[6]

Microbiota is a collection of all microorganisms present in the human body. Approximately 5% of the body weight is the microbiota that inhabits the human intestine. One gram of feces contains about 2 billion microbiota cells and consists of 500 types. The number of genes in the gut microbiota has 100-150 times greater than a person's genome.[12]

The use of synbiotics (a combination of probiotic and prebiotic) to change the gut microbiota composition is a new approach to reduce the risk of obesity and glucose intolerance.[13–15] But no study has examined whether the supplementation's positive effect is still there after the termination of the supplementation. Hence, this study aims to examine the effect of synbiotics supplementation on body weight and glucose tolerance of obese and lean subjects during and 2 months after cessation of the treatment. Besides, we also want to know whether the synbiotic supplement can affect body weight and fasting blood glucose of underweight lean subjects.

Materials and Methods

Study Participants, Clinical Trial Design and Synbiotic Supplement

This double-blind, randomized controlled trial (RCT) was conducted at the Faculty of Medicine, Muhammadiyah University of Makassar, and Hasanuddin University Medical Research Unit (HUMRC) Hasanuddin University Teaching Hospital. Participants who participated in the study were assessed for eligibility if they met the inclusion criteria: individuals with a BMI of ≥ 25 kg / m2 and a BMI of <18.5 kg / m2. Exclusion criteria include the following: subjects with type 1 and 2 diabetes, taking drugs that interfere with blood sugar levels or gut-microbiota composition such as corticosteroids, antibiotics, prebiotics, probiotics, or synbiotics 6 months before. All participants gave written consent to participate in the study, which was approved by the ethics committee of Hasanuddin Makassar University (Approval number: 719/UN4.6.4.5.31/PP36/ 2019). The clinical trial has been registered at ClinicalTrials.gov (NCT number: 04642482).

Participants were initially evaluated for baseline characteristics (anthropometry, fasting blood glucose, FBG). Body mass index (BMI) was calculated using body weight and height measured with bare feet and minimal clothing using a stadiometer and an electronic scale. FBG was measured from the cubital blood vein after 10 hours of overnight fasting. Participants were allocated with randomization into 3 groups: the Obese group with synbiotic supplementation, the obese group with placebo, and the underweight lean group. Participants and researchers were blinded to the type of intervention. Each participant group with synbiotic supplementation received 1 pack of Rillus® synbiotic (containing 10^9 CFU of live cells: Lactobacillus Plantarium 8.55 mg, Streptococcus Thermophillus 8.55 mg, Bifidobacterium bifidum 2.5 mg and 480 mg Fructooligosaccharide for 8 weeks. The control obese participants group received a placebo supplement containing maltodextrin similar to the appearance and the same energy

content as the synbiotic supplement. After 8 weeks of treatment and 4 weeks after cessation of the treatments, we re-evaluated body weight, BMI dan FBG.

Statistical analysis

The statistical test used SPSS, v.25. The data normality test was carried out before performing the statistical test. All data have normal distributions. Statistical tests were performed using the One way ANOVA test for baseline characteristics and post-hoc Tukey and repeated ANOVA tests with post-hoc Bonferroni pairwise comparison test to assess differences of body weight, BMI, and Fasting blood glucose before the intervention, 8 weeks after the intervention, and 4 weeks after the intervention was stopped. The results were expressed as mean ± SD, and mean differences were considered significant at $p < 0.05$

Results

In this placebo-controlled intervention clinical trial, the effects of the synbiotic supplement on body weight, BMI, and FBG were evaluated in human subjects during 8 weeks supplementation and 4 weeks after the supplement's cessation.

Fifty participants enrolled in this study from October 2019 to December 2019. Twenty-six participants were excluded for the following reasons: 16 not meeting inclusion criteria, 6 declined to participate, and 4 for other reasons. The remaining 24 participants were randomly assigned into 3 groups: 8 obese subjects with the synbiotic supplement, 8 control obese subjects, and 8 lean subjects with the synbiotic supplement.

Baseline characteristic of the study groups

At the beginning of the study, the 3 groups; obese participants with synbiotic treatment (obese+syn), obese participants with placebo treatment (Control obese), and lean participants with synbiotic treatment (Lean+syn), were examined for anthropometry (height, body weight,

and body mass index (BMI)) and fasting blood glucose. The average age of the participants was 20.16 years and was comparable between all groups. Gender was equally distributed among and within groups. The average Body weight (BW) and Body mass index (BMI) of the obese groups were not significantly different, but they were higher than those of the lean group (Table 1). The obese+syn and control obese groups had BMI of 32.88±5.21 kg/m^2 and 32.53±3.15 kg/m^2, respectively, whereas the lean+syn group had a BMI of 17.63±1.64 (p<0.001). The BMI difference between the obese and the lean groups reflected a significant difference in their fasting blood glucose (FBG). The obese+ syn and control obese groups had FBG of 113.12±8.03 mg/dL and 106.63±6.47, respectively, whereas the lean+syn group had FBG of 104.31±4.19 (p<0.033)

Effects of synbiotics supplementation on body weight and BMI

There were no significant alterations of body weight and BMI in obese subjects (Table 2 and Figure 1) and lean group (Table 2 and Figure 3) after 8 weeks supplementation with synbiotics and 4 weeks after cessation of the supplementation. In contrast, significant weight gain of 3.375 kg (p<0.001) and increased BMI of 1.373 (p<0.002) were observed in the control obese group treated with placebo (Table 2 and Figure 2).

Effects of synbiotics supplementation on fasting blood glucose

There was a significant reduction of FBG in obese subjects supplemented with synbiotic by 6.125 mg/dL (p<0.003) on week12 (Table 2 and Figure 2), but there was no significant change of FBG in the control obese group treated with placebo (Table 2 and Figure 2) and neither in the lean group with synbiotic supplementation (Table 2 and Figure 3).

Side effects

During the experiment, all groups showed no adverse effects as a result of being given synbiotics. In addition, there are no unwanted clinical symptoms, including diarrhea and constipation.

Discussion

This study examined the comparative effect of synbiotics on the anthropometric profile, and glycemic control among treated obese, control obese and lean subjects.

The gut microbiota plays an important role in normal bowel function and health maintenance.[16] Studies in animal models and humans have shown that a high-fat diet modulates gut microbiota and increases circulating LPS levels.[17] Previous research has also shown that synbiotics can alter appetite.[18] In this study, 4 out of 8 subjects in the obese group with synbiotic supplementation also reported decreased appetite but no weight loss. However, they were able to maintain their body weight throughout the study period. Similar trends in BW and BMI were observed in the lean group treated with synbiotics. This is in line with the recent meta-analysis results reporting that oral supplementation with probiotics or synbiotics has a small effect of reducing waist circumference but no effect on body weight or BMI.[19] In contrast, other studies found a significant decrease over time of body mass, BMI, waist circumference, and body fat mass after 3 months of synbiotic supplementation, and these were associated with a decrease in *Bifidobacterium* abundance.[13,20,21] On the other hand, in the obese control group of this study, there was a slight increase yet significant in body weight until 4 weeks after the study intervention was terminated. Interestingly, FBG significantly decreased in the obese+synbiotic group but not in the lean+synbiotic group. Similarly, Sergeev et al. found an association between a decrease over time in blood glucose and an increase in *Lactobacillus* abundance, particularly in the obese+synbiotic group.[13,20]

As BW and BMI increased, FBG also significantly increased in the obese control group in week 8 but not in week 4 after the termination of intervention. Body weight and BMI in obese subjects tend to increase over time and deteriorate FBG and may lead to type 2 diabetes or other metabolic syndrome's components.[22]

Conclusions

Although body weight and BMI were unaltered by synbiotic supplement, it may prevent body weight increase over time in obese subjects. Synbiotic supplementation may lower fasting blood glucose in obese subjects, yet body weight and BMI do not decrease. There were no significant effects of synbiotic supplementation on body weight, BMI, and fasting blood glucose in lean subjects.

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Conflict of Interest

The authors declare no conflict of interest.

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Tabla (Table)

Table 1. Baseline anthropometry and fasting blood glucose in study groups

Parameters	Groups			
	Obese + Synbiotic	Control Obese	Lean + Synbiotic	*p*
n	8	8	8	NA
Men	4	4	4	NA
Women	4	4	4	NA
Age (year)	20.25±0.71	20.50±1.20	19.75±0.46	0.09
Height (m)	1.57±0.39	1.58±7.10	1.62±0.06	0.095
Body weight (kg)	81.25±13.23	88.80±7.10	46.63±6.76	< 0.001
BMI (kg/m^2)	32.88±5.21	32.53±3.15	17.63±1.64	< 0.001
FBG (mg/dL)	113.12±8.03	106.63±6.47	104.31±4.19	0.033

Data were expressed as mean ± SD. Statistical analysis with One way ANOVA. $p < 0.05$ was considered significant. BMI, Body Mass Index; FBG, Fasting Blood Glucose. NA, not applicable

Table 2. Post-hoc analysis of baseline anthropometry and fasting blood glucose in study groups

Parameter	Group	Difference in mean (95% CI)	*p*
BW (kg)	OS vs CO	-0.38 (-11.61-12.36)	0.997
	OS vs LS	34.63 (22.64-46.61)	<0.001
	CO vs LS	34.25 (22.27-46.23)	<0.001
BMI (kg/m^2)	OS vs CO	0.35 (-4.24-4.94)	0.979
	OS vs LS	15.26 (10.67-19.85)	<0.001
	CO vs LS	14.90 (-4.94-4.24)	<0.001
FBG (mg/dL)	OS vs CO	6.49 (-14.59-1.61)	0.132
	OS vs LS	8.81(0.71-16.91)	0.032
	CO vs LS	2.32 (-5.78-10.42)	0.754

Data were expressed as mean ± SD. Statistical analysis with one way ANOVA and post-hoc tukey. $p < 0.05$ was considered significant. BMI, Body Mass Index; FBG, Fasting Blood Glucose. OS: Obese + Synbiotics; CO: Control Obese; LS: Lean + Synbiotics.

Table 3. Anthropometric changes and glycemic parameters before intervention (0), 8 months after intervention (8) and 1 month after intervention was terminated (12)

Parameter	Obese + Synbiotics			*p*	Obese control			*p*	Lean +Synbiotics			*p*
	0	8	12		0	8	12		0	8	12	
BW (kg)	81.25±13.23	81.88±11.74	82.25±12.33	0.365	80.88±7.10	83.25±7.14	84.25±6.54	0.001	46.62±6.76	47.25±6.67	47±6.16	0.432
BMI (kg/m^2)	32.88±5.20	33.16±4.79	33.32±5.06	0.335	32.53±3.15	33.50±3.31	33.90±3.16	0.002	17.63±1.48	17.86±1.48	17.78±1.39	0.425
FBG (mg/dL)	113.12±8.03	108.56±4.66	107.00±4.62	0.003	106.63±6.47	106.74±6.50	106.75±6.45	0.066	104.31±4.19	104.99±4.27	103.72±3.34	0.331

Data were expressed as mean ± SD. Statistical analysis with Repeated ANOVA and post-hoc paired wise test. $p < 0.05$ was considered significant. BMI, Body Mass Index; FBG, Fasting Blood Glucose.

Figura (Figure)

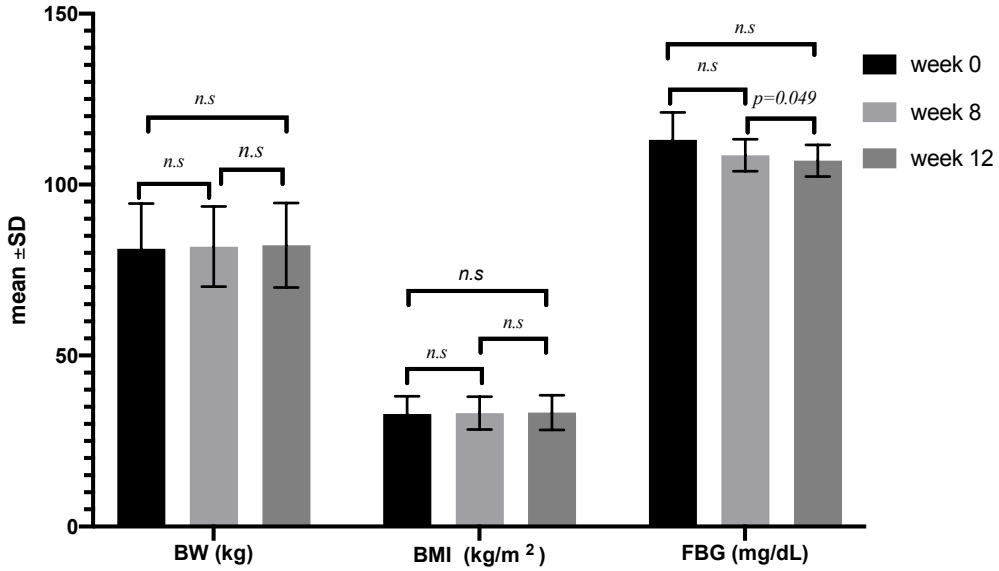

Figure 1. Alteration in Body Weight (BW), Body Mass Index (BMI), and Fasting Blood Glucose (FBG) before treatment (week 0), 8 weeks after treatment (week 8), and 4 weeks after treatment termination (week 12) in obese subjects with synbiotics treatment. Statistical analysis with Repeated ANOVA and post-hoc Bonferroni pairwise comparison test. *n.s*, not significant.

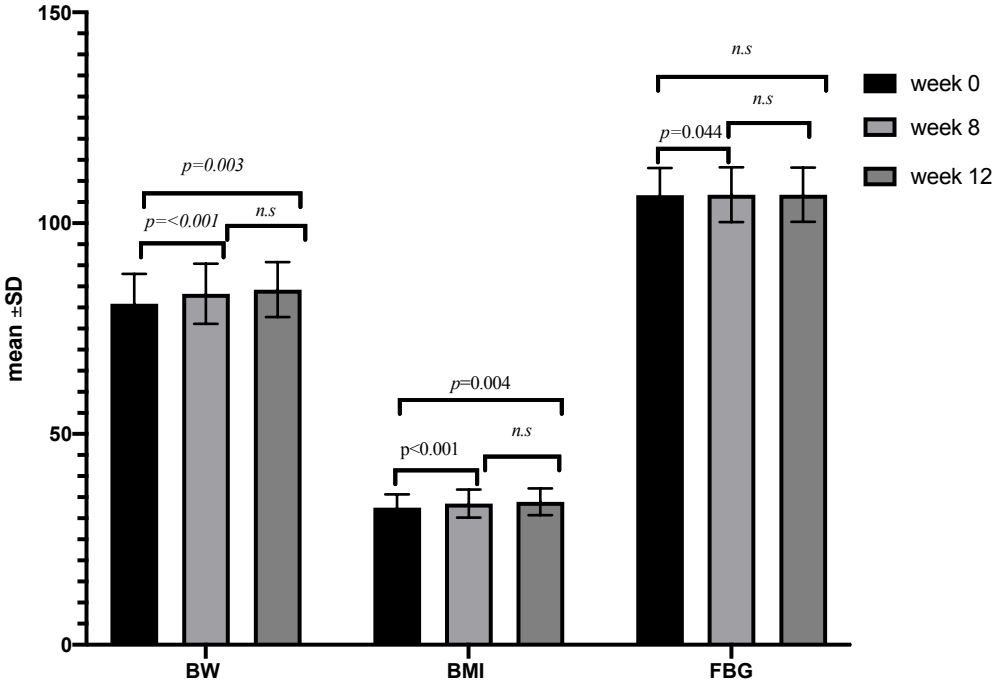

Figure 2. Alteration in Body weight (BW), Body Mass Index (BMI), and Fasting Blood Glucose (FBG) before treatment (week 0), 8 weeks after treatment (week 8), and 4 weeks after treatment termination (week 12) in control obese subjects with placebo treatment. Statistical analysis with Repeated ANOVA and post-hoc Bonferroni pairwise comparison test. *n.s*, not significant.

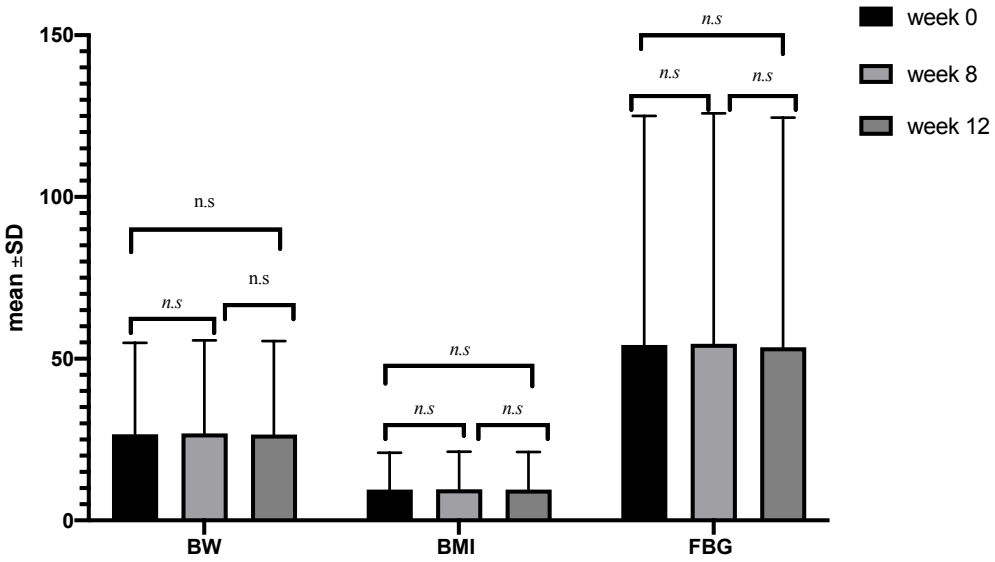

Figure 3. Alteration in Body weight (BW), Body Mass Index (BMI), and Fasting Blood Glucose (FBG) before treatment (week 0), 8 weeks after treatment (week 8), and 4 weeks after treatment termination (week 12) in non-obese subjects with synbiotics treatment. Statistical analysis with Repeated ANOVA and post-hoc Bonferroni pairwise comparison test. *n.s*, not significant.