



Randomised Controlled Trial

Effects of synbiotic supplement on body weight and fasting blood glucose levels in obesity: A randomized placebo-controlled trial

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ABSTRACT

Background: Obesity and diabetes are related. The role of gut microbiota disruption in obesity has been reported as a cause of several metabolic diseases including diabetes.

Objectives: Evaluate the effects of synbiotic supplementation (a combination of probiotic and prebiotic) on body weight (BW), Body Mass Index (BMI), and Fasting Blood Glucose (FBG) in obese subjects.

Methods: This study was a randomized, double-blind placebo-controlled. Participants were allocated with randomization into 2 groups: the obese group with synbiotic supplementation and the obese group with placebo; each group consists of 8 participants. BW, BMI, and FBG level were measured at baseline, 8 weeks after supplementation, and 4 weeks after terminating the supplementation.

Results: There were no significant change of body weight and BMI after 8 weeks synbiotics supplementation and 4 weeks after supplement discontinuation, but there were significant increases in body weight by 3.38 kg and BMI by 1.37 kg/m² in the control group. Fasting blood glucose levels were significantly decreased by 6.125 mg/dL after synbiotic supplementation. FBG did not resume 4 weeks after terminating the supplementation. In contrast, there was a significant increase of FBG in control group on week 8 and was further increased 4 weeks after placebo was discontinued.

Conclusions: Synbiotic supplementation may prevent increase of body weight and BMI in obesity and this may be related with lower fasting blood glucose levels.

1. 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]. As many as 39% or more than 1.9 billion of adults aged 18 years and over were overweight. Overall, about 13% of the world's adult population were obese [1]. Obesity and type 2 diabetes are closely related. Like 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 worldwide, or 8.8% of adults aged 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 combining 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% [4]. Moreover, it is known that comparable food intake and physical activity can lead to different weight gain or loss [5]. Beside genetic factors, 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

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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 bloodstream 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, induces 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 bodyweight 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, but the results were still conflicting [13–15]. Besides, no study has examined whether the supplementation's beneficial effects remain exist after the supplementation's termination. Hence, this study aimed to examine the effect of synbiotics supplementation on body weight, BMI, and fasting blood glucose of obese subjects after 8 weeks supplementation and 4 weeks after cessation of the treatment without dietary and activity interventions. Our hypothesis was that body weight, BMI, and fasting blood glucose would decrease after the treatment but resume after the termination of synbiotic supplementation.

2. Methods

2.1. Participants and trial design

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 Makassar, Indonesia. Forty participants with obesity (BMI of ≥ 25 kg/m²) according to Asia Pacific standard were recruited [16]. Subjects with type 1 or type 2 diabetes, taking drugs that interfere with blood glucose levels or gut-microbiota composition such as corticosteroids, antibiotics, prebiotics, probiotics, or synbiotics 6 months before were excluded. Sample size was calculated and participants were randomly allocated using permuted block randomization with 4,6,8 block sizes and divided into 2 randomized obese and control groups (20 participants each). Number of participants who finally completed the study was 8 participants in each group; the obese group with synbiotic supplementation (OS) and the control obese group with placebo (CO). There was no intervention for diet and activity, but the participants were asked not to change their usual diet and activity level and were remained every day. Participants and researchers who measured and analyzed the outcomes were blinded to the intervention type.

2.2. Interventions

Each participant group with synbiotic supplementation received 1 sachet of Rillus® synbiotic (containing 10⁹ CFU of live cells:

Lactobacillus Plantarum 8.55 mg, *Streptococcus thermophilus* 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. Participants were remained every day to take the supplement and placebo.

2.3. Bodyweight, BMI, and fasting blood glucose

Participants were initially evaluated for baseline characteristics (body weight, BMI, 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 h of overnight fasting. After 8 weeks of treatment and 4 weeks after cessation of the treatments, we re-evaluated body weight, BMI dan FBG.

2.4. Procedures

All participants gave written consent to participate in the study, which was approved by the ethics committee of Faculty of Medicine, Hasanuddin University (Approval number: 719/UN4.6.4.5.31/PP36/2019). The clinical trial has been registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT number: 04642482).

2.5. 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 student's *t*-test for baseline characteristics and repeated ANOVA tests with post-hoc Bonferroni pairwise comparison test to assess differences of BW, BMI, and FBG before the intervention, 8 weeks after the intervention, and 4 weeks after the intervention was discontinued. The results were expressed as mean \pm SD, and mean differences were considered significant at $p < 0.05$.

3. Result

Of the 40 obese-participants recruited in this study from October 2019 to December 2019, 8 participants were excluded as they were either not meeting inclusion criteria or declined to participate. Thirty-two participants were randomized into two groups; sixteen participants in the obese + synbiotic group (OS) and an equal amount in the control obese group (CO) with placebo. Eight participants each in OS and CO groups were discontinued due to loss of follow-up, health condition and incompliance reasons. Sixteen participants completed the entire trial (OS group, $n = 8$; and CO group, $n = 8$). The flowchart of the trial is presented in Fig. 1.

3.1. Baseline characteristic of the study groups

At the beginning of the study, the 2 groups; obese participants with synbiotic treatment (obese + synbiotics) and obese participants with placebo treatment (Control obese) were examined for anthropometry (height, body weight, and body mass index (BMI)) and fasting blood glucose. The participants' average age 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 two obese groups were not significantly different (Table 1). The obese with synbiotic supplement and control obese groups had BMI of 32.88 ± 5.21 kg/m² and 32.53 ± 3.15 kg/m², respectively; $p < 0.979$ (Table 1). The obese + synbiotics and control obese groups had FBG of 113.13 ± 8.03 mg/dL and 106.63 ± 6.47 , respectively, and they were not significantly different; $p = 0.132$ (Table 1).

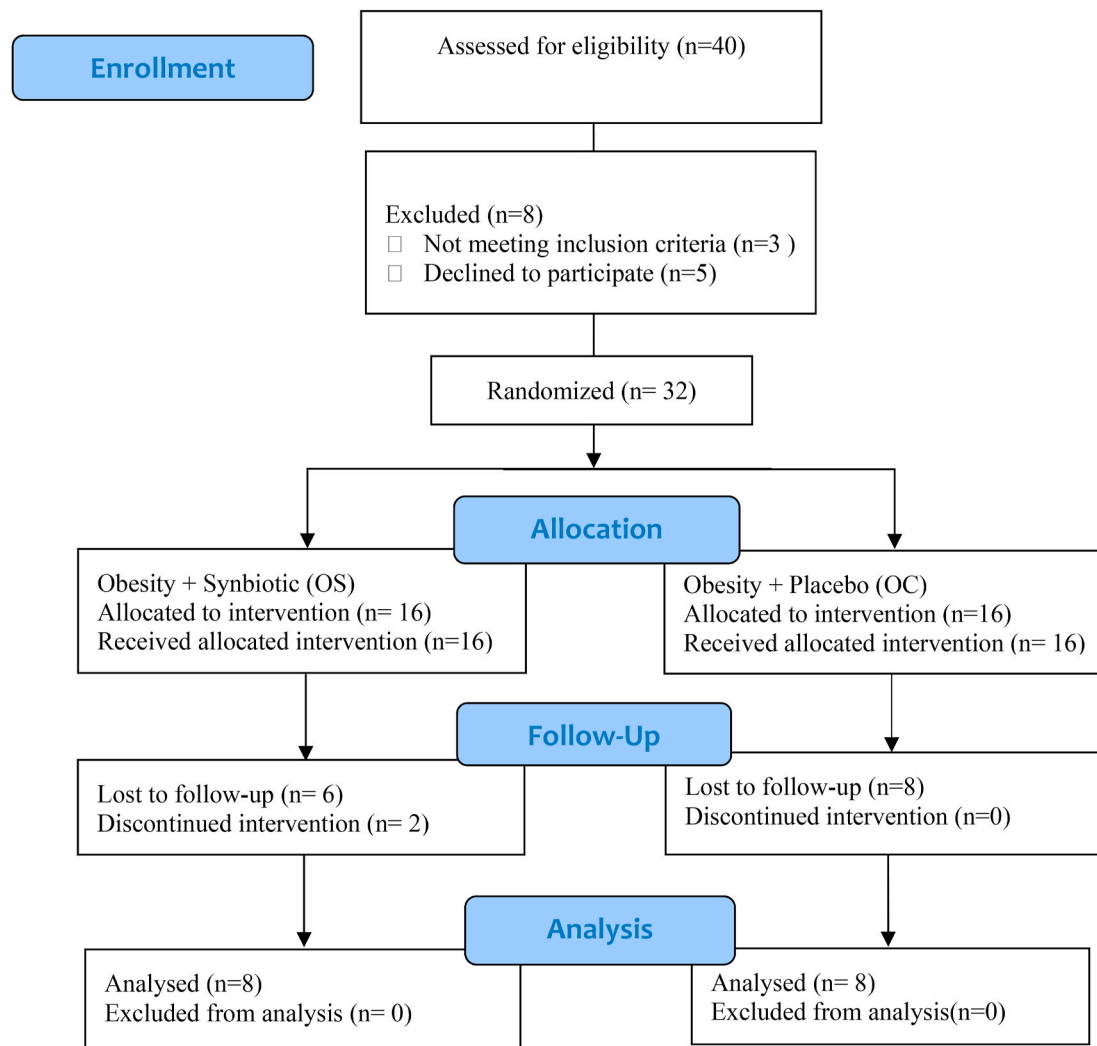


Fig. 1. CONSORT Flow Chart of participants' recruitment, randomization and allocation.

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

Parameters	Groups		
	Obese + Synbiotic (OS)	Control Obese (CO)	<i>p</i>
n	8	8	NA
Men	4	4	NA
Women	4	4	NA
Age (year)	20.25 ± 0.71	20.50 ± 1.20	0.619
Height (m)	1.57 ± 0.03	1.58 ± 0.04	0.757
Body weight (kg)	81.25 ± 13.23	80.88 ± 7.10	0.997
BMI (kg/m ²)	32.88 ± 5.21	32.53 ± 3.15	0.979
FBG (mg/dL)	113.13 ± 8.03	106.63 ± 6.47	0.132

Data were expressed as mean ± SD. Statistical analysis with student's *t*-test. *p* < 0.05 was considered significant. BMI: Body mass Index; FBG: Fasting blood glucose; NA: Not applicable.

3.2. Effects of synbiotics supplementation on body weight and BMI

There were insignificant increase of BW and BMI in obese subjects (Table 2 and Fig. 2) after 8 weeks supplementation with synbiotics (increased by 0.63 kg, *p* = 1.000) and 4 weeks after cessation of the supplementation (increased by 0.37 kg, *p* = 0.855), with total increase of BW was 1 kg, *p* = 0.721 and total increase of BMI was 0.434, *p* = 0.662. In contrast, significant weight gain on week 8 by 2.375 kg, *p* < 0.001 and 4 weeks after cessation of the placebo increased by 1 kg, *p* = 0.099, with

total weight gain was 3.375 kg (*p* < 0.001) and a significant total increase of BMI was 1.373 (*p* < 0.002) were observed in control obese group treated with placebo (Table 2 and Fig. 3).

3.3. Effects of synbiotics supplementation on fasting blood glucose

There was a significant reduction of FBG in obese subjects supplemented with synbiotic by 4.56 mg/dL on week 8 and was further decreased by 1.56 mg/dL after 4 weeks termination of synbiotic treatment (week 12), and a total decrease by 6.12 mg/dL (*p* < 0.003; Table 2 and Fig. 2). In contrast, there was a significant increase of FBG in control obese group treated with placebo on week 8 (increased by 0.11 mg/dL, *p* = 0.044) and further increased by 0.01 mg/dL on week 12, and a total increase of 0.12 mg/dL; *p* = 0.06 (Table 2 and Fig. 3).

4. Discussion

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

There were no significant alterations of body weight and BMI in obese subjects after 8 weeks supplementation with synbiotics and 4 weeks after cessation of the supplementation. In contrast, significant weight gain by 3.375 kg and an increase of BMI by 1.373 kg were

Table 2

Anthropometric and glycemic parameters before intervention (week 0), 8 weeks after intervention (week 8) and 4 weeks after intervention was terminated (week 12).

Parameters	Obese + Synbiotics (OS)			p	Control Obese (CO)			p
	Week 0	Week 8	Week 12		Week 0	Week 8	Week 12	
BW (kg)	81.25 ± 13.23 ^{ab}	81.88 ± 11.74 ^{ab}	82.25 ± 12.33 ^{ab}	0.365	80.88 ± 7.10 ^{ab}	83.25 ± 7.14 ^{cd}	84.25 ± 6.54 ^{cd}	0.001
BMI (kg/m ²)	32.88 ± 5.21 ^{ab}	33.16 ± 4.79 ^{ab}	33.32 ± 5.06 ^{ab}	0.335	32.53 ± 3.15 ^{ab}	33.50 ± 3.3 ^{cd}	33.90 ± 3.16 ^{cd}	0.002
FBG (mg/dL)	113.13 ± 8.03 ^{ab}	108.56 ± 4.66 ^{bc}	107 ± 4.62 ^{ad}	0.003	106.63 ± 6.47 ^{ab}	106.74 ± 6.50 ^{cd}	106.75 ± 6.45 ^{ac}	0.066

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. Mean values with both superscript letters are different were statistically significant.

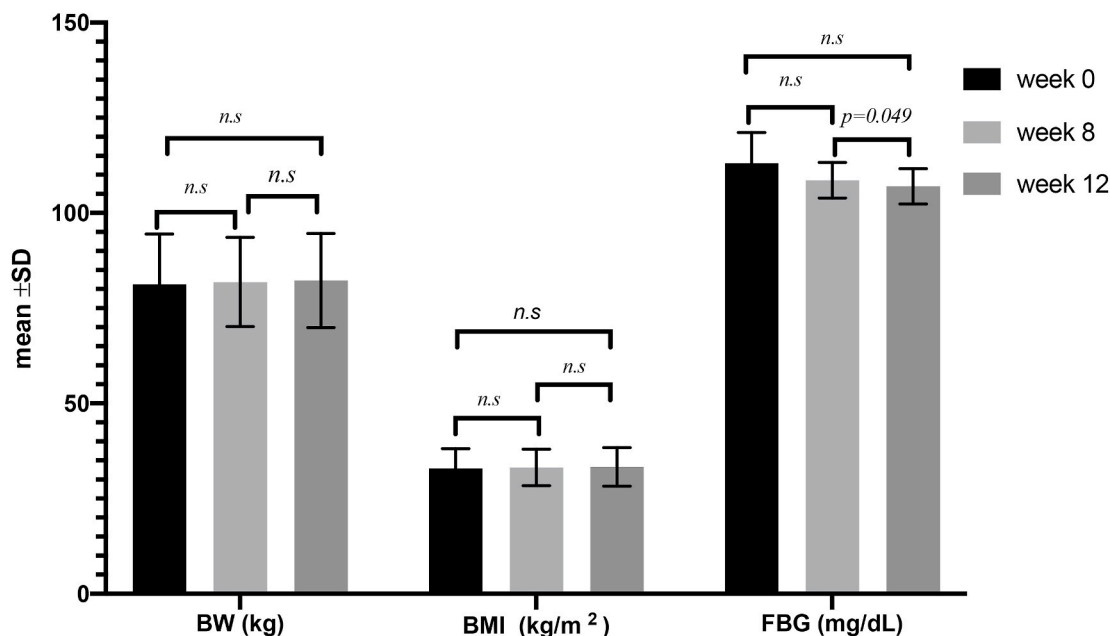


Fig. 2. Alteration in body weight (BW), body mass index (BMI), and fasting blood glucose (FBG) before treatment (week 0), 8 weeks after treatment (week 8), and 4 weeks after treatment termination (week 12) in obese subjects with synbiotics treatment. Statistical analysis with Repeated ANOVA and post-hoc Bonferroni pairwise comparison test. *n.s.*: not statistically significant.

observed in the control obese group treated with placebo. Furthermore, there was a significant reduction of FBG in obese subjects supplemented with synbiotic on week 8 and on week 12 and total decrease of 6.125 mg/dL, but there was significant increase of FBG in control obese group treated with placebo on week 8 and week 12. Thus, 8 weeks administration of synbiotic was effective in reducing FBG despite no decrease of BW and BMI. FBG was continued to decline after 4 weeks of synbiotic discontinuation.

The gut microbiota plays an important role in normal bowel function and health maintenance [17]. Studies in animal models and humans have shown that a high-fat diet modulates gut microbiota and increases circulating LPS levels [18]. Previous research has also shown that synbiotics can alter appetite [19]. 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 could maintain their body weight throughout the study period and might need longer treatment for weight loss. 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 [20]. 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 [13,21,22]. On the other hand, in the obese control group of this study, there was a slight increase yet significant in body weight on week 8 until week 12 or 4 weeks after the study intervention was terminated. Interestingly, FBG significantly decreased in the obese with 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 with a synbiotic group [13,21]. Our study also used 2 microbiota from *Lactobacillus* genera.

As BW and BMI increased, FBG also significantly increased in the obese control group in week 8 but not in week 12 after the 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 [23].

Adverse events associated with probiotic and synbiotic intervention were reported in previous studies but the events were equally distributed in control groups and other studies reported no adverse events [20]. We also found no adverse events in this study.

The study's limitation is that the number of participants who completed the study was relatively small. We did not evaluate waist circumference, dietary intake, and activity level, but we reminded the participants not to change their typical diet and activity level. Moreover, it may need a longer time to see a clear effect of synbiotic supplement on body weight, BMI and FBG as suggested in the previous studies where most studies with 8–12 weeks supplementation result in insignificant outcomes [13,20–22]. In addition, FBG may be affected by insulin level; thus HOMA-IR need to be evaluated. Our data support the previous studies reporting that the synbiotic supplementation improved glucose metabolism [13,19,21].

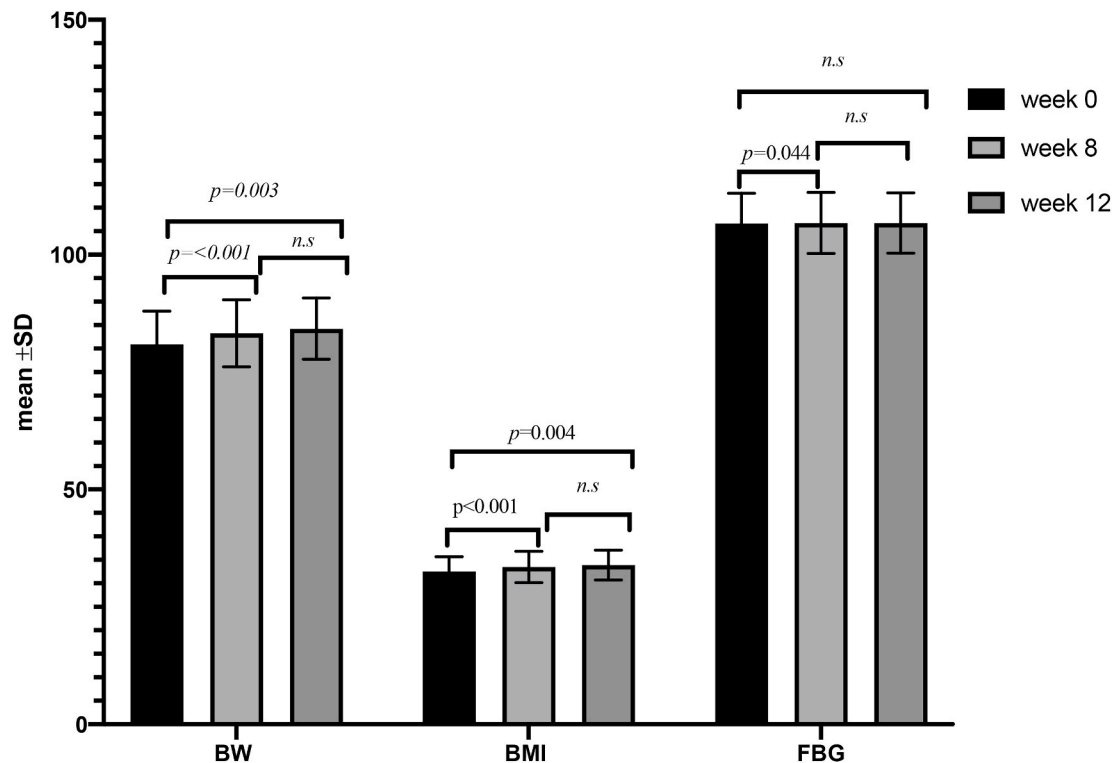


Fig. 3. Alteration in body weight (BW), body mass index (BMI), and fasting blood glucose (FBG) before treatment (week 0), 8 weeks after treatment (week 8), and 4 weeks after treatment termination (week 12) in control obese subjects with placebo treatment. Statistical analysis with Repeated ANOVA and post-hoc Bonferroni pairwise comparison test. *n.s.*: not statistically significant.

5. Conclusion

Although body weight and BMI were not decreased by synbiotic supplement, it may prevent body weight increase over time in obese subjects or may need more time to decrease. Synbiotic supplementation might lower fasting blood glucose in obese subjects before body weight and BMI were changed. Those beneficial effects of synbiotic supplement on BW, BMI and FBG in obese subjects persisted after 4 weeks of supplement termination. The role of synbiotic on anthropometric, body composition, and metabolic parameters requires further large-scale and long-term studies.

Funding

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Ethical approval

All procedures for human experiment has been approved by The Ethics Committee of Faculty of Medicine, Hasanuddin University. Approval Number: 719/UN4.6.4.5.31/PP36/ 2019.

Consent

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission to use their prospective database and files for research work.

Author contribution

ASA, MNM, FH, AA and AB participated in the study concept and design. ASA performed data collection. ASA, MNM, FH, AB contributed

in data analysis and interpretation. ASA and AB writing the papers. ASA, FH, SA, AB conducted statistical analysis. All authors read and approved the final manuscript.

Registration of research studies

Name of the registry: ClinicalTrials.gov

Unique Identifying number or registration ID: NCT number: 04642482

Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://clinicaltrials.gov/ct2/results?cond=&term=04642482&cntry=&state=&city=&dist=>.

Guarantor

Andi Salsa Anggeraini.

Declaration of competing interest

The Authors have no competing interest.

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