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The combination of isomalto-oligosaccharides (IMO)-based dietary fiber and hypocaloric high-protein diet could improve the anthropometric profile and fasting plasma glucose of healthy adults: A repeated single-arm clinical trial

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ABSTRACT

Background and aims: Meals with high protein and fiber could reduce weight and improve diabetes risk factors. Isomalto-oligosaccharide (IMO), a form of dietary fiber, could induce the afferent signal that causes appetite suppression. However, the direct effect of fiber supplementation in the form of IMO combined with a high-protein diet (HPF) on those parameters is still unknown. This study aims to investigate the effect of HPF on anthropometric parameters and blood glucose regulation of healthy subjects.

Methods: Thirteen healthy subjects were given a hypocaloric high protein diet (HPD) mixed with their prepared meals for two weeks. Followed by the HPF diet for another two weeks. Their anthropometric parameters, such as body composition (total body weight, body fat percentage, and fat-free mass), BMI and waist circumference, and fasting plasma glucose, were measured.

Results: Compared to pre-intervention, HPF could significantly ($p \leq 0.004$) reduce the anthropometric parameters and fasting plasma glucose. Compared to HPD, HPF could significantly ($p \leq 0.005$) reduce more total body weight, body fat percentage, and BMI. In addition, HPF could induce more satiety than HPD (higher VAS score).

Conclusion: HPF could improve the subject's anthropometric parameters which is obviously beneficial in preventing the risk of developing diabetes.

1. Introduction

The prevalence of overweight and obesity is rapidly increasing in every region worldwide. People who are overweight and obese have a higher risk of suffering from metabolic diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) [1]. Many people in the last decade have widely practiced high protein diets (HPD) as a means to reduce the risk of metabolic diseases. Nevertheless, despite their popularity, the result of recent research on HPD on several anthropometric and metabolic parameters showed only slight benefit [2]. HPD could reduce total body weight while maintaining or increasing muscle mass [3].

Combining HPD with high dietary fiber (DF) can be a reasonable approach. DF has played an important role in the human diet since prehistoric times, such as maintaining energy balance [4,5], improving cardiometabolic health [5–7], improving insulin sensitivity [8], preventing cancer [9,10], and promoting optimized immune and inflammatory signaling required for human health and weight control [11].

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Daily intake of DF could also improve glycemic response and lower the risk of diabetes by inhibiting the digestion and absorption of metabolizable energy in the gastrointestinal tract, maintaining satiety, and reducing caloric intake [12,13]. Therefore, the current recommended dietary fiber intake is around 25–35 g per day [14]. DF is defined basically as a carbohydrate with three or more monomeric units, which cannot be hydrolyzed by the endogenous enzymes of the human small intestine, including naturally occurring non-starch polysaccharides (NSP) and oligosaccharides found in food, isolated from food raw material, and synthetic forms. Because the human small intestine cannot hydrolyze it, it can pass unchanged into the colon, where it will be digested or fermented by the colonic microbiota [15].

Nevertheless, DF intake is still below the recommended level in many countries [14,16,17]. Low DF intake is associated with a low intake of fruits, vegetables, or whole grains, as the natural source of dietary fiber [18]. To overcome this problem, DF in the form of a food supplement may be used to augment a low-DF diet. Isomalto-oligosaccharides (IMO) is a novel dietary fiber that is a mixture of α-(1 → 6) and α-(1 → 4)-linked glucose oligomers, synthesized by an enzymatic reaction from starch [19]. IMO have been widely used in food industries owing to their stabilities, low calorigenic, and prebiotic properties.

Interestingly, there is no publication regarding the effect of IMO-based dietary fiber and high protein diet supplement combination on anthropometric profile and fasting plasma glucose. The fiber supplementation in the form of IMO combined with a high-protein diet (HPF) should have a positive synergistic effect on several anthropometric parameters and blood glucose regulation. To answer these hypotheses, we conducted a preliminary repeated single-arm clinical trial with HPD, followed by HPF intervention in thirteen metabolically healthy adults with a body mass index (BMI) of $\geq$25. The results show that HPF significantly improves the subject's body composition by reducing the total body weight, BMI, body fat percentage, and fasting plasma glucose, which is obviously beneficial to preventing the risk of developing diabetes and other metabolic diseases.

2. Material and methods

2.1. Subjects

Thirteen (n = 13) healthy subjects were voluntarily recruited. Inclusion criteria were body mass index (BMI) of $\geq$25.0, age between 18 and 50 years old, men or women, normal diet, not pregnant, not under any medication, and not having any disease or acute infection.

2.2. Trial design, intervention, and supplementation

This experiment adapted a single-arm trial analysis (see Supplementary Fig. 1). For the first two weeks, subjects were given hypocaloric prepared meals with high protein content but low DF contents (HPD). It contains less than 15 g/d of DF and protein content 30–40% of total calories. Meal total calorie is 60% of estimated energy requirements (EER), which is calculated with the formula developed by Institute of Medicine (IOM) [20]. At the end of the first two weeks, waist circumference, total body weight, body composition, and fasting plasma glucose were measured. After two weeks of washing, all of the subjects were given hypocaloric prepared meal (60% of EER) containing high protein and high DF (HPF). It contains 25–30-g DF and protein content between 30 and 40% of total calories. At the end of the interventions, waist circumference, body weight, body composition, and fasting plasma glucose were measured again. Half of DF content in food comes from occurring natural fiber from fruit, vegetables, and whole grains, the other half (50%) come from IMO-based fiber supplement (Fibercreme®, PT. Lautan Natural Krimerindo, Mojokerto, Indonesia; detailed composition sees Supplementary Table 1) which is added into the prepared meal.

2.3. Body composition measurement and blood sampling

Body weight, Body Mass Index (BMI), Fat-Free Mass (FFM), and Body Fat Percentage (BFP) were measured using Tanita Bioelectrical Impedance Analyzer (BIA) from Tanita Corporation (Illinois, USA). Before measurement, subjects were instructed not to drink coffee, tea, or alcohol and not to do moderate-to-vigorous physical activity. Waist circumference (WC) was measured using body girth tape. Capillary blood samples were taken for analysis of glucose concentration using the FreeStyle Optium glucose monitoring system (Abbot Laboratories, California, USA) for the fasting plasma glucose (FPG) parameter. The measurement of fasting plasma glucose concentration was performed twice: [1] in the morning on the first day of dietary intervention (day 1) for the pre-intervention group, and [2] in the morning on the final day of dietary intervention (day 15) for the post-intervention group. The difference between pre-and-post-groups in the different interventions was analyzed separately.

2.4. Visual analog scale (VAS)

Visual analog scales (VAS) are reliable tools to evaluate hunger and satiety at the point of food consumption [21]. To acquire the VAS-score, the subjects completed a defined questionnaire after every meal and submitted to the research facility on the next day. This procedure was done every day during the dietary intervention period.

2.5. Calculation of absolute body fat mass, measured fat loss, predicted fat loss, and discrepancy of measured-predicted fat loss calculation

Absolute body fat mass was calculated by multiplying body fat percentage, which is measured using Tanita Bioelectrical Impedance Analyzer, with total body weight in kilograms. Measured fat loss is the difference between pre- and post-intervention absolute body fat mass. On the other hand, predicted fat loss is calculated by dividing the total calorie deficit after two weeks of dietary intervention by 7700, assuming that 1 kg of body fat stores 7700 kilocalories of energy [22]. The measured-predicted fat loss discrepancy is the difference between measured fat loss mentioned above and predicted fat loss.

2.6. Statistical analysis

The data were analyzed statistically using paired-samples T-Test methods. The data were presented graphically as the mean ± standard deviation (SD) using GraphPad Prism™ 5.0 (San Diego, USA). All results were interpreted as significant if $p < 0.05$.

3. Results

3.1. Subjects' characteristics

All subjects have completed the trial. Their characteristics, which consist of age, body weight, body height, body mass index (BMI), sex, and estimated energy requirements (EER), are shown in Table 1.

3.2. HPF intervention could improve anthropometric parameters, particularly body fat percentage

The anthropometric parameter analysis and fasting plasma glucose analysis are shown in Fig. 1. In all parameters, no significant difference was observed between male and female subjects. Pre-and-post-intervention body weight and BMI are presented in Fig. 1A and B, respectively. The reduction of body weight, BMI, and percentage of body weight reduction are presented in Fig. 1F and G, and Supplementary Fig. 1, respectively. A significant reduction of body weight pre-and-post-intervention in HPD, from 81.78 ± 4.52 Kg to 80.67 ± 4.47 Kg (p = 0.000) and HPF, from 81.38 ± 4.51 Kg to 79.33 ± 4.45 Kg (p = 0.000)

Table 1
Subjects characteristics.

Characterics	Mean (Value ± SD)		
	Male	Female	All
Total samples	6	7	13
Age (years)	32.00 ± 4.05	28.00 ± 3.27	29.85 ± 4.06
Body weight (Kg)	96.7 ± 10.29	69.00 ± 5.46	81.78 ± 4.52
Body height (cm)	172.50 ± 6.03	160.14 ± 5.73	165.85 ± 8.52
Body Mass Index (Kg/m^2)	32.54 ± 3.49	26.98 ± 2.67	29.55 ± 4.18
Waist Circumference (cm)	110.50 ± 6.03	92.20 ± 6.06	98.46 ± 13.06
Daily calorie intake (60% EER[a])	1933.83 ± 184.46	1360.71 ± 118.13	1625.23 ± 331.04

Adult Male EER: 661.8 - 9.53 x Age [y] x Physical Activities x (15.91 x Weight [kg]) + 539.6 x Height [m].
Adult Female EER: 354.1 - 6.91 x Age [y] x Physical Activities x (9.36 x Weight [kg]) + 726 x Height [m].
All trial subjects had sedentary activities, their Physical Activities values are 1.0.
[a] EER: Estimated Energy Requirements calculated with formula as follows[37].

were observed. Nevertheless, the body weight reduction is significantly higher in HPF than in HPD (−2.05 ± 0.27 Kg vs. −1.11 ± 0.16 Kg, p=0.000). There is also a significant reduction in BMI pre-and-post-intervention in HPD, from 29.55 ± 1.14 kg/m^2 to 29.14 ± 1.12 kg/m^2 (p=0.000) and HPF, from 29.40 ± 1.14 kg/m^2 to 28.65 ± 1.12 kg/m^2 (p = 0.000). The reduction in BMI is significantly higher in HPF than in HPD (−0.75 ± 0.10 kg/m^2 vs. −0.41 ± 0.06 kg/m^2, p=0.0002). Body weight reduction in HPF is 2.55 ± 0.35% from pre-intervention body weight, significantly higher than body weight reduction in HPD (2.55 ± 0.35% vs. 1.35 ± 0.22%, p = 0.000).

Pre-and-post-intervention WCs between different experimental groups were presented in Fig. 1C. There is a significant reduction of waist circumference pre-and-post-intervention in HPD, from 102.18 ± 3.36 cm to 99.05 ± 3.10 cm (p = 0.000) and HPF, from 100.59 ± 3.82 cm to 96.59 ± 3.62 cm (p = 0.000). The WC reduction between different dietary intervention was presented in Fig. 1H. There is no significant difference in the reduction of waist circumference between different experimental groups.

Pre-and-post-intervention BFPs between different experiment groups were presented in Fig. 1D. There is a significant reduction of BFP pre-and-post-intervention in HPD, from 33.66 ± 1.32% to 33.24 ± 1.29% (p = 0.019) and HPF, from 33.52 ± 1.26% to 32.65 ± 1.30% (p = 0.0003). The BFP reduction between different dietary intervention was presented in Fig. 1I. The reduction of BFP in HPF is significantly higher than in HPD (−0.88 ± 0.15% vs. −0.42 ± 0.18%, p = 0.005).

Pre-and-post-intervention FFM between different experimental groups were presented in Fig. 1E. There is a significant reduction of FFM post-intervention in HPF compared to its pre-intervention, from 51.51 ± 3.40 Kg to 50.77 ± 3.36 Kg (p = 0.000). The muscle reduction between different dietary intervention was presented in Fig. 1J. The reduction of FFM in HPF group is significantly higher than in HPD group (−0.74 ± 0.11 Kg vs. −0.22 ± 0.12 Kg, p=0.002).

3.3. HPF intervention could induce fasting plasma glucose (FPG) reduction

Pre-and-post-intervention FPG between different experimental groups were presented in Fig. 2A. There is a significant reduction of FPG pre-and-post-intervention in HPF, from 90.38 ± 3.36 mg/dL to 82.54 ± 1.93 mg/dL (p = 0.004). The reduction of FPG between different dietary intervention was presented in Fig. 2B. There is no significant difference in FPG reduction between different experiment groups.

3.4. HPF intervention could increase the satiety of test subjects

The visual analog scale (VAS), which indicates a subjective feeling of satiety, was analyzed daily during the dietary intervention period. The VAS mean of each dietary intervention were presented in Fig. 1N. VAS score in HPF group is significantly higher than in HPD group (9.23 ± 0.17 vs. 8.23 ± 0.23, p=0.002) (Fig. 3). There is no significant difference

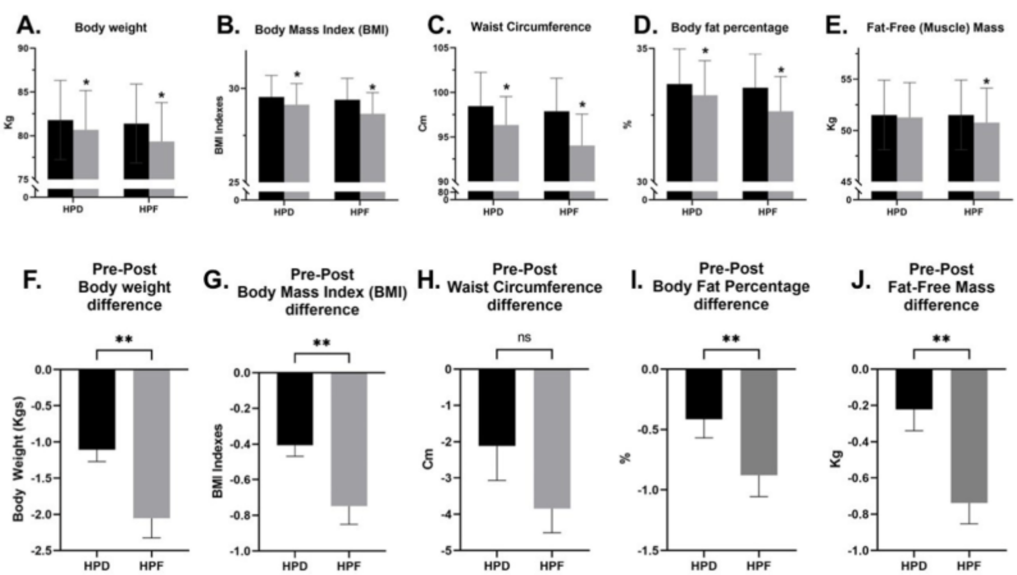

Fig. 1. Anthropometric parameters improvement after HPD and HPF interventions.
A–E: Comparison of pre- (black bar) and post-(grey bar) intervention parameters. F–J: Pre-post difference between different dietary intervention: HPD (black bar) and HPF (grey bar). The anthropometric parameters are A, F: Body weight analysis; B, G: Body mass index (BMI); C, H: Waist Circumference; D, I Body Fat percentage; E, J Fat-Free (Muscle) Mass.
HPD: High-protein diet, HPF: High-protein and High-Fiber Diet, Statistical symbols for all graphics: *$p < 0.05$; **$p \leq 0.001$ compared to Pre-post intervention (for A-E) or to each dietary intervention groups (for F-J).

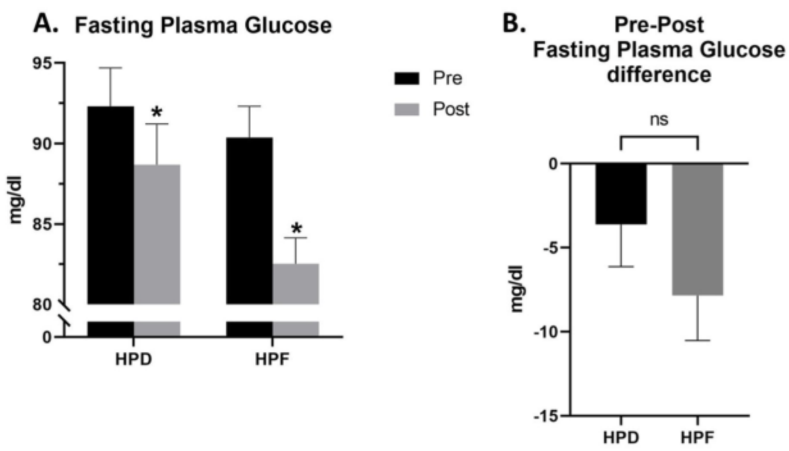

Fig. 2. Fasting plasma glucose (FPG) reduction in HPD and HPF interventions.
A: Comparison of pre- (black bar) and post-(grey bar) intervention parameters. B: Pre-post difference between different dietary intervention: HPD (black bar) and HPF (grey bar).
HPD: High-protein diet, HPF: High-protein and High-Fiber Diet, Statistical symbols for all graphics: $^{*}p < 0.05$; $^{**}p \leq 0.001$ compared to Pre-post intervention (for A) or to each dietary intervention groups (for B).

in VAS scores between both sexes.

3.5. HPF intervention could reduce body fat mass closer to its predicted value

The average of the measured fat loss in HPF is 1.38 ± 0.21 kg, which is significantly higher ($p = 0.000$) than the value in HPD, which is 0.72 ± 0.16 kg (Fig. 4A). There is a discrepancy between measured fat loss and predicted fat loss. Predicted fat loss after being corrected by total calories from snacking is 1.63 ± 0.09 kg and 2.04 ± 0.12 kg for HPD and HPF, respectively. Predicted fat loss is significantly higher than measured in both HPD and HPF (p=0.000). The discrepancy between measured and predicted weight loss is 50.76 ± 12.28% in HPD, which is significantly higher ($p = 0.001$) than the value in HPF, which is 25.22 ± 12.34% (see Fig. 4B).

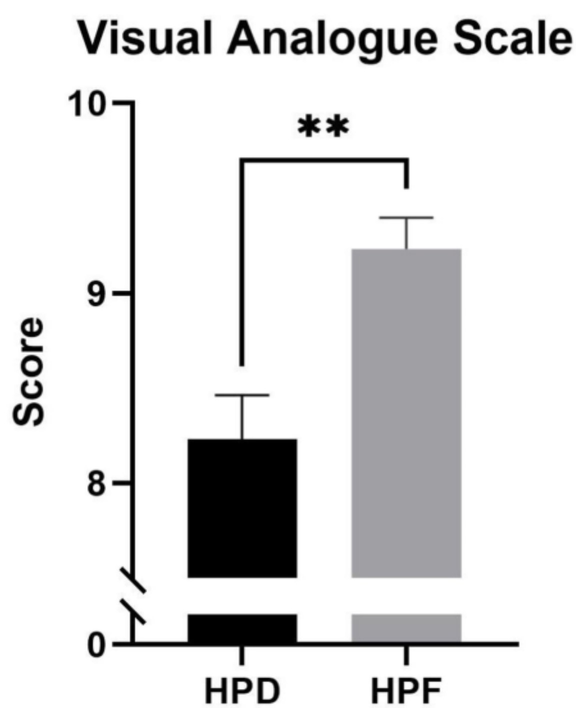

Fig. 3. VAS score in HPD and HPF interventions.
The satiety index of each intervention was quantified as a visual analogue scale (VAS) using a standard questionnaire. HPD: High-protein diet (black bar), HPF: High-protein and High-Fiber Diet (grey bar); $^{**}p \leq 0.001$.

3.6. There is no significant correlation between body weight reduction and FFM reduction in HPF intervention

The reduction in subjects' body weight is strongly followed by the reduction in BFP, both in HPD and HPF ($r = 0.691$, $p = 0.009$, and $r = 0.770$, $p = 0.002$, respectively). The correlation between body weight reduction and BFP reduction in HPD and HPF are presented in Supplementary Figs. 2A and 2B, respectively. Nevertheless, there is no significant correlation between body weight reduction and FFM reduction. The reduction of FFM does not consistently follow the reduction of body weight.

4. Discussion

4.1. HPF intervention could improve the anthropometric parameters and increases the subject's live quality

Due to the fact that diabetes could manifest through the unhealthy diet correlated with bad anthropometric parameters, the supplementation of HPF as a novel dietary intervention could significantly improve the subject's anthropometric parameters. Indeed, this hypothesis has been confirmed in Fig. 1. Compared to hypocaloric high protein diet (HPD), hypocaloric high-protein and fiber diet (HPF) could reduce more total body weight, body fat percentage, and BMI (see Fig. 1A–E). Additionally, significant differences in total body weight (BW), body fat percentage (BFP), and BMI pre-and-post-intervention between different dietary intervention was observed (Fig. 1F–J). The waist circumference (WC) was also reduced after two weeks in both dietary interventions (HPF and HPD), compared to baseline (pre-intervention). Based on the fact that WC represents visceral fat [23], this study shows that HPD and HPF have a comparable effect in reducing visceral fat, particularly after two weeks of continuous intervention. However, WC reduction in HPF tends to be higher than HPD. For subjects who have WC within obese criteria (WC ≥ 102 cm for males and WC ≥ 88 cm for females), there is a WC reduction of as much as 3.15 ± 0.70 cm for HPD and 4.10 ± 0.73 cm for HPF. There is no significant difference in WC reduction between HPD and HPF in obese subjects based on WC criteria. These comparable results might be ascribed to the short duration of intervention.

Although the reduction of fat-free mass (FFM) in HPF is also higher

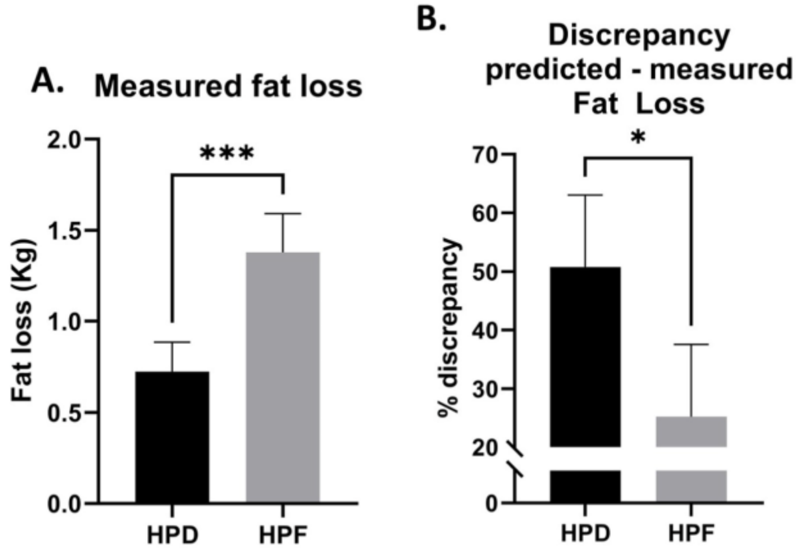

Fig. 4. Measured fat loss and measured-predicted fat loss discrepancy in HPD and HPF interventions.
A: Comparison of measured fat loss. B: Comparison of discrepancy between predicted and measured fat loss (in percentage).
HPD: High-protein diet (black bar), HPF: High-protein and High-Fiber Diet (grey bar); $*p < 0.05$; $***p \leq 0.000$.

compared to HPD (Fig. 1J), there is no significant correlation between FFM and BW reduction in HPD and HPF intervention. These results indicate that body weight reduction is not consistently followed by the reduction of muscle mass, which is an integral part of FFM. Indeed, previous studies showed that the reduction of FFM during a short course of hypocaloric dietary intervention is likely attributed to body water content [24]. Otherwise, there is a significant and strong correlation between the reduction of BFP and BW in HPD and HPF (Supplementary Fig. 2). Furthermore, the WC (see Fig. 1C,H) and BFP changes (see Fig. 1D and I) strongly indicate that HPF could induce reduction in abdominal or visceral adiposity.

4.2. Role of HPF-intervention in a reduction of the fasting plasma glucose (FPG)

In line to the previous study conducted by Pickard et al. which showed that fiber intake could improve FPG [25], our results (see Fig. 2) showed that the reduction of fasting plasma glucose (FPG) (7.85 ± 2.68 mg/dL) after two weeks of intervention caused by HPF tends to be two times higher than FPG reduction in HPD (3.62 ± 2.51 mg/dL). The dietary fiber tends to have an additional effect to a hypocaloric high-protein diet on fasting plasma glucose in the short duration of intervention and non-diabetic subjects. The plausible explanation for these result are mentioned below.

There is a discrepancy between predicted and measured fat loss after two weeks of dietary interventions. Based on the fact that 1 kg of fats stores up to 7700 kcal and 40% calorie deficit after 14 days. After being corrected by calories intake from snacks, it should induce 1.41 ± 0.08 kg and 1.85 ± 0.11 kg for HPD and HPF, respectively. However, the measured fat loss in HPD and HPF are 0.72 ± 0.16 kg and 1.38 ± 0.21 kg, respectively (Fig. 4A). It the discrepancy between predicted and measured fat loss in HPD and HPF are 50.76 ± 12.28% and 25.22 ± 12.34%, respectively (Fig. 4B). This discrepancy is most likely caused by the fall in resting and non-resting energy expenditure due to the underfeeding or hypocaloric diet, and are defined as adaptive thermogenesis [26].

4.3. HPF-intervention could induce fat loss and increase the satiety

The measured-predicted fat loss discrepancy in HPF is significantly lower than HPD. This phenomenon is caused by the lower total calories intake from snacking in HPF than HPD. These results supported our other observation regarding the increased satiety feeling induced by HPF (see Fig. 3, VAS Score). Previous observations showed that IMO supplementation could promote the growth of *lactobacilli* that, leads to an increase in short-chain fatty acid (SCFA) production [27–29]. Furthermore, SCFA could upregulate the synthesis and secretion of the hunger-suppressing or anorexigenic hormones such as leptin, peptide YY, and glucagon-like peptide 1 [30,31]. Based on those studies, we assume that HPF (which contains IMO) could suppress appetite and snacking reduction, as demonstrated in this manuscript. Furthermore, HPF might reduce energy harvesting and chronic low-grade inflammation through modulating gut microbiota as a beneficial manifestation of IMO-supplementation [29,30]. However, further investigation is required to understand the detailed mechanism. A previous study revealed that a change in Firmicutes and Bacteriodes ratio (F/B ratio) in colonic microbiome was associated with an additional energy harvest of 150 kcal per day [32]. In addition, SCFA produced by IMO fermentation could, in principle, improve intestinal barrier integrity, reducing LPS level in blood circulation [29,33,34]. Those previous studies might explain the reduction of fasting plasma glucose in HPF, which tends to be higher than that in HPD [35].

5. Conclusions

This study observed that IMO-based dietary fiber supplementation combined with a hypocaloric high-protein diet could increase satiety, induce weight loss, reduce body fat percentage, reduce peripheral adiposity, and improve the subject's body composition and fasting plasma glucose better than hypocaloric high-protein diet alone. This is obviously beneficial as a potential diet supplement to prevent the risk of developing diabetes and other metabolic diseases.

Ethics approval and clinical trial registration

This research was approved by the Health Research Ethics Committee of Widya Mandala Catholic University Surabaya (No.0295/WM12/KEPK/DSN/T/2022) and registered on clinicaltrials.gov (reg no. NCT05455164).

Author contributions

H.W. designed the experiments, performed the experiments, analyzed and interpreted the data, and wrote the manuscript. H.W and Y.T. performed the experiments and analyzed and interpreted the data. Y.H., L.H.T., K.F., C., H.W., D.A.S., and B.D.N analyzed and interpreted the data.

Declaration of competing interest

The author declares no conflict of interest.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2022.101049.

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