The Effect of Fibre Intervention on Serum and Faecal Short-Chain Fatty Acids in Human with Overweight or Obesity: A Systematic Review of Human Intervention Studies

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Abstract
Overweight/obesity is associated with many related comorbidities, such as type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD). Nutritional interventions focusing on dietary fibre and prebiotics interventions have been implemented. Fibre has been suggested to modulate gut-derived metabolites short-chain fatty acid (SCFA). We conducted a systematic review on fibre (including prebiotics) interventions to depict its effect on SCFA from faecal and blood using standard methodologies. Pubmed, Cochrane, Embase, CINAHL, and Scopus databases were systematically searched to yield peer-reviewed articles published until 31 October 2021. We included 17 articles describing fibre (including prebiotics) intervention in adult individuals with overweight/obesity. These interventions were broadly described into 3 groups: (i) fibre type food items (n = 8); (ii) fibre supplementations (i.e. prebiotics) (n = 8); (iii) prebiotic supplementation combined with CRD (n = 1). Fibre type food items intervention mostly affected the changes of acetate in faecal, whilst propionate mostly changed in the blood. Interestingly, intervention with fibre supplementation affects more the increase in faecal and blood acetate. Furthermore, fiber intervention might have an impact on the gut microbiota. Nevertheless, more well-controlled human studies are needed, with a more personalized approach perhaps based on obesity phenotype and gut microbiota profiles.

Keywords: fibre; prebiotics; SCFA; obesity; gut microbiota

INTRODUCTION
Over the last decades, the prevalence of obesity was about 13% of the adult population (11% of men and 15% of women) were obese. According to the Organization for Economic Cooperation and Development report data, obesity has reached epidemic proportions in developed and developing countries. An imbalance between energy intake and energy expenditure results in obesity. More recently, dietary content of high-fat and low fibre, sedentary lifestyle, and the gut microbiome are also involved in the development of obesity.

Obesity is strongly associated with many related comorbidities, such as type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD).
Bodyweight control by increasing physical activity and dietary-induced weight loss is still an important strategy to prevent obesity-related disorders.8–10 Of interest, various dietary components, such as fibre, that modulate metabolic health have been of growing interest in recent years. Dietary fibre may be contributed to additional mechanisms to maintain a bodyweight that may not be mediated solely by caloric content.11

Growing evidence supports the critical role of dietary fibre intake as a major contributor to gut microbiota-accessible carbohydrates in managing obesity-related metabolic disorders.12 The positive interaction between dietary fibre and the gut microbiome might improve metabolic health in humans with overweight or obesity. These mechanisms may partly be explained by the beneficial metabolites of fermentation (i.e. short-chain fatty acids (SCFAs) acetate, propionate, and butyrate).13 More interestingly, It has been reported that the SCFAs can also be transported across the gut into the circulation.14

Animal studies suggest that SCFAs have an important role in preventing and treating obesity-associated disorders.15,16 However, the effect of dietary fibre on SCFAs concentration in humans with overweight/obesity is not entirely consistent. For instance, Van der Beek et al., 2018 have demonstrated that prebiotic inulin increases only serum acetate but not with other SCFAs, and does not affect on faecal SCFAs.17 In contrast, other fibre supplementation studies have increased acetate and propionate levels in faecal samples of humans overweight or obesity.18,19

Of the two types of dietary fibre, water-soluble and insoluble, most soluble fibre are more fermentable and produces higher amounts of SCFAs compared to insoluble fibre.20 For example, mixed fibre, such as yellow pea fibre, is composed of cellulose, hemicellulose, and pectin and contains a mixture of soluble and insoluble fibre with a more significant proportion of insoluble.21 In addition to that, more recent definitions have included oligosaccharides as dietary fibre. Prebiotics is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gut microbiota that benefits the host's metabolic health.22 Prospective cohort studies indicate clearly that high fibre intakes are associated with a low risk of cardiovascular diseases (CVDs).23 However, data on adult individuals with obesity is relatively mixed.24 Thus, it may be that the physiological effects of dietary fibre related metabolite SCFAs might not be uniform in obesity. Although the link between dietary fibre and SCFAs levels has been indicated, its effect on faecal and serum concentrations from different intervention studies is still not wholly overviewed. The current systematic review was aimed to determine the effect of fibre interventions that may modulate faecal and serum SCFAs of adult individuals with overweight or obesity.

METHODS

Study design

We utilized a systematic review design to comprehensively describe dietary fibre interventions for modulating SCFAs in adult individuals with overweight or obesity and determine pertinent knowledge gaps in this critical research area. This systematic review was guided using an approach based on the methodological framework by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).25 Ethical approval was not sought as we have only used published data for this review.

The PICOS (Patients, Intervention, Comparison/Control, Outcome, Study design) framework was also used to develop inclusion criteria.26 We included only studies with adult individuals with overweight or obesity as participants. This review has operationalized intervention definition as dietary fibre or fibre type prebiotics supplementation. The group comparison in included studies was placebo/control. The outcome was the levels of SCFAs in faecal and serum from adult individuals with overweight or obesity following dietary fibre/fibre supplementation intervention. We included only studies with broad types of intervention study design.

Exclusion criteria were as follows: (1) any observational studies/ review/ acute test; (2) studies in animal models; (3) study intervention non-dietary fibre/fibre supplementation; (4) patient/participants were healthy and already developed type 2 diabetes (T2D); (5) study performed in children and adolescents (<18 years).

Literature search strategy and study selection

We conducted our systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and used the newest version of the checklist.27 The outcome of interest was the faecal and serum SCFAs levels in adults with overweight or obesity as a result of dietary fibre types intervention.

A comprehensive literature search PubMed/Medline (Medical Literature Analyses and Retrieval System Online), Cochrane Library, Web of Science, Embase database (OVID), and SCOPUS (ScienceDirect) was performed to identify articles until the 31st of October 2021. The main keywords used were “short-chain fatty acids”, “scfa”, “dietary fibre”, “prebiotic”, “obesity”, and “overweight”. These keywords were combined with Boolean operators (e.g. OR, AND, NOT), and All Fields or Medical subject subheading (Mesh) terms. The search terms for Pubmed were: (((fiber[All Fields]) OR (“dietary fiber”[All Fields])) AND (“scfa”[All Fields])) OR (“short chain fatty acids”[All Fields])) AND (“obesity”[All Fields]).

Following the search, duplicates were removed. Two authors (A.P. and R.A.) independently screened titles and abstracts. Based on the inclusion criteria, the final study selection was done by two authors (A.P and R.A.) and approved by other authors (E.R.N., M.M., D.N.A., A.C.K). All stages from searching and data extraction and qualitative/quantitative synthesis are described in (Figure 1). Any disagreements between the authors were resolved through discussion between authors.

Data extraction and management

By using standardized forms, data were extracted regarding study characteristics, all PICOS details including patients, inclusion criteria of subjects, sample size, description of intervention of each study (either dietary fibre or fibre supplementation), comparison/control, SCFA measurements, all outcome
measures of the intervention (serum and faecal SCFA), as well as other relevant outcomes. Data were extracted by two authors (A.P. and R.A.). The studies were subsequently classified according to the focus and outcomes to establish key discussion areas of this review.

RESULTS

Study characteristics

Study identification and selection are detailed in the PRISMA diagram for systematic reviews (Figure 1). The initial search strategy generated 1444 articles, out of which 278 were excluded as duplicates. After analysis of titles and abstracts, 843 records were excluded, including review articles or book chapters, in vitro studies, animal studies, and protocols, and 46 articles were selected for full-text review. Among these, 29 studies were excluded according to exclusion criteria. Thus, a total of 17 studies were included in the qualitative synthesis (Table 1).

The majority of studies (14 studies) included both sexes (male and female); the remaining three studies only included male (2 studies) or female (1 study) participants. BMI cut-offs vary between studies, 1 study included participants with BMI <28.7 kg/m².27 1 study with BMI ≤32 kg/m².28 and the remaining studies (15 studies) included BMI ranging from 25 – 45 kg/m².28,29,30,31,32,33,34,35,36,37,38,39,40 Furthermore, the majority of studies (11 out of 17) included adults individual with overweight/obesity without comorbidities, whereas six studies included adults overweight/obesity with comorbidities such as hypercholesterolemia,27,29,32 hypertriglyceridemia,28 metabolic syndrome,31 prediabetes,32 and non-alcoholic fatty liver disease/NAFLD.33 Three studies have conducted the research with a randomized crossover design.28,29,40 However, two out of 3 crossover trials did not conduct a washout period. In addition, thirteen studies were designed to parallel randomized trials, and one study by Bridges et al, 1992 was a non-randomized intervention.

Types of fibre intervention for the adult individuals with overweight and obesity mostly can be grouped into (i) fibre type food items; (ii) fibre supplementation (i.e., prebiotics); and (iii) prebiotic supplementation and calorie restriction diet mode of intervention. The dietary fibre (including prebiotics supplementation) was provided alone or combined with other modes of intervention such as a caloric restriction diet (CRD). Eight studies provided fibre type food items (e.g., wheat bran, oat bran, fruit (avocado; jucara berry), whole-grain cereal, yacon flour, Mediterranean diet, RS2-enriched wheat roll).27,28,31,34-36,38,40 Meanwhile, eight studies used fibre supplementation only (i.e., prebiotics). The types of fibre supplementation in these eight studies consisted of inulin, galactooligosaccharides (GOS), inulin-propionate ester, yellow pea fibre, arabinobioxylan, inulin-type fructans (ITF), resistant starch, and wheat bran with reduced particle size (WB RPS) fraction.18,19,29,30,32,33,37,41 Dosages used for fibre supplementation had ranged from 10 g/d to 20 g/d, whereas food type dietary fibre doses ranged from 14 g/d to 34 g/d. Duration of intervention ranged from 1 to 12 weeks. The most common intervention duration was 12 weeks (n = 8), followed by 6 weeks (n = 4), 3 weeks (n = 2) and 1/4/8 weeks (n = 1 for each study time) (Table 1).

Ten studies analyzed short-chain fatty acids (SCFAs) only in faecal samples, four studies only in the serum, and the three others analyzed both in faecal and serum. Analysis techniques used to determine faecal as well as serum SCFAs, including gas chromatography (GC), gas chromatography equipped with a flame ionization detector (GC-FID), liquid chromatography-mass spectrometry (LC-MS/MS), gas chromatography-mass spectrometry (GC-MS), and high-performance liquid chromatography (HPLC). Similar techniques were used to characterize the serum (serum) SCFAs, except for 1 study that examined using a direct enzymatic spectrophotometer for acetate analysis.27

Type of fibre for supplementation based on fermentation rate in colon

Eight out of the nine studies that used fibre supplementation/combined with CRD were analyzed SCFAs in the faecal. They were further classified based on the degree of fermentation of the type of fibre used, according to Wang et al. 2019.42 Seven studies employed inulin, GOS, or arabinobioxylan, all of which had fast fermentation rates, whereas one used pea fibre containing resistant starch, which had slow fermentation rates. From 5 studies that reported significant changes in faecal SCFAs levels, it used fibre and prebiotics supplementation with a fast fermentation rate type. In contrast, only one study reported an elevation in acetate levels, which have used a fibre intervention with a slow fermentation rate type (Table 2).

The effect of fibre type food items on the blood SCFAs in human overweight/obesity

Three studies used fibre type food items and analyzed SCFA levels in the blood.27,31,36 The intervention group in one study had a significant increase in serum acetate. Only one study found a significant increase in serum propionate levels,31 even though two studies reported a change in serum propionate levels. The intervention group's postprandial plasma butyrate levels were also found to be significantly increased.36 Based on these findings, it can be summarized that fibre from food items intervention can raise blood SCFA levels, including acetate, propionate, and butyrate (Table 3).

The effect of fibre type food items on the faecal SCFAs in human overweight/obesity

Five out of eight studies that used fibre type food items, measured faecal SCFA levels. Two studies found a substantial rise in acetate,24,35 while one study by Noakes et al, 1996 found a significant increase in butyrate among the three that showed an increase in SCFA in the intervention group. In two other research,38,40 SCFA levels were found to be lower or there was no difference between the intervention and control groups (Table 3).

The effect of fibre supplementation/combined with CRD on the blood SCFAs in human overweight/obesity

Noakes et al, 1996 found a significant increase in serum acetate.
There were four studies that analyzed blood SCFA out of the total of nine that used fiber supplementation. Only one study reported a positive effect on SCFA, an increase in acetate levels and total SCFA in the intervention group. Two other research showed a decrease in butyrate levels or no change in the blood SCFA levels, while one study could not detect the presence of SCFA in blood samples (Table 3).

The effect of fibre supplementation/combined with CRD on the faecal SCFAs in human overweight/obesity

There were eight studies that used fibre supplements and measured faecal SCFA levels. Three of eight studies showed a significant increase in acetate levels. In contrast to faecal propionate levels which were reported to be increased by two studies, none of the studies reported changes in faecal butyrate levels (Table 3).

The effect of fibre intervention on gut microbiota

Furthermore, some studies (not all) have also demonstrated the gut microbiota change following fibre interventions. Table 3 described the eleven studies (out of 18) that have investigated the gut microbiota changes. Interestingly, the acetate bacteria producer such as Bifidobacterium, Akkermansia, Faecalibacterium, Lachnospira, as well as the butyrate bacteria producer such as Ruminococcus and Bacteroides, were among the gut microbiota genus that was altered following fibre intervention in the adult individuals with overweight/obesity. The majority of the changes in SCFA levels may be partly explained by alteration of the gut microbiota, depending on the duration of intervention. This suggests that fibre supplementation, through the gut microbiota, could stimulate the production of SCFA, particularly acetate, which is thought to play a role with metabolic regulation in overweight or obese individuals.

DISCUSSION

This review aimed to describe and determine the effect of dietary fibre/prebiotics intervention on faecal or serum short-chain fatty acids (SCFAs) production in adult individuals with overweight or obesity. About seventeen studies were identified and deemed appropriate for inclusion in our systematic review, highlighting the dearth of recent interventional modes undertaken to modulate SCFAs levels for adult individuals with overweight or obesity. Obesity, per se, may alter the gut microbial composition, with a marked reduction in some microbiota and commensal strains, reducing the production of its metabolites. The consumption of dietary fibre from diet or supplements has been proposed as an effective dietary strategy for obesity control.

In our review, fibre supplementation (i.e. prebiotics) comprised approximately 50% (9 studies) of interventions discussed. They were representative of the best options available in their respective dietary supplement categories. For instance, inulin, galactooligosaccharides (GOS), and resistant starch are fibre supplement options. Roughly 40% (8 studies) of the included articles, the interventions were administered as fibre type food intervention such as wheat bran, oat bran, fruit (avocado; juçara berry), whole-grain cereal, and Mediterranean diet are among of the diet can be prescribed due to high fibre content.

Benefits of dietary fibre can be observed in a recent systematic review and meta-analysis of data from 185 prospective studies and 58 clinical trials with 4635 adult participants were included in the analyses, demonstrating a 15-30% decrease in all-cause and cardiovascular-related mortality and incidence of coronary heart disease, stroke incidence and mortality, type 2 diabetes, and colorectal cancer. Furthermore, it has been suggested that adherence to dietary patterns focusing attention on fibre and polyphenols can modulate human gut microbiota. Indeed, it has been shown that fibre plays a role in alleviating obesity-related health issues, potentially by modulating gut-derived metabolites SCFAs.

Our outcome analysis focused only on SCFA levels, either from faecal and serum samples of adult individuals with overweight or obesity. The majority SCFAs in the form of acetate, butyrate, and propionate have been widely investigated and may have relevance in overweight or obesity interventions. It has been suggested that a decrease in absorption or greater SCFAs utilization by colonocytes may contribute to increased transport of SCFAs to the systemic circulation. Furthermore, these parameters may be altered, potentially due to modulation of the gut microbiota following specific dietary fibre intervention.

However, not all outcomes of SCFAs levels showed similar improvements following dietary fibre interventions in adult individuals with overweight or obesity. In this review, it seems that acetate level was predominantly increased as compared with other SCFAs following dietary fibre interventions in overweight or obese individuals. Interestingly, this increased acetate level was observed in the faecal and serum samples, followed by propionate and butyrate. An improvement in this acetate, propionate, and butyrate might be partly explained by modulation of microbiota acetate, propionate, and butyrate producer (e.g. Bifidobacterium, Firmicutes, Prevotella, Akkermansia) following fibre supplementation in individuals with overweight and obesity as shown in gut microbiota data of included studies.

Of note, differential responses to SCFA levels might also be attributable to the baseline characteristics of gut microbiota. Indeed, a recent human study showed that microbiota characteristics prior to prebiotic intervention determined the outcome of gut-derived metabolites (i.e. SCFAs). Next to that, the cross-feeding mechanisms during dietary fibre intervention may also play a role in the SCFAs modulation by gut microbiota. Thus may argue that the fibre (including prebiotics) are not “one size fits all”; it may be due to variation in the SCFA production capacity of individuals’ gut microbiota across the tested fibre (including prebiotics).

Furthermore, the mode of administration or colonic fermentation site of fibre (including prebiotics) is a crucial determinant of the metabolic response. It has been shown that slowly fermentable fibres have a higher potential for influencing host metabolism, given the much higher SCFA release by the distal intestines. Next to that, in this systematic review, many included studies have used faecal SCFA as a biomarker of gut-derived
SCFA production. However, the body rapidly absorbs gut microbially produced SCFA. Consequently, faecal measurements may not represent in vivo colonic production, which is influenced by prebiotics or other colonic substrates (i.e. dietary fibre), colonic pH and microbiota composition. This may have implications for developing nutritional strategies to modulate SCFA production and improve metabolic health. Perhaps further studies should be focused on dietary fibres/prebiotics intervention that can reach the distal colon and based on more personalized baseline gut microbiota characteristics.

Our systematic review possesses a few strengths. The number of articles included is relatively modest (17 studies), with substantial total sample size and includes only human interventional studies, ensuring recent evidence is presented. We have made every effort to incorporate relevant articles by not imposing limitations on the types of dietary fibre interventions and definitions. The review process is rigorously detailed in the Methods section to ensure the transparency and clarity of the systematic review.

On the other hand, a few limitations to our review can be identified. Systematic reviews generally involve a broad range of sources, including online databases, grey literature, electronic search engines, data archives and written scientific texts. We have performed only from major database searches, which may reduce the number of studies under consideration. The systematic review framework utilized for the review recommended electronic databases and manual hand searching of reference lists, which has been performed extensively in our review. This review only includes studies written in English, allowing a possibility of language bias. The included studies were also not subjected to critical appraisal; hence, the individual studies quality is unknown.

CONCLUSION

Various dietary fibre interventions compasses of food type fibre and prebiotics supplementation to improve metabolic health among adult individuals with overweight or obesity have been attempted. The majority of studies result in improved SCFA levels in faecal and serum samples. Particularly acetate levels are predominantly elevated following the dietary fibre intervention. Future research should focus on the fibre (including prebiotics) supplementation mode that can reach the distal colonic site and a more personalized approach by considering baseline individual phenotype and gut microbiota characteristics. The findings of this review might be used as a reference for the community, particularly Indonesians who have low fibre intake, to increase fibre consumption through dietary fibre intake or fibre supplementation.

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