REVIEW

Effects of Weight-Loss Interventions on Short-Chain Fatty Acid Concentrations in Blood and Feces of Adults: A Systematic Review

Solomon A Sowah,[1,2] Lena Riedl,[1] Antje Damms-Machado,[1] Theron S Johnson,[1] Ruth Schübel,[1] Mirja Graf,[1] Ece Kartal,[3,4,5] Georg Zeller,[4] Lukas Schwingshackl,[6] Gabriele I Stangl,[7] Rudolf Kaaks,[1] and Tilman Kühn[1]

[1]German Cancer Research Center (DKFZ), Division of Cancer Epidemiology, Im Neuenheimer Feld 581, Heidelberg, Germany; [2]Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Germany; [3]Faculty of Biosciences, Heidelberg University, Heidelberg, Germany; [4]European Molecular Biology Laboratory (EMBL), Structural and Computational Biology Unit, Heidelberg, Germany; [5]Molecular Medicine Partnership Unit (MMPU), Heidelberg, Germany; [6]Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Nuthetal, Germany; and [7]Institute of Agricultural and Nutritional Sciences, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

ABSTRACT

Short-chain fatty acids (SCFAs, mainly acetate, propionate, and butyrate), which are primarily derived from the gut microbiome, may exert anti-inflammatory and immunomodulatory effects, and regulate energy homeostasis. It has been suggested that weight loss may affect SCFA metabolism, but a systematic review of intervention studies is lacking. We aimed to systematically assess the effects of dietary, physical activity–based, and surgical weight-loss interventions among overweight [body mass index (BMI) 25–29.9 kg/m^2)] or obese (BMI ≥30 kg/m^2) adults (≥18 y) on concentrations of acetate, propionate, butyrate, and total SCFAs in blood, urine, or feces. We conducted a systematic literature search in PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to April 30, 2018 for randomized and nonrandomized weight-loss trials among overweight or obese adults, in which the concentrations of individual and total SCFAs were assessed. A total of 9 studies consisting of 2 randomized parallel-arm trials, 4 crossover trials, and 3 nonrandomized clinical or surgical trials were included. In the majority of studies, changes in fecal SCFA concentrations were assessed, whereas changes in serum SCFAs were reported from 1 trial. Individual and total SCFA concentrations either remained unchanged or decreased significantly following weight loss. Three of the dietary interventions that resulted in decreased SCFA concentrations were low (≤5% of energy) in total carbohydrates. Most of the studies had a high risk of bias. Decreases in SCFA concentrations may accompany weight loss induced by bariatric surgery or dietary restriction among overweight or obese adults, particularly when carbohydrate intake is reduced. However, findings were inconsistent and based on studies with high to unclear risk of bias, and small sample sizes. Because measurements of fecal SCFAs may not be ideal due to limited sample standardization, well-powered trials with repeated blood measurements of SCFAs are required. This review was registered at PROSPERO as CRD42018088716. *Adv Nutr* 2019;10:673–684.

Keywords: weight loss, short-chain fatty acids, calorie restriction, bariatric surgery, physical activity, obesity, overweight, adults

Introduction

SCFAs, i.e., mainly acetate, propionate, and butyrate, are the major products of anaerobic fermentation of primarily nondigestible carbohydrates by the gut microbiome (1, 2). Beyond their established role as nutrients, laboratory-based mechanistic studies have shown that SCFAs may exert anticarcinogenic effects on the colonic epithelium through the inhibition of histone deacetylases and induction of apoptosis (3). Epidemiologic findings to suggest protective effects of fiber intake against colon cancer have been attributed to fiber-induced increases in SCFA production in the intestine (4, 5). Moreover, SCFAs may regulate energy homeostasis and confer anti-inflammatory as well as immunomodulatory systemic effects (6–8) via activation of the orphan G protein–coupled receptors GPR41/FFAR3 and GPR43/FFAR2, which are mainly expressed in adipose tissue, immune cells, and colonic epithelial cells (9, 10).

With regard to obesity, the role of SCFAs is controversial, and both obesity-inhibiting and obesity-promoting properties of SCFAs have been described. SCFAs may stimulate the release of anorectic hormones glucagon-like protein 1, peptide tyrosine tyrosine, and leptin, which may downregulate appetite and thus reduce caloric intake (11). Caloric intake was significantly reduced among overweight or obese adults following a targeted delivery of propionate

to the colon (11), and acetate infusion among overweight or obese men resulted in reduced intracellular lipolysis, and increased energy expenditure and fat oxidation (12). At the same time, SCFAs may provide excess calories and therefore induce weight gain (2).

Notwithstanding these potential effects of SCFAs on body weight (BW), the association between SCFAs and obesity may be bidirectional, i.e., obesity may have an effect on the SCFA metabolism, although the underlying mechanism is less clear. Small cross-sectional studies have shown higher fecal SCFA concentrations among obese individuals than among their lean counterparts (13), even at similar self-reported dietary fiber and caloric intakes (14). Such differences in SCFA concentrations have also been observed between lean and obese mice, and it has been proposed that there is a potentially higher production and turnover of SCFAs among obese individuals (15). This increased turnover could be related to differences in the composition and function of the obese microbiome compared to the nonobese microbiome, with an enhanced potential for energy harvest among obese individuals (13, 15). Consequently, weight-loss interventions have been shown to induce changes to the microbiome (16), which in turn may affect energy harvest and thus SCFA production in the gut. Paradoxically, it could be argued that a decrease of SCFA is a potential adverse effect of weight loss, given the putative health benefits of SCFA outlined above. Although achieving normal weight is recommended for the prevention of various chronic diseases, including colon cancer (4, 17), impaired SCFA production upon weight loss may counteract the benefits of normal weight, at least with respect to colon cancer prevention.

Given the lack of comprehensive evidence on the effect of weight loss on SCFAs, we aimed to conduct a systematic review summarizing the findings on changes in urine, plasma, and fecal SCFA concentrations after controlled weight loss by dietary, physical activity, or surgical intervention among humans. As dietary composition is an important determinant of SCFAs (6), we also aimed to investigate the role of dietary composition during weight loss on SCFA concentrations. The Cochrane risk-of-bias (RoB) tools for randomized and nonrandomized trials were used to evaluate the quality of the evidence (18, 19).

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Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.
Address correspondence to TK (e-mail: t.kuehn@dkfz.de).
Abbreviations used: BF, body fat; BIB, bilointestinal bypass; BW, body weight; RCT, randomized controlled trial; RoB, risk of bias; ROBINS-I, Risk of Bias in Nonrandomized Studies of Interventions; VLCD, very low calorie diet; %E, percentage of energy.

Methods

This systematic review was conducted in line with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (20) and followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (21). The protocol for this systematic review was registered with PROSPERO as CRD42018088716 (available at http://www.crd.york.ac.uk/PROSPERO).

Search strategy

Three electronic databases, namely, PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), were searched up to 23 March, 2018 (and updated on 30 April, 2018) for relevant studies based on a combination of appropriate search terms (**Supplemental Table 1**). The search strategy was developed initially in PubMed and adapted for use in other databases. No calendar date or language restrictions were used during the electronic search.

References were imported into a reference manager (Endnote) and duplicates were removed in 2 steps: automatic removal with the use of the reference manager, followed by manual removal by 1 reviewer. Each retrieved article was independently assessed for eligibility by 2 reviewers (SAS and TK), and disagreements were resolved through further discussions. The reference lists of the retrieved articles were checked to identify potentially relevant studies.

Study selection

Studies that met the following criteria were included: *1*) hypocaloric dietary, physical activity–based, or surgical weight-loss interventions among overweight or obese (BMI $\geq$25 kg/m^2) adults ($\geq$18 y); and *2*) studies that assessed blood, urine, or fecal concentrations of acetate, propionate, or butyrate following a weight-loss intervention. Studies were excluded if they were: *1*) observational trials; *2*) pharmacologic intervention trials; *3*) intervention trials in individuals with a history of major cardiovascular disease events (e.g., stroke, myocardial infarction) or gastrointestinal diseases such as irritable bowel syndrome considering that pathophysiologic alterations and medication use among individuals with chronic diseases may strongly affect the microbiome and SCFA production (22–24); or *4*) in vitro experiments or studies in animal models.

Data extraction

One reviewer (SAS) used a data-extraction template to extract information on the first author, publication year, participant characteristics (age, sex, and health status), study design, type of intervention, duration of intervention, and changes in acetate, propionate, butyrate, and total SCFA concentrations. Information on the changes in BW, body fat (BF), or BMI was also recorded, where available. The

completeness of the extracted data for each study was evaluated by a second reviewer (LR).

Risk of bias assessment

An RoB assessment was conducted for each study included in this review. The Cochrane RoB tool for randomized controlled trials (RCTs) was used to assess the RoB of RCTs based on: random sequence generation, allocation concealment, selective reporting, incomplete outcome data, and blinding of participants or study personnel (18). For nonrandomized trials, RoB was assessed in 7 domains through the use of the Cochrane "Risk of Bias in Nonrandomized Studies of Interventions" (ROBINS-I) tool: bias due to confounding, selection of study participants, classification of interventions, deviations from the intended interventions, missing data, measurement of outcomes, and selection of the reported results (19).

Qualitative data synthesis

A qualitative synthesis of the findings on the changes in the concentrations of the major and total SCFAs following weight loss induced by surgery, diet, or physical activity in overweight or obese individuals is discussed in this review. Substantial heterogeneity in the selected studies precluded performing a meta-analysis.

Results

Database search

A total of 836 records were retrieved by the initial database and manual search, out of which 736 remained after duplicates were removed. The titles and abstracts of the remaining studies were screened, and a further 708 studies were excluded for not meeting the eligibility criteria. Nine full-text studies that met the review criteria were retained for inclusion in the qualitative synthesis, after 18 full-text articles (**Supplemental Table 2**) were excluded with reasons (**Figure 1**). A flowchart of the detailed study selection process is shown in Figure 1.

Characteristics of the included studies

A summary of the 9 weight-loss trials included in this review is provided in **Table 1** (RCTs), **Table 2** (randomized crossover trials) and **Table 3** (nonrandomized trials). The publication dates of the included studies ranged from 2007 (25) to 2018 (26). The sample size of the studies ranged between 19 (27) and 91 (28) adults.

Study participants

One study recruited only women (29), whereas 5 studies were carried out exclusively among men (25, 26, 30–32), and 3 studies included both sexes (27, 28, 33). For studies

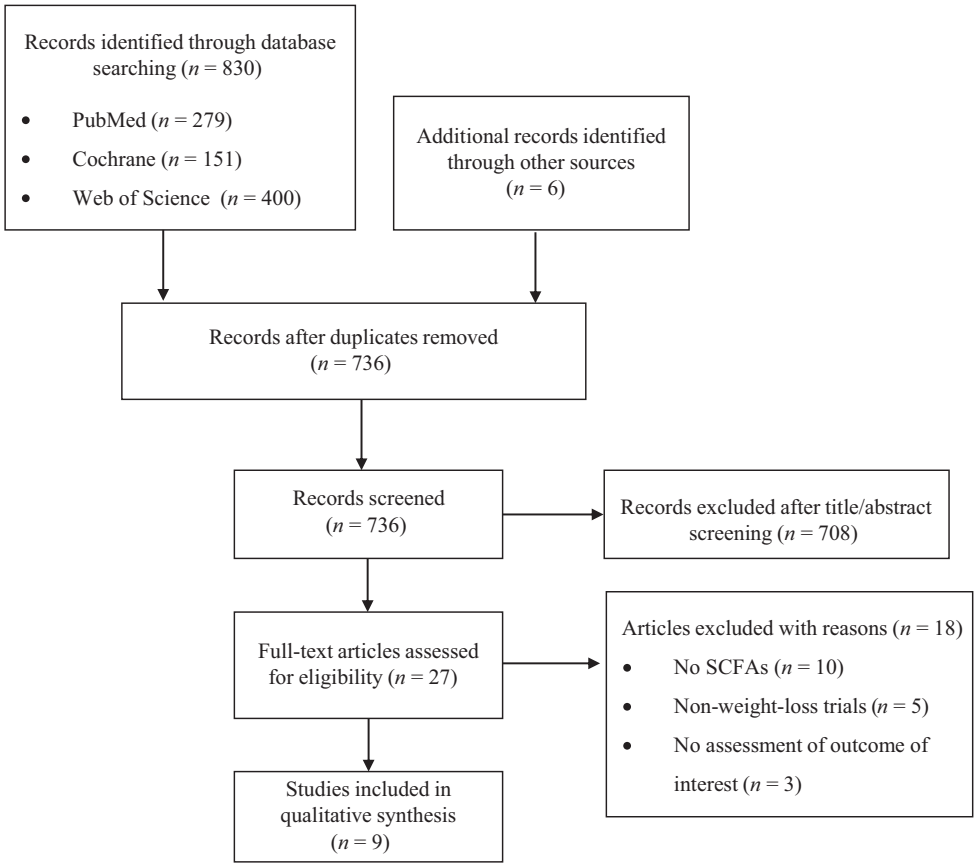

FIGURE 1 Flowchart summarizing studies evaluated and selected for the systematic review.

TABLE 1 Summary of randomized controlled trials of dietary weight-loss interventions among obese or overweight adults[1]

Study (ref)	Study design	Participant characteristics	Sample, *n*	Age,[2] y	BMI,[2] kg/m^2	Treatment (intervention, duration and level of control)	Changes in SCFA concentrations after intervention[3]				Technique and specimen	Anthropometry[4]
							Acetate	Propionate	Butyrate	Total		
Benassi-Evans et al. (30)	RCT, parallel	OW/OB men with at least 1 other risk factor for CVD	M: 33	(20–65)	(27–40)	High-protein/high red meat (35%E protein, 40%E carbohydrate) isocaloric energy-restricted dietary intervention for 12-wk intensive weight loss followed by weight maintenance for up to 52 wk	↔	↔	↔	↔	GC (feces)	9.3 ± 0.7 kg average weight loss after 12 wk for both diet groups. No significant weight change was observed from weeks 12 to 52 in either group
						High-carbohydrate (17%E protein, 58%E carbohydrate) energy-restricted dietary intervention for 12-wk intensive weight loss followed by weight maintenance for up to 52 wk. All diets were prescribed	↔	↔	↔	↔		
Brinkworth et al. (28)	RCT, parallel	OW/OB men and women with abdominal obesity and at least one other metabolic risk factor	M: 18; F: 30	50.4 ± 7.7	33.5 ± 4.1	Energy-restricted (~6–7 MJ, 30% deficit) low-carbohydrate diet (35%E protein, 61%E fat, and 4%E carbohydrate) for 8 wk. Diet was prescribed	↓	↔	↓	↓	GC (feces)	The low-carbohydrate diet group had a significantly greater weight loss than the high-carbohydrate group (7.6 ± 2.6 kg vs 6.0 ± 2.8 kg) after 8 wk
		OW/OB men and women with abdominal obesity and at least one other metabolic risk factor	M: 18; F: 25	51.0 ± 7.5	33.9 ± 4.4	Energy-restricted (~6–7 MJ, 30%E deficit) high-carbohydrate diet (24%E protein, 30%E fat, and 46%E carbohydrate) for 8 wk. Diet was prescribed	↔	↔	↔	↔		

[1] *n* = 2. BMI, body mass index; CVD, cardiovascular disease; F, female; GC, gas chromatography; M, male; OB, obese; OW, overweight; RCT, randomized controlled trial; ref, reference; SCFA, short-chain fatty acid; %E, percentage of energy.
[2] values are means ± SDs or means ± SEMs; minimum-maximum in parenthesis (all such values).
[3] ↓ = significant within-group decrease; ↑ = significant within-group increase; ↔ = no change; ∗significantly stronger decrease compared with other groups in the study.
[4] Amount of weight loss expressed as mean ± SD or mean ± SEM.

TABLE 2 Summary of randomized crossover studies of dietary weight-loss interventions among obese or overweight adults[1]

Study (ref)	Study design	Participant characteristics	Sample, *n*	Age,[2] y	BMI,[2] kg/m^2	Treatment (intervention, duration and level of control)	Changes in SCFA concentrations after intervention[3]				Technique and specimen	Anthropometry[4]
							Acetate	Propionate	Butyrate	Total		
Duncan et al. (25)	Randomized crossover design	OB healthy men	M: 19	20–57	30–42	maintenance diet (M) (13%E protein, 52%E carbohydrate, and 35%E fat) for 3 d. Diet was provided	—	—	—	—	GC (feces)	6.34 ± 2.24 and 4.35 ± 2.61 kg of weight loss with the high-protein/low-carbohydrate diet and the high-protein/medium-carbohydrate diet, respectively (34)
						High-protein/medium-carbohydrate weight-loss diet (<8.5 MJ/d) (30%E protein, 35%E carbohydrate, 35%E fat) for 4 wk. Diet was provided	↓	↓	↓	↓		
						High-protein/low-carbohydrate weight-loss diet (<8.5 MJ/d) (30%E protein, 4%E carbohydrate, and 66%E fat) for 4 wk. Diet was provided	↓	↓	↓*	↓		
Gratz et al. (26)	Randomized crossover design	OW/OB healthy men	M: 18	21–70	26.5–51.7	Normal-protein weight-loss diet (9 MJ/d) (15%E protein, 55%E carbohydrate) for 10 d after a weight-maintenance diet (13 MJ/d). Diet was provided	↔	↔	↓	↔	GC (feces)	Similar weight loss with all 3 diets (average 4.1 kg). Significant decrease from 116.4 kg on maintenance diet to 112.5 kg on NPWL, 112.15 kg on NPAAWL and 112.36 kg on HPWL
						Normal protein enriched with free amino acids and moderate amounts of carbohydrate weight-loss diet (9 MJ/d) (15%E protein, 15%E free AA, and 40%E carbohydrate) for 10 d after a weight-maintenance diet (13 MJ/d). Diet was provided	↔	↔	↓	↔		
						High protein containing moderate amounts of carbohydrate weight-loss diet (30%E protein and 40%E carbohydrate) for 10 d after a weight-maintenance diet (13 MJ/d). Diet was provided	↔	↔	↓*	↔		

(*Continued*)

TABLE 2 (*Continued*)

Study (ref)	Study design	Participant characteristics	Sample, *n*	Age,[2] y	BMI,[2] kg/m^2	Treatment (intervention, duration and level of control)	Changes in SCFA concentrations after intervention[3]				Technique and specimen	Anthropometry[4]
							Acetate	Propionate	Butyrate	Total		
Russell et al. (31)	Randomized crossover design	OB healthy men	M: 17	21–74	27.9–48.5	Weight-maintenance diet (13%E protein, 50%E carbohydrates, and 37%E fat) for 7 d. Diet was provided	—	—	—-		GC (feces)	
						High-protein and moderate-carbohydrate (28%E protein, 35%E carbohydrate, and 37%E fat) weight-loss diet (8.3 MJ/d) for 4 wk. Diet was provided.	↔	↓	↔	↔		Mean weight loss of 3.99 kg (3.59% of BW) after 4 wk
						High-protein and low-carbohydrate (29%E protein, 5%E carbohydrate, and 66%E fat) weight-loss (8.3 MJ/d) diet for 4 wk. Diet was provided	↓*	↓	↓*	↓*		Mean weight loss of 6.43 kg (5.77% of BW) after 4 wk
Salonen et al. (32)	Randomized crossover design	OW/OB men with metabolic syndrome	M: 14	27–73	27.9–51.3	Consumption of a run-in weight-maintenance (M) (427 g carbohydrate/d, 13.26 MJ/d) standardized diet for 1 wk and then after consumption of a high resistant starch diet (RS) (434 g carbohydrate/d, 13.26 MJ/d) for 3 wk and a high nonstarch polysaccharide diet (NSP) (427 g carbohydrate/d, 13.70 MJ/d) for 3 wk, both at weight maintenance. A high-protein (144.1 ± 2.31 g/d) and medium-carbohydrate (201.2 ± 9.68 g/d) weight-loss diet (8.10 MJ/d) was consumed for the final 3 wk. Uncooked food (for 30% of energy) was provided	↓	↓	↓	↓	GC (feces)	Mean BW and BF were similar during the M, RS, and NSP diet. There was a significant reduction in initial mean BW (121.1 kg) and BF (49.0) by 6.1 and 4.9 kg, respectively, after the consumption of the weight loss diet

[1] *n* = 4. BF, body fat; BMI, body mass index; BW, body weight; GC, gas chromatography; M, male; OB, obese; OW, overweight; ref, reference; SCFA, short-chain fatty acid; %E, percentage of energy.
[2] Values are ranges.
[3] ↓ = significant within-group decrease; ↑ = significant within-group increase; ↔ = no change; *significantly stronger decrease compared with other groups in the study.
[4] Amount of weight loss expressed as means ± SDs, means ± SEMs, or as a percentage.

TABLE 3 Summary of nonrandomized (dietary and bariatric surgery) weight-loss trials among obese or overweight adults[1]

Study (ref)	Study design	Participant characteristics	Sample, *n*	Age,[2] y	BMI,[2] kg/m^2	Treatment (intervention, duration, and level of control)	Changes in SCFA concentrations after intervention[3]				Technique and specimen	Anthropometry[4]
							Acetate	Propionate	Butyrate	Total		
Damms-Machado et al. (29)	Clinical trial (nonrandomized)	OB women	F: 15	48 ± 3	40.2 ± 1.0	VLCD (800 kcal/d for 12 wk, fiber 15 g/d) as part of a weight-loss program that involved exercise units, nutrition counselling, and behavior modification over 26 wk. Formula diet was provided	↔	↔	↔	↔	GC (feces)	17.2 ± 0.8% and 24.6 ± 0.8% relative weight loss after 3 and 6 months, respectively
		OB women	F: 15	48 ± 3	45.8 ± 0.9	LSG	↔	↔	↔	↔		16.1 ± 1.1% and 23.9 ± 1.6% relative weight loss after 3 and 6 months, respectively
Dao et al. (33)	Intervention (single-arm)	OW/OB healthy men and women	M: 8; F: 41	(25–65)	(25–38)	6-wk calorie restriction (1200 kcal/d for women and 1500 kcal/d for men) diet enriched with fiber and protein (35%E protein, 25%E fat, and 40%E carbohydrate) followed by a 6-wk weight stabilization period. All diets were prescribed	↓	—	—	—	NMR (serum)	Weight loss of −5.85 ± 0.3% and −5.6 ± 0.6% after 6 and 12 wk compared with baseline, respectively
Patrone et al. (27)	Intervention (single-arm)	Morbidly or severely obese patients with at least one comorbidity factor	M: 2; F: 9	(35–64)	(33.4–58.8)	Bariatric surgery (BIB)	↓	↓	↔	↔	GC (feces)	Significant decrease in BMI from 47.46 ± 7.46 to 40.68 ± 5.88 kg/m^2, 24 wk after bariatric surgery

[1] *n* = 3. BMI, body mass index; F, female; GC, gas chromatography; LSG, laparoscopic sleeve gastrectomy; M, male; NMR, nuclear magnetic resonance spectroscopy; OB, obese; OW, overweight; ref, reference; SCFA, short-chain fatty acid; VLCD, very low calorie diet; %E, percentage of energy.
[2] Values are means ± SDs or means ± SEMs; minimum-maximum in parenthesis (all such values).
[3] ↓ = significant within-group decrease; ↑ = significant within-group increase; ↔ = no change.
[4] Amount of weight loss or change in BMI expressed as means ± SDs, means ± SEMs, or as a percentage.

that reported age ranges, this was between 20 and 74 y. Participants in each study were either overweight or obese at baseline, with BMI ranging from 25 to 58.8 kg/m^2, and mean BMIs from 33.5 to 45.8 kg/m^2.

Weight-loss interventions

Six of the studies were RCTs, with either crossover or parallel-arm designs, whereas the other 3 studies were nonrandomized interventions. None of the interventions induced weight loss through physical activity alone. Weight loss was based on a dietary intervention in 7 studies (25, 26, 28, 30–33), and by bariatric surgery [biliointestinal bypass (BIB)] in 1 study (27). One other study by Damms-Machado et al. investigated the effects of both surgical and a dietary weight-loss intervention in a parallel-arm trial (29). The dietary intervention in this trial started with a 12-wk period of very low calorie diet (VLCD; 800 kcal/d), followed by a 6-wk refeeding phase, and 7-wk stabilization phase, which were paralleled by physical activity classes. Overall, the duration of dietary interventions in the included studies ranged from 3 to 12 wk, with follow-up periods of up to 52 wk (Tables 1–3). In surgical weight-loss trials, evaluation of SCFA concentrations was carried out between 12 and 24 wk postsurgery. Each study reported significant weight losses following the interventions (shown in Tables 1–3). Changes (absolute or percentage) in BW, BMI, or BF were reported relative to baseline or maintenance values (in the case of dietary interventions).

Biospecimen, analytical technique, and SCFA measured

SCFA concentrations were quantified in feces in 8 studies with the use of GC (25–32), whereas serum SCFA concentration was measured by NMR spectroscopy in 1 study (33). None of the studies assessed SCFA concentrations in urine. Concentrations of the 3 major SCFAs, acetate, propionate, and butyrate, as well as total SCFAs, were measured in all but 1 study (which assessed acetate only) (33).

Weight loss in relation to changes in SCFA

Parallel-group randomized trials.

Benassi-Evans et al. (30) found no significant changes in concentrations of total or individual SCFAs in fecal samples of 33 overweight or obese men, after an average weight loss of 9.3 ± 0.7 kg over 12 wk achieved by either a high-protein (35%E) or a high-carbohydrate (58%E) weight-loss diet, with similar fiber contents (50 g/d). Weight loss was not reported by trial arm, although the authors stated that there was no significant difference between the groups. After a maintenance phase of 40 wk, no significant changes in SCFA concentrations were observed either (30).

In another randomized controlled study by Brinkworth et al. (28), in which a total of 121 overweight or obese adults were prescribed with either an energy-restricted high carbohydrate (46%E, fiber: 31.5 ± 5.0 g/d) diet or an energy-restricted low-carbohydrate (4%E, fiber: 13.0 ± 2.0 g/d) diet (30% energy deficit for both diets) for 8 wk, no significant variations were observed in the total and major fecal SCFA concentrations in the former group. Participants in the low-carbohydrate group, who achieved greater weight loss (7.6 ± 2.6 compared with 6.0 ± 2.8 kg) than the high-carbohydrate group, had significantly reduced fecal concentrations of acetate, butyrate, and total SCFAs, although propionate concentrations did not change in comparison to baseline. The differences in the changes of acetate, butyrate, and total SCFA concentrations between the 2 groups were statistically significant. To promote compliance, uncooked and preweighed foods designed to provide 30% of total energy intake and the key macronutrients of each diet intervention were supplied to participants in this trial.

Randomized crossover trials.

In a randomized crossover trial by Gratz et al. (26), in which all foods (breakfast, lunch, and dinner) were prepared, weighed, and served to overweight or obese, but otherwise healthy men ($n = 18$), absolute concentrations of propionate, acetate, and total fecal SCFAs did not change following consumption of a normal-protein weight-loss diet (9 MJ/d, 2154.27 ± 270.14 kcal/d) for 10 d, a normal-protein weight-loss diet enriched with free amino acids and moderate amounts of carbohydrates (40%E, fiber: 19.92 ± 2.68 g/d), or a high-protein diet containing moderate amounts of carbohydrate (40%E, fiber: 18.13 ± 2.39 g/d). Absolute butyrate concentrations decreased with all 3 weight-loss diets over time, with significantly stronger decreases upon the high-protein diet containing moderate amounts of carbohydrate. Each dietary intervention achieved an average weight loss of 4.1 kg.

In another randomized crossover trial by Russell et al. (31) involving 17 obese healthy men, 4-wk intake of a high-protein (28%E) and moderate-carbohydrate (35%E) weight-loss diet that resulted in a mean weight loss of 3.99 kg (3.59% BW) did not significantly alter acetate, butyrate, and total SCFA concentrations in feces compared with a maintenance diet. A decrease in fecal propionate concentration was, however, observed following the high-protein and moderate-carbohydrate diet. In the same study, a high-protein (29%E) and low-carbohydrate (5%E) weight-loss diet, which achieved greater average weight loss (6.43 kg or 5.77% BW compared with 3.99 kg or 3.59% BW) also resulted in a significant decrease in the major and total fecal SCFA concentrations after 4 wk, with butyrate concentration decreasing by 50% (31).

In a similar crossover trial, Duncan et al. (25) randomized 19 obese but healthy men to consume a high-protein (30%E) and medium-carbohydrate (35%E) and a high-protein (30%E) and low-carbohydrate (4%E) weight-loss diet, each diet weighed and supplied for 4 wk in a crossover design. Upon entry into the trial, participants were initially provided with a 3-d energy maintenance diet. In this study, fecal concentrations of major and total SCFAs decreased significantly with weight loss (low-carbohydrate: −6.34 ± 2.24 kg, medium-carbohydrate: −4.35 ± 2.61 kg) within both intervention groups, although there was no

significant difference between the medium-carbohydrate and the low-carbohydrate high-protein diets (34).

Salonen et al. (32) observed that the concentrations of all major SCFAs and total SCFAs decreased significantly compared with both a run-in standardized and a high nonstarch polysaccharide maintenance diet in a randomized crossover trial, in which 14 overweight and obese men with metabolic syndrome consumed either a fully controlled high-protein (144.1 ± 2.31 g/d) or a medium-carbohydrate (201.2 ± 9.68 g/d) weight-loss diet (8.10 MJ/d) for 3 wk. Participants were reported to have significantly lost 6.4 and 4.9 kg of BW and BF, respectively, after the intervention. The weight-loss diet period was preceded by a run-in diet (427 g carbohydrates/d, 13.26 MJ/d) for 1 wk, a high-resistant starch diet (427 g carbohydrates/d, 13.26 MJ/d) for 3 wk, and a high nonstarch polysaccharide diet for 3 wk (434 g carbohydrates/d, 13.70 MJ/d), all fully controlled at weight maintenance (32).

Nonrandomized trials

Total and major SCFA concentrations assessed after 3 and 6 mo did not significantly change when 15 overweight or obese women exclusively consumed a very low calorie formula diet (Optifast 800 formula, Nestlé Inc.; 800 kcal/d, fiber content: 15 g/d) for 12 wk as part of a multidisciplinary weight-loss intervention (OPTIFAST 52) in a parallel-arm trial by Damms-Machado et al. (29). After 12 wk consumption of the VLCD, solid food was reintroduced for 6 wk without change in energy intake, followed by a 7-wk stabilization period during which the increase in energy intake was stepwise (exact data on energy intake in the last phase of the trial were not reported, neither were data on fiber intake after the first 12 wk of VLCD). Participants attained a relative weight loss of 17.2 ± 0.8% and 24.6 ± 0.8%, respectively, 3 and 6 mo after baseline. Just as observed in the VLCD group, participants who underwent laparoscopic sleeve gastrectomy did not show significant changes in their fecal concentrations of major and total SCFAs assessed at 12 and 24 wk after surgery in the study by Damms-Machado et al. (29). Relative weight loss of 16.1 ± 1.1% and 23.9 ± 1.6% was recorded after 3 and 6 mo, respectively, following the weight-loss surgery (29).

Patrone et al. (27) assessed fecal SCFA concentrations among 11 participants with severe (BMI >35 kg/m^2) or morbid (BMI >40 kg/m^2) obesity before and after BIB surgery which resulted in a significant decrease in BMI from 47.46 ± 7.46 to 40.68 ± 5.88 kg/m^2 after 24 wk. Following weight loss (after 24 wk), fecal butyrate and total SCFA concentrations remained unchanged although the concentrations of acetate and propionate decreased significantly (27). Average daily caloric intake postsurgery was also significantly lower than baseline (3008.11 ± 799.31 compared with 1540.28 ± 378.16 kcal) (27).

Lastly, the only study in which NMR was used to quantify SCFA in serum (33) included 49 overweight and obese but healthy participants (41 women) recruited as part of a calorie-restriction weight-loss intervention (35). Throughout the intervention, in which participants consumed prescribed calorie-restricted diets (women, 1200 kcal/d; and men, 1500 kcal/d) enriched with fiber and protein for 6 wk, followed by a 6-wk weight stabilization phase, serum acetate concentrations were shown to decrease significantly, accompanied by significant weight loss after 6 wk. Participants achieved a total weight loss of −5.85 ± 0.3% and −5.6 ± 0.6% after 6 and 12 wk, respectively, compared with baseline (33).

Risk of bias

An evaluation of the RoB was performed for the 6 RCTs (2 parallel-arm and 4 crossover trials) and the 3 nonrandomized interventions included in this review. Among the RCTs, RoB was low to high across the bias domains, with random sequence generation unclear in all the studies, and allocation concealment unclear in 5 of the studies (**Supplemental Table 3**). Unclear RoB pertained mostly due to inadequate description of the random sequence generation and the concealment of allocation in the RCTs. Selective reporting was low in 6 studies, and all of the studies had low RoB with respect to blinding of outcome assessment. Bias due to incomplete outcome data was also low in 6 of the studies. Overall RoB was high in all the RCTs, mainly contributed by the lack of blinding in the RCTs. The nonrandomized interventions also showed low to moderate RoB across the 7 domains of bias based on the ROBINS-I tool (**Supplemental Table 4**) (19). Two of the nonrandomized interventions were judged to have moderate RoB overall, and 1 study had an overall low RoB.

Discussion

In this systematic review, we evaluated and summarized the evidence on alterations in blood and fecal SCFA metabolite profiles following weight-loss interventions. Overall, the number of intervention studies on weight loss and SCFA was small, with only 9 smaller studies meeting the inclusion criteria. Weight loss was induced with a dietary intervention in 7 studies, of which 4 were randomized crossover trials (25, 26, 31, 32), 2 were randomized parallel-arm trials (28, 30), and 1 was a parallel-arm trial that also included a surgical arm (29). Bariatric surgery (BIB) was used to induce weight loss in 1 study (27).

With regard to total SCFAs, concentrations were shown to decrease with weight loss in 3 studies (25, 28, 32), whereas no significant changes were reported in 4 studies (26, 27, 29, 30). One other study reported decreased concentrations of total SCFAs after a low-carbohydrate weight-loss diet and unchanged concentration after a weight-loss diet containing higher carbohydrate amounts (31). Analyses of changes in fecal butyrate in response to weight loss showed that butyrate concentrations decreased in 2 studies (25, 32), and remained unchanged in 3 studies (27, 29, 30). Both decreased and unchanged concentrations were reported in 3 studies, with the decreased concentrations achieved with low-carbohydrate diets in 2 of the studies (28, 31) and with

a moderate amount of carbohydrates in the other study (26). For acetate, 5 studies reported decreased concentrations following the weight-loss intervention (25, 27, 28, 31, 32). Again, 2 studies comparing weight-loss diets with different carbohydrate amounts showed stronger decreases in acetate with lower carbohydrate amounts (28, 31). Three other studies did not find any changes in the concentrations after weight loss (26, 29, 30). Finally, with respect to propionate, whereas reduced concentrations upon weight loss were reported in 4 studies (25, 27, 31, 32), 4 studies did not find any changes (26, 28–30). The only study on serum SCFAs showed that acetate concentrations decreased throughout the weight-loss intervention (33).

Several of the studies reviewed here suggest that beyond weight loss per se, weight loss induced by diets with a low carbohydrate amount may lead to decreases in fecal SCFA, particularly butyrate (25, 26, 28, 31). In light of evidence that SCFAs, and especially butyrate, potentially exert anticarcinogenic effects in the intestine (3, 36), these studies indicate that weight-loss diets should contain sufficient amounts of fiber. However, in a dietary intervention study among obese children, the concentrations of all the major SCFAs decreased significantly after 30 d despite the weight-loss diet containing standardized high amounts of nondigestible carbohydrates (37). A recent meta-analysis also found no effect of dietary fiber consumption on total fecal SCFA concentrations among healthy adults (38). Moreover, in a study that compared women 9.4 y after they had undergone either Roux-en-Y gastric bypass or vertical banded gastroplasty with matched obese controls, SCFA concentrations were found to be reduced in the Roux-en-Y gastric bypass and vertical banded gastroplasty women despite similar total fiber intakes (39).

Alternatively, the tendency of SCFA concentrations to decrease upon weight-loss may be an indication of reduced efficiency with which energy is harvested from dietary SCFAs during weight loss among overweight or obese individuals (15). Consistent with this theory, lower fecal concentrations of major and total SCFAs have been associated with the lean phenotype in observational human studies (13, 14, 40). In addition to reduced efficiency in energy harvest from undigested food, increased mucosal absorption and utilization of SCFAs in peripheral tissues and colonocytes in response to prolonged calorie restriction has been proposed to explain the lower fecal or plasma SCFA concentrations observed after weight loss. Acetate and propionate are hepatically oxidized to yield energy and incorporated into intestinal gluconeogenesis, respectively, whereas butyrate is rapidly absorbed and used as fuel by colonic epithelial cells (6, 41). Taken together, the amounts of SCFAs quantified in feces or plasma could represent a balance between the amounts produced in the large intestine and that which is absorbed or utilized in vivo (42). A greater degree of weight loss may therefore be associated with increased absorption and utilization of SCFAs in vivo, and thus lower concentrations quantified in plasma or feces during weight loss.

Strengths and limitations

This is the first study to systematically summarize the evidence on alterations in blood and fecal SCFA metabolite profiles following a weight-loss intervention. Studies of interest were retrieved and assessed independently by 2 reviewers and from 3 databases by a prespecified protocol. The high risk of overall bias within the RCTs reviewed relates to the lack of blinding of participants and study personnel in the studies (Supplemental Tables 2 and 3), although this is extremely difficult to achieve in these types of studies (43, 44). More importantly, most of the studies had small sample sizes, with SCFA concentrations assessed in an exploratory manner, hence differences in the metabolite concentrations before and after intervention may have been difficult to detect as a result of insufficient power. Some of the studies were further carried out among participants, who were heterogeneous regarding key characteristics such as age and BMI (with wide ranges in some of the included trials), and important subgroup analyses were not possible given the smaller sample sizes. Geographic diversity, a determinant of microbiome composition, was not accounted for. In addition, the studies had short durations, with the exception of 1 study, in which SCFA concentrations were assessed 1 y after the intervention (30). Another limitation of the included studies is that SCFAs were mostly measured in fecal samples. The diverse fecal sample collection, preservation, and processing methods are all significant sources of variation in the quantification of SCFAs in a complex biological sample such as feces, which may have obscured findings from the included studies. With regard to serum SCFAs, it can be questioned whether concentrations in the peripheral blood stream reflect microbiome-derived SCFAs, as these may be mainly transported within the enterohepatic circulation and metabolized by the liver. Furthermore, acetate in the serum may be produced endogenously through glucose, fatty acid as well as amino acid metabolism (45). However, assessment of SCFA concentrations in blood sampled from the portal vein, which may be more accurate, is burdensome and has only been carried out in patients undergoing surgery (41), and sudden death victims (1). Nonetheless, there was consistency in the analytic technique used to quantify SCFAs as 8 out of the 9 studies used GC.

How shifts in the gut microbial composition, which were assessed in 7 of the studies, may have mediated the observed alterations in the concentrations of SCFAs was not discussed, as it was beyond the scope of this present review. Such information will nevertheless improve understanding of the gut microbiome's role in weight loss through SCFA production. It is further noteworthy that the anticarcinogenic effects of butyrate are putative, and there are mechanistic studies to suggest that butyrate may rather promote the development of colonic tumors (the so-called "butyrate paradox") (31). As such, fecal or circulating SCFAs cannot be considered as established biomarkers of intermediate disease risk at this time. Therefore, the findings of this review should be interpreted in consideration of the inherent limitations of the included original studies, and clearly points to the

need for more comprehensive, longer randomized trials with larger numbers of participants.

Conclusions

This systematic review suggests either a lowering or neutral effect of diet- or surgery-induced weight loss on individual and total SCFA concentrations in feces, although published studies are small and may have a high risk of bias. Lower SCFA concentrations during weight loss may be related to lower SCFA production in response to lower carbohydrate intake, or decreased energy harvest from the diet, or increased mucosal absorption. Interventions with varying and controlled fiber consumption during weight loss may help to determine to what degree changes in SCFA concentrations are a result of weight loss, changes in fiber intake, or a combination of these effects. Future prospective studies on SCFAs and colon cancer risk should take possible effect modification by obesity into account.

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