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Dairy proteins, dairy lipids, and postprandial lipemia in persons with abdominal obesity (DairyHealth): a 12-wk, randomized, parallel-controlled, double-blinded, diet intervention study[1–3]

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ABSTRACT

Background: Abdominal obesity and exaggerated postprandial lipemia are independent risk factors for cardiovascular disease (CVD) and mortality, and both are affected by dietary behavior.

Objective: We investigated whether dietary supplementation with whey protein and medium-chain saturated fatty acids (MC-SFAs) improved postprandial lipid metabolism in humans with abdominal obesity.

Design: We conducted a 12-wk, randomized, double-blinded, diet intervention study. Sixty-three adults were randomly allocated to one of 4 diets in a 2 × 2 factorial design. Participants consumed 60 g milk protein (whey or casein) and 63 g milk fat (with high or low MC-SFA content) daily. Before and after the intervention, a high-fat meal test was performed. We measured changes from baseline in fasting and postprandial triacylglycerol, apolipoprotein B-48 (apoB-48; reflecting chylomicrons of intestinal origin), free fatty acids (FFAs), insulin, glucose, glucagon, glucagon-like peptide 1 (GLP-1), and gastric inhibitory polypeptide (GIP). Furthermore, changes in the expression of adipose tissue genes involved in lipid metabolism were investigated. Two-factor ANOVA was used to examine the difference between protein types and fatty acid compositions, as well as any interaction between the two.

Results: Fifty-two participants completed the study. We found that the postprandial apoB-48 response decreased significantly after whey compared with casein ($P = 0.025$) independently of fatty acid composition. Furthermore, supplementation with casein resulted in a significant increase in the postprandial GLP-1 response compared with whey ($P = 0.003$). We found no difference in postprandial triacylglycerol, FFA, insulin, glucose, glucagon, or GIP related to protein type or MC-SFA content. We observed no interaction between milk protein and milk fat on postprandial lipemia.

Conclusion: We found that a whey protein supplement decreased the postprandial chylomicron response compared with casein in persons with abdominal obesity, thereby indicating a beneficial impact on CVD risk. This trial was registered at clinicaltrials.gov as NCT01472666. *Am J Clin Nutr* 2015;101:870–8.

Keywords: dairy, milk protein, whey, casein, milk fat, medium-chain saturated fatty acid, abdominal obesity, postprandial lipemia, apoB-48, incretin, adipose tissue gene expression

INTRODUCTION

Obesity leads to exaggerated postprandial lipemia, an independent risk factor for cardiovascular disease (CVD)[4] and death (1–3). Lifestyle factors, including inappropriate dietary behavior, are fundamental to the development of obesity. The consumption of dairy products is found to reduce the risk of CVD, diabetes, obesity, and total mortality; however, conflicting findings have been reported (4–8). Given the varying composition of dairy products, it is important to investigate the effects of individual nutritional components as well as their potential interactions.

Dairy products are rich in proteins (whey and casein) that possess latent beneficial health effects. Whey protein provides high satiety (9), lowers blood pressure (10), stimulates insulin (11) and incretin release (12), and reduces postprandial blood

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[4] Abbreviations used: apoB-48, apolipoprotein B-48; *CD36*, cluster of differentiation 36 (fatty acid translocase); CH, casein + high medium-chain SFA; CL, casein + low medium-chain SFA; CVD, cardiovascular disease; E%, energy percentage; *FABP4*, fatty acid binding protein 4; *FAS*, fatty acid synthase; FDR, false discovery rate; FFA, free fatty acid; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; *GPR120*, G protein–coupled receptor 120; LC-SFA, long-chain SFA; *LPL*, lipoprotein lipase; MC-SFA, medium-chain SFA; T2D, type 2 diabetes; WH, whey + high medium-chain SFA; WL, whey + low medium-chain SFA.

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glucose (11). Furthermore, we have previously shown that a whey protein supplement to a fat-rich meal decreases postprandial triacylglycerol responses compared with other protein types in subjects with type 2 diabetes (T2D) (13).

In addition, dairy products contain high amounts of SFAs. SFAs traditionally have been linked to an increased risk of CVD. However, recent meta-analyses do not support this (14, 15), and focus cannot purely be on "total SFA" content given the diversity of compositions of SFAs in different food items (16). Milk fat is rich in medium-chain SFAs (MC-SFAs) (chain length C6–C12), which can be increased by changing the cattle feeding regimen (17–19). Interestingly, the biological effects of MC-SFAs are different from those of long-chain SFAs (LC-SFAs) (chain length ≥C14) (20). The gastrointestinal hydrolysis and absorption of MC-SFAs are faster than that of LC-SFAs. The majority of absorbed MC-SFAs is transported directly to the liver (20), whereas LC-SFAs are first incorporated into chylomicrons with the apolipoprotein apoB-48. After hydrolysis of triacylglycerol, chylomicrons are called chylomicron remnants, which take part in the formation of atherosclerotic plaques (21). Some studies show beneficial effects of MC-SFAs on weight control, glucose, and lipid metabolism (20), but results remain conflicting (22, 23).

We hypothesized that whey protein and milk fat enriched in MC-SFAs have beneficial and synergistic effects on the postprandial lipid metabolism. The aim of the present human intervention study was primarily to investigate the long-term effects of whey and MC-SFA supplementation on postprandial plasma concentrations of apoB-48, triacylglycerol, and free fatty acids (FFAs) and on the expression of genes involved in the lipid metabolism in the subcutaneous adipose tissue.

METHODS

Study design

The study was performed as a randomized, parallel-controlled, double-blinded, 12-wk diet intervention study. The study participants were randomized in a 2 × 2 factorial design to one of 4 diets: whey + low MC-SFA (WL), whey + high MC-SFA (WH), casein + low MC-SFA (CL), or casein + high MC-SFA (CH). The randomization was performed according to 2 randomization lists created by STATA version 12 (StataCorp LP). One randomization list was created for abdominally obese participants with metabolic syndrome and one for abdominal obese participants without metabolic syndrome. Each randomization code was packed in individually sealed and numbered envelopes. By mistake, one envelope with a CH code was skipped during the study, resulting in only 14 participants being randomly allocated to CH, whereas 17 participants were randomly allocated to WH.

The study was maintained strictly double-blinded throughout the entire period through coding of test products. The codes for the protein types and for the fatty acid composition of the butter were kept under lock at Arla Foods Ingredients Group P/S (Viby J., Denmark) and the Danish Cattle Research Centre (Foulum, Denmark), respectively.

The primary outcome, postprandial lipemia, was evaluated by triacylglycerol, apoB-48 responses, and FFAs. The secondary outcomes were postprandial insulin, glucose, glucagon, glucagon-like peptide 1 (GLP-1), and gastric inhibitory polypeptide (GIP) responses as well as adipose tissue gene expressions. **Figure 1** presents the study design and visit schedule.

The screening visit and the meal test days were all fasting visits. Smoking was not permitted at the fasting visits, and alcohol consumption was not permitted during the 2 d before the fasting visits. Anti-inflammatory drugs were not allowed 4 d before the meal test days, and no strenuous exercise was permitted the day before the fasting visits.

Study participants

Sixty-three abdominally obese Caucasian participants were recruited through local newspapers and electronic advertisement to participate in the study. The study was conducted at the Department of Endocrinology and Internal Medicine, Aarhus University Hospital, between October 2011 and December 2012. After receiving written and oral information, all participants gave their written informed consent before participating in the study. Participants were screened on the basis of their medical history and a physical examination. The inclusion criteria were as follows: ≥18 y of age, an abdominal circumference of ≥94 cm for men or ≥80 cm for women, and weight stability (±5 kg) for at least 3 mo before inclusion. The exclusion criteria were T2D; severe cardiovascular, renal, endocrine, or psychiatric disease; drug abuse; or pregnancy or lactation. Blood donation was not allowed for 3 mo before or during the intervention. All participants continued taking their regular medication without dose changes throughout the study period.

A total of 52 participants completed the study (see **Figure 2** for flowchart). Because of technical difficulties, no intravenous access was obtained at the postintervention meal test and oral glucose tolerance test on one of the completing participants. Fat biopsy specimens were not obtained from 3 participants (2 due to bleeding and 1 would not participate in the postintervention biopsy). Furthermore, adipose tissue samples from 2 participants were damaged due to early defrosting.

The study protocol was carried out in accordance with the Helsinki Declaration of 1975 as revised in 1983 and was approved by the Central Denmark Region Committees on Health Research Ethics. The study was registered with clinicaltrials.gov as NCT01472666.

Production of dietary supplements and dietary assessment

Each day during the 12-wk intervention period, the participants had to consume 60 g trial protein (whey or casein) as well as 2 rolls, 1 cake, and 25 g butter, which provided a total of 63 g milk fat/d. The protein was administered as powder (delivered from Arla Foods Ingredients Group P/S) with either whey isolate (Lacprodan DI-9224) or casein (Miprodan 30) and ready to mix with water.

Fifty Holstein cows at the Danish Cattle Research Centre (Foulum, Denmark) were used to produce the 2 different compositions of milk fat for the study. Cows were fed a low-fat diet during a 2-wk period, and milk was collected during week 3 for butter manufacturing. The low-fat diet should ensure a high de novo synthesis of MC-SFAs (24). Afterward, the cows were fed a diet supplemented with fractionated palm fat, 40 g/kg dry matter intake, and milk was collected for the low MC-SFA butter production. Butter was produced and packed at Thise Mejeri (Roslev, Denmark). The production of rolls and muffins was performed at the industrial kitchen at Aarhus University Hospital.

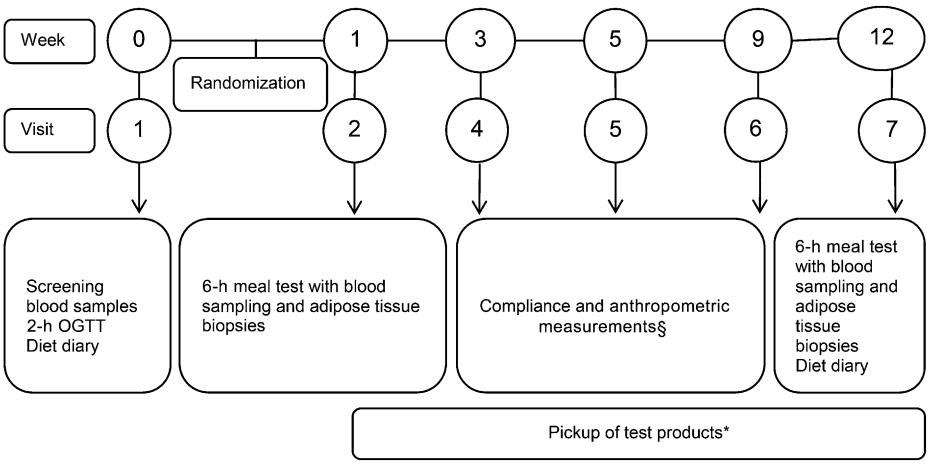

FIGURE 1 Study design; visits and examinations during the 12-wk intervention. §If problems with weight stability occurred during the study, additional visits were scheduled where a new 3-d weighed food diary was completed and dietetic guidance was given. *Test products were picked up at the research facility by the study participants every week to every fourth week according to the participants' preferences. OGTT, oral-glucose-tolerance test.

In total, the daily energy content of our test products was 6200 kJ/d [with the following energy percentage (E%) distribution: 42 E% as fat, 21 E% as protein, and 37 E% as carbohydrate].

After instruction by dietitian (KVR), all participants completed a 3-d weighed food diary before the intervention (2 weekdays and 1 day on a weekend). The diary was used to calculate daily energy intake and macro- and micronutrient contents by using the Master Dietist System, version 1.235 (2007), based on the Danish National Food administration database. Moreover, the study participants' energy requirement was calculated from their basal metabolic rate and their physical activity level (25). Based on this, our dietitian instructed the participants on how to incorporate the test products into their regular diet and how to maintain weight stability.

Visits and the test meal

At the screening visit (visit 1), the study participants attended the clinic at 0800 after an overnight fast. At first, their fasting body weight was measured on a regularly calibrated scale (WB-100A Class 111; Tanita). Then, a catheter was inserted into a cubital vein for blood sampling. A standard 2-h oral glucose tolerance test (75 g D-glucose) was performed to rule out T2D. Additional fasting laboratory measurements were performed (alanine aminotransferase, hemoglobin A1c, fasting glucose, triacylglycerol, thyroid-stimulating hormone, sodium, potassium, creatinine, and hemoglobin).

A meal test was performed before and after the intervention. After an overnight fast, the study participants arrived at the clinic at 0730. A catheter was placed in a cubital vein for blood sampling, and afterward an adipose tissue biopsy was performed. After the biopsy, baseline blood samples were drawn (at time 0 min), and then the test meal was consumed within the next 20 min. The test meal consisted of bread, egg, butter, bacon, cheese, salami, milk, and decaffeinated coffee. The meal had the following E% distribution: 65 E% as fat, 19 E% as carbohydrates, and 16 E% as protein. The energy content of the meal was 4500 kJ. During the following 6 h, blood samples were drawn at specified time points: triacylglycerol and FFA at 0, 60, 120, 180, 240,

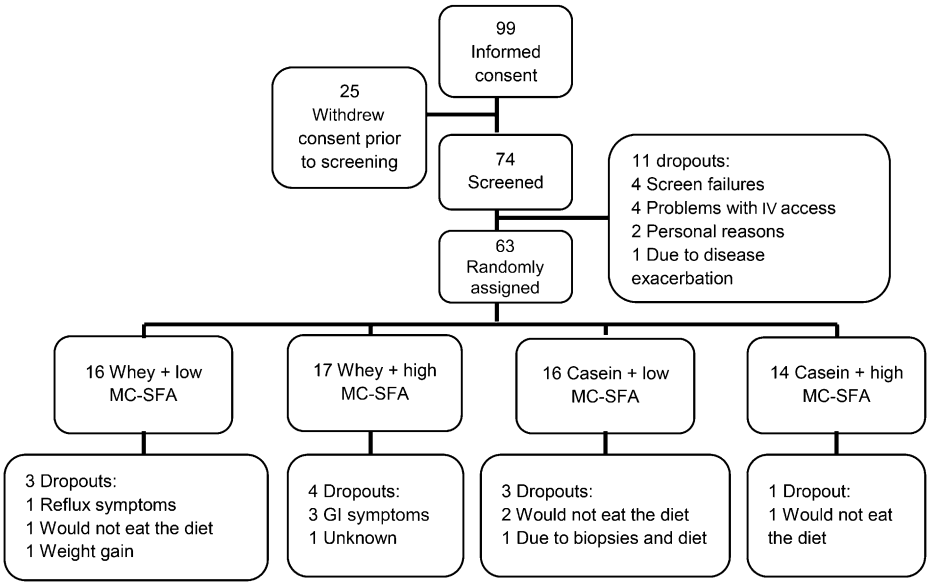

FIGURE 2 Flowchart showing the number of participants in the study. GI, gastrointestinal; IV, intravenous; MC-SFA, medium-chain SFA.

and 360 min; GLP-1 and GIP at 0, 15, 30, 60, 120, 240, and 360 min; insulin, glucose, and glucagon at 0, 15, 30, 60, and 120 min; and apoB-48 at 0, 120, 240, and 360 min. Except for apoB-48 analysis, all blood samples were immediately centrifuged at 2000 × *g* for 15 min at 4°C; thereafter, the plasma samples were frozen at −20°C and the next day stored at −80°C. The apoB-48 blood samples were mixed by hand, left at room temperature for 30–60 min, and then centrifuged for 10 min at 2000 × *g* and frozen at −80°C.

Fat biopsies and gene expression analyses

Fat biopsy specimens were taken at baseline and 240 min postprandial from the abdominal subcutaneous adipose tissue. The biopsy specimens were taken with Bergström needle through a small skin incision under local analgesia with 10–15 mL lidocaine (20 g/L). The adipose tissue was cleaned for blood with sterile saline, snap-frozen in liquid nitrogen, and stored at −80°C. RNA was isolated from ∼250 mg adipose tissue by using an acid guanidinium thiocyanate-phenol-chloroform extraction method (Trizol Reagent 15596–018; Invitrogen). AROS Applied Biotechnology AS performed the gene expression analyses by using Fluidigm BioMark real-time reverse transcriptase–polymerase chain reaction system. Predesigned primers and TaqMan Gene Expression Assay probes from Applied Biosystems (Life Technologies) were used. Cycle threshold values were measured in duplicates.

Blood analyses

The measurement of apoB-48 was performed with an ELISA method by using the Human ApoB-48 ELISA kit manufactured by Shibayagi Co. Ltd. ApoB-48 in serum was stable for up to 5 cycles of freeze and thaw (<−70°C). Intra- and interassay precision was 2.1% and 7.4%, respectively.

Plasma triacylglycerol and FFA concentrations were measured with enzymatic colorimetric assays by using commercial kits [no. 04657594190 (Roche Diagnostics Gmbh) for triacylglycerol; code 270–7700 (Wako Chemicals Gmbh) for FFA]. Measurements of both parameters were made on the cobas c111 system. The intra- and interassay precision was 1.1% and 2.3% for triacylglycerol, respectively. The intra-assay precision for FFA was 1.5%. Plasma glucose was measured by a glucose oxidase method with a GOD-PAP glucose kit (no. 11491253216; Roche Diagnostics Gmbh). Serum insulin was measured with an ELISA technique (code K6219; Dako Denmark A/S). Glucagon was measured by radioimmunoassay with glucagon antibody and ^{125}I-glucagon (cat. GL-32K; Millipore).

Concentrations of total GLP-1 were measured by using a radioimmunoassay specific for the C-terminal of the GLP-1 molecule (antiserum no. 89390) (26). Total GIP was analyzed by using an assay with a C-terminally directed antiserum (code no. 80867) (27).

Statistical analysis

The power calculation was based on previous results from our group and made to detect a difference in our primary outcome (i.e., postprandial triacylglycerol response) of 20% between diets (13, 28). The number of participants needed to complete the study and achieve a statistical power of 80% was calculated to be 52 ($\alpha < 0.05$, $\beta = 0.80$). A 2-factor ANOVA model was used to examine the effect of specific protein type and the specific fatty acid composition, as well as the interaction between protein and fat. If data were not normally distributed or variances were unequal (evaluated by histograms, Bland-Altman, and Q-Q plots), data were logarithmically transformed, with results given as medians ± 95% CIs. Postprandial response data are given as incremental AUCs for 360 min for apoB-48, triacylglycerol, GLP-1, and GIP; as total AUCs for 360 min for FFA; and as incremental AUCs for 120 min for glucose, insulin, and glucagon. $P < 0.05$ was considered statistically significant. Results are given as means ± 95% CIs, unless otherwise stated. However, gene expressions are all given as medians ± 95% CIs. Statistical calculations on gene expression were performed on RNA values normalized to the mean of 2 reference genes (*β2-microglobulin* and *RNA polymerase II*). Changes in fasting gene expression after intervention are reported as percentage changes (±95% CIs) from the fasting baseline gene expression. A 1-sample mean comparison *t* test was used to test whether post-intervention fasting gene expression was significantly different from the baseline. Change in postprandial gene expression is reported as a percentage relative to the fasting gene expression. A 2-sample mean comparison paired *t* test was used to estimate whether the postprandial responses (before and after intervention) were significantly different from each other. The false discovery rate (FDR) correction (29) was used to overcome the problem of multiple statistical testing of the genes. All statistical calculations were performed with STATA version 12 (StataCorp LP), and GraphPad Prism 6 (GraphPad Software) was used to generate the graphical elements.

RESULTS

Baseline characteristics

Table 1 presents baseline characteristics of the 52 completing participants by group.

Fatty acid composition of the butter

The mean daily intake of C6–C12 fatty acids was 8.5 ± 0.3 g in the high–MC-SFA group and 6.9 ± 0.2 g in the low–MC-SFA group. The difference obtained in the content of C6–C12 fatty acids was 1.6 g/d (a daily 24% relative increase in the high–MC-SFA group).

Dietary data

Dietary data are provided in **Table 2**. At baseline, no significant differences were found in dietary variables between the groups. Although all groups increased their energy intake, the casein-supplemented groups increased their energy intake with a mean of 1556 kJ/d (95% CI: 384, 2728; $P = 0.010$) more than the whey-supplemented groups. The difference remained after adjusting for age and sex ($P = 0.013$) and was independent of the fatty acid composition.

No other changes in dietary variables were related to a specific protein type or fatty acid composition. No interactions were found between protein and fat regarding any changes in dietary parameters.

TABLE 1
Baseline characteristics of the 52 completing participants with abdominal obesity[1]

Characteristic	Whey + low MC-SFA	Whey + high MC-SFA	Casein + low MC-SFA	Casein + high MC-SFA
Female sex, *n* (%)	13 (62)	13 (46)	13 (46)	13 (54)
Age, y	61.1 (55.1, 67.0)[2]	50.0 (40.6, 59.4)	56.7 (46.1, 67.3)	59.0 (50.7, 67.3)
Weight, kg	85.1 (75.6, 94.6)	86.2 (78.2, 94.2)	85.7 (76.7, 94.8)	87.8 (80.0, 95.6)
Statin use, *n*	6	2	3	0
Metabolic syndrome, *n* (%)	7 (54)	7 (54)	6 (46)	6 (46)
Smoking, *n*	2	4	1	2

[1]MC-SFA, medium-chain SFA.
[2]Mean; 95% CI in parentheses (all such values).

Body weight

For WH, CL, and CH, the weight increased by 2.0 kg (95% CI: 1.0, 3.1; $P = 0.001$), 1.5 kg (95% CI: 0.6, 2.4; $P = 0.003$), and 1.4 kg (95% CI: 0.7, 2.1; $P = 0.001$), respectively. In the WL group, the mean body weight tended to increase ($P = 0.087$) by 1.0 kg (95% CI: −0.2, 2.1). The increase in body weight was not a result of a specific protein type ($P = 0.829$) or fatty acid composition ($P = 0.186$), and it did not differ between groups ($P = 0.401$). Adjusting the increase in body weight for age and sex did not significantly alter the results.

Fasting and postprandial changes

The fasting and postprandial changes (including baseline values) in apoB-48, triacylglycerol, FFA, glucose, insulin, glucagon, GLP-1, and GIP are given in **Table 3**. After the intervention, whey compared with casein significantly ($P = 0.025$) decreased the postprandial apoB-48 response by 4310 mg/L (95% CI: 559, 8060) independently of the fatty acid composition. The effect of whey on postprandial apoB-48 compared with casein remained after adjustment for age, sex, weight change, baseline blood pressure, and statin intake.

Neither fasting nor postprandial triacylglycerol or FFA responses changed significantly in relation to type of protein or fatty acid composition during the intervention. Casein consumption increased the GLP-1 postprandial response by 878 pmol/L × 360 min (95% CI: 312, 1444; $P = 0.003$) compared with whey consumption. The change in postprandial GLP-1 was independent of the specific fatty acid composition. The fasting GLP-1 concentrations were not differentially altered by the type of

TABLE 2
Daily energy intake and macro- and micronutrient content based on a 3-d weighed food diary, baseline and change during the 12-wk intervention[1]

					Two-factor ANOVA, *P* value		
Characteristic	Whey + low MC-SFA (*n* = 13)	Whey + high MC-SFA (*n* = 12)	Casein + low MC-SFA (*n* = 13)	Casein + high MC-SFA (*n* = 13)	Protein	Fatty acid composition	Interaction
Energy (kJ/d), baseline	8357 (7118, 9596)	8806 (8008, 9605)	8448 (6497, 10,399)	7169 (6087, 8251)			
Energy (kJ/d), change	1377 (50, 2704)	1436 (115, 2756)	3084 (1803, 4366)	2841 (1640, 4041)	0.010	0.875	0.799
Carbohydrate (E%), baseline	45.7 (41.8, 49.6)	44.8 (40.5, 49.2)	45.6 (39.5, 51.7)	46.9 (41.8, 51.9)			
Carbohydrate (E%), change	−7.1 (−10.1, −4.0)	−6.4 (−11.6, −1.3)	−5.5 (−11.5, 0.6)	−8.0 (−12.5, −3.5)	0.988	0.666	0.482
Protein (E%), baseline	17.0 (15.6, 18.4)	17.6 (15.0, 20.2)	16.4 (14.0, 18.7)	16.5 (14.8, 18.2)			
Protein (E%), change	2.8 (1.6, 3.9)	1.7 (−0.7, 4.1)	2.2 (−0.4, 4.8)	3.0 (1.2, 4.8)	0.719	0.885	0.331
Fat (E%), baseline	33.6 (30.8, 36.5)	36.8 (33.0, 40.7)	36.2 (31.8, 40.6)	34.1 (29.3, 38.8)			
Fat (E%), change	6.0 (3.2, 8.7)	3.3 (−1.4, 7.9)	4.0 (−0.7, 8.8)	5.9 (1.3, 10.6)	0.857	0.839	0.254
SFA (g/d), baseline	25.5 (19.7, 31.2)	27.1 (21.5, 32.7)	26.8 (20.9, 32.7)	23.7 (15.4, 32.1)			
SFA (g/d), change	22.4 (15.3, 29.6)	24.3 (16.2, 32.5)	28.2 (23.3, 33.0)	25.8 (18.9, 32.6)	0.260	0.937	0.499
MUFA (g/d), baseline	22.7 (18.4, 27.0)	23.9 (18.9, 28.9)	22.6 (17.3, 27.8)	20.8 (14.6, 26.9)			
MUFA (g/d), change	5.9 (1.5, 10.2)	6.2 (−0.6, 13.1)	12.7 (6.8, 18.6)	9.3 (2,2, 16.5)	0.084	0.589	0.513
PUFA (g/d), baseline	9.0 (7.5, 10.5)	9.2 (6.7, 11.6)	8.7 (6.1, 11.2)	9.6 (7.1, 12.1)			
PUFA (g/d), change	−2.0 (−4.1, 0.2)	−0.8 (−1.2, 2.9)	0.9 (−1.2, 2.9)	−2.5 (−5.3, 0.2)	0.648	0.366	0.062
Vitamin D (μg/d), baseline[2]	3.5 (2.0, 6.0)	2.7 (1.4, 5.6)	2.5 (1.4, 4.5)	1.9 (1.0, 3.7)			
Vitamin D (μg/d), change[3]	0.9 (0.4, 1.7)	1.2 (0.6, 2.6)	1.2 (0.6, 2.3)	1.6 (0.7, 3.9)	0.406	0.320	0.947
Sodium (mg/d), baseline	2539 (2179, 2899)	2428 (1922, 2934)	2369 (1915, 2823)	2227 (1556, 2897)			
Sodium (mg/d), change	−529 (−1149, 91)	−845 (−1194, −497)	−297 (−915, 321)	−376 (−910, 157)	0.162	0.426	0.635
Calcium (mg/d), baseline	691 (554, 828)	953 (728, 1179)	730 (587, 872)	737 (530, 944)			
Calcium (mg/d), change	−23 (−285, 238)	−346 (−667, −25)	−169 (−333, −6)	−173 (−325, −21)	0.903	0.142	0.146

[1]Values are means; 95% CIs in parentheses unless otherwise indicated. E%, energy percentage; MC-SFA, medium-chain SFA.
[2]Values are medians; 95% CIs in parentheses.
[3]Values are median ratios; 95% CIs in parentheses (week 12/week 0).

TABLE 3
Baseline and change during intervention of fasting and postprandial plasma apoB-48, lipids, incretins, glucose, insulin, and glucagon[1]

Characteristic	Whey + low MC-SFA (n = 13)	Whey + high MC-SFA (n = 12)	Casein + low MC-SFA (n = 13)	Casein + high MC-SFA (n = 13)	Two-factor ANOVA, P value		
					Protein	Fatty acid composition	Interaction
ApoB48 fasting (μg/L), baseline[2]	6164 (4344, 8748)	4515 (3605, 5655)	4624 (3315, 6448)	5748 (4163, 7938)			
ApoB48 fasting (μg/L), change	−2 (−674, 669)	68 (−1003, 1140)	632 (−1125, 2390)	169 (−874, 1212)	0.500	0.715	0.632
ApoB48 iAUC (mg/L × 360 min), baseline[2]	2314 (1983, 2699)	2217 (1825, 2692)	1987 (1529, 2583)	1883 (1412, 2513)			
ApoB48 iAUC (mg/L × 360 min), change	−2486 (−6856, 1884)	−1162 (−4263, 1940)	670 (−1984, 3324)	4349 (−1138, 9836)	0.025	0.182	0.534
TG fasting (mmol/L), baseline[2]	1.05 (0.84, 1.52)	1.20 (0.94, 1.52)	0.97 (0.78, 1.20)	1.08 (0.80, 1.47)			
TG fasting (mmol/L), change[3]	0.97 (0.83, 1.13)	1.00 (0.85, 1.17)	1.09 (0.94, 1.26)	0.98 (0.91, 1.06)	0.418	0.547	0.316
TG iAUC (mmol/L × 360 min), baseline[2]	201 (134, 302)	159 (100, 253)	190 (133, 272)	172 (119, 247)			
TG iAUC (mmol/L × 360 min), change[3]	0.94 (0.73, 1.21)	1.10 (0.86, 1.42)	0.99 (0.76, 1.28)	1.21 (0.97, 1.50)	0.528	0.113	0.868
FFA fasting (mmol/L), baseline	0.34 (0.26, 0.43)	0.39 (0.21, 0.57)	0.32 (0.25, 0.38)	0.32 (0.24, 0.40)			
FFA fasting (mmol/L), change	−0.01 (−0.06, 0.04)	0.02 (−0.09, 0.13)	0.02 (−0.04, 0.08)	0.06 (−0.03, 0.15)	0.358	0.356	0.925
FFA tAUC (mmol/L × 360 min), baseline	132 (112, 153)	130 (104, 156)	127 (118, 137)	123 (96, 151)			
FFA tAUC (mmol/L × 360 min), change	−4.55 (−18.64, 9.55)	1.55 (−18.64, 21.74)	−8.24 (−24.88, 8.40)	−10.92 (−28.38, 6.55)	0.310	0.836	0.578
GLP-1 fasting (pmol/L), baseline	10.4 (8.6, 12.1)	9.9 (8.3, 11.5)[4]	8.7 (7.1, 10.2)	8.9 (7.9, 10.0)			
GLP-1 fasting (pmol/L), change[3]	1.1 (0.9, 1.2)	1.0 (0.9, 1.2)[4]	1.1 (0.9, 1.2)	0.9 (0.8, 1.1)	0.411	0.143	0.209
GLP-1 iAUC (pmol/L × 360 min), baseline	4161 (3285, 5036)	3444 (2339, 4549)[4]	2552 (1825, 3279)	3098 (2033, 4162)			
GLP-1 iAUC (pmol/L × 360 min), change	−835 (−1549, −120)[2]	−753 (−1515, 9)[4]	97 (−481, 675)	67 (−350, 484)	0.003	0.934	0.846
GIP fasting (pmol/L), baseline[2]	11.1 (9.0, 13.8)	12.6 (9.5, 16.8)	11.7 (9.7, 14.0)	13.1 (10.3, 16.8)			
GIP fasting (pmol/L), change[3]	1.1 (0.9, 1.4)	1.0 (0.8,1.4)	1.0 (0.9,1.1)	0.9 (0.7,1.2)	0.272	0.380	0.971
GIP iAUC (pmol/L × 360 min), baseline	25,348 (19,783, 30,912)	22,811 (18,481, 27,141)	26,346 (23,508, 29,184)	23,727 (17,249, 30,205)			
GIP iAUC (pmol/L × 360 min), change	−1084 (−5170, 3002)	443 (−4066, 4953)	−493 (−5479, 4492)	371 (−3163, 3905)	0.892	0.545	0.867
Glucose fasting (mmol/L), baseline	5.56 (5.29, 5.82)	5.55 (5.26, 5.85)	5.58 (5.26, 5.90)	5.53 (5.20, 5.86)			
Glucose fasting (mmol/L), change	0.03 (−0.16, 0.21)	0.03 (−0.22, 0.27)	−0.14 (−0.32, 0.04)	0.11 (−0.07, 0.28)	0.610	0.167	0.177
Glucose iAUC (mmol/L × 120 min), baseline	69.37 (46.43, 92.32)	63.48 (45.76, 81.21)	70.17 (58.79, 81.54)	74.47 (54.49, 94.44)			
Glucose iAUC (mmol/L × 120 min), change	10.17 (−14.74, 35.08)	−1.09 (−22.08, 19.90)	25.28 (4.11, 46.45)[2]	7.04 (−17.30, 31.39)	0.269	0.163	0.742
Insulin fasting (pmol/L), baseline[2]	25.79 (17.87, 37.23)	30.51 (15.07, 61.79)	22.57 (9.56, 53.17)	22.55 (9.56, 53.17)			
Insulin fasting (pmol/L), change[3]	0.91 (0.54, 1.55)	0.77 (0.36, 1.68)	1.02 (0.67, 1.53)	1.18 (0.70, 1.99)	0.311	0.987	0.538
Insulin iAUC (pmol/L × 120 min), baseline[2]	11,400 (8321, 15,619)	11,764 (7051, 19,628)	13,806 (10,086, 18,897)	14,492 (10,000, 21,003)			
Insulin iAUC (pmol/L × 120 min), change[3]	1.29 (1.10, 1.51)[2]	1.29 (0.94, 1.79)	1.20 (0.88, 1.63)	1.28 (0.99, 1.66)	0.726	0.773	0.808
Glucagon fasting (pg/mL), baseline[2]	67.44 (56.43, 80.60)	61.44 (53.39, 70.70)	67.42 (52.29, 86.92)	65.23 (56.19, 75.73)			
Glucagon fasting (pg/mL), change[3]	1.07 (0.93, 1.24)	0.98 (0.84, 1.16)	1.14 (0.92, 1.41)	1.02 (0.94, 1.11)	0.491	0.170	0.865
Glucagon iAUC (pg/mL × 120 min), baseline[2]	2123 (1538, 2931)	2617 (1801, 3803)	2344 (1811, 3033)	1987 (1406, 2809)			
Glucagon iAUC (pg/mL × 120 min), change[3]	1.01 (0.68, 1.51)	0.83 (0.62, 1.12)	0.96 (0.66, 1.39)	1.07 (0.79, 1.44)	0.566	0.791	0.341

[1]Values are means; 95% CIs unless otherwise indicated. FFA, free fatty acid; GIP, gastric inhibitory polypeptide; GLP-1, glucagon like peptide-1; iAUC, incremental AUC; MC-SFA, medium-chain SFA; tAUC, total AUC; TG, triacylglycerol.
[2]Medians; 95% CIs in parentheses.
[3]Median ratios; 95% CIs in parentheses (week 12/week 0).
[4]n = 11.

protein or the fatty acid composition after the intervention. Adjusting for sex and age did not significantly alter the results.

Neither fasting nor postprandial GIP was affected by the type of protein or the fatty acid composition. Fasting glucose, insulin, and glucagon, as well as the postprandial responses of these parameters, were not differentially affected by the type of protein or fatty acid composition. No interaction between protein and fat was seen regarding apoB-48, triacylglycerol, FFA, GLP-1, GIP, glucose, insulin, or glucagon.

Gene expressions

We investigated the expression of the following genes: lipoprotein lipase (*LPL*); G protein–coupled receptor 120 (*GPR120*); cluster of differentiation 36 (*CD36*), also known as fatty acid translocase; fatty acid binding protein 4 (*FABP4*); and fatty acid synthase (*FAS*) before and after the dietary intervention in both the fasting and the postprandial state. **Figure 3** shows the relative changes in gene expression of *LPL*, *GPR120*, and *CD36* in the fasting and the postprandial states.

Interaction between protein and fat was observed regarding all gene expressions. Therefore, no independent effect of whey/casein or amount of MC-SFA could be detected. The fasting gene expressions of *LPL*, *GPR120*, and *CD36* were all upregulated after the intervention in the CH group by 42% (95% CI: 21, 66; $P < 0.001$), 59% (95% CI: 24, 104; $P = 0.002$), and 24% (95% CI: 12, 38; $P < 0.001$), respectively, whereas the gene expression of *GPR120* and *CD36* was downregulated postprandially in the CH group by 25% (95% CI: 2, 53; $P = 0.034$) and 9% (95% CI: 2, 17; $P = 0.017$), respectively. All above changes remained significant after FDR correction. No fasting or postprandial changes in gene expression were observed in the CL group, whereas a 17% (95% CI: 0, 33; $P = 0.045$) upregulation of the postprandial *LPL* gene expression was seen in the WH group. However, this was not significant after FDR correction. The fasting gene expressions of GPR120 and CD36 were upregulated in the WL group by 19% (95% CI: 3, 37; $P = 0.023$) and 11% (0, 23; $P = 0.038$), respectively, after intervention, whereas we found a downregulation in postprandial *LPL* and *GPR120* gene expressions by 9% (95% CI: 1, 18; $P = 0.038$) and 21% (95% CI: 5, 39; $P = 0.015$), respectively. All changes in the WL group were still significant after FDR correction. We detected no changes in *FAS* or *FABP4* gene expressions in either the fasting or the postprandial conditions (data not shown).

DISCUSSION

The present study investigated the long-term effect of milk proteins (whey and casein) and milk fat with a low or high content of MC-SFAs on postprandial lipemia in abdominally obese human subjects.

Interestingly, we found a markedly reduced postprandial apoB-48 response to a fat-rich standard meal after 12-wk intake of whey compared with casein. ApoB-48 reflects the numbers of chylomicron particles. Chylomicrons are transformed into chylomicron remnants that have the ability to penetrate the arterial wall, accumulate within the subendothelial space, and thereby take part in the pathogenesis of atherosclerosis (21, 30, 31). Whether the difference in apoB-48 responses is related to changes in the chylomicron secretion or clearance remains to be clarified. The lower apoB-48 response to whey compared with casein supplementation may be related to differences in the uptake of triacylglycerol. Thus, we recently found that whey protein delays the uptake of triacylglycerol compared with casein (32). The differential postprandial apoB-48 response depended on the protein type and not on the amount of MC-SFAs in the butter. It is noteworthy that MC-SFAs are not incorporated into chylomicrons, in contrast to LC-SFAs (33). The relatively limited difference between the high and low amount of MC-SFAs in our study (a difference of 1.6 g/d in C6–C12) may be too small to provoke differences in fasting or postprandial triacylglycerol responses. However, it should be stressed that the difference between a high and low amount of MC-SFAs in our diets reflects what could be obtained naturally in the butter by using a targeted cattle feeding regimen (19).

Plasma concentrations of apoB-48 have been found to be reduced by statin treatment (34). Therefore, it could be argued that it would have been preferable to have used lipid-lowering drugs as an exclusion criterion. However, our study participants were receiving stable doses of statins throughout the study, and

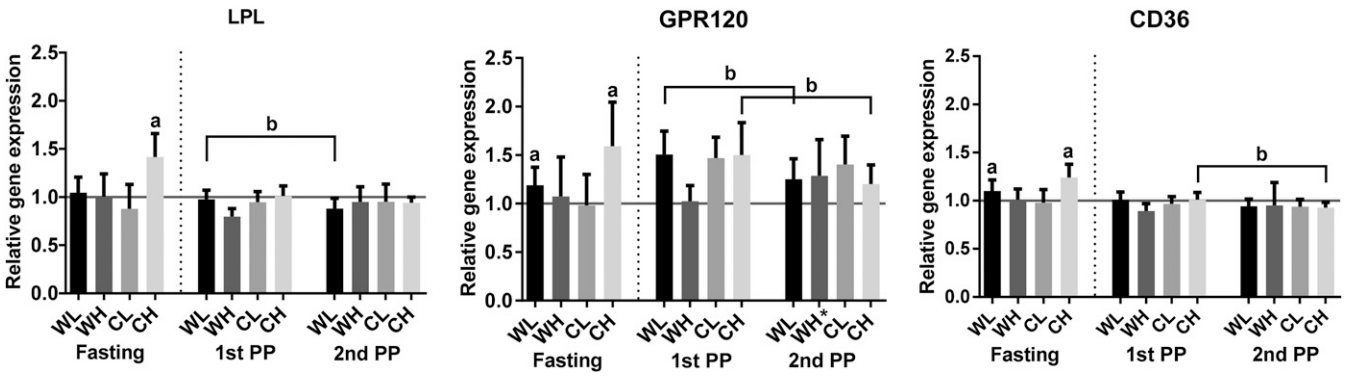

FIGURE 3 Relative changes in the gene expression of *LPL*, *GPR120*, and *CD36* in abdominal adipose tissue (geometric means ± 95% CIs). *Fasting* represents fasting postintervention gene expression relative to preintervention fasting gene expression. "1st PP" and "2nd PP" represent relative changes from the fasting gene expression to the postprandial gene expression at the pre- and postintervention meal test, respectively. [a]One-sample mean comparison *t* test; fasting gene expression preintervention compared with postintervention, $P < 0.05$ after the FDR correction. [b]Two-sample mean comparison paired *t* test; relative postprandial gene expression preintervention compared with postintervention, $P < 0.05$ after the FDR correction. WL, CL, and CH ($n = 12$). WH ($n = 11$). WH* ($n = 10$). CH, casein + high medium-chain SFA; CL, casein + low medium-chain SFA; FDR, false discovery rate; WH, whey + high medium-chain SFA; WL, whey + low medium-chain SFA.

adjustment for statin treatment did not affect our results. The reduction in postprandial apoB-48 after whey supplementation was not reflected in a change in postprandial triacylglycerol (our primary outcome). This may suggest that the total amount of triacylglycerol in the postprandial phase is incorporated into fewer chylomicrons after whey than after the casein supplementation. Another explanation could be that hepatically produced triacylglycerol may have diluted the circulating triacylglycerol and made a triacylglycerol difference of intestinal origin difficult to detect. To our knowledge, the present study is the first to study the long-term effect of a whey supplementation on postprandial lipemia.

Both whey and casein can stimulate the postprandial release of GLP-1 (12), and high pharmacologic doses of GLP-1 receptor agonists attenuate the postprandial rise in triacylglycerol and apoB-48 (35, 36). It is, however, unlikely that the protein-induced difference in endogenous GLP-1 responses is related to the apoB-48 secretion, because casein elicited a higher GLP-1 response than whey. Only few studies, and to our knowledge no long-term studies, have investigated the effect of whey and casein on postprandial GLP-1, and results have been inconsistent (37, 38). Despite a postprandial difference in the GLP-1 response between the casein- and whey-supplemented groups, we found no difference in postprandial glucose or insulin related to the protein type. This is in line with our previous acute studies in obese nondiabetic (38) and T2D subjects (13).

To gain insight into metabolic changes in insulin-sensitive tissue, we investigated the effects of the different MC-SFA content and milk protein supplementation on the expression of genes involved in the lipid metabolism in abdominal subcutaneous adipose tissue. We found changes in *LPL*, *GPR120*, and *CD36* gene expressions in one or more of the groups in both fasting and postprandial conditions after intervention, which illustrates differential gene expression changes in the adipose tissue. However, the findings were dispersed, and the interaction between the milk protein and milk lipids made it difficult to determine whether the changes could be explained by our diet intervention.

The present study is strong because of the double-blinded, randomized, and long-term design. However, it has some limitations. We aimed to keep the participants' diets isocaloric and maintain weight stability by regular guidance by the dietitian. We did not succeed in this, which may have affected our outcomes. However, the weight change did not significantly differ between groups, and the positive effect of whey on postprandial apoB-48 compared with casein remained after adjustment for the weight change.

We also found an unintended reduction in the intake of calcium after the intervention. Calcium from dairy products can increase fat excretion by forming insoluble calcium–fatty acid soaps with the ingested lipids (39). A lower intake of calcium as a result of our intervention may have lowered the fatty acid excretion and thereby have contributed to a greater increase in postprandial lipemia than would have been expected if the calcium intake had not changed (40). However, Hjerpsted et al. (41) found that a large difference in the intake of calcium from dairy foods did not alter fecal fat excretion in healthy participants. Given that we did not measure fecal fat content, we do not know if the fat excretion was changed during the intervention. Furthermore, we cannot entirely rule out a possibility of bias caused by the dropout subjects, because the proportions of women and of subjects without metabolic syndrome were higher in the dropout group than in the completers group. If dropout rates are similar across groups, the bias will disappear when we examine the differences between the 4 groups. However, because of the limited number of subjects in each of the 4 groups, it is not statistically possible to compare the dropout rates across the 4 groups.

As in other studies, the completion of the study generates unanswered and interesting questions. What is the minimal and optimal dose of whey to improve postprandial apoB-48 responses? Why does whey improve the postprandial apoB-48 response but not the triacylglycerol response? What is the physiologic mechanism that underlies the improvement of apoB-48?

In conclusion, the present study shows that a 12-wk dietary supplement of whey protein reduces the postprandial apoB-48 response, which reflects a reduced number of chylomicron particles after a fat-rich meal compared with casein. Thus, a long-term whey supplement may have a beneficial effect on the risk of developing CVD. However, more studies are needed to fully evaluate the apoB-48–lowering effect of whey protein.

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