Table 2 Fecal parameters before and after 4 weeks supplementation with flaxseed fibers (FF) and/or dairy calcium (Ca) in addition to alli®*

	FF-		FF+			*P*-values**	
						Intervention	
	Ca- ($n = 6$)	Ca + ($n = 13$)	Ca- ($n = 10$)	Ca + ($n = 10$)	Baseline	FF	Ca
Defecation frequency (n/d)							
Baseline	1.43 ± 0.17	1.78 ± 0.32	1.21 ± 0.15	1.21 ± 0.11	0.50	0.07	0.79
Week 4	1.24 ± 0.14	1.47 ± 0.26	1.24 ± 0.10	1.39 ± 0.18			
Fecal wet weight (g/d)							
Baseline	169.8 ± 45.9	184.9 ± 31.2	141.5 ± 35.6	152.4 ± 35.6	0.81	0.09	0.04*
Week 4	129.5 ± 36.5	187.1 ± 24.8	144.7 ± 28.3	199.6 ± 28.3			
Fecal dry matter (%)							
Baseline	27.6 ± 2.2	28.7 ± 1.4	30.9 ± 1.5	30.8 ± 1.8	0.56	0.78	0.54
Week 4	29.8 ± 1.8	29.0 ± 1.2	30.5 ± 1.1	30.3 ± 1.7			
Fecal fat excretion (g/d)							
Baseline	17.7 ± 3.2	18.6 ± 2.2	18.6 ± 2.5	15.3 ± 2.5	0.75	0.02*	0.04*
Week 4	15.4 ± 4.3	20.8 ± 2.9	21.0 ± 3.3	25.6 ± 3.3			
Fecal fat excretion (%)							
Baseline	24.5 ± 6.3	31.7 ± 4.3	32.1 ± 4.9	24.9 ± 3.8	0.38	0.08	0.07
Week 4	24.1 ± 10.3	37.1 ± 7.0	36.0 ± 8.0	48.1 ± 8.0			

*$n = 39$; completers only population
**P-values refer to an ANCOVA model with adjustment for baseline value, sex and age

accompanied by changes in ratings of gastrointestinal symptoms apart from a tendency towards an increase in severity, but not frequency, of diarrhea with Ca. The fecal fat excretion was ~10 g/d higher with FF and Ca (~25 g/d) compared to fecal fat excretion with orlistat alone (~15 g/d). which is a marked increase from the ~155 g/d of fecal fat excretion with orlistat alone.

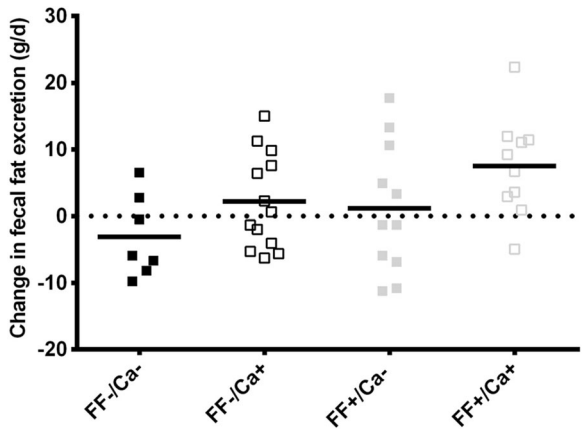

Fig. 3 Fecal fat excretion. Individual and mean change in fecal fat excretion (g/d) from baseline (orlistat treatment only) to week 4 (orlistat plus placebo (FF-/Ca-) or flaxseed fibers (FF) and/or dairy Ca (Ca) supplements). * Indicate a significant effect of Ca ($p = 0.02$) and # indicate a significant effect of FF ($p = 0.04$) compared to control in an ANCOVA

Orlistat diminishes fat absorption by inhibiting the activity of the gastrointestinal lipase resulting in an increased amount of intact non-hydrolyzed triacylglycerols in the intestine. Ca is proposed to form insoluble soaps with these triacylglycerols [25], which may occur more distally, thus, orlistat may not affect the ability of Ca to form soaps, but rather result in an increased amount of lipids available for soap formation. FF are highly viscous dietary fibers [26] and as such, they are proposed to increase the viscosity of the intestinal contents which both thickens the unstirred water-layer along the mucosal barrier as well as slows digestive enzyme activity, including lipases [14]. Thus, both mechanisms of action appear to act in combination with orlistat, which does not appear to affect magnitude of effect of the supplements. Orlistat alone resulted in a fecal fat excretion of 25-30% of intake, and fecal fat excretion depends on dose of orlistat, although not in a linear manner [4]. Thus, components exerting their effects via different mechanisms may exceed this plateauing at a given dose, as suggested by our results. However, the combination of FF and Ca without orlistat treatment has not been tested; thus it is unknown whether orlistat may in fact facilitate some of the effects observed by increasing the intestinal triacylglycerol content.

As previously reported, attrition rates are high for orlistat treatment [3], and the present study was no exception. Overall, 33% of the participants dropped out of the

Table 3 Cardiometabolic risk markers before and after 12 weeks supplementation with flaxseed fibers (FF) and/or dairy calcium (Ca) in addition to alli®*

						P-values**		
		FF-		FF+			Intervention	
		Ca- (*n* = 6)	Ca + (*n* = 12)	Ca- (*n* = 10)	Ca + (*n* = 10)	Baseline	FF	Ca
Body weight (kg)	Baseline	98.9 ± 8.4	103.4 ± 5.2	91.2 ± 3.9	95.6 ± 2.8	0.30		
	Week 12	94.0 ± 9.9	98.9 ± 4.9	87.4 ± 3.8	91.4 ± 2.4		0.46	0.80
WC (cm)	Baseline	111.0 ± 4.8	111.3 ± 3.4	104.5 ± 2.6	104.2 ± 3.2	0.56		
	Week 12	104.9 ± 6.3^{ab}	107.5 ± 3.2^{a}	101.8 ± 2.7^{a}	98.4 ± 2.9^{b}		FF × Ca: 0.03*	
Systolic BP (mmHg)	Baseline	116 ± 6	118 ± 2	113 ± 2	123 ± 4	0.52		
	Week 12	116 ± 5	114 ± 3	115 ± 3	129 ± 5		0.58	0.70
Diastolic BP (mmHg)	Baseline	82 ± 3	81 ± 3	78 ± 2	84 ± 2	0.23		
	Week 12	80 ± 4	79 ± 2	75 ± 3	84 ± 2		0.03*	0.61
TAG (mmol/L)	Baseline	0.85 ± 0.33	1.46 ± 0.23	1.65 ± 0.25	0.99 ± 0.25	0.15		
	Week 12	0.85 ± 0.18	1.27 ± 0.14	1.17 ± 0.14	0.92 ± 0.14		0.42	0.56
T-C (mmol/L)	Baseline	4.87 ± 0.39	5.29 ± 0.28	5.31 ± 0.30	5.62 ± 0.30	0.52		
	Week 12	2.39 ± 0.38	4.94 ± 0.27	4.95 ± 0.30	5.11 ± 0.30		0.95	0.87
LDL-C (mmol/L)	Baseline	2.94 ± 0.33	3.24 ± 0.24	3.31 ± 0.26	3.28 ± 0.26	0.82		
	Week 12	2.52 ± 0.30	3.09 ± 0.21	3.12 ± 0.24	2.98 ± 0.24		0.98	0.62
HDL-C (mmol/L)	Baseline	1.45 ± 0.10	1.30 ± 0.07	1.18 ± 0.06	1.65 ± 0.09	0.17		
	Week 12	1.35 ± 0.15	1.15 ± 0.05	1.18 ± 0.06	1.52 ± 0.08		0.19	0.81
Glucose (mmol/L)	Baseline	5.38 ± 0.19	5.34 ± 0.13	5.24 ± 0.15	5.42 ± 0.15	0.84		
	Week 12	5.29 ± 0.20	5.34 ± 0.14	5.30 ± 0.16	5.19 ± 0.16		0.40	0.32
Insulin (pmol/L)	Baseline	83.9 ± 26.6	103.3 ± 18.8	102.4 ± 20.6	73.4 ± 20.6	0.67		
	Week 12	62.0 ± 38.3	114.6 ± 24.7	83.0 ± 27.1	70.0 ± 27.1		0.52	0.25
HOMA-IR	Baseline	2.92 ± 0.58	3.54 ± 0.63	3.65 ± 1.21	2.59 ± 0.41	0.68		
	Week 12	2.10 ± 0.46	3.99 ± 1.31	2.96 ± 0.80	2.34 ± 0.47		0.97	0.67
HbA1c (%)	Baseline	5.32 ± 0.05^{a}	5.59 ± 0.08^{b}	5.50 ± 0.09^{ab}	5.57 ± 0.12^{b}	0.03*		
	Week 12	5.38 ± 0.10	5.48 ± 0.08	5.48 ± 0.09	5.47 ± 0.10			
hsCRP (pg/mL)	Baseline	3.23 ± 1.76	3.11 ± 1.15	4.81 ± 1.43	7.61 ± 2.41	0.92		
	Week 12	3.93 ± 0.70	2.07 ± 0.45	5.06 ± 1.61	5.80 ± 1.90		0.03*	0.61

Abbreviations: *BMI* body mass index, *BP* blood pressure, *HDL-C* HDL cholesterol, *hsCRP* high sensitivity C-reactive protein, *HOMA-IR* Homeostasis Model of Assessment - Insulin Resistance, *HbA1c* glycated hemoglobin, *LDL-C* LDL cholesterol, *TAG* triacylglycerol, *T-C* total cholesterol, *WC* waist circumference

*$n = 39$; completers only population

**P-values refer to an ANCOVA model with adjustment for baseline value, sex and age. Columns with different superscript letters are significantly different; $P<0.05$

study, and ~40% (6 participants of which 5 dropped out after randomization) of these were directly related to gastrointestinal side effects. Only one participant receiving Ca dropped out, whereas three participants receiving FF dropped out indicating that the supplements affected gastrointestinal symptoms differently; however the study was too small to assess differences in attrition rates and thus this warrants further investigations. Nonetheless, the compliance to alli® was very high, which may be related to the fact that a few participants consumed a larger amount of alli® than instructed, likely because they know that a higher dose of orlistat could be taken without increased risk. The compliance to the dietary supplements was lower, likely due to its effect on palatability of the foods in which they were applied. However, a large proportion of the drop outs occurred during week 4, where dietary records and fecal collections took place. Thus, some of the dropouts may be related to the cumbersome procedures the participants were requested to follow, rather than the intervention itself.

Surprisingly, FF supplementation resulted in increased diastolic blood pressure and hsCRP, which is in contrast to previous reports on anti-inflammatory effects of flaxseeds among obese individual [26, 27]. Mean baseline blood pressure was within the normal range in the current study, whereas mean hsCRP concentrations were very high indicating an at risk population. However, in the subset of participants with hsCRP < 10 pg/mL, the effect was

attenuated; thus the pro-inflammatory effect of FF is not a robust finding. Moreover, we conducted multiple comparisons i.e. the secondary end-points without adjustments, which makes it likely that these findings are spurious and a matter of chance. The findings need to be replicated in independent studies.

Overall, compliance with both orlistat and dietary supplements was good, but tended to be best with Ca, whereas larger variations were observed in the FF supplemented groups. FF are viscous dietary fibers, and form highly viscous solutions immediately upon hydration. Thus the distribution of the FF as powders to be dissolved in liquids or sprayed on foods, e.g. yoghurt, may have given rise to less palatable foods, which may have affected compliance. This is not the case for Ca, which is solubilized and affects the taste of the food, but not the texture and thus it may have been better tolerated.

Few studies have examined the effect of dietary components on orlistat-induced fecal fat excretion and gastrointestinal symptoms. In contrast to the current findings, 6 g of psyllium given three times daily in conjunction with 120 mg orlistat was found to decrease occurrence of gastrointestinal events compared to placebo in a crossover study in 30 obese participants; however, fecal fat excretion was not assessed [17]. Psyllium and FF are both highly viscous dietary fibers, but the dose of psyllium was ~3 times higher than the FF dose used in the present study, which may explain why the results differ. Furthermore, a crossover design may be preferable when assessing subjective ratings of symptoms as inter-individual variation then can be eliminated. In the present study, we were not able to control type of fat; however, amount of fat consumed did not differ between groups and only decreased by few grams during the study, thus we do not believe fat intake to have affected our results, where patterns of relative fecal fat excretion (% of intake) followed that of fecal fat excretion in absolute amounts. A highly controlled study revealed that foods high in dietary fibers given in conjunction with 3×80 mg orlistat did not affect fecal fat excretion patterns differently than low-fiber foods, whereas extracellular fat (rendered lard) increased fecal fat excretion compared to intracellular fat (un-rendered lard) [16]. These results suggest that fat type in the background diet may be of great importance for the efficacy of orlistat whereas the content of dietary fibers, in natural food matrices, may vary considerably without affecting fat absorption.

Major strengths of the present study are the 2x2 factorial design, which enabled us to study interactions; that the intervention was well-controlled and resulted in a high compliance in all participants; and that that both gastrointestinal symptoms and fecal fat excretion were assessed and could thus be compared. However, the small sample size, partly caused by a large attrition rate, limits our ability to make firm conclusions based on these results.

Conclusions

The present findings do not support alleviation of orlistat-induced gastrointestinal side effects by supplementation of FF and/or Ca as hypothesized. However, fecal fat excretion was increased with both FF and Ca in the absence of a worsening of symptoms and to the greatest extent when both FF and Ca were consumed indicating a substantial additive effect.

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