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ARTICLE

Effect of whole milk compared with skimmed milk on fasting blood lipids in healthy adults: a 3-week randomized crossover study

Sara Engel[1] · Mie Elhauge[1] · Tine Tholstrup[1]

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Abstract

Background/objectives Dietary guidelines have for decades recommended choosing low-fat dairy products due to the high content of saturated fat in dairy known to increase blood concentration of LDL cholesterol. However, meta-analyses including observational studies show no association between overall dairy intake and risk of cardiovascular disease and even point to an inverse association with type 2 diabetes. The objective was to compare the effects of whole milk (3.5% fat) with skimmed milk (0.1% fat) on fasting serum blood lipids, insulin, and plasma glucose in healthy subjects.

Subject/methods A randomized, controlled 2 × 3-week crossover dietary intervention in 18 healthy adults randomly assigned to a sequence of treatments consisting of 0.5 L/d of whole milk and skimmed milk as part of their habitual diet. A total of 17 subjects completed the intervention.

Results Whole milk increased HDL cholesterol concentrations significantly compared to skimmed milk ($P < 0.05$). There were no significant differences between whole milk and skimmed milk in effects on total and LDL cholesterol, triacylglycerol, insulin, and glucose concentrations.

Conclusions Intake of 0.5 L/d of whole milk did not adversely affect fasting blood lipids, glucose, or insulin compared to skimmed milk. Moreover, intake of whole milk increased HDL cholesterol concentration compared to skimmed milk. These findings suggest that if the higher energy content is taken into account, whole milk might be considered a part of a healthy diet among the normocholesterolemic population.

Introduction

Dairy is a source of saturated fat (SFA) and dietary recommendations for choosing low-fat dairy products are mainly based on predicted effects of macronutrients, such as SFA, which are known to increase LDL cholesterol concentration in the blood. However, there is disagreement between dietary guidelines [1, 2] and results from meta-analysis of prospective cohort studies reporting no association between dairy and risk of cardiovascular disease (CVD) [3] and an inverse association with type 2 diabetes (T2D) [4]. A meta-analysis including studies comparing diets of equal SFA content from cheese and butter reported a beneficial effect of cheese on LDL cholesterol [5]. Moreover, a comparison between regular and reduced fat cheese found no difference in effect on LDL cholesterol and risk markers of the metabolic syndrome [6], although a significantly higher SFA content in the regular fat cheese diet. This could suggest that the expected effect on LDL cholesterol was mediated by a combination of nutrients or bioactive components in the cheese matrix. Every day, people make a choice between whole milk and skimmed milk in the super market. Thus, a comparison between these high and low-fat dairy products is a real-life practical issue for the consumer that makes it possible to further examine the effect of milk fat on health. Two studies compared milk with different fat content and found no difference in changes in LDL and HDL cholesterol; one between two control diets with semi-skimmed and skimmed milk (1.9 vs. 0.3%) [7] and another between whole milk and skimmed milk (3.4 vs. 0.2%) but with only eight participants and therefore

✉ Sara Engel
saraengel@nexs.ku.dk

[1] Faculty of Science, Department of Nutrition, Exercise and Sports, University of Copenhagen, Rolighedsvej 30, DK-1958, Frederiksberg, Denmark

underpowered [8]. Current evidence from randomized controlled trials (RCTs) indicate that milk consumption has no effect on risk of T2D in terms of fasting insulin and glucose concentrations [7, 9–11], although not consistently [12]. The aim of this study was to investigate the effects of whole milk compared with skimmed milk on serum total, LDL, and HDL cholesterol, and triacylglycerol concentration and secondarily on glucose and insulin concentrations in healthy subjects. We hypothesized that whole milk would increase fasting blood cholesterol concentration moderately compared to skimmed milk.

Methods

Subjects

Subjects were recruited through postings on the Internet and around university campus area in Copenhagen. A total of 25 subjects were screened through telephone calls, 19 were assessed for eligibility, 18 were enrolled in the study, and 1 subject dropped out after randomization (see participant flowchart in Fig. 1). Exclusion criteria were: previous or current CVD, diabetes, or other severe chronic disease; BMI (in kg/m ^{2}) < 18.5 and >30; age < 20 years and >70 years; pregnancy or planning of pregnancy during study period; excessive physical activity (>10 h/wk); milk allergy or lactose intolerance; blood donations <1 mo prior to and during study period; use of supplements, lipid-lowering medication, as well as medicine that might affect study outcomes; known or suspected abuse of alcohol, medication, or drugs; blood pressure >140/90 mmHg; and inability to follow study protocol. After receiving oral and written information about the study all subjects gave their informed consent in writing and completed a lifestyle questionnaire including questions about current and previous disease.

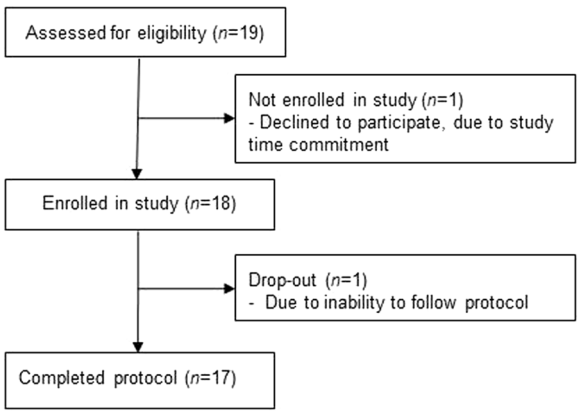

Fig. 1 Participant flowchart

Study design

The study was a crossover RCT. The two intervention periods of whole milk and skimmed milk (in random order) were 3 weeks long with no wash-out period, as the lipids in the blood are known to adjust after 2 weeks [13]. The study was not blinded as the appearance of the test beverages could not be concealed. However, analyses of blood samples as well as statistics were done blinded. Sample size was based on a previous study on dairy fat in which butter significantly increased LDL cholesterol compared with olive oil (control) (difference in concentration 0.17 mmol/L) [14]. Thus, with a standard deviation (SD) of 0.19 mmol/L, a total of 12 subjects had to be included in order to detect a similar difference (assuming a significance level of 5 and 80% power). The study was carried out at the Department of Nutrition, Exercise, and Sports, Faculty of Science, University of Copenhagen, Frederiksberg, Denmark from 3 October to 17 December 2015. The study was approved by the Municipal Ethical Committee of Copenhagen (Report H-15011908) and conducted according to the Helsinki Declaration.

Intervention

The test foods were provided to the study subjects, consisting of 0.5 L conventional skimmed milk (0.1%, Arla Foods, Denmark) and whole milk (3.5%, Arla Foods, Denmark) from cows and from the same season. The energy content and macronutrient composition of the milks are shown in Table 1. Subjects were instructed not to consume yoghurt, ice-cream, or milk besides the test milk. For other dairy products such as cheese and butter and for cooking oils subjects were instructed to keep the same dietary pattern throughout the intervention. Apart from the test foods

Table 1 Composition of 0.5 L of whole and skimmed milk and the calculated differences

	Whole	Skimmed	Difference
Energy/d (kJ)	1345	750	595
Fat (g)	17.5	1.5	16
SFA	11.5	1	10.5
MUFA	4	0.5	3.5
PUFA	0.5	0.0	0.5
Protein (g)	17	17.5	0.5
Carbohydrates (g)	24	23.5	0.5

Note: Danish Food Composition Databank (http://frida.fooddata.dk), Version 2, 2016, National Food Institute, Technical University of Denmark 2016

and restrictions in dairy intake the remaining diet was self-selected and study subjects were asked to maintain their usual diets and their regular level of physical activity throughout the intervention periods. Subjects were instructed in how to substitute the test foods for food items from their habitual diets (usually the milk they normally drank). Weekly subjects visited the department to collect the milk and for weighing and follow-up making sure they adhered to the test diet and kept a stable body weight during intervention periods. Compliance was measured as a percentage of milk consumed according to a diary kept throughout the intervention compared with the milk handed out. Subjects completed 3-d dietary records the last week of each period and were instructed to include 1 weekend day and 2 weekdays to take account of differences in nutrient intake. Dietary intake was assessed using Dankost Pro dietary assessment software (Dankost).

Clinical investigations

Fasting blood samples were taken at baseline, after 3 weeks and after 6 weeks. Prior to the blood sampling subjects fasted (12 h) and were asked to refrain from smoking (12 h), extreme sports (36 h), alcohol or medicine (24 h). Blood samples were drawn for assessment of following: serum lipids (total, LDL, and HDL cholesterol and triacylglycerol), insulin, and plasma glucose. Samples for assessment of blood lipids and insulin were collected into dry tubes, and samples for glucose were collected into tubes with a 1×3 mL-fluoride citrate mixture. To coagulate blood samples were stored at room temperature for 30 min. Further, blood samples for assessment of blood lipid and insulin concentrations were centrifuged at 2754×*g* for 10 min at 4 °C and stored at −80 °C until the concentration was analyzed. For glucose, samples were centrifuged at 2754×*g* for 10 min at 20 °C and stored at −80 °C until the concentration was analyzed. LDL and HDL cholesterol concentrations were assessed by enzymatic colorimetric procedure (ABX Pentra LDL Direct CP and ABX Pentra HDL Direct CP, respectively; Horiba ABX). Concentration of total cholesterol was assessed by enzymatic photometric test (CHOD-PAP from ABX Pentra Cholesterol CP). Triacylglycerol and glucose concentrations were assessed by enzymatic colorimetric procedure (ABX Pentra Triglycerides CP and ABX Pentra Glucose HK CP; Horiba ABX, respectively). Blood lipid concentration was analyzed on an ABX Pentra 400 Chemistry Analyzer (Horiba ABX). Interassay CVs for total, LDL and HDL cholesterol, triacylglycerol, and glucose were 2.2, 2.7, 2.0, 2.6, and 2.5%, respectively. Intra-assay CVs for total, LDL and HDL cholesterol, triacylglycerol, and glucose were 0.9, 0.7, 1.2, 3.8, and 1.1%, respectively. Insulin concentrations were assessed by the solid-phase enzyme-labeled chemiluminescent immunometric assay with an Immulite 2000 XPi (Siemens Medical Solutions Diagnostics). Interassay and intra-assay CVs for insulin were 3.5 and 4.2%, respectively.

Insulin resistance was evaluated by using homeostasis model assessment—insulin resistance (HOMA-IR) with the following formula: HOMA-IR = Fasting serum insulin (μU/mL) x fasting plasma glucose (mmol/L)/22.5 [15].

Fasting body weight was measured at baseline, 3 and 6 weeks to the nearest 0.1 kg wearing light clothing and having emptied their bladder in advance. Height, body weight for BMI calculation, and waist circumference were also measured at screening. Height was measured without shoes to the nearest 0.5 cm with a wall-mounted stadiometer (Seca) and waist circumference was measured horizontally at the midpoint between the bottom rib and the top of the hip bone.

Statistical analysis

Statistical differences for outcome measures were analyzed with linear mixed models that incorporated systematic effects of period and treatment and their interaction. Approximate *F*-tests were used to evaluate the interaction between time and treatment and if non-significant to evaluate a time-independent treatment effect. Baseline values and relevant covariates: sex, age, waist circumference, and baseline-BMI were included. Subject-specific random effects were included to account for inter-subject variability and to adjust for non-specific differences that could not be explained by the explanatory variables included. For dietary records statistical differences were based on paired *t*-test or Wilcoxon Signed Rank test for non-parametric variables. Treatment differences were reported in terms of unadjusted mean levels with corresponding standard errors. All models were validated by graphical assessment of normal quantile plots and residual vs. fitted plots. When departure was detected logarithmic transformation of the variables were made. Variance homogeneity was visually inspected and showed similar variance. Concentration of glucose and insulin were correlated to blood lipid responses using Pearson correlation test or Spearman correlation test for non-parametric variables. A two-tailed P-value < 0.05 was considered significant. The statistical software R version 3.1.3 2015 was used for all statistical evaluations.

Results

Subjects

Of the 18 recruited subjects, 1 dropped out in the first period because of inability to follow study protocol. Baseline

characteristics of the 17 subjects who completed the study are outlined in Table 2. No difference was observed in body weight during the intervention between whole milk and skimmed milk periods ($P = 0.59$). The compliance for intake of milk during the first and second period was 99.7 and 98.5%, respectively.

Table 2 Baseline characteristics of the 17 subjects who completed the intervention

	Value
Sex, *n* (%)	
Men	6 (35)
Women	11 (65)
Smoking, *n* (%)	1 (6)
Age (years)	25.7 ± 2.3
Height (cm)	174.1 ± 11.1
BMI (kg/m ^{2})	21.8 ± 1.5
Waist circumference (cm)	75.9 ± 6.2
Systolic blood pressure (mmHg)	114 ± 7.5
Diastolic blood pressure (mmHg)	70.3 ± 7.0
Total cholesterol (mmol/L)	4.35 ± 0.72
LDL cholesterol (mmol/L)	2.34 ± 0.49
HDL cholesterol (mmol/L)	1.61 ± 0.37
Triacylglycerols (mmol/L)	1.00 ± 0.34
Insulin (pmol/L)	42.87 ± 20.86
Glucose (mmol/L)	5.28 ± 0.35
HOMA-IR	1.42 ± 0.75

Note: Mean ± SD (all such values)

HOMA-IR homeostasis model assessment—insulin resistance

Table 3 Results after skimmed milk and whole milk periods

	Skimmed	Whole	*P*
Total cholesterol (mmol/L)	4.31 ± 0.15[a]	4.45 ± 0.15	0.06
LDL cholesterol (mmol/L)	2.27 ± 0.11	2.33 ± 0.11	0.54
HDL cholesterol (mmol/L)	1.63 ± 0.10	1.69 ± 0.10	0.04
Total:HDL cholesterol	2.74 ± 0.13	2.73 ± 0.12	0.82
Triacylglycerols (mmol/L)	0.98 ± 0.08	1.06 ± 0.08	0.24
Insulin (pmol/L)[b]	41.99 ± 4.13	45.66 ± 4.23	0.22
Glucose (mmol/L)	5.24 ± 0.07	5.32 ± 0.09	0.38
HOMA-IR[b]	1.37 ± 0.14	1.50 ± 0.14	0.23

HOMA-IR homeostasis model assessment—insulin resistance

[a]All values are mean ± SE. Statistical differences are based on linear mixed models with baseline values as covariates and adjustments for sex, age, BMI, and waist circumference ($n = 17$)

[b]$n = 16$ because one sample was below the detection limit (14.4 pmol/L) and was removed from the analysis

Blood lipids

Results from fasting blood lipid measurements at the end of each period are listed in Table 3. HDL cholesterol was significantly higher with whole milk than with skimmed milk ($P < 0.05$). There were no significant differences between the periods for any of the other blood lipids. For total cholesterol there was a tendency for a higher concentration with whole milk than with skimmed milk ($P = 0.06$).

Insulin and glucose

Results of glucose and insulin concentrations measured at the end of each period as well as calculated HOMA values are listed in Table 3. There were no significant differences between the periods for any of these outcomes. However, correlation analysis with skimmed milk showed that insulin and LDL cholesterol were moderately positively correlated ($r = 0.54$, $P < 0.05$) and with whole milk that glucose and HDL cholesterol were moderately negatively correlated ($r = 0.52$, $P < 0.05$).

Dietary intake

Results from the dietary records are listed in Table 4. Total energy intake was significantly higher with whole milk than with skimmed milk ($P < 0.05$). Fat intake (in grams and percentage of energy) was significantly higher with whole milk than with skimmed milk ($P < 0.001$). Also, the intake of saturated, monounsaturated, and polyunsaturated fat was

Table 4 Average daily consumption of energy, macronutrients, and calcium during the skimmed and whole milk periods

	Skimmed	Whole	*P*
Total energy (kJ)	8817 ± 359	10,261 ± 672	0.02
Energy density (kcal/g)	1.3 ± 0.0	1.4 ± 0.1	0.32
Fat (% of energy)	32.7 ± 1.3	37.6 ± 0.8	<0.001
Fat (g)	77.9 ± 4.1	103.6 ± 6.4	<0.001
Saturated fat	27.0 ± 2.0	39.8 ± 2.5	<0.001
Monounsaturated fat	28.5 ± 1.7	35.0 ± 2.3	0.02
Polyunsaturated fat	13.1 ± 1.0	16.7 ± 1.2	0.02
Carbohydrate (% of energy)	48.9 ± 1.4	44.8 ± 1.1	0.002
Protein (% of energy)	17.4 ± 0.5	16.6 ± 0.6	0.43
Calcium (mg)	1147 ± 48	1185 ± 57	0.47
Alcohol (g)	2.9 ± 0.9	4.0 ± 1.3	0.50
Dietary fiber (g)	28.7 ± 2.5	29.8 ± 2.7	0.49

Note: All values are mean ± SE. Statistical differences are based on paired *t*-test or Wilcoxon Signed Rank test for non-parametric variables (saturated fat and protein). $n = 17$. Data were assessed with a 3-d weighed dietary record. Estimated by using Dankost Pro dietary assessment software (Dankost)

significantly higher with whole milk than with skimmed milk ($P < 0.001$, $P < 0.05$, and $P < 0.05$, respectively). Intake of carbohydrate was significantly higher with skimmed milk than with whole milk ($P < 0.01$). There were no differences between the periods for intake of protein, calcium, alcohol, and dietary fiber.

Discussion

In the present study we showed that a daily intake of 0.5 L whole milk for 3 weeks did not increase LDL cholesterol compared to an equal intake of skimmed milk in healthy subjects. Moreover, although small, a significant increase in HDL cholesterol concentration was shown with whole milk compared to skimmed milk, which was significantly, moderately, and negatively correlated with glucose concentration. None of the other outcome measurements showed a difference between the periods. The increase in HDL cholesterol following intake of whole milk was expected due to the higher content of SFAs known to increase HDL and LDL cholesterol concentrations [16]. The Nordic Nutrition Recommendations as well as the American Dietary Guidelines advice that SFA should be limited to less than 10 E% [1, 2], due to the predicted effect on LDL cholesterol. In comparison, the amount of SFAs in the whole milk diet was almost 5 E% above and in the skimmed milk diet close to recommendation (14.4 and 11.3 E%, respectively), according to the dietary records. Thus, the result of no difference in LDL cholesterol was unexpected and opposite to the dietary guidelines and our hypothesis, despite of the dominating macronutrient content of SFA with whole milk. Studies of the association between HDL cholesterol concentration and CVD has shown that HDL is protective [17, 18]. However, it is necessary to be cautious when interpreting low concentration of HDL cholesterol as a CVD risk factor. Mendelian randomization studies have shown that genetically decreased HDL cholesterol was not associated with increased risk of myocardial infarction, questioning the causality of an association between low HDL concentration and CVD [19–21]. Still, HDL cholesterol concentration, as a marker of cardiovascular health, should be taken into consideration when interpreting the effect of dairy or SFAs in the diet.

Our results are in line with two previous intervention studies from 2009 and 1994 comparing milk of different fat content that also showed no effect on total and LDL cholesterol concentration after 12 months and 6 weeks with similar milk intake (500 and 660 mL/d, respectively); however, contrary to our results also no effect on HDL cholesterol [7, 8]. Fonolla et al. compared semi-skimmed milk and skimmed milk and therefore a smaller difference in milk fat (1.9 vs. 0.3%), which could explain the lack of difference in HDL cholesterol compared to the present study [7]. Steinmetz et al., the more comparable study and of good quality, also compared skimmed milk with whole milk in a crossover design, but in a background diet designed to meet the AHA recommendations. Steinmetz et al. reported a significantly higher concentration of total and LDL cholesterol with whole milk compared to skimmed milk [8]. However, the statistical analysis was not adjusted for baseline measurements, and thus not adjusted for differences between periods, and in addition the sample size was small ($n = 8$). Still, the analysis of difference in change from baseline between the two diets was also reported which showed no difference between total and LDL cholesterol, in line with our results. Nevertheless, the study reported higher Apolipoprotein B concentrations with whole milk compared to skimmed milk known to be a predictor of cardio metabolic risk [22].

Although the dietary records showed a significantly higher energy intake with whole milk compared to skimmed milk, it seems that the study subjects compensated for the extra energy with whole milk by lowering their intake of carbohydrate which was significantly lower compared to skimmed milk. The content of calcium and protein were similar in the two milk types, but whole milk has a higher content of milk fat globule membranes (MFGM), which encloses the fat. A possible matrix effect of MFGMs was suggested in a recent study showing an impaired lipoprotein profile after a butter oil diet, low in MFGMs, compared with a whipping cream diet, high in MFGMs [23]. One proposed mechanism, based on a mice study, is through lowering of cholesterol absorption by inhibition of cholesterol micellar solubility possibly due to presence of sphingomyelin in MFGM fragments [24]. Thus, one could speculate that an expected higher LDL cholesterol concentration after whole milk may be modified by a dairy matrix effect of MFGM.

The strength of the present RCT was the imitation of real-life settings by not matching the diets for energy content or macronutrient composition, which made it possible to directly compare whole milk and skimmed milk as whole foods. The free-living design of the study was a limitation, thus allowing the presence of potential confounding by other lifestyle and dietary factors. However, the crossover design minimizes this potential confounding as study subjects were their own control.

In conclusion, the results indicate that intake of 0.5 L/d of whole milk does not adversely affect fasting blood lipids, glucose, or insulin compared to skimmed milk in healthy adults. Moreover, intake of whole milk increased HDL cholesterol concentration compared to skimmed milk. These findings suggest that if the higher energy content is taken into account, whole milk can be considered as part of a healthy diet among the normocholesterolemic population.

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Compliance with ethical standards

Conflict of interest TT has received research grants from Arla Foods, Denmark; The Danish Dairy Research Foundation; and the Dairy Research Industry, Rosemont, IL. The remaining authors declare no competing interests.

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