Examine.com

Research Digest

Exclusive Sneak Peek

Click here to purchase ERD

Table of Contents

Got Milk(fat globule membrane)?

Potential role of milk fat globule membrane in modulating plasma lipoproteins, gene expression, and cholesterol metabolism in humans: a randomized study

Introduction

Cardiovascular disease (CVD) is a general term for any pathological condition that involves the heart or blood vessels. Many of these diseases, and certainly those most commonly associated with Western societies, are a result of atherosclerosis – the thickening of artery walls through the buildup of plaques of fatty material. Although CVD was once thought to be primarily due to elevated cholesterol levels, it is now recognized that inflammation of the arteries is a necessary prerequisite for plaque formation.

That said, LDL infiltration of the artery walls is a major cause of inflammation, and there is little debate among the medical community that high levels of LDL-cholesterol (LDL-c) is a risk factor for CVD. Two recent meta-analyses support this view. The first looked at over 38,000 patients taking statins and found a significant reduction in risk as LDL-c levels moved from above 175 mg/dL to below 50 mg/dL. Achieving an LDL-c below 100 mg/dL through statin therapy was associated with a 44% reduced risk of having a major CVD event, while levels below 50 mg/dL were associated with a 56% reduced risk. The second analysis looked at data from over 10,000 patients enrolled in 24 randomized, placebo-controlled trials of PCSK9 inhibitors and found that

treatment reduced LDL-c by nearly half while simultaneously reducing the number of heart attacks by 51% and the odds of death from any cause by 55%.

What these studies serve to illustrate is that we now have two completely different drug therapies, statins and PCSK9 inhibitors, which reduce LDL-c by different methods and reduce the risk of CVD-related events. It stands to reason that other methods that reduce LDL may also reduce the risk of CVD. A first line of defense for the management of blood cholesterol levels is dietary intervention.

Dairy fat is typically around 70% saturated fat and makes up about a fifth of total saturated fat intake in the U.S. diet, making it a prime target for nutritional interventions. However, results from observational and experimental trials that evaluate the impact of dairy products on blood cholesterol levels are not conclusive. Notably, there is a lot of evidence from randomized controlled trials that diets high in saturated fat derived largely from butter fat increases LDL-c, whereas cheese intake results in lower LDL-c compared with butter of equal fat content, and may not increase LDL compared with a diet lower in saturated fat. Similarly, the results are fairly consistent in showing that whole milk

> " Dairy fat is typically around 70% saturated fat and makes up about a fifth of total saturated fat intake in the U.S. diet, making it a prime target for nutritional interventions. "

increases LDL-c more than low-fat or skim milk, while whole-fat yogurt may reduce LDL-c.

The inconsistent findings with regard to dairy fat's effects on blood cholesterol have been hypothesized to be owed, at least in part, to the milk-fat globule membrane (MFGM) – a three-layered membrane composed of proteins, lipids, and numerous minor bioactive sterols that encloses the milk fat globules. Figure 1 shows the basic processes used to make different dairy products. The MFGM is a very fragile compound that is preserved in cream and cheese, but destroyed during mechanical processing, such as the churning required to make butter or the homogenization of milk. It has been suggested to have numerous health benefits, including cholesterol-lowering effects. The current study was an attempt to test the hypothesis that the effect of dairy fat on serum cholesterol levels is mediated by the presence (or absence) of the MFGM.

Observational and experimental evidence investigating the effect of dairy fat on serum cholesterol levels is conflicting and depends on the dairy product consumed. An intact milk-fat globule membrane (MFGM) present in some dairy foods, such as non-homogenized cream and cheeses, may explain the inconsistencies. The study under review tested this hypothesis.

Who and what was studied?

Local advertising at Uppsala University Hospital, Sweden was used to recruit overweight but otherwise healthy men and women to undergo an eight-week, single-blinded randomized trial. The participants were 50-65 years old, had an average BMI of 28, did not regularly engage in heavy exercise (more than 3 times per week), and had no abnormal blood chemistry. After being stratified by baseline sex, age, LDL-c, and habit-

Figure 1: Dairy products in a nutshell
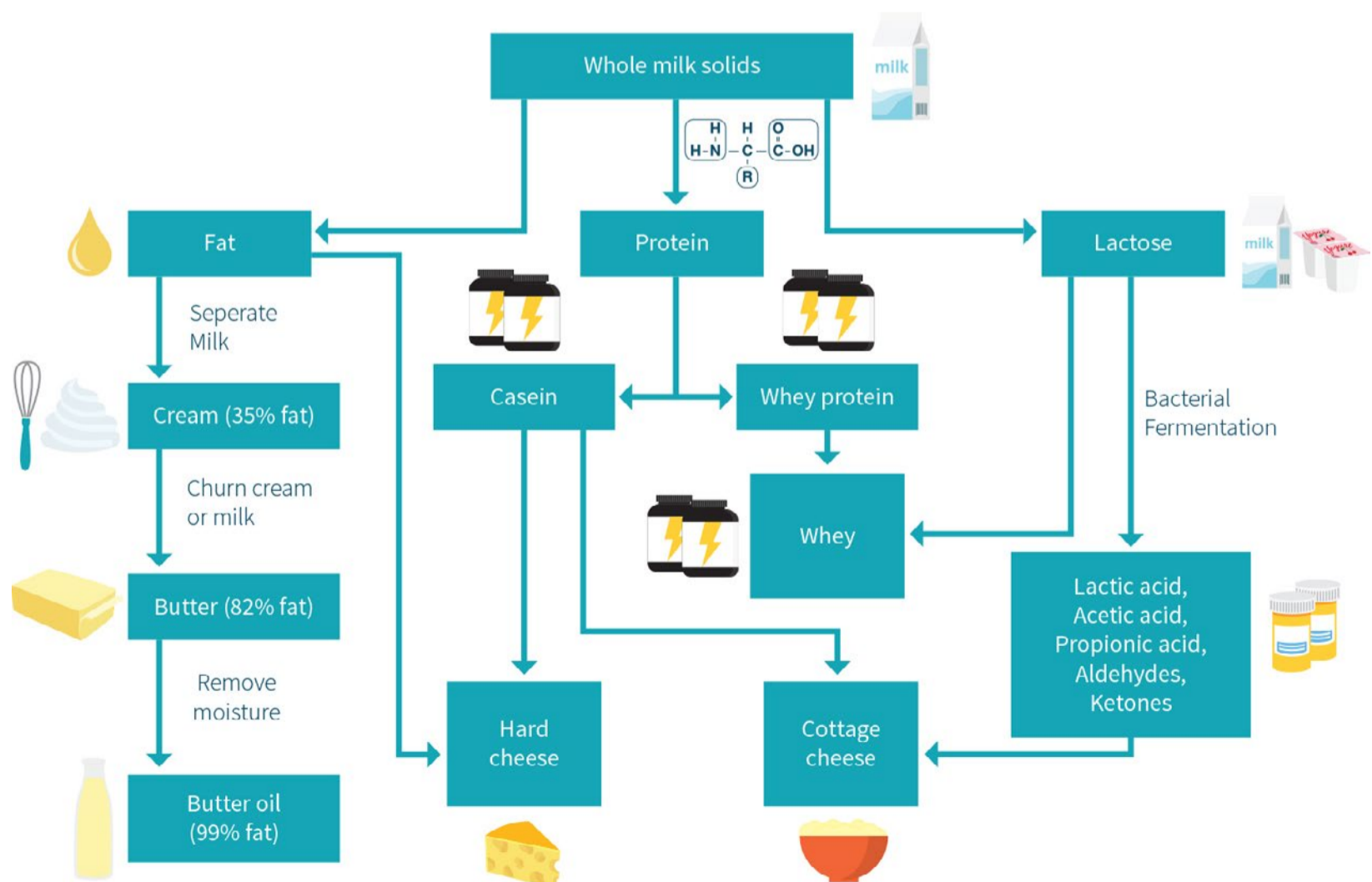
ual dairy intake (high vs. low), the participants were randomized to a MFGM or control group. Stratification means that the participants were put into categories based on the aforementioned variables, helping ensure an even distribution between groups. A total of 46 people completed the study (26% men and 74% women).

The dietary interventions were essentially the same except for the source of dairy fat. Both groups consumed 100 grams (just under ½ cup) of fat-free milk and one scone prepared by the research staff. The MFGM group also consumed 100 grams (about 6.5 tablespoons) of whipping cream (40% fat) per day, which was confirmed to have intact MFGMs, while the control group consumed 40 grams (about three tablespoons) of butter oil that had no MFGMs present, and a few grams of whey protein isolate to match up the protein and calcium content of the groups. The butter, oil, and whey were baked into the scones of the control participants. All participants were allowed to eat their food however and whenever they wanted through the day, provided the whipping cream was not heated, mixed, or whipped.

The participants were all free-living adults who visited the research clinic weekly for weight measurement, food distribution, and general support. They were instructed not to change their usual dietary habits, but to avoid consuming any dairy or margarine products not provided by the researchers.

Table 1: Nutrient content of the intervention food items

	MFGM diet	Control diet
Energy, kcal	805	794
Carbohydrate, g	88.9	86
Fat, g	41.8	41.4
Protein, g	16.7	16.7
Phospholipids, mg	19.8	1.3
Cholesterol, mg	100	120
Calcium, mg	687	677

What were the findings?

The researchers evaluated numerous metabolic biomarkers, but the treatment affected only a few, which are shown in Figure 2. While the control group showed

Figure 2: Significant differences between study groups
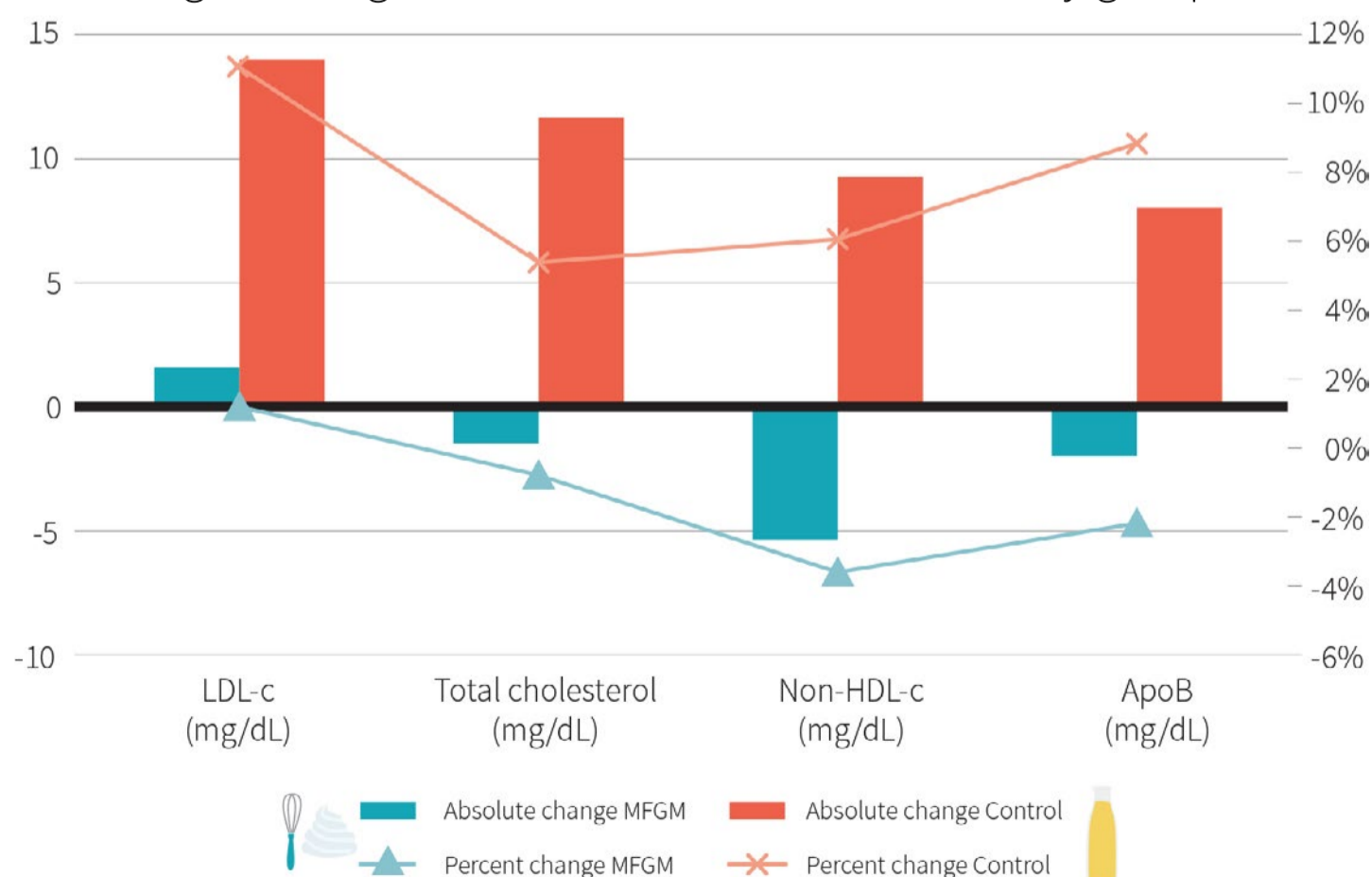
a rise in total-, LDL-, and non-HDL-cholesterol and apolipoprotein (Apo) B, the MFGM group did not, and there was a significant difference between the groups after the eight week intervention.

The researchers also analyzed peripheral blood mononuclear cell (PBMC) gene expression in the women of each group and found the expression of 19 genes to be significantly reduced in the MGFM group and increased in the control group. Changes in most of these genes correlated with changes in one or more of the changes in blood lipids. Though the scientific understanding of most these genes is poor, some of them have been implicated in the regulation of the cell life cycle, including apoptosis (programmed cell death), and in the regulation of protein breakdown within cells.

What does this really tell us?

This is a limited but informative study. It shows that replacing the habitual dairy fat intake of older over-weight-obese Swedish men and women with 40 grams of dairy fat from pasteurized but not homogenized cream has no effect on blood cholesterol levels and down-regulates the expression of numerous PBMC genes. However, replacing dairy fat with butter oil significantly increases blood cholesterol levels and PBMC gene expression. The small sample size, ethnical and geographical homogeneity, and inability to know how, when, and with what exactly the test products were consumed are significant limitations to the study. Although the presence of the MFGM in the cream is a plausible explanation for the outcomes, it is also possible that the physical state of the fats (fat globules vs. isolated fat) influenced the results.

Nonetheless, a strength of this study is that the results are directly translatable to common foods, although the effects may have been different if butter, rather than butter oil, was used in the control group. Still, the LDL-c-raising effects of butter oil are in line with those observed with butter. Of the most commonly con-

> " The small sample size, ethnical and geographical homogeneity, and inability to know how, when, and with what exactly the test products were consumed are significant limitations to the study. "

sumed sources of dairy fat, butter and butter oil have the lowest MFGM content (see FAQ).

Another strength of the study was that plasma phospholipid and cholesterol fatty acid composition were unchanged in both diets throughout the intervention without any differences between the diet groups, suggesting that the milk fat dose used (40 grams a day) was

similar to the habitual dairy fat intake of the participants. This helps minimize the possibility that changes in dietary fat intake influenced the results.

In sedentary, overweight-obese Swedish people, consuming pasteurized but non-homogenized cream instead of butter oil prevented increases in blood cholesterol concentrations, possibly due to the intact MFGM within the cream. However, the small sample size and lack of geographic and ethnic diversity makes it difficult to generalize the results of this study.

Big picture

The potential mechanisms through which MFGM counteracts the cholesterol-raising effects of dairy fat are not well established, but animal models suggest that it involves reduced cholesterol absorption or phospholipid-induced alterations in liver gene expression. For instance, rats fed a high-fat diet supplemented with MFGM phospholipids display a 15% to 30% increase in fecal cholesterol excretion and a 20% to 60% decrease in liver cholesterol. In a separate rodent study, where

the consumption of phospholipids was set to the estimated intake of a typical human, overall and per meal cholesterol absorption were reduced by half. Although the current study did measure surrogate markers of cholesterol absorption and synthesis and found no changes among the participants, the possibility of reduced cholesterol absorption and increased cholesterol excretion cannot be ruled out until more direct measurements in humans are made.

Rats that consume a high-fat diet supplemented with MFGM-rich milk extract display a reduction in liver fat accumulation and blood lipid levels attributed to a significant reduction in the expression of hepatic genes that regulate cholesterol synthesis (HMG-CoA reductase), bile acid synthesis (cholesterol 7α-hydroxylase), and fatty acid synthesis. This is in accord with the current study, which found all 15 tested PBMC genes to be down-regulated in the MFGM group. It has been suggested that PBMC gene expression after dietary interventions reflect changes within the liver and can be used for studying the response of certain genes related to fatty acid and cholesterol metabolism.

> " The potential mechanisms through which MFGM counteracts the cholesterol-raising effects of dairy fat are not well established, but animal models suggest that it involves reduced cholesterol absorption or phospholipid-induced alterations in liver gene expression. "

The current study is novel in its attempts to test the MFGM hypothesis, but falls short of providing concrete evidence that the group differences are owed to it. Unfortunately, there are no other human studies on the MFGM. The main confounding variable was the different dairy sources used, which could be overcome in future trials by using products only differing in their level of processing (e.g., homogenized vs. non-homogenized whole milk). Of course, adding more strict dietary control would also aid in isolating the MFGM. Allowing the consumption of MFGMs through their natural food sources provides a degree of generalizability to the foods themselves. Future trials should also evaluate if supplementation with a MFGM extract would have similar effects on blood cholesterol and interact with other fat sources in the diet.

> " The world enjoys gravitating to the extremes of issues, and blood cholesterol levels are no exception. "

Frequently Asked Questions

If inflammation is a necessary prerequisite for atherosclerosis, then why worry about LDL-c?
The world enjoys gravitating to the extremes of issues, and blood cholesterol levels are no exception. Although many "anti-mainstream" nutrition enthusiasts claim that hypercholesterolemia doesn't play a role in heart disease, understanding how arterial plaque forms may aid in illustrating why we should care about LDL-c and especially LDL particle count (LDL-p).

After an artery is damaged through any of the many risk factors for CVD (hypertension, free radicals, etc.), it begins to express certain proteins that allow for the accumulation of white blood cells. As the white blood cells arrive, they begin releasing chemicals (cytokines; this is the inflammation part) that signal more of their brethren to stop by. Under normal circumstances, the damage would resolve and the blood cells would leave: mission accomplished. However, under conditions of continuous damage through, for example, chronic inflammation, the artery will never fully repair and the white blood cells will continue to accumulate. This is where LDL-c and LDL-p come into play.

LDL-cholesterol enters the damaged area, where it is more prone to becoming oxidized. The oxidation signals to the white blood cells that they need to eat it, so as to protect the body. But this LDL-c-engulfing process turns white blood cells into "foam cells," which can be thought of as obese white blood cells. That is, they are giant lipid-filled cells that can't function properly and are ultimately part of what forms the plaque seen in atherosclerosis. So while inflammation is indeed necessary, if there there are fewer LDL particles with overall lower LDL cholesterol in the blood, then there is a reduced likelihood of it entering the damaged area and being oxidized and consumed. Similarly, if someone has a boatload of LDL-c in their blood along with high LDL-p, there is a far greater likelihood that some of it will become oxidized and consumed by white blood cells, even if the damaged area is only temporarily (i.e. no systemic inflammation present) damaged. So, the best bet against heart disease is keeping both inflammation and LDL-c / LDL-p low.

What dairy products contain an intact MFGM?

The MFGM in dairy fat prevents lipid droplets from grouping together, therefore they remain dispersed in the milk. Only after destruction of the structure of the MFGM through mechanical force like churning do lipid droplets aggregate and subsequently form large fat clumps (i.e., butter). This is why MFGMs are only present in dairy products that contain dairy fat and have not been mechanically altered through churning or homogenization. For example, whole milk, cream, and cheese all contain MFGMs, whereas butter, butter oil, butter milk, whey protein, and any fat-free dairy products do not.

That being said, MFGM is only one of the many differences between dairy products that may influence their differential impacts on heart disease. For example, cheese and milk are more nutrient-dense than butter. Additional differences are shown in Figure 3.
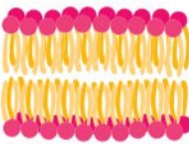
What is the difference between butter and butter oil?
Butter oil is the fat concentrate obtained primarily from butter or cream by the removal of practically all the water and proteins. The terms anhydrous milk fat, dry butterfat, and dehydrated butter fat are used synonymously with butter oil, but the raw material used for their preparation is mainly cream. Ghee is also a form of butter oil.

What should I know?

Non-homogenized milk fat (cream) does not increase cholesterol levels, which, ironically, is the main reason we are told to avoid high-fat dairy foods. The MFGM may explain the inconsistencies of observational and experimental studies evaluating the impact of dairy fat on blood lipid levels, and this study provides preliminary evidence to support this hypothesis. However, no concrete conclusions can be made because of a handful of study limitations, such as the physical state of the dairy products used. Animal research suggests any potential effects may be owed to the ability of the MFGM to reduce cholesterol absorption and synthesis and increase excretion. ◆

Figure 3: Differences between butter and cheese impact health effects

	CHEESE	BUTTER
CHOLESTEROL EFFECT	LOW/ MODERATE	MODERATE/ HIGH
MFGM	HIGH	LOW
PROTEIN	MODERATE	ABSENT
VITAMIN	MODERATE	ABSENT
FERMENTATION	PRESENT	ABSENT

Turns out that demonizing "Dairy" as a category probably isn't the best approach. Maybe demonizing isn't the best approach, in general. Head over the Facebook ERD forums to talk about dairy and heart disease.