

Dairy product consumption and the metabolic syndrome

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The metabolic syndrome is an important risk factor for type 2 diabetes mellitus and CVD. Epidemiological studies have now suggested protective effects of dairy product consumption on the development of this syndrome. Here we review the physiological effects and possible mechanisms involved of three main dairy constituents (Ca, protein, fat) on important components of the metabolic syndrome. Ca supplements improve the serum lipoprotein profile, particularly by decreasing serum total and LDL-cholesterol concentrations. They also lower systolic and diastolic blood pressure. Insufficient evidence exists for a significant role of Ca supplements or dairy in body-weight management. Effects of Ca may be related to intestinal binding to fatty acids or bile acids, or to changes in intracellular Ca metabolism by suppressing calciotropic hormones. Dietary proteins may increase satiety in both the short and longer term, which may result in a reduced energy intake. They have also been reported to improve the serum lipoprotein profile as compared with carbohydrates. Dairy proteins are precursors of angiotensin-I-converting enzyme-inhibitory peptides, which may lower blood pressure. Such effects, however, have inconsistently been reported in human studies. Finally, conjugated linoleic acid, which effectively lowers body weight in animals, has no such effect in humans in the quantities provided by dairy products. To reduce the intake of SFA, the consumption of low-fat instead of high-fat dairy products is recommended. In conclusion, more research is warranted to better understand the physiological effects and the mechanisms involved of dairy products in the prevention and treatment of the metabolic syndrome.

Dairy products: Metabolic syndrome: Calcium

Introduction

The metabolic syndrome dramatically enhances the risk of developing CVD and type 2 diabetes mellitus. It consists of a combination of different metabolic abnormalities, such as abdominal obesity, atherogenic dyslipidaemia, elevated blood pressure, insulin resistance, glucose intolerance, impaired endothelial and haemostatic function, and a low-grade inflammatory state⁽¹⁾. The prevalence of the metabolic syndrome among the adult population exceeds 20 % in many Western societies and is expected to increase in the very near future⁽²⁾. Without doubt, this will have important economic and health consequences, and unfortunately no straightforward approach exists to prevent or treat the metabolic syndrome.

However, it is well established that both energy restriction and dietary composition play an important role in this respect. More specifically, several studies have suggested that dairy food products have a positive impact on the prevention of the metabolic syndrome. The aim of the

present review is now to briefly summarise findings from epidemiological studies on the relationship between dairy product consumption and the metabolic syndrome and to discuss the results from intervention studies on the effects of dairy products and dairy constituents on features of this syndrome. In addition, attention is paid to underlying mechanisms. We hereby focused on studies carried out during the last decade.

Dairy product consumption and the metabolic syndrome

A number of epidemiological studies have investigated the relationship between dairy product consumption and the prevalence or incidence of the metabolic syndrome. In 2000, Mennen *et al.*⁽³⁾ showed in a cross-sectional study that consumption of dairy products was inversely related with the prevalence of the metabolic syndrome in men (aged 30–64 years), but not in women. Men who consumed more than one portion of dairy products per d had a 40 % lower

Abbreviations: ACE, angiotensin-I-converting enzyme; CLA, conjugated linoleic acid.

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prevalence of the metabolic syndrome compared with men who did not consume dairy products at all. In another cross-sectional study, Azadbakht *et al.* ⁽⁴⁾ demonstrated an inverse association between dairy product consumption and the metabolic syndrome in healthy Tehranian subjects aged 18–74 years. In the group with the highest dairy product intake (≥ 3.1 servings/d of milk, yogurt, cheese and milk-based desserts) the prevalence of the metabolic syndrome was 7% lower compared with the group with the lowest dairy product intake (< 1.7 servings/d). In addition, Elwood *et al.* ⁽⁵⁾ have recently found a negative relationship between milk and dairy product intake and the prevalence of the metabolic syndrome in a study among 45- to 49-year-old men. Similar results were observed by Ruidavets *et al.* ⁽⁶⁾, who showed in a cross-sectional sample of 45- to 64-year-old men that intake of dairy products (milk and cheese) was negatively related to the prevalence of the metabolic syndrome. However, a cross-sectional study by Beydoun *et al.* ⁽⁷⁾ among 4519 US adults showed that the various dairy products may have different associations with the metabolic syndrome. While cheese consumption showed a positive relationship with the prevalence of the metabolic syndrome, the intake of yogurt resulted in a negative relationship. In contrast, in an elderly Dutch population, Snijder *et al.* ⁽⁸⁾ did not find associations between dairy product consumption and the metabolic syndrome. Also, after differentiation between low-fat and high-fat dairy products, no significant associations were found. In the same population, baseline dairy product consumption was also not related to the risk of developing the metabolic syndrome in the next 6.4 years ⁽⁹⁾. However, in the prospective Coronary Artery Risk Development in Young Adults (CARDIA) study ⁽¹⁰⁾ among more than 3000 young (aged 18–30 years) men and women, it was found that in overweight subjects dairy product consumption was inversely associated with the development of all components of the metabolic syndrome over the next 10 years. In another prospective study by Lutsey *et al.* ⁽¹¹⁾, dairy product consumption was inversely associated with the incidence of the metabolic syndrome in more than 9500 US subjects (aged 45–64 years) after 9 years of follow-up.

Though not consistent, the majority of epidemiological studies do suggest that dairy products may play a role in the prevention and development of the metabolic syndrome. However, which of the components from dairy products may be responsible for these possible positive effects is not clear, neither are the mechanisms behind these effects. However, several intervention studies have been performed on the effects of single nutrients from dairy products on the different features of the metabolic syndrome. In this respect, much attention has been paid to Ca, protein and fat.

Calcium

Dairy products are an important source of Ca ^(12,13). High intakes of dietary Ca may be associated with a lower prevalence of the various risk markers belonging to the metabolic syndrome, as indicated by epidemiological studies ^(14,15). A number of intervention studies also showed beneficial effects of Ca on features of the metabolic syndrome.

Effects of calcium on the serum lipid profile

Ca may affect the serum lipoprotein profile. Ca provided as a food supplement has been found to increase serum HDL-cholesterol concentrations ⁽¹⁶⁾, and to decrease serum total cholesterol ⁽¹⁷⁾ and LDL-cholesterol concentrations ⁽¹⁸⁾. As a consequence, Ca intake also improved the HDL:LDL-cholesterol ratio, which may be an even better marker to predict cardiovascular risk than LDL or HDL *per se*. Reid *et al.* ⁽¹⁶⁾ found beneficial effects on circulating lipid levels after 12 months of Ca supplementation. Two hundred and twenty-three postmenopausal women were given 1 g Ca daily as calcium citrate or placebo. HDL-cholesterol and the HDL:LDL-cholesterol ratio significantly increased by 0.13 mmol/l and 0.06, respectively. No statistically significant decreases in total cholesterol (-0.18 mmol/l) and LDL-cholesterol (-0.29 mmol/l) were observed. In the cross-over study of Ditscheid *et al.* ⁽¹⁷⁾, thirty-one healthy adults received 1 g Ca daily, supplied as pentacalcium hydroxy-triphosphate in bread, or non-supplemented bread for 4 weeks. A significant decrease in total cholesterol (-0.24 mmol/l), and non-significant decreases in LDL-cholesterol (-0.14 mmol/l) and the LDL:HDL-cholesterol ratio (-0.85) were found. Shahkhalili *et al.* ⁽¹⁸⁾ observed significantly decreased serum LDL-cholesterol concentrations (-0.32 mmol/l) and a non-significant decrease in total cholesterol (-0.34 mmol/l). In this study, ten healthy men received Ca-supplemented chocolate (900 mg Ca per d) or non-supplemented chocolate for 2 weeks in a cross-over design. On the contrary, Bostick *et al.* ⁽¹⁹⁾ did not find significant effects of Ca supplementation on the serum lipoprotein profile in 193 men and women aged 30–74 years. Subjects received 1 or 2 g Ca daily, given as calcium carbonate, for 4 months. No statistically significant differences in serum total cholesterol and HDL-cholesterol concentrations were found between the Ca and placebo groups.

A summary of human intervention studies on the effects of Ca supplements on the serum lipid profile is given in Table 1.

Possible mechanisms underlying the effects of calcium on the serum lipid profile

Two potential mechanisms have been proposed by which Ca might affect lipoprotein metabolism. One mechanism is the inhibition of fat absorption in the intestine (Fig. 1). Ca interacts in particular with SFA to form Ca–fatty acid soaps. The formation of these insoluble complexes increases faecal fat excretion. Evidence for this interaction comes from a number of human studies ^(18,20–22). More recently, however, Boon *et al.* only observed a tendency towards an increased faecal fat excretion on high-Ca (1200 or 2500 *v.* 400 mg) diets ⁽²³⁾. In support of a decreased fat absorption, Lorenzen *et al.* ⁽²⁴⁾ have shown that Ca from dairy products (milk and low-fat yogurt), in contrast to supplementary Ca, diminished the TAG content of chylomicrons postprandially. This suggests either an increase in chylomicron clearance, or a decrease in fat absorption. As there is no evidence in the literature suggesting that Ca interferes with chylomicron clearance, effects on fat absorption are very likely. However,

Table 1. Overview of recent intervention studies on the effects of dairy product and calcium supplementation on serum lipid profile, blood pressure and glucose metabolism

Component of the metabolic syndrome	Subjects	Design	Additional Ca intake (mg/d) and source	Control	Effects	Study reference
Lipid profile	223 elderly women	Randomised, 1 year	1000 (calcium citrate)	Placebo	TC -0.18 mmol/l LDL-C -0.29 mmol/l HDL-C +0.13 mmol/l* HDL:LDL ratio +0.06* TAG -0.02 mmol/l TC -0.24 mmol/l*	Reid <i>et al.</i> (2002) ⁽¹⁶⁾
Lipid profile	Thirty-one healthy adults	Cross-over, double-blind, 2 x 4 weeks	1000 (pentacalcium hydroxy-triphosphate in bread)	Non-supplemented bread	LDL-C -0.14 mmol/l LDL:HDL ratio -0.85 TC -0.34 mmol/l	Dietscheid <i>et al.</i> (2005) ⁽¹⁷⁾
Lipid profile	Ten healthy men	Randomised, double-blind, cross-over, 2 x 2 weeks	900 (supplemented chocolate)	Non-supplemented chocolate	LDL-C -0.32 mmol/l*	Shahkhalili <i>et al.</i> (2001) ⁽¹⁸⁾
Lipid profile	193 healthy adults	Randomised, double-blind, 4 months	1000 or 2000 (calcium carbonate)	Placebo	TC -0.07 mmol/l	Bostick <i>et al.</i> (2000) ⁽¹⁹⁾
Blood pressure	Thirty-four obese adults	Randomised, 24 weeks	700 (dairy products)	Low-Ca, low-dairy product diet	HDL +0.01 mmol/l SBP -6.99 mmHg*	Zemel <i>et al.</i> (2005) ⁽⁴³⁾
Blood pressure	459 healthy adults	Randomised, 8 weeks	820 (dairy products in diet rich in fruits and vegetables)	Diet rich in fruits and vegetables	DBP -4.37 mmHg*	Appel <i>et al.</i> (1997) ⁽⁷⁷⁾
Blood pressure	Thirty-four obese adults	Randomised, 12 weeks	600 (dairy products in energy-deficit diet)	Low-Ca, energy-deficit diet	DBP -1.9 mmHg*	Zemel <i>et al.</i> (2005) ⁽³⁰⁾
Blood pressure	193 healthy adults	Randomised, double-blind, 6 months	1000 or 2000 (calcium carbonate)	Placebo	SBP -2.59 mmHg DBP -4.37 mmHg*	Bostick <i>et al.</i> (2000) ⁽¹⁹⁾
Glucose metabolism	Thirty-four obese adults	Randomised, 24 weeks	700 (dairy products)	Low-Ca, low-dairy product diet	SBP -0.8 mmHg DBP -0.4 mmHg	Zemel <i>et al.</i> (2005) ⁽⁴³⁾
Glucose metabolism	Thirty-two obese adults	Randomised, 24 weeks	1200–1300 (dairy products in energy-deficit diet)	Low-Ca, low-dairy product, energy-deficit diet	Fasting insulin -19.7 pm* Glucose AUC ↓* Fasting insulin ↓*	Zemel <i>et al.</i> (2004) ⁽²⁸⁾

TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; AUC, area under the curve; ↓, reduced. **P* < 0.05.

the reason for the difference between the effects of dairy and supplemental Ca is not clear. The authors suggested that other properties of dairy products may be responsible for the different effects, such as the chemical form of Ca (calcium phosphate in dairy products *v.* calcium carbonate in supplements) or the synergistic action of other dairy components.

SFA are known to increase total and LDL-cholesterol, most probably by suppressing LDL-receptor activity⁽²⁵⁾. The reduced absorption of SFA may, at least in part, contribute to the LDL-cholesterol-lowering effects of Ca. Some studies have suggested that this mechanism may be less effective under high-protein conditions, because protein would increase the intestinal absorption of Ca^(22,26). Whether or not this decreases the amount of Ca that is available for binding to fatty acids has, however, not been investigated. In fact, Ca is only partially absorbed and it may be speculated that the Ca content of high-dairy diets is high enough to leave sufficient amounts of Ca in the gastrointestinal tract for binding to fatty acids. Another possible mechanism is that Ca binds to bile acids (Fig. 1). Indeed, in some human studies, Ca increased the faecal excretion of bile acids^(17,18,27). In this way, reabsorption of bile acids into the enterohepatic circulation is inhibited, leading to an increased conversion of cholesterol to bile acids in the liver and ultimately to decreased LDL-cholesterol levels.

Effects of calcium and dairy products on body weight and fat mass

Ca may exert its effects on the metabolic syndrome by mediating body weight and fat mass. Observational as well as intervention studies suggest that high Ca intakes are associated with lower body weight and fat mass. Zemel *et al.* were among the first to report beneficial effects of Ca on body weight and fat mass. Furthermore, they have proposed that Ca from dairy sources exerts larger effects than Ca from non-dairy sources. In a 6-month trial⁽²⁸⁾, thirty-two obese subjects were maintained on energy-deficit (-500 kJ/d) diets and randomised to control (zero to one servings of dairy products per d supplemented with placebo, providing 400–500 mg Ca per d), high-Ca (control diet supplemented with 800 mg Ca per d as calcium carbonate) or high-dairy (three servings per d supplemented with placebo, providing 1200–1300 mg Ca per d) diets. Both weight loss and fat loss were higher on the high-Ca diet than on the control diet, but even higher on the high-dairy diet. Additionally, the largest percentage of fat from the trunk was lost on the high-dairy diet, shifting the distribution of body-fat loss to a more favourable pattern. Thus, dairy products exerted a substantially larger effect on both fat loss and fat distribution compared with an equivalent amount of supplemental Ca. This has been attributed to additional bioactive compounds in dairy products that may act synergistically with Ca to modulate body weight and fat mass⁽²⁹⁾. Although the macronutrient composition of the diets was similar and the diets only differed in Ca content, the observed effects might partly be due to differences in protein source, for example. The augmentation of weight loss by dairy products was also observed in another study, in

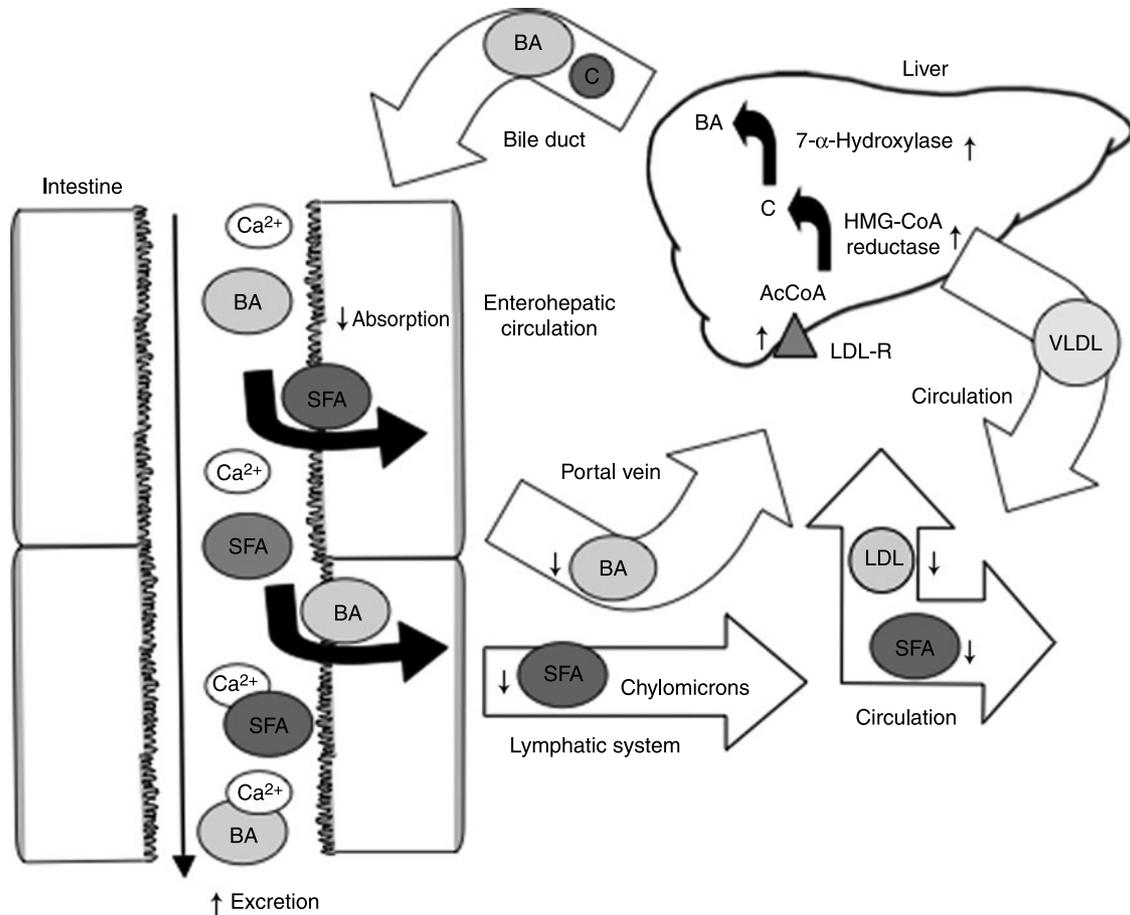


Fig. 1. One of the proposed mechanisms of action of dietary Ca. Ca binds to SFA or bile acids (BA) in the intestine, inhibiting their absorption. SFA raise LDL-cholesterol, probably by decreasing LDL-receptor (LDL-R) activity. Reduced absorption of SFA can therefore lower serum LDL-cholesterol. In the liver, cholesterol is converted into BA. Lowering the absorption of BA in the intestine will therefore lead to an increased conversion of cholesterol and reduced serum LDL-cholesterol levels. C, cholesterol; ↑, increased; HMG, 3-hydroxy-3-methyl-glutaryl; ↓, reduced; AcCoA, acetyl-CoA.

which an energy-deficit yogurt diet (1100 mg Ca) was compared with an energy-deficit control (400–500 mg Ca) diet⁽³⁰⁾. While macronutrients were held constant and only Ca contents differed, it cannot be concluded whether the effects are due to Ca alone or also to other bioactive components in dairy products.

Despite these positive results^(28,30), many other studies did not provide evidence for weight- or body fat-reducing effects of Ca. Recently, Lanou & Barnard⁽³¹⁾ thoroughly reviewed forty-nine randomised controlled trials on the effects of dairy product and Ca intake, with or without energy restriction, on body weight and adiposity. Of seventeen studies on dairy product intake, fifteen showed no effect on body weight, while two reported weight gain. Nineteen trials used Ca supplements and found no effect on weight, while one study showed weight loss and one study found a lower rate of weight gain on Ca treatment. They identified six trials using dairy products in combination with reduced energy intake, of which three reported no effects and three showed body-weight loss. Of the five studies on Ca supplementation combined with energy restriction, four found no effect and one study observed weight loss. The authors therefore concluded that the majority of the current evidence from

clinical trials does not support the hypothesis that Ca or dairy product consumption promotes weight or fat loss.

There is no clear explanation for the discrepancy between the positive results from the studies by Zemel^(28,30) and the large number of studies reporting no weight-reducing effects of Ca and dairy product consumption. It has been proposed that the effects of Ca on body weight are only present in populations with low habitual intakes, and that at Ca consumption above 800 mg per d, no additive beneficial effects of increasing dietary Ca will occur⁽³²⁾. However, Lanou & Barnard⁽³¹⁾ also included trials among populations with suboptimal Ca intakes, which does not support this threshold hypothesis. It might also be speculated that dairy products and Ca supplements reduce body weight and fat mass only when part of an energy-restricted diet. This reasoning is, however, also not supported by the majority of studies⁽³¹⁾.

Possible mechanisms underlying the effects of calcium on body weight and fat mass

For the effects of Ca on body weight and body composition, the ability of Ca to bind fatty acids and thereby inhibit fat

absorption, as discussed above, is proposed as one possible mechanism of action. Another way by which Ca might affect body composition is by regulating intracellular Ca levels, as hypothesised by Zemel *et al.* (Fig. 2)⁽²⁹⁾. Intracellular Ca levels are regulated by calcitropic hormones, such as parathyroid hormone and 1,25-hydroxyvitamin D (calcitriol). High dietary Ca depresses the levels of calcitriol, thereby decreasing intracellular Ca. This results in a stimulation of lipolysis. Additionally, low intracellular Ca inhibits the expression of fatty acid synthase, which is a key enzyme in *de novo* lipogenesis^(29,33). Therefore, Ca intake may directly affect the storage and breakdown of fat in adipose tissue. This mechanism has been demonstrated in human adipocytes *in vitro*, in which calcitriol increased intracellular Ca concentrations and inhibited lipolysis. Additionally, in transgenic mice, a high-Ca diet reduced lipogenesis and stimulated lipolysis, resulting in reductions in body weight and adipose tissue mass⁽³⁴⁾. However, this concept has not yet been shown in humans. In fact, in a series of trials performed by Boon *et al.*, the various steps of the Zemel hypothesis could not be confirmed. Although high Ca/high dairy product intake did affect calcitriol metabolism⁽³⁵⁾, and although changes in intracellular Ca did change lipolysis⁽³⁶⁾, changes in serum calcitriol did not alter fat metabolism *in vivo*⁽³⁵⁾.

Effects of calcium on blood pressure

Epidemiological as well as intervention studies have shown an inverse relationship between Ca intake and blood pressure^(37,38). Several potential mechanisms may explain the positive effect of Ca on blood pressure, including reduced membrane permeability to monovalent and divalent

cations, reduced intracellular Ca levels, decreased concentrations of Ca-regulating hormones, reduced sympathetic nervous system activity, and altered metabolism of other electrolytes, for example, increased Na excretion⁽³⁹⁾. Again, the effect of Ca might be mediated by suppression of the hormone calcitriol. Suppression of this hormone could lower intracellular Ca levels in vascular smooth muscle cells, thereby reducing peripheral resistance and blood pressure⁽⁴⁰⁾. Although it has been shown that calcitriol increases intracellular Ca in arteries of rats⁽⁴¹⁾, and that an association exists between calcitriol and blood pressure in normotensive men⁽⁴²⁾, this hypothesised mechanism has not yet been demonstrated in humans. A summary of human intervention studies on the effects of dairy and Ca supplements on blood pressure is given in Table 1.

Effects of calcium on glucose metabolism

Finally, one study showed a significant decrease in insulin levels in subjects consuming a high-dairy diet compared with subjects on a low-dairy diet⁽⁴³⁾. Thirty-four obese African-American adults were maintained on a low-Ca (500 mg/d)/low-dairy (<one serving per d) or a high-dairy (1200 mg Ca per d diet including three servings of dairy) diet for 24 weeks. Circulating insulin decreased by 19.7 pM in subjects on the high-dairy diet compared with the low-dairy diet ($P < 0.05$). Although no differences in body weight were observed, subjects on the high-dairy diet showed a decrease in body fat and an increase in lean mass, which might be related to the improved insulin sensitivity. Another report from this laboratory showed similar results in thirty-two obese adults⁽²⁸⁾. Fasting glucose levels were unaffected by diet, but a 27% decrease in the area under the glucose curve and a 44% decrease in fasting plasma insulin levels was observed on the high-dairy diet, while these were unaffected on the low-dairy diet. However, in this study it was not possible to discern whether these are direct effects of the high-dairy diet, or secondary effects of the greater weight and fat loss found on this diet. Although in both studies the diets only differed in Ca content, it cannot be excluded that differences in the source of protein, for example, could have influenced the observed effects of dairy product consumption.

Table 1 shows an overview of these studies of dairy products on glucose metabolism.

Conclusion

Ca supplements improve the serum lipid profile, most likely by decreasing total and LDL-cholesterol, thereby improving the HDL:LDL-cholesterol ratio. Ca and dairy products also reduce blood pressure. While some studies have reported positive effects of dairy products and Ca on body weight and body composition, the majority of trials do not support these findings. Ca may exert its effects by intestinal binding to fatty acids and bile acids, or by depressing calcitropic hormones and changing intracellular Ca metabolism, although the evidence for the latter mechanism is limited.

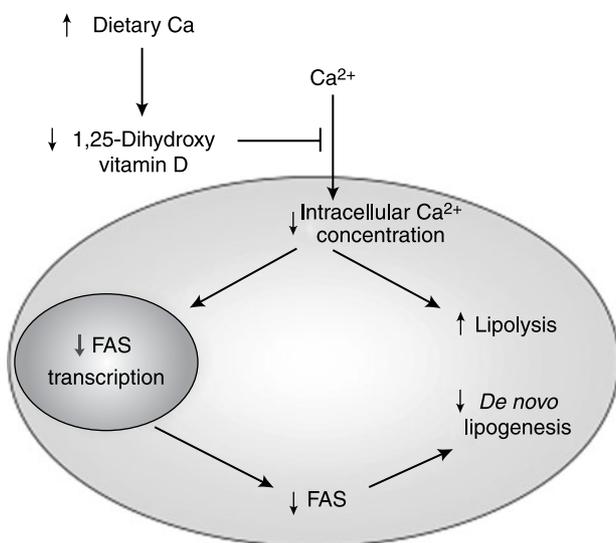


Fig. 2. Hypothesised mechanism of stimulation of lipolysis and inhibition of lipogenesis by dietary Ca. Increased dietary Ca intake lowers the level of the hormone 1,25-dihydroxy vitamin D, thereby lowering the uptake of Ca^{2+} into the cell. Decreased levels of intracellular Ca stimulate lipolysis and decrease the transcription of fatty acid synthase (FAS), resulting in the inhibition of lipogenesis.

Dairy protein

Dairy products are an important source of protein. Nowadays, more and more attention is paid to the role of protein in metabolic diseases.

Effects of protein on the serum lipid profile and body-weight regulation

Recent evidence suggests that protein added to the diet at the expense of carbohydrates has favourable effects on serum lipoprotein profiles. Krauss *et al.* found a slight increase in both LDL- and HDL-cholesterol, but a decrease in the total:HDL-cholesterol ratio by proteins replacing carbohydrates⁽⁴⁴⁾. In general, other studies also reported a decrease in the total:HDL-cholesterol ratio on high-protein diets⁽⁴⁵⁾. However, in the OmniHeart trial, a high-protein diet decreased serum total cholesterol, LDL-cholesterol, HDL-cholesterol and TAG concentrations⁽⁴⁶⁾.

Another interesting property of protein is its role in body-weight regulation, which consists of different aspects. First, protein increases satiety, which may result in a decreased energy intake. In the short term, i.e. after an acute meal, consumption of high-protein meals (60–81 % of energy from protein) resulted in higher satiety compared with low- or moderate-protein meals^(47–50) and a reduced energy intake^(48,49,51). Also in the longer term, high-protein diets in studies lasting up to 4 d caused a continuously higher satiety throughout the day^(52,53). In this respect, the effects of high-protein diets do not seem to depend on the type of macronutrient that is substituted. However, effects may be different for diverse types of protein. For example, it was shown that satiety was acutely increased and energy intake was decreased after a whey diet compared with a casein diet⁽⁵⁴⁾.

Furthermore, high-protein diets may preserve or increase fat-free mass and reduce fat mass during weight loss and weight regain, contributing to an improved body composition and metabolic profile. Layman *et al.*⁽⁵⁵⁾ found an improved body composition during weight loss in adult women, when proteins replaced carbohydrates. In a trial by Westerterp-Plantenga *et al.*⁽⁵⁶⁾, overweight and obese subjects who consumed 18 % of energy as protein regained less weight (1 kg) during 3 months after a weight-loss period than subjects who consumed 15 % of energy from protein (2 kg). In addition, body composition of the regained body mass was more favourable in the high-protein group, in which no fat mass, but only fat-free mass was regained, resulting in a lower percentage of body fat.

Effects of bioactive peptides on blood pressure and coagulation

Milk contains two major protein groups: caseins and whey proteins. Caseins are a mixture of related phosphoproteins, characterised as one of the most nutritive milk proteins, containing all of the common amino acids and being rich in the essential ones. They are a heterogeneous family of proteins, mainly α_{S1} -, α_{S2} -, β - and κ -caseins. Caseins account for almost 80 % of total protein in bovine milk and exist primarily as calcium phosphate-stabilised micellar

complexes⁽⁵⁷⁾. Whey protein is the name for a collection of globular proteins that can be isolated from whey, a by-product of cheese manufactured from cows' milk. Whey proteins account for 20 % of total milk protein, and are also a heterogeneous group of proteins. They mainly consist of α -lactalbumin, β -lactoglobulin and serum albumin⁽⁵⁷⁾.

Both caseins and whey proteins are precursors of many different biologically active peptides. These peptides are inactive within the protein sequence, requiring enzymic proteolysis for release of the bioactive fragment from the protein precursor. These fragments can be released either during gastrointestinal digestion or during food processing, for example, during fermentation with bacteria such as *Lactobacillus helveticus*^(58,59).

One class of bioactive peptides derived from dairy protein is the group of the angiotensin-I-converting enzyme (ACE) inhibitory proteins. ACE is a multifunctional enzyme that plays a key physiological role in the regulation of peripheral blood pressure. Associated with the renin-angiotensin system, ACE converts angiotensin I to the highly potent vasoconstrictor angiotensin II. Inhibition of this enzyme prevents the formation of angiotensin II and will therefore result in reduced blood pressure. ACE-inhibitory peptides are present in the amino acid sequences of caseins, as well as in whey proteins^(59,60). In this way, blood pressure is one feature of the metabolic syndrome that could be affected by dairy protein (Fig. 3). However, most studies on the ACE-inhibitory effects of milk peptides have been performed *in vitro*, and the number of human studies is limited. Aihara *et al.*⁽⁶¹⁾ performed a 4-week trial with forty subjects with high-normal blood pressure and forty mild hypertensive subjects, receiving either powdered fermented milk tablets (12 g) or placebo tablets. They found decreases in systolic and diastolic blood pressures by 3.2 mmHg (non-significant) and 5.0 mmHg ($P < 0.05$), respectively, in the high-normal subjects. In the mild hypertensive subjects, systolic blood pressure was decreased by 11.2 mmHg ($P < 0.05$) and diastolic pressure by 6.5 mmHg ($P = 0.055$). In the study of Mizuno *et al.*⁽⁶²⁾, forty-eight subjects with high-normal blood pressure and eighty-three mild hypertensive subjects received casein hydrolysate (3.6 mg/d) or placebo tablets for 6 weeks. In the high-normal group, non-significant changes in both systolic (-3.1 mmHg) and diastolic (-0.3 mmHg) blood pressure were observed. Systolic blood pressure decreased significantly by 11.8 mmHg in the mildly hypertensive subjects, while diastolic blood pressure was decreased by 2.9 mmHg. In a trial with thirty-nine hypertensive patients performed by Seppo *et al.*⁽⁶³⁾, skimmed milk fermented with *Lactobacillus helveticus* (150 ml/d) seemed to cause a reduction in blood pressure after 21 weeks, compared with skimmed milk fermented with *Lactococcus* sp. However, after intention-to-treat analysis, no significant differences between the test-product group and control group were observed. In addition, in a recent placebo-controlled trial in 135 mildly hypertensive subjects by Engberink *et al.* no effects of milk-derived peptides on blood pressure, ACE activity or plasma angiotensin II concentrations were found after 8 weeks of treatment⁽⁶⁴⁾. Also, bioavailability of these peptides is questionable⁽⁵⁸⁾, although one study has demonstrated the uptake of intact lactotripeptides⁽⁶⁵⁾. Finally, the amount of

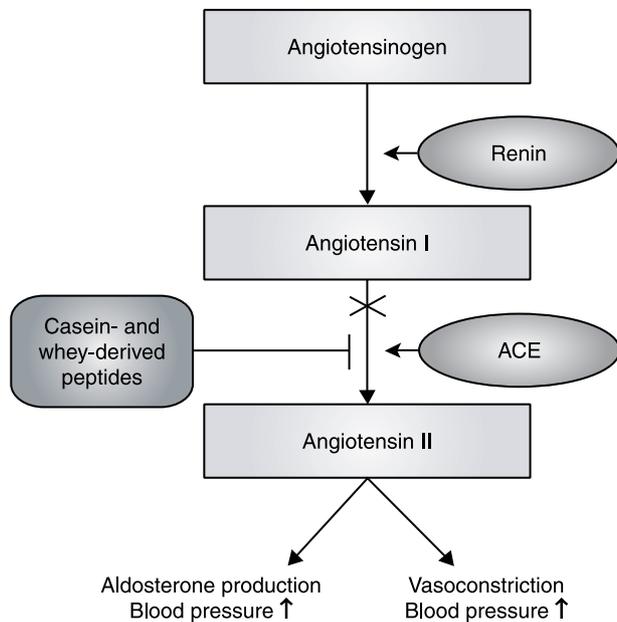


Fig. 3. Inhibition of conversion from angiotensin I to angiotensin II by bioactive peptides derived from milk proteins. These peptides block the action of angiotensin-converting enzyme (ACE) and may, in this way, lower blood pressure.

ACE-inhibitory peptides in non-enriched dairy products may simply be too low to play a significant role in blood pressure regulation. Taken together, human studies do currently not provide unequivocal evidence that bioactive peptides from dairy protein lower systolic or diastolic blood pressure.

Additionally, bioactive peptides in dairy protein can exert beneficial effects on the prothrombotic state characterising the metabolic syndrome. A large number of similarities between blood clotting and milk clotting exist, including sequence identities between fibrinogen and some milk proteins, and some functional similarities. Casoplatelins are peptides derived from κ -casein that display anti-thrombotic activity. They show some sequence similarity to the interacting region of the fibrinogen γ -chain in platelet aggregation. Their inhibitory effect is probably due to the competition between anti-thrombotic peptides and the fibrinogen γ -chain for platelet receptors^(59,66). Again, much of this anti-thrombotic activity has been measured *in vitro*, which does not necessarily imply anti-thrombotic activity *in vivo*. Human studies are lacking, but *in vivo* anti-thrombotic activity of milk peptides has been shown in some animal studies⁽⁶⁷⁾.

An overview of the effects of dairy protein on metabolic syndrome components found in human studies is presented in Table 2.

Conclusion

In conclusion, protein can play a role in body-weight regulation by increasing satiety, resulting in reduced energy intake. In body-weight loss and regain, protein may improve body composition by preserving or increasing fat-free mass and reducing fat mass. It also affects the serum lipid profile

when compared with carbohydrates by decreasing both LDL- and HDL-cholesterol, but it improves the total:HDL ratio. Furthermore, dairy proteins are precursors of bioactive peptides, which can inhibit ACE activity and thereby reduce blood pressure, but evidence for such effects is currently not provided by human studies.

Dairy fat

The Western diet provides approximately 90 g fat per d. Of this daily fat consumption, a substantial proportion is supplied by dairy products⁽¹³⁾. High-fat dairy products are relatively rich in SFA, especially in myristic (14:0), palmitic (16:0) and stearic (18:0) acids⁽⁶⁸⁾. While stearic acid has little effect on the serum lipoprotein profile, myristic and palmitic acids are known to increase serum LDL- and HDL-cholesterol concentrations. Intervention studies have also shown that replacing SFA by *cis*-unsaturated fatty acids lowers the risk of CVD⁽⁶⁹⁾. To improve an atherogenic lipoprotein profile, the current recommendation is to reduce the intake of SFA.

It is hypothesised that fat in milk, butter and cheese affects blood lipids differently due to matrix effects. Tholstrup *et al.* could not confirm different effects of fat in milk and butter, but found a moderately lower LDL-cholesterol concentration after a cheese diet compared with a butter diet⁽⁷⁰⁾. Biong *et al.*⁽⁷¹⁾ observed significantly lower total cholesterol concentrations after a cheese diet than after a butter diet, while the difference in LDL-cholesterol almost reached statistical significance. These observations could be related to the fact that the diets differed in Ca content, with the highest Ca intake from the cheese diet. Similar results were found by Nestel *et al.*⁽⁷²⁾ in mildly hypercholesterolaemic subjects. The macronutrient composition of the diets was similar, but no data on Ca contents were given.

Effects of conjugated linoleic acid

Recently, much attention has been paid to conjugated linoleic acid (CLA). CLA is a positional and geometric conjugated isomer of linoleic acid. Two common isomers of CLA exist, *trans*-10, *cis*-12-CLA (*t10,c12*-CLA) and *cis*-9, *trans*-11-CLA (*c9,t11*-CLA), which may have distinct metabolic effects. The *c9,t11* isomer accounts for over 90% of the total CLA intake from food. Milk fat is relatively rich in *c9,t11*-CLA, although levels are still low (less than 0.5% of total milk fat). Many animal studies have shown positive effects of CLA on body weight and fat deposition^(73,74). In addition, some animal trials reported cholesterol-lowering effects of CLA⁽⁷⁵⁾. However, results of human studies are less consistent. In a recent meta-analysis, it was found that, given at a dose of 3.2 g/d, CLA produces a modest loss in body fat in human subjects⁽⁷⁶⁾. In contrast, a number of reviews concluded that CLA is not effective in reducing body weight and plasma cholesterol concentrations in humans, and that especially *t10,c12*-CLA may actually adversely affect human health, for example, by inducing insulin resistance⁽¹⁷⁾. In addition, effects, if any, are only observed at high intakes (> 3 g/d). Therefore, the amount of CLA in dairy fat is too low to play a significant role in the prevention of the metabolic syndrome.

Table 2. Overview of recent intervention studies on the effects of fermented dairy products or dairy protein on components of the metabolic syndrome

Component of the metabolic syndrome	Subjects	Design	Intervention	Control	Effects	Study reference
Blood pressure	Forty HN + forty MH subjects	Randomised, double-blind, 4 weeks	Six powdered fermented milk tablets (12 g)	Placebo tablets	HN: SBP - 3.2 mmHg DBP - 5.0 mmHg* MH: SBP - 11.2 mmHg* DBP - 6.5 mmHg*	Alhara <i>et al.</i> (2005) ⁽⁶¹⁾
Blood pressure	Forty-eight HN + eighty-three MH subjects	Randomised, single-blind, 6 weeks	Casein hydrolysate, 3.6 mg/d	Placebo tablets	HN: SBP - 3.1 mmHg DBP - 0.3 mmHg MH: SBP - 11.8 mmHg* DBP - 2.9 mmHg	Mizuno <i>et al.</i> (2005) ⁽⁶²⁾
Blood pressure	Thirty-nine hypertensive patients	Randomised, 21 weeks	Skimmed milk fermented with <i>Lactobacillus helveticus</i> , 150 ml/d	Skimmed milk fermented with <i>Lactococcus sp.</i> , 150 ml/d	SBP - 5.0 mmHg DBP - 2.5 mmHg	Seppo <i>et al.</i> (2003) ⁽⁶³⁾

HN, high-normal blood pressure subjects; MH, mild hypertensive subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure.

* $P < 0.05$.

Conclusion

To reduce cardiovascular risk, it is important to limit the intake of SFA. Therefore, the consumption of low-fat instead of high-fat dairy products is strongly recommended. While different responses to fat from different dairy products have not been confirmed, other dairy constituents, such as Ca, seem to influence the effects. It is not likely that CLA, in the amounts present in dairy products, has any risk-reducing effects.

Overall conclusion

Several epidemiological studies have suggested that the consumption of dairy products contributes to a decreased risk of developing the metabolic syndrome. If so, an important question is which components of dairy products are actually responsible for the favourable effects. Ca and protein have been reported to positively affect several components of the metabolic syndrome. The fat fraction of dairy products does not seem to contain any bioactive compounds in this respect. The different components may act synergistically, leading to augmented beneficial effects, but this certainly warrants further investigation. Without doubt, the intake of SFA should be limited. Therefore, it is important to focus on low-fat instead of high-fat dairy products.

Taken together, evidence exists that dairy products may play a role in the prevention and treatment of the metabolic syndrome. However, most of the studies focused on single features of the metabolic syndrome. In addition, not all features of the syndrome (for example, the inflammatory and prothrombotic state) have been studied in depth. Furthermore, most research focused on single dairy constituents, while studies on the effects of dairy products mainly had an observational design. Therefore, as yet, there is insufficient evidence to decisively conclude that dairy products play a role in the development of the metabolic syndrome. Hence, more experimental research is needed to fully elucidate the physiological effects of an increased consumption of dairy products as related to the metabolic syndrome, as well as the mechanisms involved.

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