REVIEW

Dairy Foods and Dairy Fats: New Perspectives on Pathways Implicated in Cardiometabolic Health

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ABSTRACT

Low-fat and nonfat dairy products have been promoted as part of a healthy dietary pattern by both US dietary guidelines and professional organizations for several decades. The basis for this recommendation stems in part from the putative negative cardiometabolic effects associated with saturated fat consumption. However, as nutrition research has shifted from a single nutrient to a whole-food/dietary pattern approach, the role of dairy foods and dairy fat in the diet–disease relationship is being reexamined. Most observational and experimental evidence does not support a detrimental relationship between full-fat dairy intake and cardiometabolic health, including risks of cardiovascular disease and type 2 diabetes. Indeed, an expanded understanding of the dairy food matrix and the bioactive properties of dairy fats and other constituents suggests a neutral or potentially beneficial role in cardiometabolic health. To consider how consuming dairy foods, including full-fat dairy, is associated with cardiometabolic health, this review provides an innovative perspective on mechanisms that link dairy consumption to 3 main biological systems at the core of metabolic health, the gastrointestinal, hepatic, and vascular systems. *Adv Nutr* 2020;11:266–279.

Keywords: dairy, saturated fat, cardiometabolic disease, vascular health, type 2 diabetes, dietary calcium

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. In recent years, there has been a substantial global increase in cardiometabolic diseases such as type 2 diabetes (T2D), hypertension, and obesity (1). In fact, the American Society of Endocrinology, the National Cholesterol Education Program, and the WHO, among others, now recognize cardiometabolic syndrome as a disease entity. Cardiometabolic disease is a combination of metabolic dysfunctions characterized by insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, and central obesity, and its presence markedly increases CVD morbidity and mortality (2). Diet, among other lifestyle factors such as physical activity and smoking, has an established link with cardiometabolic health (3, 4). Over the past decade, nutrition research related to health outcomes has shifted from a focus on individual nutrients to complete dietary patterns and whole foods. This is reflected by evidence-based dietary recommendations such as the Dietary Guidelines for Americans (DGA). The 2015–2020 DGA specifically identified low-fat and fat-free dairy foods as components of healthy eating patterns (5). Public health recommendations to emphasize low-fat and fat-free dairy are attributed, in part, to the putative negative health effects of saturated fats. Yet, the evidence linking dietary saturated fat with CVD risk and risk indices is far from settled, with many studies demonstrating no association (6–13). Furthermore, the majority of observational and experimental evidence does not support a detrimental relationship between consuming full-fat dairy and cardiometabolic health outcomes, including CVD or T2D [e.g., (12, 14–21)]. In addition, consideration of the health impact of dairy fats and dairy foods must take into account their complex matrix (e.g., milk oligosaccharides, calcium, live and active cultures in yogurt, milk fat globule membranes and polar lipids, and bioactive peptides), which contribute to the gastrointestinal (GI) tract milieu of diet-derived factors that influence the host and microbiome. With these considerations in mind, there is a critical need to revisit current concepts related to dairy fats (and other dairy components) with respect to how they associate with physiological systems relevant to whole-body cardiometabolic health. In contrast to other recent reports that broadly focus on specific dairy foods or dairy-containing diet patterns and CVD disease risk or T2D [e.g.,

(11, 12, 14, 17–19, 22)] the current review aims to consider new perspectives on mechanisms that link dairy-containing diet patterns (or specific dairy components) to 3 main biological systems at the core of metabolic health, the GI, hepatic, and cardiovascular systems. Using this approach, one can build an integrative picture of how dairy foods may impact the splanchnic and vascular systems, which are episodically and chronically exposed to factors associated with individual meals and food patterns.

Current Status of Knowledge

Dairy consumption and gastrointestinal tract function

Dairy foods can broadly affect immune function via specific mechanisms in the gut. The GI tract is closely linked with immune function and maintains homeostasis with the gut microbiota via the mucosal layer, intestinal barrier, and immunocytes (23). These systems affect cardiovascular health via direct effects on GI tract immune cells and/or the flux of microbial antigens and metabolites into the bloodstream, which impact whole-body and vascular site inflammation (24, 25). Dendritic cells in the gastrointestinal tract sample microbial antigens, migrate to the mesenteric lymph nodes and induce the activation of T cells (26). Intestinal activation of Toll-like receptor 4 (TLR4) by endotoxin increases proinflammatory T cell populations and cytokine production (27). In contrast, commensal bacteria may stimulate barrier function and/or produce metabolites (e.g., propionate and butyrate) that dampen intestinal inflammation (28, 29). There are multiple avenues through which the GI tract, and dietary components that modify its structure or function, may have substantial effects on cardiometabolic health. Notably, animal studies have contributed extensively to the current understanding of this area. Although some humans have polymorphisms conferring lactase persistence, laboratory rodents gradually lose intestinal lactase activity after weaning (30, 31). Lactase activity is typically not described in rodent studies. Since undigested lactose can be fermented in the GI tract by gut microbiota, intestinal lactase activity may be an important variable to consider when interpreting results from animal models.

Metabolic endotoxemia and cardiovascular health. Immune homeostasis in the intestine is achieved in part through cellular responses to the gut microbiota. Translocation of gut-derived endotoxins, e.g. lipopolysaccharides (LPS), from Gram-negative bacteria generate a proinflammatory response by activating TLR4 (32, 33). Consumption of dietary emulsifiers or high-fat challenge meals can, under some circumstances, activate postprandial inflammation by coabsorption of LPS and lipids (34, 35). Collectively, chronic low-grade LPS exposure is described as "metabolic endotoxemia." This phenomenon has been implicated in obesity and insulin resistance by inducing chronic inflammatory responses (36, 37) that may increase risk of cardiovascular disease (38, 39).

Postprandial inflammation and cardiovascular health. Recognition of the link between postprandial lipemia, inflammation, and CVD has led to further investigation of how inflammation could develop in the postprandial state. Initially, postprandial lipemia was observed in individuals with coronary artery disease after consuming a high-fat, high calorie (HFHC) challenge meal consisting of heavy whipping cream, chocolate syrup, and sugar (729 kcal/m^2) (40). Subsequently, postprandial lipemia induced by an HFHC meal was associated with inflammation. In healthy individuals, an HFHC challenge meal (white bread, ham, margarine, coffee, and whole milk providing 602 kcal/m^2) increased NF-κB activation in peripheral blood mononuclear cells (PBMCs) after 6–9 h (41).

The postprandial inflammatory response is determined by the metabolic state of the individual (e.g., obese or lean) and by the macronutrients in the test meal (42). It has been shown that both predominately carbohydrate-based and lipid-based meals may induce postprandial inflammation (42). Carbohydrate consumption increases postprandial glucose, which by itself is sufficient to induce oxidative stress and increase circulating IL-6 (43). Impaired glucose tolerance exacerbates inflammation in response to glucose ingestion (43). Lipid consumption alone induces postprandial endotoxemia in rodents (44). Endotoxins are coabsorbed with lipids, and emulsified lipids increase postprandial lipemia and endotoxemia relative to unemulsified fat intake (44, 45). The majority of studies that have utilized high-fat meals to induce postprandial inflammation include carbohydrates (46), so both lipid- and glucose-mediated mechanisms that lead to postprandial inflammation should be considered. A recent analysis of the literature on HFHC meals and postprandial inflammation concluded that the inflammatory response was not associated with the proportion of fat (46). The

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Abbreviations used: ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; AhR, aryl hydrocarbon receptor; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DGA, Dietary Guidelines for Americans; FMD, flow-mediated dilation; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HFHC, high-fat, high calorie; HFM, high-fat meal; hsCRP, high-sensitivity CRP; LBP, LPS-binding protein; MFGM, milk fat globule membrane; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFDM, nonfat dry milk; PBMC, peripheral blood mononuclear cell; SDMA, symmetric dimethylarginine; SM, sphingomyelin; T2D, type 2 diabetes; TLR4, Toll-like receptor 4.

postprandial inflammatory response was also inconsistent among studies of HFHC meals. While postprandial IL-6 was increased in 32 of 45 studies, blood IL-1β, TNF-α, and C-reactive protein (CRP) were not consistently induced by a high-fat meal (HFM) (46). Others have suggested that leukocyte markers of inflammation are more consistent in the postprandial state than concentrations of plasma cytokines (47). This implies that cell-based markers of inflammation may be more robust indicators of inflammatory status in the postprandial state than circulating cytokines. Since few studies have comprehensively assessed cell-based markers of postprandial inflammation, a complete understanding of the immune response to different dietary components is limited. Recently, the concept that saturated fatty acids robustly activate macrophage inflammation under normal conditions, or even after an HFM, has been challenged (46, 48).

Dairy and postprandial inflammation.

In the context of an HFHC challenge meal, emulsified dairy fats can induce postprandial inflammation, and thus, dairy foods (typically cream, butter, cheese, or milk) have been included in the majority of challenge meals to study postprandial inflammation (46). In fresh milk, the fat is stabilized by the milk fat globule membrane (MFGM). Subsequent processing by the addition of emulsifying ingredients can alter the physical state of fats in dairy products by redistributing naturally occurring phospholipids and proteins, which may affect the postprandial response. Emulsifying ingredients are also added to dairy foods to achieve desired textures. In a randomized crossover study, obese or normal-weight individuals consumed a mixed meal consisting of 40 g milk fat, 50 g bread, and 160 mL skimmed milk (251 kcal) after an overnight fast (45). The dairy fat was consumed as an emulsification in the milk (emulsified with milk protein) or spread on the bread (unemulsified). Endotoxemia was not evident in normal-weight individuals ($n = 8$) after either treatment. The emulsified dairy fat substantially increased LPS activity 60 min after the test meal, but the unemulsified dairy fat spread had no effect on postprandial endotoxemia in obese individuals ($n = 8$) (45).

Other studies using a combination of dairy cream and sugar have yielded inconsistent results on postprandial inflammation. For instance, a 300-kcal intake of cream alone induced postprandial endotoxemia and TLR4 expression in mononuclear cells (49). In another example, a cream, sugar, and water mix that provided 954 kcal increased postprandial IL-6 in healthy men, but this increase was no different than the increase occurring after a lower-calorie meal (50). In a double-blind randomized crossover intervention study, postprandial IL-8 was increased by a high-fat shake (53% wt/vol) fresh cream, 3% (wt/vol) sugar and 44% (wt/vol) water with a macronutrient composition of 6 g protein, 95 g total fat (54 g saturated), 22 g carbohydrates, and 954 kcal relative to an average breakfast shake containing 43% (wt/vol) full cream milk, 48% (wt/vol) full cream yogurt, 4% (wt/vol) lemonade, 4% (wt/vol) fantomalt (a high-energy carbohydrate oral supplement) (Nutricia BV), and 1% (wt/vol) wheat fiber with a macronutrient composition of 17 g protein, 14.5 g total fat (9 g saturated), 49.5 g carbohydrates, 2.3 g fiber, and 400 kcal (50). In contrast, 1200 kcal provided from milk, cream, sucrose, and protein or 150 kcal from ice cream and whipping cream had no effect on postprandial inflammation (51, 52).

Several studies have evaluated whether dairy products can prevent postprandial inflammation. Schmid et al. compared the effects of an HFHC dairy meal (including cheese and butter), an HFHC nondairy control meal, and an HFHC nondairy meal supplemented with full-fat milk on postprandial inflammatory and metabolic responses in healthy men (53). Endotoxemia, IL-6, and TNF-α concentrations were not different after the dairy-supplemented meals compared with the nondairy HFHC meal (53). A subsequent study provided acidified milk or a probiotic yogurt (containing *Lactobacillus rhamnosus* GG) to healthy men ($n = 14$, BMI 18.0 to 25.0 kg/m^2) after 2-wk consumption of dairy products prior to the HFHC meal (54). Both the milk and yogurt (400 g/d) reduced the postprandial IL-6 and TNF-α integrated AUC, relative to the preintervention baseline HFHC meal (54). These changes were in parallel with alterations of the gut microbiota during each dietary phase. *Bilophila wadsworthia* decreased with milk consumption, while *Lactobacillus delbrueckii* spp. *bulgaricus* and *Streptococcus salivararius* spp. *thermophilus* increased after yogurt intake (54). Further analysis of these changes found that yogurt intake altered the expression of 747 genes in the blood transcriptome at 2 h after consumption (55). In contrast, 55 and 4 genes were changed by the intervention at 4 and 6 h, respectively. Yogurt dampened postprandial genes associated with immune activation, as well as the aryl hydrocarbon receptor (AhR). Targeted analysis of AhR ligands identified a positive correlation between circulating xenometabolite indole-3-acetaldehyde and *AhR* gene expression (55). Yogurt consumption increased microbe-derived indole derivatives relative to acidified milk, which may explain the differential effects of these 2 products on the AhR (56).

Another study compared the consumption of low-fat, sweetened yogurt to an isocaloric nondairy control snack in obese and nonobese women (57, 58). Premeal yogurt consumption inhibited the increase of postprandial IL-6 in both obese and nonobese women ($n = 30$ per group) after an HFHC meal (57). Yogurt consumption also reduced postprandial LPS-binding protein (LBP): sCD14, a marker of endotoxin exposure (57). Premeal yogurt consumption has also been shown to reduce postprandial hyperglycemia in obese women (58). Additional daily consumption of 340 g yogurt for 9 wk further decreased postprandial LBP: sCD14 in obese women, although postprandial IL-6 was similar to the acute effect (58).

Collectively, these studies suggest that yogurt and acidified whole milk consumption reduce postprandial inflammation in the context of HFHC challenge meals. In contrast,

consumption of significant amounts of emulsified fat may exacerbate postprandial inflammation in obese individuals. Excessive intake of cream contributes to postprandial inflammation in some cases. Therefore, the dose, metabolic state of the individual and food matrix all impact how dairy affects postprandial inflammation.

Mechanisms by which dairy affects GI tract function. Studies of dairy in animal models suggest that a number of components could impact GI tract function in a manner that modulates intestinal immune function. For example, after 4 wk, serum LPS activity and fecal Gram-negative bacteria were reduced in mice fed a high-fat diet (45% kcal from fat from soybean oil and anhydrous milk fat) modified to contain 0.25% (wt/wt) milk sphingomyelin, a polar lipid in milk fat (59). Supplementation of 1.5 g/kg/d milk fat globule membrane by daily gavage for 15 d reduced bacterial translocation and increased the expression of claudin tight junction proteins in the ileum of rats with small-bowel resection (60). Low-fat, sweetened yogurt powder also inhibits intestinal barrier dysfunction by increasing tight junctions in human intestinal Caco-2 cells exposed to inflammatory cytokines (61). Probiotics commonly found in fermented dairy products, milk proteins, and peptides have also been shown to directly improve intestinal barrier function through tight junction stabilization in Caco-2 cell culture models (62–66). Results from intervention studies in humans suggest that consumption of 400 g/d fermented milk for 2 wk can alter gut microbiota and microbial xenometabolites that may improve barrier function (54–56, 67). However, a complete understanding of the impact of the dairy matrix on microbiota composition and function is lacking.

Dairy consumption and hepatic function

Relationship of liver function with cardiometabolic health. The liver is a multifunctional organ, which plays a critical role in health and disease as a hub for whole-body nutrient metabolism, as well as a major site of detoxification enzymes, hormone production, and immune functions. The liver is a major site of lipid biosynthesis, including the production of bile acids, fatty acids, and cholesterol. In many species, it is the major organ responsible for the secretion of endogenous lipids in the form of VLDL and the clearance of circulating lipoproteins, including LDL. Often referred to as the hepatic manifestation of metabolic syndrome, nonalcoholic fatty liver disease (NAFLD) has recently emerged as the most common liver disorder worldwide and is present in the majority of obese individuals (38). NAFLD includes a broad spectrum of conditions occurring in the absence of significant alcohol use, including steatosis, nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma. NASH is expected to become the most common indication for liver transplantation in the future (38). Beyond the liver, NAFLD also worsens health outcomes associated with obesity by increasing the risk for CVD (68). This is thought to be due to liver dysfunction contributing to systemic inflammation, oxidative stress, and dyslipidemia (69).

Overview of liver lipid metabolism in health and disease. NAFLD is thought to be driven by hepatic insulin resistance. Ectopic lipid deposition of lipid metabolites (e.g., ceramide, diacylglycerol) and inflammation are thought to contribute to hepatic insulin resistance in NAFLD. Insulin is responsible for 2 primary actions in the liver: *1*) increasing de novo lipogenesis and *2*) reducing gluconeogenesis. Insulin transcriptionally suppresses gene expression of gluconeogenic enzymes and induces the transcription of several genes involved in de novo lipogenesis, by transcriptional and posttranslational actions on the lipogenic transcription factors (70–72). Hepatic insulin resistance is associated with impairments of selective branches of the insulin signaling pathway, with the capacity for insulin to stimulate de novo lipogenesis retained at the same time as the inability to suppress hepatic gluconeogenesis (73). In parallel with increases in hepatic de novo lipogenesis are reductions in β-oxidation. Insulin-induced lipogenesis leads to increased malonyl-CoA production, which in turn inhibits carnitine palmitoyl transferase-1, and as a result, fatty acid oxidation is reduced (74). Consequently, this altered lipid handling further contributes to the progression of liver injury and NAFLD (75).

Hepatic insulin resistance is also related to increased VLDL-triglyceride production, which contributes to atherogenic dyslipidemia (76). LDL receptors are abundant in the liver, and this organ plays a major role in LDL clearance from circulation (77). The cholesterol content of LDL cholesterol is well established as a predictor of cardiovascular events and the primary target of lipid-lowering therapy (78). The liver is also the primary source responsible for the elevated plasma CRP concentration observed in NAFLD (79, 80). Circulating high-sensitivity CRP (hsCRP) is an independent predictor of future myocardial infarctions (81) and cardiovascular events (82). Thus, liver dysfunction has systemic implications for cardiometabolic health, with both lipid and inflammatory contributors to its sequelae.

Clinical studies using dairy products on NAFLD-related measures. *Dairy compared with nondairy diet interventions.* The effects of dairy products on liver-derived lipoprotein concentrations have been studied extensively and reviewed previously (83, 84). However, few dietary interventions have examined the effects of dairy products as the primary intervention variable on NAFLD-related measures or in NAFLD patients. NAFLD may be diagnosed in humans through a liver biopsy, considered the gold standard, but is most commonly examined via imaging and other noninvasive diagnostic measures of liver injury, such as serum alanine transaminase (ALT) and aspartate transaminase (AST) (85). Observational studies have inversely linked NAFLD with low-fat dairy intake (86, 87). Thus, dietary patterns which incorporate dairy, such as the DASH (Dietary Approaches

to Stop Hypertension) diet, may be useful in mitigating this disease. An 8-wk parallel intervention study demonstrated benefits of following a calorie-restricted DASH diet ($n = 30$), which incorporated at least 3 servings of low-fat dairy daily, on lowering BMI, serum ALT, HOMA-IR, hsCRP, and serum triglycerides, among other variables, compared to a calorie-restricted control diet ($n = 30$) in patients with NAFLD (88). However, other differences in the DASH diet compared to the control diet, such as greater fruit and vegetable intake and lower simple sugar intake, likely also contributed to the observed benefits. A 4-wk crossover study in overweight/obese adults ($n = 47$) showed a diet rich in low-fat dairy (4–6 servings/d) increased insulin resistance (HOMA-IR) compared to a diet high in lean red meat with minimal dairy (<1 serving/d) (89); however, there was no effect on serum inflammation markers (90). In contrast, in a 6-wk randomized crossover study in adults with metabolic syndrome ($n = 37$), the consumption of 3 servings of low-fat dairy daily (296 mL 1% milk, 170 g nonfat yogurt, 56.7 g 2% cheese) compared to isocaloric carbohydrate-based control foods (42.5 g granola bar and 355 mL juice) significantly lowered plasma ALT, AST, hepatic steatosis index, and mRNA expression of IL-6 and IL-1β in PBMCs. In this study, dairy intake had no effect on HOMA-IR or other plasma inflammatory biomarkers measured (91). Body weight, waist circumference, and BMI were lower after the low-fat dairy period in women but not men. The authors speculated that the observed decrease in plasma aminotransferases may be due to attenuation of hepatic apoptosis and improvement in hepatocyte function by branched-chain amino acids from casein in milk, and/or an effect of increased circulating vitamin D concentrations following dairy consumption. The specific mechanisms by which at least some dairy foods impact liver fat and liver health indices remain to be elaborated.

Yogurt clinical studies. Gut microbiota have been linked with liver function and the development of NAFLD in both rodents (92) and humans (93). Yogurt has been investigated for its effects on liver function measures as both conventional (live starter cultures) and probiotic-containing yogurt (i.e., yogurt with starter cultures and added probiotics). In a recent 24-wk open-label randomized, controlled, clinical trial, NAFLD patients were instructed to follow a healthy lifestyle and consume either 300 g daily of a synbiotic yogurt containing 1.5 g inulin and *Bifidobacterium animalis* subsp. *lactis* ($n = 34$), 300 g of a conventional yogurt ($n = 34$), or no yogurt as a control ($n = 34$) (94). After 24 wk, liver steatosis and liver span (a measure of hepatomegaly) assessed by ultrasonography were both shown to be reduced to a significantly greater extent with the synbiotic yogurt group compared to the other 2 groups. The synbiotic yogurt group also had greatly improved serum liver enzymes, with significantly lower levels of ALT, AST, gamma-glutamyl transferase, and alkaline phosphatase. These changes were also observed with reductions in HOMA-IR and serum lipids (cholesterol, triglycerides, and LDL cholesterol) compared to controls. Relative to controls, grade of steatosis, liver function variables, and lipid profiles improved with conventional yogurt, but to a lesser degree than with synbiotic yogurt. Probiotic yogurt was also shown to be more effective than conventional yogurt in another study in NAFLD patients. In a parallel intervention study, NAFLD patients who consumed 300 g/d of a probiotic-containing yogurt (B. *lactis* Bb12 and *Lactobacillus acidophilus* La5) ($n = 36$) for 8 wk had significant reductions in weight, BMI, ALT, AST, LDL cholesterol, and insulin compared to patients consuming a conventional yogurt ($n = 36$) (95). A growing body of evidence suggests that probiotic-containing yogurt can reverse or improve liver steatosis indices relative to conventional yogurt and controls, whereas conventional yogurt only modestly improves or has no effect on these indices compared with no yogurt intake.

Cheese, whey, and human liver function. Currently, there are no controlled trials that have specifically examined the effects of cheese intake in NAFLD patients. However, relative to other full-fat dairy products such as butter, cheese intake has not been shown to raise LDL cholesterol concentrations in human intervention studies (96–98), suggesting an effect on the liver's function in lipoprotein secretion or clearance from circulation. A 12-wk randomized parallel intervention study in adults with ≥2 metabolic syndrome risk factors ($n = 139$) demonstrated no significant effects of a diet incorporating 80 g/d of regular-fat cheese ($n = 45$) on body composition, serum lipids, nuclear magnetic resonance–lipoprotein profiles, HOMA-IR, or hsCRP compared to reduced-fat cheese ($n = 48$) or low-cheese control diets ($n = 46$) (99, 100).

High-protein diets containing whey protein have been investigated for their potential benefits in liver function. In particular, the high cysteine content of whey protein may be beneficial in supporting hepatic levels of the antioxidant glutathione, which has been shown to be lower in livers of NAFLD patients (101). However, data from well-controlled trials are sparse in this area. In a randomized, double-blind, placebo-controlled trial, elderly women ($n = 166$; 70–80 y) consumed 30 g/d of whey protein–supplemented beverage ($n = 82$) or an energy-matched, low-protein, high-carbohydrate control beverage ($n = 84$) for 2 y (102). After 2 y, there were no significant differences in weight, waist circumference, BMI, insulin, glucose or HOMA-IR between groups. Additionally, there were no significant differences in hepatic steatosis between the treatments, as measured by computed tomography scans, although hepatic steatosis significantly worsened from baseline in the control but not the protein-treated groups. Strong inferences about the effects of cheese and whey intake on liver function and NAFLD are limited by the paucity of studies currently available on this topic, which warrants further investigation.

Animal models using dairy bioactive components on liver function and NAFLD development.

Whole dairy. Whole-dairy foods and dairy bioactive components have been investigated for their effects on liver

function and NAFLD, mostly in rodent models. Adams and colleagues (103) investigated the effects of high-calcium diets with and without nonfat dry milk (NFDM) on metabolic and inflammatory outcomes in diet-induced obese C57BL/6 mice. Male mice were fed an obesogenic soy protein–based high-fat diet (45% kcal as fat, 0.5% wt/wt calcium) for 8 wk, then randomized to consume for an additional 8 wk either the same diet (control; $n = 29$), a high-fat diet with 1.5% (wt/wt) calcium (high-Ca; $n = 30$), or a high-fat diet with high calcium (1.5% wt/wt) from NFDM (NFDM; $n = 30$). Mice fed the NFDM diet had improved glucose tolerance and lower liver triglycerides compared to both the high-calcium and control groups, suggesting the noncalcium dairy matrix components are responsible for benefits seen in these outcomes. Accordingly, feeding studies in rats have shown benefits of cheese on hepatic lipid content in some, but not all, studies (104). Interestingly, diets containing 10% (wt/wt) ripened cheese (15 d and 35 d) reduced hepatic lipids in obese diabetic mice (*db/db*) compared to a diet with 10% (wt/wt) unripened cheese (105), suggesting the duration of ripening affects the cheese matrix and health response.

Polar lipids from dairy and MFGM. In its natural state, milk fat is encased in a tri-layer milk fat globule membrane (MFGM), which is composed of proteins, cholesterol, and polar lipids (106). Polar lipids comprise approximately 1% of the total lipids of milk, and include glycerophospholipids (e.g., phosphatidylcholine) and sphingolipids (e.g., sphingomyelin), which emulsify triglyceride in the aqueous phase of milk (107). The polar lipid content of dairy products can vary considerably due to processing (108). Importantly, these MFGM components may impact the health effects of milk fat triglycerides and cholesterol in dairy products. In particular, sphingomyelin and its sphingolipid metabolites have been examined extensively in rodent models for their properties in inhibiting the intestinal absorption of other lipids (e.g., cholesterol, fatty acids) (). Due to their putative inhibition of the intestinal absorption of other lipids, as well as being a source of choline for liver health, polar lipids from MFGM have been investigated for potential benefits on liver function (109).

Blesso and colleagues have shown that feeding purified dietary sphingomyelin (SM; 0.1–0.25%, wt/wt diet) chronically to high-fat diet–fed C57BL/6 mice attenuates hepatic steatosis (59, 110). However, Yamauchi et al. (111) reported that supplementing 1% (wt/wt) of milk SM for 4 wk did not significantly alter hepatic lipids in genetically obese KK-Ay or low-fat diet–fed C57BL/6 mice. Wat et al. (112) and Kamili et al. (113) reported that chronic supplementation with various milk polar lipid extracts (0.25%–0.35% SM, wt/wt diet) significantly attenuated hepatic steatosis by lowering cholesterol and triglycerides in livers of C57BL/6 mice fed high-fat diets (21% butter fat, 0.15% cholesterol by weight). Effects were also observed in genetically obese KK-Ay mice with polar lipid–supplemented diets (0.5%–1.7% wt/wt) (114). However, some rodent studies have not shown effects on hepatic triglycerides. Supplementing an MFGM isolate (0.5% polar lipids, 0.1% SM by weight of diet) to AIN-76A diet-fed rats for 12 wk significantly reduced hepatic cholesteryl ester content, with no change in hepatic TG (115). Furthermore, supplementing palm oil–based high-fat diet with 1.2% (wt/wt) milk polar lipids did not impact hepatic lipids in C57BL/6 mice after 8 wk (116). More research should be conducted on the effects of milk polar lipids, particularly those provided as components of whole dairy compared to those which are provided as an isolate. Further research is warranted in the clinical realm, as well, to test how MFGM and other dairy lipids impact human liver phenotypes.

Odd-chain fatty acids from dairy. The odd-chain saturated fatty acids, pentadecanoic acid (15:0) and heptadecanoic acid (17:0), are xenolipids ("nonself" lipid molecules that are derived from microbes) produced by the gut microbiota in ruminant animals and may serve as circulating biomarkers of dairy fat intake in humans (117). Odd-chain fatty acids comprise ∼1.5% of milk fat, with 15:0 being twice as abundant as 17:0 (118). Interestingly, serum concentrations of 15:0 and 17:0 were negatively correlated with NAFLD activity scores and hepatocyte ballooning scores in a cohort of NAFLD patients ($n = 106$) (119). Serum 15:0 was also negatively correlated with the severity of fibrosis and AST, while serum 17:0 was negatively correlated with both AST and ALT. Mice fed methionine-choline–deficient diets supplemented with 15:0 (5% wt/wt) for 4 wk were partially protected from liver injury. Supplementation with 15:0 attenuated elevations in serum AST, normalized liver weights of animals, and reduced the number of ceroid-laden macrophages (119). These results suggest that odd-chain fatty acids found in milk fat may influence liver function; however, more research is needed to confirm these initial findings and to understand if physiologically relevant intakes or systemic levels influence metabolic health or liver function.

Protein and/or bioactive peptides from milk. Administration of whey protein has been shown to improve liver function and reduce NAFLD-related outcomes in mice (120), and in rats in some studies (121), but not others (122). Male Wistar rats fed various whey protein mixtures (whey protein isolate, whey hydrolysate) or individual isolated whey proteins (α-lactalbumin, β-lactoglobulin, or glycomacropeptide) by oral gavage (∼1 g/kg body weight) for 28 wk had lower ALT concentrations and hepatic malondialdehyde, with some whey proteins also improving body weight (whey isolate, α-lactalbumin, and β-lactoglobulin) and hepatic glutathione levels (whey isolate, whey hydrolysate, and β-lactoglobulin) (121). In another study, female C57BL/6 J mice were fed high-fat diets for 11 wk, with or without 100 g whey protein isolate per liter drinking water (120). Compared to high-fat diet controls, mice fed the whey protein isolate had fewer hepatic lipid droplets evaluated by histological analysis, as well as lower concentrations of nonpolar lipids (mainly triglycerides) in

livers. However, a recent study in low-fat diet–fed male Wistar rats reported that while orally administering a whey protein concentration (WPC-80) at 0.5 g/kg body weight for 21 d increased hepatic glutathione concentrations and induced liver injury compared to saline ingestion, including significantly increasing ALT, AST, hepatic malondialdehyde, IL-1β and TGF-β1 concentrations (122). Further studies are needed to clarify these contrasting effects of whey protein in some rodent studies. In addition to whey protein, hydrolyzed casein derived from dairy products may also be a source of bioactive compounds/peptides for protection of liver function. The inclusion of an extensively hydrolyzed form of casein, instead of nonhydrolyzed casein, to a high-fat, high-sucrose diet (45% kcal as mainly lard) was shown to lower body weight, serum lipids, and macrovesicular steatosis in LDLr$^{-/-}$.Leiden mice after 21 wk (123).

Probiotics found in dairy products. Kefir, a fermented milk product and potential source of probiotics, has been reported in rodents to have beneficial effects on liver outcomes in NAFLD induced by high-fat diet (124), high-fructose corn syrup–enriched diet (125), and genetic deficiency of leptin (*ob/ob* mice) (126). The isolation and administration of a potential probiotic from fermented milk was reported to have beneficial effects on NAFLD in rats (127). *Lactobacillus paracasei* Jlus66 (4×10^{10} cfu) administered to 60% kcal high-fat diet–fed rats for 20 wk decreased body and liver weights, serum ALT, and NAFLD lesion score compared to control animals fed a high-fat diet.

Calcium. Due to the putative effects of calcium on forming insoluble fatty acid soaps in the GI tract and increasing fecal fat excretion (128), dietary calcium may be an important dairy component which affects liver fat accretion. Accordingly, male C57BL/6 mice that were fed a calcium-adequate high-fat diet (0.5% calcium, 20% corn oil wt/wt) for 18 mo had significantly lower NAFLD-related liver injury (hepatic inflammation, fibrosis, and overall NAFLD activity scores) and greater gut microbial diversity than mice fed a calcium-deficient high-fat diet (0.04% calcium wt/wt) (129). Furthermore, in male Wistar rats that were overfed as pups, feeding a diet that was 2-fold enriched in calcium (10 g/kg of diet) for 2 mo significantly improved histological steatosis scores and liver oxidative stress markers (130).

Dairy consumption and cardiovascular function

Diets containing higher levels of dairy foods have been reported to be associated with neutral or lower risks for CVD-related morbidity and mortality (14, 131, 132). A mediating benefit of higher dairy food intakes on CVD risk is attributed to its blood pressure–lowering effects, which have been reviewed (133) and are the focus of several systematic reviews and meta-analyses (134–137). However, reduced blood pressure is unlikely to fully explain the mechanisms by which dairy foods may lower CVD risk. Evidence from controlled trials that will be discussed herein support that dairy foods improve vascular function independent of any blood pressure–lowering effect.

The challenge to evaluating dairy foods with regard to CVD risk relates to the decades-long development of this disorder. However, vascular dysfunction has an early etiologic origin and mediates the progression of CVD. Brachial artery flow-mediated dilation (FMD) is a well-established method to evaluate vascular function and has prognostic value to predict cardiovascular events (138–140). This technique in combination with measures of cardiometabolic biomarkers has been applied in controlled clinical studies to help establish the mechanistic benefit of dairy foods.

Postprandial effects.

In the acute setting, the controlled administration of dairy foods or their bioactive components have been examined for their impact on vascular health in the postprandial period. In a double-blind, randomized controlled trial with cross-over design, persons with metabolic syndrome ingested 1% low-fat milk (474 ml) or an isocaloric volume of rice milk that was matched for micronutrients but had a higher proportion of its energy from carbohydrate (40 g compared with 24 g) in lieu of less protein (1 g compared with 16 g) (141). During the 3-h postprandial period, FMD responses were unaffected by low-fat milk, whereas FMD decreased following rice milk ingestion; blood pressure was unaffected regardless of treatment. The vasoprotective activity of low-fat milk was attributed to its lack of impact on postprandial hyperglycemia-induced oxidative stress that otherwise limits nitric oxide bioavailability. Indeed, rice milk significantly increased circulating glucose in association with increasing lipid peroxidation. Rice milk also increased postprandial levels of asymmetric dimethylarginine (ADMA) relative to arginine (ADMA/ARG). In contrast, low-fat milk did not increase postprandial lipid peroxidation and actually increased circulating ARG. This suggests that its limited impact on hyperglycemia protects against oxidative stress, which is otherwise known to increase arginase-mediated catabolism of ARG (142). These biochemical findings are consistent with evidence that FMD responses are at least, in part, mediated in a nitric oxide-dependent manner (143).

Controlled feeding trials.

Based on postprandial hyperglycemia mediating vascular dysfunction, a randomized cross-over trial in persons with prediabetes examined the vasoprotective activities of nonfat dairy milk or its casein and whey proteins when co-ingested with glucose (144). While glucose alone (75 g) decreased FMD responses, glucose-induced decreases in FMD during the 3-h postprandial period were prevented when nonfat milk (474 ml containing 16 g total protein) or isonitrogenous amounts of either casein or whey protein were co-ingested with glucose. Consistent with the co-ingestion of whey or casein with carbohydrate similarly attenuating acute hyperglycemia in individuals with prediabetes (145), each dairy-based treatment similarly lowered areas under

the curve ($AUC_{0-3\,h}$) for plasma glucose while increasing cholecystokinin (144). This suggests that hyperglycemia was attenuated by delaying glucose absorption. Further, the lipid peroxidation biomarkers malondialdehyde and F_2-isoprostanes (that were otherwise increased by glucose) were attenuated by all dairy-based treatments in association, with lower methylglyoxal and endothelin-1. $AUC_{0-3\,h}$ of nitric oxide metabolites were similarly higher among all dairy-based treatments, which occurred coincident with greater ARG availability and lower ADMA/ARG, and with symmetric dimethylarginine relative to ARG (SDMA/ARG) but without affecting tetrahydrobiopterin redox status.

In a similarly designed controlled trial in individuals with prediabetes, postprandial vascular function and metabolic health was examined in response to dairy milk fat per se (146). Participants ingested glucose alone or glucose with either nonfat dairy milk (0.4 g fat) or full-fat dairy milk (16.2 g fat) prior to assessing FMD and cardiometabolic biomarkers during the 3-h postprandial period. Despite prospective observational reports linking dairy fat with CVD risk (147, 148), findings of this controlled study (146) showed that dairy milk, regardless of its fat content, similarly protected against glucose-induced impairments in vascular function. In agreement with others (141, 144), the vasoprotective mechanism was likely attributable to limiting glucose-induced oxidative stress: the latter decreases ARG and increases both ADMA/ARG and SDMA/ARG. Together, these findings support that dairy milk, mediated through its proteins and without any detriment of its lipid fraction, helps to promote vascular function by improving nitric oxide bioavailability.

Potential mechanisms of action: gut–vessel interactions. Evidence from a large-scale prospective observational study indicated that 2-h blood glucose following a glucose tolerance test, but not fasting glucose, predicted CVD-related mortality in persons with impaired glucose tolerance or those with overt diabetes (149). This further highlights that postmeal glucose excursions may be important to regulate vascular function. Although insulinotropic effects of milk proteins ($\geq$20 g/serving) have been observed (150), the doses are generally higher than typical consumption patterns of dairy foods. Thus, rather than due to enhanced glucose clearance, the glucose-lowering effects of dairy foods are at least partly mediated at the level of the gut. This is consistent with dairy milk or milk proteins increasing circulating cholecystokinin (146) in agreement with separate clinical studies suggesting slower gastric emptying (145, 151). Further, C-peptide concentrations increased among individuals with prediabetes following the acute ingestion of whey protein isolate (50 g) compared with maltodextrin (145). Both whey protein isolate and sodium caseinate also increased glucose-dependent insulinotropic polypeptide to a greater extent than maltodextrin, but neither dairy-derived protein affected glucagon-like peptide-1 (GLP-1) levels. However, the effects of whey protein on GLP-1 may be dose dependent, consistent with a higher dose (70 g) but not a lower dose (30 g) increasing peak GLP-1 during a 3-h postprandial period (151). Overall, the evidence from controlled studies supports the cardioprotective benefits of dairy milk along the gut–vessel axis. Whether the attenuation of oxidative stress by dairy foods contributes to changes in vascular function remains unknown. Limited evidence indicates that, at least acutely, nitro-γ-tocopherol is unaffected by low-fat dairy milk ingestion (141). That this nitrative stress biomarker increases by proinflammatory responses (152) suggests that dairy foods protect against acute vascular dysfunction independent of inflammation, but further study is needed.

Potential mechanisms of action: microcirculation. The microcirculation controls 80% of systemic vascular resistance, and dysfunction of the microcirculation is highly predictive of long-term CVD risk (153, 154). One of the earliest detectable functional manifestations of CVD is remodeling of the resistance vasculature and an attendant loss of endothelium-dependent vasodilation due to a reduction in nitric oxide. Thus, the mechanistic impact of dairy on microcirculatory control is a relatively unexplored area of investigation.

Independent of blood pressure reduction, dairy-derived bioactive proteins protect vascular endothelial function through multiple putative mechanisms, including acting as free-radical scavengers (155, 156), reducing NADPH oxidase (157), inhibiting lipid peroxidation (158), and improving antioxidant enzyme capacity through increased expression and activity (159, 160). The majority of the studies that have mechanistically demonstrated these effects have been performed in isolated cell and animal models (161, 162). Collectively, the results of these studies suggest that dairy proteins can preserve endothelial function by limiting reactive oxygen species (ROS).

An additional proposed mechanism underlying the protective effects of dairy on microcirculatory control involves angiotensin-converting enzyme (ACE) inhibition (163–165). In particular, casein-derived lactotripeptides including Val-Pro-Pro and Ile-Pro-Pro exhibit modest ACE-inhibitory properties. In a study involving stage I hypertensive men ($n = 24$), in a double-blind placebo controlled design, 1 wk of supplementation with casein hydrolysate improved vascular responsiveness during reactive hyperemia (166). Subsequent microarray analysis of the aorta in a spontaneously hypertensive rat model indicated the target changes in gene expression related to vascular function were increases in endothelial NO synthase and connexin 40, and alterations in pro/anti-inflammatory transcription factors, including NF-κB and peroxisome proliferator–activated receptor γ, respectively (167).

To date, few studies have interrogated the putative mechanisms underlying the impact of whole dairy foods on microcirculatory control in humans. In observational studies, low-fat milk, yogurt, and cheese consumption was associated with improved retinal microvascular quality in subjects with elevated CVD risk (168). However, in prospective studies,

acute low-fat milk consumption resulted in reduced NO-dependent vasodilation in the skin compared to both a water control and a eucaloric rice beverage comparison. The human cutaneous circulation has emerged as a representative vascular bed for assessing mechanisms mediating vascular dysfunction and is a validated in vivo model for assessing endothelial function in the microcirculation (169–171). Despite observing a reduction in NO-dependent vasodilation, the total magnitude of the vasodilator response remained unchanged (172). These data suggest that other non-NO–dependent pathways, including vasoprotective hyperpolarizing factors, may be modulated by dairy in the acute (single meal) setting.

The matrix and fat composition of dairy may protect the microvasculature from the detrimental effects of sodium. Independent of the effects on blood pressure, sodium reduces NO in the microcirculation through increasing superoxide production through NADPH oxidase (173, 174). However, recent data demonstrate that detrimental effects of sodium are mitigated when ingested in a dairy complex (natural cheese) (173). NO-dependent vasodilation in the cutaneous microcirculation was impaired 90 min after sodium ingestion at 560 mg and 1120 mg from a pretzel snack and 560 mg from nondairy cheese (soya), which was ameliorated with the localized treatment of the nonspecific antioxidant ascorbate. Similar to the animal and cell culture studies, the conclusions from this study suggest that the mechanisms mediating this vasoprotective effect are through decreasing oxidant stress (175). However, the exact component of the dairy cheese matrix mediating this effect or the influence of the dairy fat composition on these responses are unknown. Longer-term controlled and free-living studies incorporating low- and full-fat dairy cheese as a source of bioactive peptides and sodium in a sustainable dietary pattern are needed, to determine the precise mechanisms underlying these vascular effects.

Conclusions

Considerations of how specific foods or food components may impact whole-body health and function will benefit from an integrative perspective: one that takes dietary patterns, food matrices, and multitissue physiology into account. In this review, we have considered how full-fat dairy and other forms of dairy foods impact systems directly relevant to cardiometabolic health, including the gastrointestinal tract, liver, and vasculature. This unique perspective, bolstered by epidemiological and observational literature, generally supports the concept that dairy foods (including full-fat dairy) included as part of healthy dietary patterns do not negatively impact factors such as chronic or postprandial inflammation, CVD risk markers, vascular function, or liver fat homeostasis. In fact, on balance, epidemiological, randomized controlled trials and mechanism-based evidence points to a neutral-to-protective association of dairy with respect to cardiometabolic health. This unique perspective, complemented by epidemiological and observational literature, generally supports the concept that dairy foods (including select forms of full-fat dairy such as milk, yogurt, and cheese) included as part of healthy dietary patterns does not contribute to deterioration of metabolic health, e.g. by negatively impacting factors such as chronic or postprandial inflammation, CVD risk markers, vascular function or liver fat homeostasis. In fact, on balance, epidemiological and mechanism-based evidence points to a neutral to protective association of dairy with respect to cardiometabolic health.

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