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Associations between dairy foods, diabetes, and metabolic health: potential mechanisms and future directions

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Abstract

Epidemiological evidence supports an inverse relationship between adequate intake of dairy foods and susceptibility to type 2 diabetes (T2D). The biological mechanisms responsible for this association remain to be established. This review provides a current perspective on proposed mechanisms that may underlie these effects, and highlights how randomized clinical trials can be applied to investigate these relationships. Results from epidemiological studies generally support that consumption of milk and dairy products is associated with a lower incidence of T2D or improvements in glucose homeostasis indices, and studies of animal and cell models support a positive effect of dairy-rich diets or components on metabolic and inflammation factors relevant to T2D and insulin resistance. Emerging evidence indicates that dairy components that alter mitochondrial function (e.g., leucine actions on silent information regulator transcript 1 (SIRT1)-associated pathways), promote gut microbial population shifts, or influence inflammation and cardiovascular function (e.g., Ca-regulated peptides calcitonin gene-related peptide [CGRP] or calcitonin) should be considered as possible mechanistic factors linking dairy intake with lower risk for T2D. The possibility that dairy-derived trans-palmitoleic acid (tC16:1) has metabolic bioactivities has also been proposed. Pre-clinical and clinical studies focusing specifically on these parameters are needed to validate hypotheses regarding the potential roles of dairy products and their components on the determinants of glucose tolerance, particularly insulin sensitivity, pancreatic endocrine function, and inflammation in individuals at-risk for T2D development. Such experiments would complement epidemiological studies and add to the evidence base for recommendations regarding consumption of dairy products and their individual components.

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Keywords

type 2 diabetes mellitus; metabolic syndrome; prediabetes; Dietary Guidelines for Americans

Introduction

Rapidly rising rates of type 2 diabetes (T2D) and other cardiometabolic disorders pose a significant threat to human health and raise healthcare costs worldwide. Data collected by the Centers for Disease Control and Prevention (CDC) shows that 26 million Americans have diabetes, and approximately one third of U.S. adults are classified as having prediabetes and/or metabolic syndrome [1, 2]. The health complications associated with diabetes are extremely taxing at both the individual and healthcare system levels. For instance, according to the CDC, diabetes is the leading cause of adult blindness in the U.S. and is also responsible for 44% of end-stage renal disease cases and 60% of lower limb amputations. The treatment and management of diabetes costs an estimated \$176 billion annually in the U.S. alone, and the estimated indirect cost from disability, loss of work, and premature death related to diabetes is \$69 billion [3]. Trends in the prevalence of obesity and T2D among pediatric and adolescent populations have also become a major public health concern. Obesity, a major risk factor for developing T2D and metabolic syndrome, has more than doubled in children and tripled in adolescents living in the U.S. over the past two decades [4, 5]. During this time, the percentage of pediatric cases of diabetes classified as T2D has risen from less than 3% to 45% [6]. Diet and lifestyle interventions are the preferred treatment modality for these groups, and pharmacotherapy is only indicated if supervised lifestyle intervention fails [7, 8]. In light of these sobering statistics, it is imperative that the clinical and scientific communities identify modifiable factors that can help prevent or mitigate T2D and other cardiometabolic diseases.

Recently, the relationship between dairy consumption, reduced T2D risk, and improved metabolic health has received increasing attention. The potential role for dairy consumption to reduce T2D risk was recognized in the 2010 Dietary Guidelines for Americans (DGA), which recommend 3 cups of fat-free or low-fat (1%) milk and milk products daily for individuals aged 9 years and above [9]. The DGA, established jointly by the U.S. Departments of Agriculture and Health and Human Services, are designed to provide science-based advice for Americans aged 2 years and above to help prevent chronic diseases and promote health. Recommendations for milk product intake have traditionally been based on their role as key contributors of essential nutrients, as well as on moderate evidence of a link to improved bone health. In 2010, the Dietary Guidelines Advisory Committee addressed a number of questions related to diet and disease risk using an evidence-based review process, and one of these questions was “What is the relationship between the intake of milk and milk products and incidence of T2D?” [10]. The Committee considered a systematic review with meta-analysis of four prospective studies, which reported that relative risk for T2D was 10% lower in people who had a high milk intake relative to those with low consumption [11]. Based on this, the Committee concluded that “Moderate evidence shows that milk and milk products are associated with a lower incidence of type 2 diabetes in adults,” and in the Implications section, noted that “Research since 2004 shows

that under-consumption of milk and milk products may lead to an increase in type 2 diabetes” [10].

This review aims to summarize recent meta-analyses that evaluated these potential links, to explore possible mechanisms, and to identify knowledge gaps to provide guidance and insight for future studies.

Summary of Recent Epidemiological Evidence

Since the publication of the 2010 DGA report, studies have been published that support a possible protective effect of dairy product consumption on T2D incidence. In the following publications, the evidence reviewed is based on observational data obtained primarily through validated food-frequency questionnaires. While there is some variation among the dairy items included, the majority of studies defined total dairy intake as the combined intake of individual low-fat (skim milk, 1% milk, skim chocolate milk, sherbet, yogurt, cottage/ricotta cheeses) and high-fat (whole milk, cream, sour cream, ice-cream, butter, cream cheese and other cheeses) dairy products.

Tong et al. [12] completed a meta-analysis of studies on dairy consumption and risk of T2D, with seven cohort studies identified from a systematic literature review. When comparing the highest with the lowest dairy product intake, the combined diabetes risk ratio (RR) was 0.86 (95% CI, 0.79–0.92), with little evidence of heterogeneity. For subgroup analysis, the combined RRs were 0.82 (95% CI, 0.74–0.90), 1.00 (95% CI, 0.89–1.10), 0.95 (95% CI, 0.86–1.05) and 0.83 (95% CI, 0.74–0.93) for intake of low-fat dairy, high-fat dairy, whole milk and yogurt, respectively. Dose-response analysis showed that T2D risk could be reduced 5% for each one serving per day of total dairy products and 10% for each one serving per day of low-fat dairy products.

Kalergis et al., in a recent evidence-based review, reported that dairy intake is significantly associated with a reduced T2D risk and the relationship is dose-dependent [13]. There was consistent evidence to support an association between low-fat dairy consumption and T2D risk reduction, but a beneficial impact was also suggested for regular-fat dairy. The authors concluded that the roles of specific dairy products need to be clarified and that mechanistic studies should be conducted to expand on the current research. Another evidence-based review examining studies published just after the 2010 DGA report arrived at essentially the same conclusions [14].

Aune et al. [15] conducted a systematic review and dose-response meta-analysis of 17 cohort studies related to dairy intake and T2D risk. Summary RRs were estimated with a random-effects model. In the dose-response analysis, the summary RRs (95% CIs) were 0.93 (0.87–0.99) per 400 g total dairy products/day, 0.98 (0.94–1.03) per 200 g high-fat dairy products/day, 0.91 (0.86–0.96) per 200 g low-fat dairy products/day, 0.87 (0.72–1.04) per 200 g milk/day, 0.92 (0.86–0.99) per 50 g cheese/day, and 0.78 (0.6–1.02) per 200 g yogurt/day. Nonlinear inverse associations were observed for total dairy products, low-fat dairy products, cheese, and yogurt, with a flattening of the curves at higher intakes. The authors concluded that there is a significant inverse association between intakes of dairy

products, low-fat dairy products, and cheese and risk of T2D. Similarly, another recent meta-analysis of 14 studies [16] concluded that for 200 g/day total or low-fat dairy consumption, RRs for T2D risk were 0.94 (0.91–0.97) and 0.88 (0.84–0.93), respectively. For 30 g/day cheese and 50 g/day yogurt the RRs were 0.80 (0.69–0.93) and 0.91 (0.82–1.00), respectively.

Thus, these recent population-based observational findings support an inverse relationship between dairy consumption and T2D risk. However, there is ambiguity surrounding the effects of different dairy products, the specific dairy food components involved, as well as the potential mechanisms by which this association occurs. Since not all dairy intervention studies have demonstrated improvements in glycemic control indices (e.g., [16, 17]), there is a need for further clinical trials to explore mechanisms and to determine if there are phenotypic subsets of the population that would most benefit from the metabolic effects of dairy foods.

Dairy and Cardiometabolic Health: Potential Mechanisms

In addition to the epidemiological evidence supporting a positive role for dairy-rich diets and cardiometabolic health, results outlined below from rodent obesity models or cell culture models support the concept that dairy-associated factors could improve insulin sensitivity, reduce adiposity, and/or attenuate inflammation or oxidative stress markers. The degree to which these outcomes can be replicated in human populations remains to be established; yet insights related to potential mechanisms of action for dairy foods may be gleaned from these models. Despite several plausible mechanistic models, and some emerging ideas worth consideration, large knowledge gaps remain with respect to our basic understanding of how dairy diets influence metabolism and inflammation.

Calcium and calcitriol

Evidence from cell culture models has provided *in vitro* support for the hypothesis that *in vivo*, dietary calcium attenuates inflammatory cytokine production, oxidative stress, and fat cell lipid accumulation. The basic premise is that suboptimal dietary calcium results in elevated production and blood levels of the calcium-regulating vitamin D derivative calcitriol (1,25-dihydroxyvitamin D₃), which in turn has pro-inflammatory and obesogenic activities (reviewed in: [18, 19]). Calcitriol increased pro-inflammatory cytokine gene expression and secretion from adipocytes and macrophages, and was associated with higher intracellular Ca accumulation and reactive oxygen species generation [20]. A high Ca diet reduced inflammation and adiposity in the aP2-agouti obese mouse model [21]. Despite these promising results, the role of calcium and calcitriol on obesity- and inflammation-associated phenotypes *in vivo* remains an open question. For instance, high calcium feeding in isolation without a dairy matrix does not consistently reduce adiposity in diet-induced obese (DIO) rodent models (e.g., [22–24] and references therein), and in some cases promotes obesity and adipose tissue inflammation despite lowered blood calcitriol [23]. Protein source (nonfat dry milk (NFD) or whey), and not dietary Ca level or changes in calcitriol, corresponded best to adiposity differences in DIO mice and rats [25, 26]. With respect to inflammation, recent results from a DIO mouse model (fed adequate or high Ca,

or high Ca with a NFDM matrix) indicated that in a group of 90 mice, adipose macrophage infiltration (and inflammation generally) closely correlated with adiposity regardless of diet [23]. In humans, calcitriol had *anti*-inflammatory actions in *ex vivo* studies of monocytes from persons with type 1 and type 2 diabetes, with no effect in non-diabetics [27]. The reason for the latter was not ascertained, but likely was because of the demonstrated very low inflammatory state innate to the control monocytes vs. the diabetic subjects. Therefore, dietary calcium-associated reductions in calcitriol alone are not necessary and sufficient to drive anti-inflammatory and anti-obesity properties of dairy products.

Leucine, Silent Information Regulator Transcript 1 (SIRT1), and Mitochondrial Function

Insulin resistance and T2D are characterized by sub-optimal *in situ* mitochondrial function in muscle and perhaps other metabolically important tissues such as liver. Evidence for this includes increased tissue and blood indices of mismatched fatty acid fuel delivery relative to mitochondrial oxidative capacity (e.g., [28, 29]), metabolic flux measurements suggestive of lower muscle TCA cycle capacity [30–32], and decreased metabolic flexibility (switching between fat and carbohydrate oxidation) [33]. The etiologies of these phenotypes are not established, but might include TCA cycle anaplerotic/cataplerotic imbalance [29, 34] and/or reduced tissue mitochondrial capacity [35], which together or in combination would promote incomplete fuel catabolism and accumulation of metabolites that promote inflammation or insulin resistance outcomes [36]. Recent evidence points to the possibility that dairy protein-derived components such as leucine may counter mitochondrial dysfunction. It has been suggested that anti-obesity properties and improvements in metabolic sequelae may be derived from the whey protein fraction [37], a rich source of leucine. Leucine promoted fat oxidation in cultured myotubes [38] and increased mitochondrial mass in myotubes, adipocytes, and hepatocytes [39, 40]. Leucine has been reported to increase expression/activity of SIRT1, an NAD⁺-sensitive protein deacetylase implicated in activating fat oxidation, mitochondrial biogenesis, improving insulin sensitivity and reducing oxidative stress [39–41]. This activation led to increases in downstream metabolic gene targets such as peroxisome-proliferator activated receptor gamma coactivator-1 α (PGC-1 α) [39–41]. Strikingly, effects were generally replicated in cells treated with serum from human subjects who had consumed 3 daily whey protein-based smoothies for 28 days, an effect not seen with serum from soy protein-based diets [41]. Leucine is also an activator of mammalian target of cellular rapamycin (mTOR), a nutrient-sensitive factor that affects mitochondrial biogenesis and function in part through modifying yin-yang 1 (YY1) interactions with PGC-1 α [42]. It is notable that in mouse DIO models, leucine, whey protein isolate, or a NFDM-based diet matrix reduced feed efficiency and/or increases energy expenditure [23, 24, 43–45], suggestive of changes in mitochondrial activity and activation of thermogenic systems. Thus, it is plausible that dairy protein contributes to metabolic health outcomes through mitochondrial changes involving leucine-associated SIRT1 and/or mTOR activation in muscle and other tissues. This concept requires clinical experimental evaluation of mitochondria *in situ* with concurrent assessments of insulin action and oxidative stress indices.

Trans-palmitoleate (tC16:1n-7)

Full-fat dairy may contain bioactive lipids that regulate metabolic and inflammatory pathways, and tC16:1n-7 (derived from rumen bacteria and relatively high in ruminant-derived foods) has been proposed as a candidate. This idea emerged from large epidemiological cohorts indicating that higher circulating concentrations of tC16:1n-7 are consistently associated with significantly reduced risk for development of T2D [46, 47]. While blood tC16:1n-7 levels may simply be marking dietary tC16:1n-7 intake (e.g., [48]), the possibility that tC16:1n-7 has protective effects on dysfunctional metabolism has been proposed [46, 47], based on the observation that administration of the *cis*-isomer cC16:1n-7 (an endogenously-produced stearoyl-CoA desaturase-1 product) can promote insulin sensitivity in cultured rat myotubes and in rodents *in vivo* [49, 50]. The notion that dairy-derived tC16:1n-7 plays a similar role is worth consideration; however, there are a variety of observations that temper this perspective. First, tC16:1n-7 is also rich in beef [48] and yet in contrast to dairy, epidemiologic studies do not support a protective role for red meat consumption and incident diabetes (e.g., [51]), with the caveat that any putative tC16:1n-7 positive metabolic effects may be impacted by factors present in red meat and not dairy products. Second, from a biochemical standpoint it is not certain that tC16:1n-7 and cC16:1n-7 isomers would behave similarly in the body. Third, although administration of cC16:1n-7 promotes insulin action and glucose homeostasis in rodents, and in some human studies higher blood concentrations correspond to insulin sensitivity [52, 53], the latter observation is far from uniform ([54] and references therein). Furthermore, plasma cC16:1n-7 was found to be 2.8-fold higher in T2D women compared to weight- and age-matched obese counterparts despite obvious insulin resistance in the former [55]. Thus, the evidence remains equivocal on the role for dairy-derived tC16:1n-7 in protecting against transition into the pre-diabetic or T2D state.

Dairy Effects on Gut and Liver

Little is known about the impact of dairy on liver health, and in particular the steatosis that often accompanies the dysmetabolic obesity of metabolic syndrome or T2D. Accumulation of liver fat is associated with insulin resistance and inordinately high hepatic glucose output, and can progress to non-alcoholic hepatosteatosis or non-alcoholic fatty liver disease. In two studies in which DIO mice were fed a 45% fat diet with a dairy matrix (NFDM protein and lactose carbohydrate), liver fat was dramatically reduced compared to DIO mice fed a soy protein and sucrose-based diet; this effect appeared to be independent of weight [23, 24]. Fermented dairy products had a similar effect in *db/db* mice [56]. It remains to be seen if these results translate to the human condition, and the mechanisms underlying the dairy effects are not known. Based on initial observations that a NFDM-based diet significantly alters gut microbial populations in DIO mice [57], a strong possibility is that dairy components (e.g., oligosaccharides: [58, 59]) alter the microbiome. This could change host-gut microbe signals that impact host metabolism, as originally speculated by the Cani group [56].

Calcitonin Gene-Related Peptide (CGRP)

An intriguing yet understudied possibility is that dairy Ca in part modifies inflammation and blood pressure via changes in local or systemic actions of the hormone CGRP. In addition to conveying signals in an afferent manner away from peripheral tissues (pain, temperature, proprioception, noxious chemical signals), some peripheral neurons act in an efferent fashion to secrete CGRP, which can impinge upon inflammation and hemodynamics (see [60, 61]). CGRP expression by spinal cord neurons is up-regulated by dietary Ca in the rat [62] and expression is reduced by calcitriol treatment of C-cells or thyroid cells in culture [63–65]. This calcium- and inflammation-regulated peptide appears to have important immunomodulatory actions by 1) tempering inflammation through NFκB inhibition and 2) increasing endothelial production of PGI₂, a prostaglandin with anti-inflammatory activities [61]. Interestingly, CGRP is expressed in rodent and human white adipose tissue (WAT), where Linscheid et al. showed it can be induced by pro-inflammatory insults (e.g., [66, 67]). The peptide is also a powerful vasodilator, and CGRP has been proposed to contribute to the beneficial effects of dietary calcium/dairy in thwarting hypertension [68, 69]. The importance of CGRP in dairy-associated metabolic, inflammation, and blood pressure effects remains to be confirmed, however. For instance, CGRP mRNA in a mouse DIO model was not changed by dietary Ca in WAT [23] or in nodose ganglia containing peripheral neuron cell bodies from the same mice (T.N. Dunn, S.H. Adams, unpublished data) despite reduced plasma calcitriol.

Considerations for Future Trials of Dairy Consumption and T2D Risk

Although the available evidence from observational data and laboratory studies suggest a consistent inverse association between dairy intake and T2D risk or metabolic dysfunction with several biologically plausible explanations, additional supporting evidence from randomized controlled trials is needed. This will inform dietary recommendations with respect to dose and types of dairy foods (full-, low-, or no-fat foods and beverages, fermented and non-fermented products, and cheeses) to optimize metabolic health. Pre-clinical and clinical mechanistic studies are needed to test hypotheses regarding the potential roles of dairy products and their components such as minerals, vitamin D, proteins, and peptides liberated during digestion, on the determinants of glucose tolerance in both healthy individuals and those with risk factors for T2D development (e.g., prediabetes, obesity, insulin resistance, metabolic syndrome). Nutrients including calcium, magnesium, potassium, vitamin D, and protein/peptides unquestionably have important potential roles in the physiological effects of dairy. However, results from studies investigating their relationships with diabetes risk or metabolic phenotypes have been inconsistent [12, 70–72]. In addition to the direct effects of dairy products, consideration should be given to displacement effects, as individuals who consume more dairy foods/beverages will typically consume less of other foods that might also impact diabetes risk (e.g., sugar-sweetened beverages).

A framework that may be helpful to furthering our understanding of the role of dairy foods in T2D was provided by DeFronzo in his 2009 Banting Lecture [73]. He reviewed the evolution of the understanding of the metabolic defects associated with T2D and suggested

expanding the traditional triumvirate of defects in skeletal muscle (insulin resistance), liver (insulin resistance and excessive hepatic glucose output) and pancreatic beta-cells (insufficient glucose-stimulated insulin secretion) to include five additional contributions, terming the metabolic defects associated with diabetes the “Ominous Octet” [73] (Table 1). Investigation into the influences of dairy foods and their components on this octet of metabolic defects is in very early stages at present. Below are some suggestions for investigation within the framework of DeFronzo’s “Ominous Octet.”

The Influences of Dairy Products and Dairy Components on Insulin Resistance and Pancreatic Beta-Cell Function

Fundamentally, hyperglycemia results when the pancreatic beta-cells are unable to produce a sufficient quantity of insulin to maintain normal glucose uptake. In some cases this is thought to result from insulin resistance, requiring compensatory hyperinsulinemia, and eventually leading to pancreatic beta-cell “exhaustion.” An alternate perspective is that hyperinsulinemia begets or contributes to peripheral insulin resistance (reviewed in [74]).

Regardless, because pancreatic beta-cell response is tied to the level of insulin sensitivity/resistance through a negative feedback loop (greater insulin resistance necessitates a larger insulin response to maintain normoglycemia), beta-cell function can only be assessed in conjunction with insulin sensitivity. It has been hypothesized that dairy proteins, in particular whey, may impart glucose-regulating properties through triggering gut hormones and incretins that regulate insulin release and gut motility (reviewed in [75]). Limited evidence suggests that insulin sensitivity can be improved in subjects consuming higher dairy compared to lower dairy diets [76, 77]. In one study [77], 40 overweight or obese adults with metabolic syndrome were randomly assigned to receive adequate or low dairy diets for 12 weeks. Significant improvements were observed in the adequate dairy arm, relative to the low dairy arm, in fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR). These changes were accompanied by reductions in several markers of inflammation and oxidative stress, as well as a statistically significant 55% increase from baseline in adiponectin, a hormone secreted by adipose tissue. Blood levels of adiponectin have been inversely associated with insulin resistance, metabolic syndrome and risk for developing T2D, suggesting a possible mechanistic link between dairy consumption and improved insulin sensitivity mediated by enhanced adiponectin secretion [78, 79]. However, results from other studies evaluating the influence of dairy intake on adiponectin levels have shown mixed results, one supportive of an increase [80] and another showing no effect [17]. The latter controlled feeding trial indicated no effect of adequate dairy intake on HOMA-IR, glucose or insulin in previously low-dairy consumers. Considering these mixed outcomes, additional intervention studies are needed to fully assess the impacts of dairy consumption on insulin sensitivity and beta-cell function, as well as the association of these phenotypes with changes in metabolically relevant adipocyte-derived hormones such as adiponectin.

A review of the methods available for assessing whole body, as well as peripheral (mainly skeletal muscle and adipose tissue) and hepatic insulin resistance, and pancreatic beta-cell function is beyond the scope of this review, and the interested reader is referred to papers by Muniyappa et al. [81] and Borai et al. [82]. An important consideration for such clinical

investigations is the comparison condition, e.g. to evaluate the effects of greater dairy food consumption in place of other products with similar macronutrient composition (e.g., yogurt compared with eggs), as well as other alternatives that consumers might choose (e.g., fluid milk compared with sugar-sweetened beverages).

The Influences of Dairy Products and Dairy Components on Functions of the Gastrointestinal Tract that Influence Glucose Homeostasis

In recent years, knowledge of the influences of the gastrointestinal tract on glucose homeostasis has progressed substantially. The incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) play important roles in maintaining glucose homeostasis, in part by enhancing pancreatic beta-cell responsiveness to glucose [83, 84]. As much as 25% of the postprandial insulin response has been suggested to be attributable to the effects of incretins. Individuals with T2D have lower than normal postprandial GLP-1 concentrations, and have resistance to the effects of GIP. GLP-1 deficiency, in particular, has become a target for therapy, with availability of drugs that act as GLP-1 analogues or that reduce GLP-1 degradation by inhibiting the enzyme dipeptidylpeptidase-4 [85]. Various lines of evidence indicate that GLP-1 production by small intestinal and colonic L-cells is influenced by specific nutrients, and may respond to foods that provide substrate for certain species of colonic microbiota [86]. In particular, prebiotic fibers and resistant starches have been shown to alter gut microbiota, and such changes have been associated with improvements in whole body insulin sensitivity and higher postprandial blood concentration of GLP-1 [87–89]. Some dairy products have the potential to alter gut microbiota through probiotic effects of live cultures used during fermentation, and others may do so through the prebiotic effects of dairy oligosaccharides [59, 90]. Thus, the influences of consuming dairy foods and dairy food components on gut microbiota, and potential links to incretin and other signaling responses warrant investigation [91].

Effects on Pancreatic Alpha-cell, Adipose Tissue, and Central Nervous System (CNS) Function as it Relates to Glucose Homeostasis

As DeFronzo [73] described, one of the metabolic defects of T2D is excessive release of glucagon by pancreatic alpha-cells. The secretion of glucagon in response to protein in patients with diabetes is often increased [92, 93]. It is unknown at present whether the protein type/amino acid composition of dairy products, or other dairy components, might differentially affect pancreatic alpha-cell activity. The CNS is intimately involved with regulation of peripheral glucose homeostasis (e.g., hepatic glucose output) and endocrine pancreas function [94–96], and amino acids have been demonstrated to elicit signals in the hypothalamus [97]. Effects of acute or chronic dairy food consumption on CNS function remain largely unexplored, but should be considered as a potential route by which glucose homeostasis, liver and pancreatic functions are influenced by dietary alterations.

With regard to effects on body composition, inclusion of dairy products in calorie-restricted diets has been shown, in some studies, to improve body weight, waist circumference and fat mass, while preserving lean mass [98–102]. Such outcomes would promote insulin sensitivity and reduce T2D risk. However, these findings have not been confirmed over the

long term by meta-analysis [101], and in a recent controlled-feeding weight loss trial in obese individuals, a mixed dairy- and Ca-rich diet did not produce additional fat loss or differentially alter fasting insulin sensitivity indices compared to a control diet [17]. It is not clear if controlled and matched calorie restriction *per se* masked beneficial effects of dairy on cardiometabolic indices or satiety in that experiment. For instance, some of the metabolic benefits of dairy food consumption may be due to variations in *ad libitum* energy intake, since body weight effects of calcium and vitamin D supplementation were attributable to variations in lipid and energy intake [103], and milk supplementation facilitates appetite control in the context of weight loss [104]. Additional studies that explore metabolic outcomes under weight maintenance or free-living conditions will be worthwhile to further explore these questions.

The protein component of dairy may also indirectly enhance body weight regulation and lean mass changes through enhanced satiety and promotion of skeletal muscle growth via anabolic dairy protein-derived branched-chain amino acids [13, 102]. In healthy individuals, muscle protein synthesis has been shown to increase after intense resistance exercise following ingestion of dairy proteins [105], and whey protein in particular appears to mediate these effects [75, 106]. Whether similar post-exercise skeletal muscle synthesis is as responsive to dairy protein in individuals with insulin resistance and T2D has not been fully elucidated [102]. Clinical trials examining the effects of dairy protein for muscle conservation and function in individuals with prediabetes and T2D are needed.

Biomarkers for Intake and Activities of Dairy Foods and Their Relationships to T2D Risk

Studies of dairy product intake and the risk of several chronic metabolic diseases, including not only T2D, but also metabolic syndrome, cardiovascular disease and hypertension have yielded inconsistent results. The use of biomarkers as a reflection of dairy food intake could improve the assessment of these relationships. Potential dairy fat intake biomarkers include 14:0 (myristic acid), 15:0 (pentadecanoic acid), 17:0 (margaric acid) and *16:1n-7* in plasma, plasma phospholipids, or red blood cell membranes. A limitation of these biomarkers is that they would not reflect intake of fat-free dairy products. Nevertheless, circulating levels or proportions of 15:0, 17:0 and *16:1n-7* have been associated with a more favorable T2D risk factor profile and with lower risk for T2D development [46, 47, 49, 50, 52, 53, 107].

However, results from several lines of evidence suggest that chronic high-level exposure of pancreatic-beta cells to some long-chain saturated fatty acids, especially palmitic acid (16:0), is detrimental to their function, and enhances apoptosis, which, by decreasing beta-cell mass, would potentially increase the risk for T2D [108]. Accordingly, epidemiological, pre-clinical and clinical studies are needed to more clearly define the dose-response relationship between dairy fat intakes and changes in levels of these lipid biomarkers, as well as the relationships between changes in these biomarkers to indices of glucose and insulin homeostasis and T2D risk.

Metabolomics, i.e., comprehensive metabolite analysis, lends itself to the search for new dairy intake and function biomarkers and novel metabolite signatures that may be used to characterize insulin resistance and T2D risk [109, 110]. In metabolomics investigations of the association between serum metabolites and insulin resistance or risk of T2D, alterations

in sugar metabolites, select amino acids, and choline-containing phospholipids were identified (e.g., [110, 111]). These results suggest the important role that metabolomics play in the future of diabetes research and indicate potential markers that may prove useful in the evaluation of the influence of dairy product consumption on T2D risk and metabolic actions in clinical and epidemiological studies.

Summary & Future Directions

Consistent observational results support that consumption of dairy products is linked to lower T2D and metabolic disease risk in the population. Mechanisms for the protective properties of dairy consumption remain to be fully elaborated in pre-clinical and clinical studies, but may involve chronic or acute postprandial activities of dairy-derived lipids, amino acids, and/or minerals, and could involve changes in the gut microbiome and/or hormonal cues. The strength of the relationship between intake of dairy products and protection against T2D supports the position of dairy products in dietary guidance.

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List of abbreviations used

T2D	type 2 diabetes
SIRT1	silent information regulator transcript 1
CGRP	calcitonin gene-related peptide
CDC	Centers for Disease Control and Prevention
DGA	Dietary Guidelines for Americans
RR	risk ratio
CI	confidence interval
NFDM	nonfat dry milk
DIO	diet induced obesity
PCG-1α	peroxisome-proliferator activated receptor gamma coactivator-1 α
mTOR	mammalian target of cellular rapamycin

YY1	yin yang 1
WAT	white adipose tissue

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TABLE 1

Metabolic disturbances associated with T2D – evolution from the “Triumvirate” to the “Ominous Octet” [73]

Traditional “Triumvirate” of Metabolic Defects in T2D	Additional Metabolic Defects Comprising the “Ominous Octet”
<ul style="list-style-type: none"> • Skeletal muscle insulin resistance • Excessive hepatic glucose production • Insufficient glucose-stimulated pancreatic beta-cell insulin secretion 	<ul style="list-style-type: none"> • Excessive release of free fatty acids by adipose tissues • Incretin deficiency/resistance (glucagon-like peptide-1 [GLP-1] deficiency and gastric inhibitory peptide [GIP] resistance) • Excessive release of glucagon by pancreatic alpha-cells • Dysregulated central nervous system control of insulin secretion and hepatic glucose output • Increased renal reabsorption of glucose

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