

Dairy Foods and Dairy Proteins in the Management of Type 2 Diabetes: A Systematic Review of the Clinical Evidence^{1,2}

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a growing public health concern affecting hundreds of millions of people worldwide and costing the global economy hundreds of billions of dollars annually. This chronic disease damages the blood vessels and increases the risk of other cardiometabolic ailments such as cardiovascular disease and stroke. If left unmanaged it can also lead to nerve damage, kidney damage, blindness, and amputation. For the most part, many of these symptoms can be prevented or reduced through simple dietary modifications and proper nutrition. Therefore, identifying relatively inexpensive and easily implementable dietary modifications for the prevention and management of T2DM is of considerable value to human health and healthcare modalities around the globe. Protein-rich dairy products have consistently been shown in epidemiologic studies to be beneficial for reducing the risk of developing T2DM. The clinical evidence regarding both dairy foods and dairy proteins (i.e., casein and whey protein) have shown promise for improving insulin secretion in individuals with T2DM. However, the clinical research on dairy protein supplementation in subjects with T2DM has been limited to acute studies. These studies have been mostly descriptive and have not been focused on important T2DM endpoints such as prevention, management, or treatment. Long-term studies are clearly needed to help researchers and medical professionals better understand the effects of consistent dairy protein intake on the metabolic health of humans with T2DM. *Adv Nutr* 2015;6:245–259.

Keywords: casein, cultured, dairy, fermented, glucose, insulin, milk, protein, type 2 diabetes, whey

Introduction

Type 2 diabetes mellitus (T2DM)³ is a global public health burden costing hundreds of billions of dollars annually and accounting for ~12% of all healthcare costs worldwide (1). Currently, T2DM has been estimated to afflict >350 million people globally, with projected increases to >550 million people by the year 2030 (2). The T2DM epidemic is a relatively new phenomenon, only occurring and spreading at unprecedented rates in recent history (3). Many millions of these cases could be prevented with proper dietary alterations alone (4–6). A large percentage of human dietary patterns and practices have also changed drastically in the last

few hundred years, with substantial increases in processed and refined foods and reductions in many of the nutritious staples that have traditionally sustained human populations for generations. The consumption of dairy products is one of civilization's oldest recorded dietary traditions, with these foods providing high-quality protein and several important micronutrients for various populations for over a millennium (7).

Certain chronic diseases such as T2DM create a domino effect that increases the risk of other chronic illnesses, along with several cardiometabolic risk factors such as obesity, hypertension, and dyslipidemia (8–10). The common effects of T2DM, such as an impaired insulin response and hyper- or hypoglycemia, can largely be modulated through nutrition and exercise. In Western countries, dietary modification and weight loss are the primary treatment options for individuals with T2DM, but there is still a tremendous amount of controversy surrounding the best nutrition advice and prescriptive diets for improved glycemic control. Therefore, identifying relatively inexpensive and easily implementable dietary modifications for the prevention and management of chronic and metabolic diseases is of considerable value

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³ Abbreviations used: BW, body weight; EAA, essential amino acid; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; iAUC, incremental area under the curve; T2DM, type 2 diabetes mellitus.

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to both human health and healthcare modalities around the globe.

The idea of milk as medicine is really not so far-fetched, because milk is nature's most complex food, containing all of the nutritional components necessary to support life and proper development. Additionally, milk contains numerous bioactive components such as digestion-resistant proteins (e.g., lysozyme, lactoferrin, and immunoglobulins) (11, 12), peptides [α -lactorphins, β -lactorphins, casokinins (13, 14), and oligosaccharides (15)] that can affect health and disease in ways that are only just being discovered. Of all the components in dairy milk, protein is the most abundant component linked to beneficial effects on several chronic disease risk factors (16) and reduced risk of T2DM (17, 18), whereas the naturally occurring lipids and carbohydrates in dairy products tend to be recognized as neutral factors (19–22).

Dairy proteins (i.e., casein and whey) are found in dairy foods such as milk, yogurt, and cheese, or they can be consumed as supplements in isolated or concentrated forms. When consumed in adequate amounts, casein or whey proteins provide differential health effects than when the same proteins are consumed as components of whole dairy products (16). Interestingly, casein and whey protein supplements contain fewer carbohydrates, fat, and calories by weight than whole dairy products such as milk and yogurt, but they have greater stimulatory effects on insulin and incretin secretion than their carbohydrate-containing counterparts. Additionally, the effects of whey protein in particular also tend to be less glycemic and more insulinogenic than all other regularly consumed protein-rich foods and supplements, such as milk, cheese, ham, soy, turkey, tuna, egg, egg white, casein, gluten, fish protein, and free amino acids (23–27). However, it should be noted that protein supplements do add calories to the diet, and this factor should be taken into account for overweight and obese populations who are trying to manage their weight.

The aim of this review is to examine the existing evidence from clinical trials investigating the effects of dairy foods and dairy proteins on the glycemic and insulinemic response of subjects with T2DM. Our primary search strategy (Figure 1) included the databases PubMed, EMBASE, Cab Abstracts, and Web of Science. Our secondary search strategy was to review the bibliographies of original research and review articles to harvest further applicable studies. Database searches were last conducted in August 2014. Eligible studies were included in this review if they were original works published in a peer-reviewed journal between the years 1984 and 2014. Studies were included if they involved adult participants ≥ 18 y with T2DM. All studies measured either milk, dairy products, or milk protein intake in at least one group of participants in a clinical setting (both controlled and not-controlled studies were included). Acute challenge studies, short-term studies (< 1 mo) and long-term studies (> 1 mo) were included. All included studies measured ≥ 1 quantitative outcomes relating to the target categories of blood glucose response or insulin response.

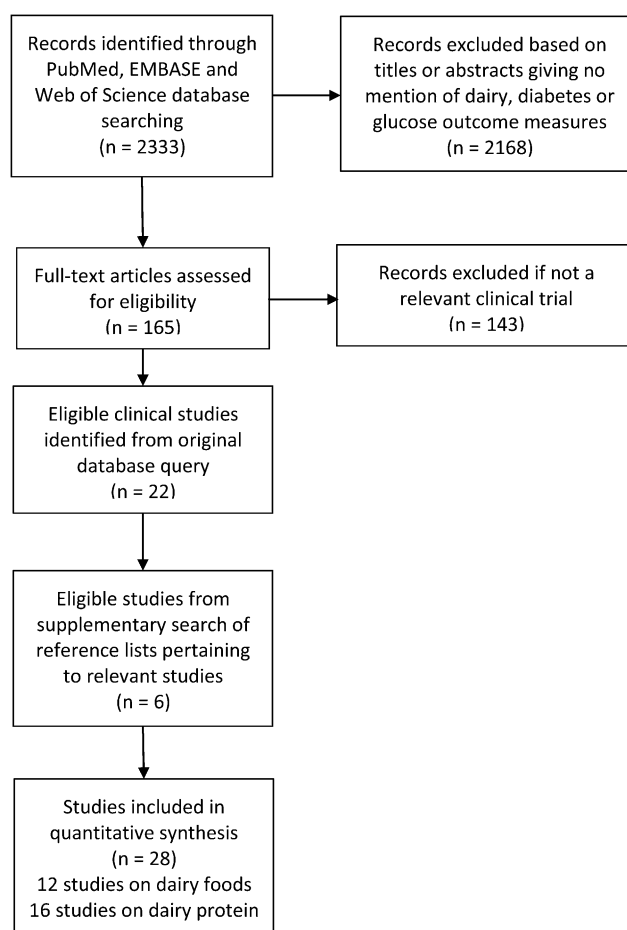


FIGURE 1 Flow chart of study selection process.

The PubMed database was used to search for relevant medical subject headings and general terms for the study population, exposures, and specific outcomes. Human milk and type 1 diabetes were excluded from the search. Initial searches were restricted to the data fields of title and abstract. Specific terms included in searches for the target population included the following: “Type 2 diabetes,” “diabetes,” “diabetes mellitus,” “diabetic,” “noninsulin-dependent,” and “NIDDM.” The following terms were used for interventions: “milk,” “dairy,” “kefir,” “yogurt,” “doogh,” “cheese,” “butter,” “whey,” and “casein.” We used the following terms for outcomes: “glucose,” “glycemic,” “glycemia/glycaemia,” “insulin,” “insulinemia/insulinaemia,” and “insulinemic.” Database searches yielded a total of 2333 seemingly relevant publications. Titles and abstracts of these studies were screened down to 165 potential studies for further evaluation with the use of the inclusion and exclusion criteria. After further review, 22 studies from the database searches met the full eligibility criteria, and another 6 studies were harvested from the reference pages of eligible studies. These 28 studies were then divided into 12 publications on dairy foods (i.e., milk, cheese, and yogurt/doogh) and 16 publications on dairy proteins (i.e., whey and casein).

Clinical Studies of Dairy Foods (Milk, Yogurt, and Cheese) in Subjects with T2DM

A large amount of the early work investigating the effects of high-protein dairy foods (i.e., milk, cheese, and yogurt) on insulin and glucose responses was pioneered by Gannon and Nuttall. These researchers have tested the effects of cottage cheese containing 25 g of protein against several other lean protein sources (i.e., turkey, lean beef, gelatin, egg white, fish, and soy) on glycemic responses to snacks and meals in subjects with T2DM (28–31). Over the last 4 decades, Gannon and Nuttall have collaborated on numerous studies investigating the effects of dietary modifications on glycemic control (32–37) and they have contributed greatly to our understanding of how shifts in the type, amount, and combination of macronutrients in the diet can modulate insulin secretion and glucose homeostasis.

Twelve studies investigated the effects of dairy foods such as milk, cheese, and yogurt on human subjects with T2DM dating back to 1984 (28–31, 38–45) (Table 1). The majority of these studies focused primarily on glycemic control and the direct effects of dairy foods on blood glucose, insulin, or incretins (28–31, 38, 40, 45), whereas the other studies focused primarily on related markers such as inflammatory markers, antioxidant status, endothelial biomarkers, and lipid profiles (39, 41–44). None of these studies addressed the specific amount or proportion of casein and whey protein in their intervention groups, but instead focused on the total amount of dairy protein consumed. Three of the 12 studies investigated the glycemic effects of adding milk to various types of meals (29, 38, 45), whereas 6 of these studies used probiotic yogurt as the intervention group (39–44), thereby introducing the effects of fermentation and various probiotic strains on T2DM as additional variables.

Fat-free milk. In 1986, Gannon et al. (29) published a seminal paper in the area of dairy and T2DM. The researchers tested the effects of fat-free milk containing 50 g carbohydrates (and 34 g protein) vs. 50 g carbohydrates from simple sugars (i.e., glucose, galactose, fructose, or lactose) on 7 subjects with a mean age of 64 ± 3 y. The researchers reported that they could accurately predict the glucose response to various meals based on the carbohydrate content of the meals in subjects with uncontrolled T2DM, but the insulin response was not accurately predictable based solely on carbohydrate form or amount in the meals. In other words, insulin response was not simply dependent on blood glucose fluctuations. For example, the insulin response from milk was 5-fold greater than predicted based on its glucose response, and it was significantly higher than from a beverage containing an equal amount of carbohydrate from lactose. In the end, there was no significant difference in glucose response between the milk and lactose groups, but both groups did show a significantly lower glucose response than did the glucose group. The authors attributed the differences in insulin

secretion between the milk and lactose meals to the insulinogenic effects of the protein in milk.

In opposition to those findings, Aro et al. (45) studied 10 subjects with T2DM and reported that when 3.3 cups (782 mL) of fat-free milk, containing 40 g carbohydrates (and 27 g protein) was consumed vs. 40 g lactose in water, the milk meal (i.e., protein + lactose) induced a lower insulin response than lactose alone. However, the milk and lactose meals both had similar effects on glucose response despite their differential influences on insulin secretion. It is unclear why the Aro et al. results differed so greatly from those of Gannon et al. (29), but the evidence from other studies on both healthy subjects and subjects with T2DM point toward a much larger insulinogenic effect from milk (i.e., protein + lactose) and milk proteins than from nondairy protein sources or simple sugars alone (23, 25, 27, 46). A limitation to these early studies is that they all used fat-free milk, and the line of study was not continued with other milk products or dosing designs. It would be valuable to see how different amounts of milk and different amounts of fat in commonly consumed milk varieties (i.e., 1%, 2%, and whole milk) affect glucose and insulin responses.

Cheese. Over the course of 10 y (1988–1998), Gannon further studied the insulin response of subjects with T2DM to protein-rich dairy foods in the form of cottage cheese (28, 30, 31). The researchers tested the effects of 25 g lean protein from cottage cheese vs. various other sources of lean protein (i.e., beef, turkey, fish, soy, and egg white) when coingested with 50 g glucose. In one study of 17 male subjects (28), it was reported that casein-rich cottage cheese and glucose meals were able to induce more insulin secretion than other lean-protein and glucose-equivalent test meals, although there was no difference in postprandial glucose concentrations between protein meals. Additionally, when the cottage cheese was coingested with 50 g glucose, it was able to induce a 3.6-fold greater insulin response than when 50 g glucose alone was consumed. In another study that compared the coingestion of 25 g protein from cottage cheese + 50 g glucose to 50 g glucose alone in 7 male subjects, the addition of cottage cheese to the glucose lowered the glycemic response by >10% compared with glucose alone (31). Furthermore, when the cottage cheese + glucose combination was compared with a similar amount of protein from egg white (25 g) + glucose (50 g), the insulin response was 3.6-fold higher in the cottage cheese + glucose group, despite a similar intake of calories, carbohydrates, fat, and protein between groups. Taken together with the earlier studies on fat-free milk, the data provide evidence that dairy foods containing ~25 g of protein can be potent insulin secretagogues and regulators of glycemic control when consumed with or without fat or carbohydrates. It should be noted that the cottage cheeses tested in these studies were all very low-fat varieties; it would be interesting to see how higher-fat cottage cheeses or other types of cheeses (especially those that have been cultured and aged) could affect insulin and glucose

TABLE 1 Clinical studies of dairy products (milk, cheese, and yogurt) in subjects with T2DM¹

Dairy product and reference	Study population and design	Intervention	Findings
Fat-free milk Uusitupa et al., 1984 (38)	10 subjects (7 male, 3 female) Age: 40–63 y BMI: N/A Acute challenge study; randomized, crossover	Subjects consumed an oatmeal breakfast (40 g oats, 10 g butter, and 2 g table salt), with 100 mL noncaloric soft drink, and either of the following: 1) 300 mL fat-free milk with the meal 2) 300 mL fat-free milk cooked into the meal	Blood glucose response was higher after the cooked milk meal than with the meal with milk taken separately. There were no differences in postprandial insulin concentrations.
Gannon et al., 1986 (29)	7 subjects (gender: N/A) Age: 64 ± 3 y BMI: 32.2 ± 1.7 kg/m ² Acute challenge study; randomized, controlled, crossover	Subjects consumed a meal consisting of 50 g carbohydrates from one of the following: 1) fat-free milk 2) glucose 3) ice cream 4) lactose	Blood glucose AUC was similar after ingestion of milk (containing 34 g protein + 50 g lactose) and 50 g lactose alone. Milk ingestion led to significantly higher insulin AUC compared with lactose alone. The insulin response from milk was ~5-fold greater than would be anticipated from its glucose response.
Aro et al., 1987 (45)	10 subjects (gender: N/A) Age: N/A BMI: N/A Acute challenge study; randomized, controlled, crossover	Subjects consumed a liquid meal containing 40 g carbohydrates from one of the following: 1) fat-free milk 2) lactose 3) glucose 4) fructose	Blood glucose responses were similar after the milk (containing 27 g protein + 40 g lactose) and 40 g lactose meals. The insulin response was significantly higher after the lactose and glucose meals than after the milk and fructose meals.
Cheese Gannon et al., 1988 (28)	17 male subjects Age: 63 ± 2 y BMI: 29 ± 1 kg/m ² Acute challenge study; randomized, double-blind, placebo-controlled, crossover	Subjects consumed a meal that contained 50 g glucose alone or 50 g glucose plus an additional 25 g protein from the following: 1) cottage cheese 2) lean beef 3) turkey 4) gelatin 5) egg white 6) fish 7) soy	There was no difference in postprandial glucose concentrations between any of the lean protein meals. Total insulin secretion was greatest following ingestion of the meal containing cottage cheese. Insulin secretion was 3.6 times higher from the glucose + cottage cheese meal than from 50 g glucose alone.
Gannon et al., 1992 (31)	7 male subjects Age: 68 ± 2.7 y BMI: 30 ± 1.3 kg/m ² Acute challenge study; randomized, controlled, crossover	Subjects consumed a breakfast meal that contained one of the following: 1) 50 g glucose alone 2) 25 g protein from cottage cheese 3) 25 g protein from egg white 4) 50 g glucose + 25 g protein from cottage cheese 5) 50 g glucose + 25 g protein from egg white	The glucose responses following ingestion of cottage cheese or egg white meals were not significantly different. The ingestion of 50 g glucose with cottage cheese or egg white protein decreased the glucose AUC by 11% and 20%, respectively. The serum insulin area response was 3.6-fold greater following ingestion of cottage cheese than with egg white.
Gannon et al., 1998 (30)	7 male subjects Age: 65 y BMI: 29 kg/m ² Acute challenge study; randomized, controlled, crossover	Subjects consumed 2 cups of decaffeinated coffee and a breakfast meal that contained one of the following: 1) 50 g glucose alone 2) 25 g fructose alone 3) 25 g protein from cottage cheese 4) 25 g fructose + 25 g protein from cottage cheese	The glucose concentration was only modestly increased and the AUCs were similar when cottage cheese, fructose, or the combination was ingested. The insulin AUC for cottage cheese was 2.5-fold greater than for fructose, and the insulin AUC for the fructose + cottage cheese meal was similar to the insulin AUC for 50 g glucose.

(Continued)

TABLE 1 (Continued)

Dairy product and reference	Study population and design	Intervention	Findings
Yogurt/doogh Shab-Bidar et al., 2011 (39)	100 subjects (43 male, 57 female) Age: 52.4 ± 8.4 y BMI: 29.3 ± 4.1 kg/m ² 12-wk study; randomized, double-blind, placebo-controlled	Subjects were assigned to consume 250 mL doogh twice a day (total = 500 mL/d) of either of the following: 1) vitamin D-fortified doogh 2) plain doogh	After 12 wk, consumption of the vitamin D-fortified doogh resulted in a significant improvement in fasting glucose compared with the plain doogh. Fasting insulin was significantly lower after 12 wk in both groups. There was a between-group intervention effect showing significantly lower fasting insulin concentrations in the vitamin D-fortified doogh group compared with the plain doogh group.
Nikooyeh et al., 2011 (40) Neyestani et al., 2012 (41) Heravifard et al., 2013 (42)	90 subjects (35 male, 55 female) Age: 50.7 ± 6.1 y BMI: 29.5 ± 5 kg/m ² 12-wk study; randomized, double-blind, controlled	Subjects were assigned to consume 250 mL doogh twice a day (total = 500 mL/d) of one of the following: 1) plain doogh 2) vitamin D-fortified doogh 3) vitamin D + calcium-fortified doogh	After 12 wk, daily intake of the vitamin D-fortified doogh, with or without added calcium, improved glycemic status compared with plain doogh. There was a significant decrease in serum glucose, insulin, HOMA-IR, and Hb A _{1c} in both the vitamin D-fortified doogh group and the vitamin D + calcium-fortified doogh group compared with the plain doogh group.
Ejtahed et al., 2011 (43) Ejtahed et al., 2012 (44)	60 subjects (23 male, 37 female) Age: 51 ± 7.5 y BMI: 29 ± 4.0 kg/m ² 6-wk study; randomized, double-blind, controlled	Participants consumed daily either of the following: 1) 300 g conventional yogurt containing <i>Lactobacillus bulgaricus</i> and <i>Streptococcus thermophilus</i> 2) 300 g probiotic yogurt containing <i>L. bulgaricus</i> , <i>S. thermophilus</i> , <i>Lactobacillus acidophilus</i> La5, and <i>Bifidobacterium lactis</i> Bb12	At the end of 6 wk, fasting blood glucose and Hb A _{1c} were significantly decreased in the probiotic yogurt group compared with the conventional group. Fasting insulin concentrations were not significantly different between groups at the end of the trial.

¹ Twelve publications produced from 9 different clinical studies, 1984–2013. Hb A_{1c}, glycated hemoglobin; N/A, not available; T2DM, type 2 diabetes mellitus.

response differently than low-fat cottage cheese. Further studies making use of a dose-response technique or longer-term study period would also add greatly to the understanding of how protein-rich dairy foods can affect insulin and glucose responses in subjects with T2DM.

Cultured dairy products (i.e., yogurt and doogh). Some of the latest clinical research in the area of dairy foods and T2DM has been conducted on a cultured milk product called doogh, which is similar to yogurt but more savory and often more carbonated than conventional yogurt. The recent studies on doogh have ranged from 6 to 12 wk in length and have included daily supplementation between 300 g/d and 500 mL/d of various fortified or cultured doogh products. In a study by Shab-Bidar et al. (39), the researchers tested the effects of 500 mL/d (2×250 mL/d) of a conventional vs. a vitamin D–fortified doogh beverage on 100 subjects (43 male and 57 female) for 12 wk. The researchers found that consumption of both beverages led to significantly lower fasting insulin concentrations after 12 wk compared with baseline concentrations, whereas only the vitamin D–fortified beverage led to a reduction in fasting glucose. Overall, the group consuming the vitamin D–fortified beverage had a significantly improved glycemic status compared with the conventional group; this effect was credited to the amelioration of poor vitamin D status in many of the participants in the vitamin D fortification group. Another 12 wk study with a similar intervention strategy (500 mL/d doogh) and dosing design (2×250 mL/d) was performed by Nikooyeh et al. (40) on 90 subjects (35 male and 55 female). This study differed from the study by Shab-Bidar et al., in that a calcium + vitamin D–fortified group was also tested. The study by Nikooyeh et al. reported that vitamin D fortification and calcium + vitamin D fortification led to significant improvements in glycemic control compared with a conventional doogh product. Additionally, a 6 wk study was performed by Ejtahed et al. (43) in 60 subjects (23 male and 37 female) that tested the effects of 300 g/d conventional yogurt vs. probiotic yogurt. Both yogurts contained *Lactobacillus bulgaricus* and *Streptococcus thermophiles*, but the probiotic yogurt was also enriched with strains of *Bifidobacterium lactis Bb12* and *Lactobacillus acidophilus La5*. The researchers reported that after 6 wk, the added probiotic strains improved fasting blood glucose and glycated hemoglobin (Hb A_{1c}) compared with the conventional group. However, fasting insulin concentrations were similar between the groups. Importantly, the data on yogurt/doogh and T2DM is limited, especially because there were no dairy-free control groups included in any of the studies. Additionally, the postprandial insulin and glucose responses were not measured in any of these studies. Therefore, there is no way to tell how these cultured dairy products affected insulin and glucose concentrations on a per-meal basis. Despite the inconsistencies in study design between the yogurt trials, such as the amount of yogurt consumed or the addition of vitamins, minerals, or probiotic strains, the results show the promise of beneficial effects

from fortified cultured dairy product consumption on glycemic control and related markers (i.e., HbA_{1c}, insulin sensitivity, lipoprotein concentrations, inflammatory molecules, endothelial biomarkers, and antioxidant status). Further studies on popular cultured dairy products such as conventional yogurts, Greek yogurt, and kefir would provide valuable insights on how various probiotic strains and nutrient fortifications may affect insulin and glucose responses differently than noncultured dairy products.

The studies on cultured (e.g., yogurt) and noncultured (e.g., milk, cottage cheese) dairy products have shown them to be uniquely insulinotropic and glucose-lowering foods with insulinemic indices ~3–6 times higher than expected based on their glycemic indices (47). In other words, these protein-rich dairy foods can directly stimulate the release of insulin from the pancreas independently of carbohydrate intake.

Clinical Studies of Dairy Proteins (Whey and Casein) in Subjects with T2DM

There have been numerous clinical studies on the dairy proteins—whey and casein—in healthy adults. Many of these studies have been conducted in athletes with an interest in outcome effects on muscle function, physical performance, and protein synthesis rates. There have also been dozens of clinical dairy protein studies investigating the chronic and acute effects on weight loss, glucose concentrations, and insulin secretion (16). However, many of these studies have been primarily focused on healthy or overweight populations with normal β cell function and without diagnosed metabolic disease. Overall, there have been several clinical studies providing evidence for positive metabolic effects with whey and/or casein protein ingestion (48), but only a few have investigated these protein fractions in subjects with T2DM, and all of the published dairy and T2DM clinical studies so far have been acute challenge studies or short-term trials.

Sixteen publications have reported on the effects of dairy proteins (whey and/or casein) in subjects with T2DM (24, 25, 49–62) (Table 2). These studies were all published between 2005 and 2014. The studies varied considerably in that they tested casein or whey protein doses ranging from 6 g to >100 g, with some assigning doses based on body weight (BW) and others assigning every subject to receive the same amount of protein. Additionally, some of the studies added variable types and amounts of carbohydrates to the test meals, whereas others did not. Most of the studies tested ~25–50 g casein or whey protein at a time. All but one of the clinical protein studies reported on subjects averaging between 55 and 65 y of age with BMIs between 24 and 30 kg/m².

Casein. Of the 16 clinical publications on whey and/or casein ingestion in subjects with T2DM reported here, 12 publications reported the effects of casein protein consumption on glucose and insulin responses (24, 49–51, 53, 54, 56–61). A majority of the clinical research on casein and T2DM has

TABLE 2 Clinical studies of dairy proteins (whey and casein) in subjects with T2DM¹

Dairy protein tested and reference	Study population and design	Intervention	Findings
Casein Manders et al., 2005 (57)	10 male subjects Age: 62 ± 2 y BMI: 27 ± 1 kg/m ² Acute challenge study; randomized, double-blind, placebo-controlled, crossover	Subjects were given continuous glucose infusions + repeated boluses of 2 mL/kg BW every 15 min for 165 min of either of the following: 1) 0.7 g carbohydrate · kg BW ⁻¹ · h ⁻¹ 2) 0.7 g carbohydrate · kg BW ⁻¹ · h ⁻¹ + 0.35 g · kg ⁻¹ · h ⁻¹ of a mixture consisting of 50% casein protein hydrolysate, 25% leucine, and 25% phenylalanine Subjects were given a single bolus of one of the following: 1) 0.7 g carbohydrate/kg BW 2) 0.7 g carbohydrate/kg BW + 0.35 g casein hydrolysate/kg BW 3) 0.7 g carbohydrate/kg BW + 0.35 g casein hydrolysate/kg BW + 0.1 g leucine/kg BW Subjects ingested 3 meals/d in a single 24 h period containing either of the following: 1) flavored water placebo 2) 0.3 g casein protein hydrolysate/kg BW + 0.1 g leucine/kg BW	Plasma glucose responses were lower in the carbohydrate + protein (casein + leucine + phenylalanine) group than in the carbohydrate alone group. Plasma insulin responses were higher in the carbohydrate + protein group than in the carbohydrate alone group. The glucose responses were lower in both the carbohydrate + casein, and the carbohydrate + casein + leucine groups, compared with the carbohydrate control. Plasma insulin responses were greater in the carbohydrate + casein, and carbohydrate + casein + leucine groups, compared with those in the carbohydrate control. The 24-h glucose concentrations in the casein + leucine group were significantly lower than with the water placebo group. The prevalence of hyperglycemia was significantly lower in the casein + leucine group than in the placebo group. Insulin was not measured in this study. Over 6 h, plasma glucose responses were lower after carbohydrate + casein ingestion than after the carbohydrate control. Plasma insulin concentrations were significantly higher in the carbohydrate + casein group than in the carbohydrate control. The 24-h glucose concentrations were similar between groups. Casein coingestion with each main meal did not reduce the prevalence of hyperglycemia. Insulin response was not reported in this study.
Manders et al., 2006 (59)	10 male subjects Age: 59.7 ± 2.6 y BMI: 26.8 ± 0.82 kg/m ² Acute challenge study; randomized, double-blind, placebo-controlled, crossover	Subjects were assigned to consume one of the following: 1) 80 g fat (control) 2) 80 g fat + 45 g carbohydrate 3) 80 g fat + 45 g casein 4) 80 g fat + 45 g carbohydrate + 45 g casein	The 45-g carbohydrate meal and the 45-g casein + 45-g carbohydrate meal caused a higher 8-h postprandial glucose response than the control or 45-g casein meals. The 45-g casein meal and the 45-g casein + 45-g carbohydrate meal increased 8 h insulin responses compared with the control meal. The largest insulin response was seen with the 45-g carbohydrate + 45-g casein meal.
Manders et al., 2006 (58)	11 male subjects Age: 58 ± 1 y BMI: 28 ± 1 kg/m ² Acute challenge study; randomized, double-blind, placebo-controlled, crossover	Subjects were given continuous glucose infusions + repeated boluses every 30 min for 6 h of either of the following: 1) 0.6 g carbohydrate · kg BW ⁻¹ · h ⁻¹ 2) 0.6 g carbohydrate · kg BW ⁻¹ · h ⁻¹ + 0.3 g · kg BW ⁻¹ · h ⁻¹ casein protein hydrolysate Subjects ingested 3 meals/d in a single 24 h period containing either of the following: 1) flavored water placebo 2) 0.4 g casein/kg BW	Over 6 h, plasma glucose responses were lower after carbohydrate + casein ingestion than after the carbohydrate control. Plasma insulin concentrations were significantly higher in the carbohydrate + casein group than in the carbohydrate control. The 24-h glucose concentrations were similar between groups. Casein coingestion with each main meal did not reduce the prevalence of hyperglycemia. Insulin response was not reported in this study.
Manders et al., 2008 (60)	10 male subjects Age: 68 ± 2 y BMI: 24.9 ± 0.4 kg/m ² Acute challenge study; randomized, double-blind, placebo-controlled crossover	Subjects were given continuous glucose infusions + repeated boluses every 30 min for 6 h of either of the following: 1) 0.6 g carbohydrate · kg BW ⁻¹ · h ⁻¹ 2) 0.6 g carbohydrate · kg BW ⁻¹ · h ⁻¹ + 0.3 g · kg BW ⁻¹ · h ⁻¹ casein protein hydrolysate Subjects ingested 3 meals/d in a single 24 h period containing either of the following: 1) flavored water placebo 2) 0.4 g casein/kg BW	Over 6 h, plasma glucose responses were lower after carbohydrate + casein ingestion than after the carbohydrate control. Plasma insulin concentrations were significantly higher in the carbohydrate + casein group than in the carbohydrate control. The 24-h glucose concentrations were similar between groups. Casein coingestion with each main meal did not reduce the prevalence of hyperglycemia. Insulin response was not reported in this study.
Manders et al., 2009 (53)	13 male subjects Age: 62 ± 2 y BMI: 28 ± 1 kg/m ² Acute challenge study; randomized, double-blind, placebo-controlled crossover	Subjects were given continuous glucose infusions + repeated boluses every 30 min for 6 h of either of the following: 1) 0.6 g carbohydrate · kg BW ⁻¹ · h ⁻¹ 2) 0.6 g carbohydrate · kg BW ⁻¹ · h ⁻¹ + 0.3 g · kg BW ⁻¹ · h ⁻¹ casein protein hydrolysate Subjects ingested 3 meals/d in a single 24 h period containing either of the following: 1) flavored water placebo 2) 0.4 g casein/kg BW	Over 6 h, plasma glucose responses were lower after carbohydrate + casein ingestion than after the carbohydrate control. Plasma insulin concentrations were significantly higher in the carbohydrate + casein group than in the carbohydrate control. The 24-h glucose concentrations were similar between groups. Casein coingestion with each main meal did not reduce the prevalence of hyperglycemia. Insulin response was not reported in this study.
Brader et al., 2010 (49)	11 subjects (7 male, 4 female) Age: 62.4 ± 3.9 y BMI: 28.9 ± 3.6 kg/m ² Acute challenge study; randomized, controlled, crossover	Subjects were assigned to consume one of the following: 1) 80 g fat (control) 2) 80 g fat + 45 g carbohydrate 3) 80 g fat + 45 g casein 4) 80 g fat + 45 g carbohydrate + 45 g casein	The 45-g carbohydrate meal and the 45-g casein + 45-g carbohydrate meal caused a higher 8-h postprandial glucose response than the control or 45-g casein meals. The 45-g casein meal and the 45-g casein + 45-g carbohydrate meal increased 8 h insulin responses compared with the control meal. The largest insulin response was seen with the 45-g carbohydrate + 45-g casein meal.

(Continued)

TABLE 2 (Continued)

Dairy protein tested and reference	Study population and design	Intervention	Findings
Geerts et al., 2011 (50)	36 subjects (27 male, 9 female) Age: 61.5 ± 5.1 y BMI: 28.1 ± 3.6 kg/m ² Acute challenge study; randomized, double-blind, placebo-controlled, partial crossover	Subjects were assigned to consume one of the following: 1) 35 g carbohydrate + 5 g fat placebo 2) placebo + 15 g unhydrolyzed casein 3) placebo + 15 g casein hydrolysate 4) placebo + 15 g casein hydrolysate + leucine	Both casein hydrolysate treatments (with leucine and without) caused lower 4-h postprandial plasma glucose concentrations compared with the placebo and unhydrolyzed casein meals. All casein meals caused higher 4-h postprandial insulin secretion than the placebo meal. The casein hydrolysate + leucine group showed the greatest insulin response.
Jonker et al., 2011 (51)	13 subjects (8 male, 5 female) Age: 58 ± 1 y BMI: 27.9 ± 0.9 kg/m ² Acute challenge study; randomized, placebo-controlled, double-blind	Subjects were assigned to consume one of the following: 1) 50 g carbohydrate + 0 g casein (control) 2) 50 g carbohydrate + 6 g casein 3) 50 g carbohydrate + 12 g casein	The 12-g casein meal decreased the 4-h postprandial glucose response compared with the control, whereas the 6-g dose did not. The 12-g casein dose increased peak insulin concentrations and the 4-h postprandial insulin response compared with the control, but the 6-g dose did not.
Manders et al., 2014 (61)	60 male subjects Age: 60 ± 1 y BMI: 30.2 ± 0.4 kg/m ² Acute challenge study; randomized, placebo-controlled, double-blind	Subjects were assigned to consume one of the following: 1) 0.7 g carbohydrate/kg BW 2) 0.7 g carbohydrate/kg BW + 0.3 g intact casein/kg BW 3) 0.7 g carbohydrate/kg BW + 0.3 g casein hydrolysate/kg BW	The plasma glucose responses were lower in both the carbohydrate + intact casein group and the carbohydrate + casein hydrolysate group than in the carbohydrate control. There was no difference in 4-h postprandial glucose response between casein groups. The insulin response was greater in the carbohydrate + intact casein group and the carbohydrate + casein hydrolysate group than in the carbohydrate control. There was no difference in 4-h postprandial insulin response between casein groups.
Whey and casein Tessari et al., 2007 (24)	12 subjects (7 male, 5 female) Age: 56.6 ± 2.3 y BMI: 24.3 ± 0.8 kg/m ² Acute challenge study; randomized, double-blind, controlled, crossover	Subjects consumed a 6-kcal/kg BW, 50% protein mixed meal containing 0.7 g protein/kg BW of one of the following: 1) mixture of free amino acids resembling the amino acid composition of micellar casein (amino acid control) 2) sweet whey protein isolate 3) micellar casein	3-h postprandial glucose AUCs were similar after whey protein and casein ingestion. Insulin response was greater with whey protein than with casein. GLP-1 response tended to be lower with casein than with whey protein. GIP concentrations were similar after whey and casein protein ingestion.
Mortensen et al., 2009 (54) and Mortensen et al., 2010 (56)	12 subjects (6 male, 6 female) Age: 64.6 ± 3.3 y BMI: 28.9 ± 3.7 kg/m ² Acute challenge study; randomized, crossover	Subjects consumed a meal containing 100 g butter, 45 g carbohydrates, and one of the following: 1) 45 g casein protein 2) 45 g whey protein 3) 45 g cod protein 4) 45 g gluten protein	The 8-h postprandial glucose AUC was lower after the whey meal than after the other protein meals. There were no significant differences reported in insulin, glucagon, GLP-1, and GIP responses between meals.

(Continued)

TABLE 2 (Continued)

Dairy protein tested and reference	Study population and design	Intervention	Findings
Whey Frid et al., 2005 (25)	14 subjects (8 male, 6 female) Age: 27–69 y BMI: 26.2 ± 3.1 kg/m ² Acute challenge study; randomized, crossover	Subjects consumed a breakfast meal consisting of 102 g white wheat bread and, 4 h later, a lunch meal containing 52.2 g mashed potatoes and 50 g meatballs, with one of the following at both meals: 1) 27.6 g whey protein 2) 96 g lean ham + 5 g lactose	There was no difference between groups in 3-h glucose AUC after breakfast. However, after lunch, the 3 h blood glucose AUC for the whey group was significantly reduced compared with the ham + lactose group. The insulin AUCs were higher after both breakfast and lunch when whey was included in the meal than with ham + lactose. Two-hour postprandial breakfast GIP AUC and 3-h postprandial lunch GIP AUCs were higher after whey ingestion than with ham + lactose. There were no differences reported in GLP-1 concentrations.
Ma et al., 2009 (52)	8 subjects (7 male, 1 female) Age: 58 ± 3 y BMI: 28.6 ± 1.3 kg/m ² Acute challenge study; randomized, controlled, crossover	Subjects consumed a preload meal of 350 mL beef soup and, 30 min later, a potato meal, with one of the following: 1) 55 g whey protein with preload meal 2) 55 g whey protein with potato meal 3) no whey protein at either meal (control)	The 5-h postprandial blood glucose response was similar between the whey protein preload and whey protein with meal. Both whey trials resulted in lower blood glucose responses than the no whey group. The 5-h postprandial insulin AUC was similar between the whey protein preload and whey protein with meal. Both whey protein trials resulted in higher insulin responses than the no whey protein group.
Mortensen et al., 2012 (55)	12 subjects (5 male, 7 female) Age: 65.8 ± 5.3 y BMI: 28.2 ± 5.3 kg/m ² Acute challenge study; randomized, single-blind, crossover	Subjects consumed a meal containing 100 g butter, 45 g carbohydrates, and one of the following: 1) 45 g whey protein isolate 2) 45 g whey protein hydrolysate 3) 45 g whey protein with α -lactalbumin 4) 45 g whey protein with caseinoglycomacropeptide Subjects were assigned to consume either of the following, followed by a 353 kcal high glycemic index breakfast: 1) 50 g whey protein 2) water-placebo	GIP concentrations were higher in the whey protein preload and whey protein meal than in the no whey protein group. GLP-1 was greatest during the 90 min after the whey protein preload. Over 3 h, the glucose response was significantly lower after the whey + caseinoglycomacropeptide meal than with the whey protein hydrolysate meal. Over 8 h, 45 g whey protein isolate and 45 g whey protein hydrolysate led to higher insulin responses compared with 45 g whey + α -lactalbumin or 45 g whey + caseinoglycomacropeptide. Over 3 h, glucose concentrations were reduced after whey protein preload compared with the placebo. Insulin response was higher with whey protein preload than with the placebo. Both total GLP-1 and intact GLP-1 concentrations were significantly higher with the whey protein preload than with the placebo.
Jakubowicz et al. 2014 (62)	15 subjects (9 male, 6 female) Age: 64.1 ± 1.4 y BMI: 26.7 ± 1.2 kg/m ² Acute challenge study; randomized, open label, placebo-controlled, crossover		

¹ Sixteen publications produced from 15 different clinical studies, 2005–2014. BW, body weight; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic peptide; T2DM, type 2 diabetes mellitus.

been reported by Manders et al. (53, 57–61). These researchers used various study designs, including different challenge doses and dosing regimens, various forms of casein, and additional amino acid mixtures. The researchers often used a carbohydrate control beverage while testing the effects of casein and carbohydrate coingestion on postprandial glucose and insulin responses up to 24 h after ingestion. They reported that in subjects with T2DM, casein coingested with carbohydrates significantly increases insulin response and blood glucose disposal, thereby reducing the postprandial rise in blood glucose associated with carbohydrate intake (57, 59–61). The researchers also found that adding the branched-chain amino acid (BCAA) leucine to casein will increase the insulin response and glucose disposal values to a greater extent than will casein coingestion alone, suggesting that the extra leucine naturally present in whey protein may be a major factor in its greater insulin secretagogue abilities over casein and other lower leucine-containing proteins. Manders et al. (53) provided further evidence for leucine's insulin stimulating abilities by testing the effects of casein hydrolysate with and without leucine intake versus a water placebo with 3 daily meals. When testing 0.4 g casein/kg BW vs. the placebo, the researchers found no significant differences in blood glucose concentrations over 24 h (8.9 ± 0.8 vs. 9.2 ± 0.7 mmol/L, respectively; $P > 0.05$). However, in a separate study in which they added 0.1 g leucine/kg BW to 0.3 g casein hydrolysate/kg BW, they reported significantly lower 24 h glucose concentrations in the intervention group vs. the water placebo (9.6 ± 0.6 vs. 10.8 ± 0.5 mmol/L, respectively; $P < 0.05$) (58).

Brader et al. (49) investigated the acute effect of consuming 45 g casein added to a high-fat control meal (80 g fat from butter) and to a fat control + carbohydrate-rich meal (80 g fat from butter + 45 g carbohydrates from white bread) in 11 subjects (7 male and 4 female) with well-controlled T2DM. Both the high-fat meal and the high-fat + carbohydrate meal were tested with and without casein, and measurements were taken for 8 h after the meal. The investigators reported that the fat + carbohydrate meal and the fat + casein meal led to a significantly higher incremental area under the curve (iAUC) for insulin compared with the fat control, whereas the fat + carbohydrate + casein meal led to the highest insulin iAUC of all meals tested. The iAUCs for glucagon were significantly higher for both casein-containing meals compared with the meals without casein, whereas only the fat + carbohydrate + casein meal showed a higher glucose-dependent insulinotropic peptide (GIP) iAUC than the fat control meal. The researchers concluded that casein did not appear to modulate incretin secretion, but that the combination of casein and carbohydrate led to an additive insulinotropic effect, potentially because of a nonincretin-dependent mechanism. However, whether the similar incretin response between all interventions tested was from the large dose of fat in the meals or from a signaling impairment of the study population because of their diabetes was inconclusive. The casein group did show a more pronounced secretion of glucagon than did the fat control and fat + carbohydrate groups, which

may have led to the higher insulin concentrations, given that glucagon is another factor that can directly stimulate insulin secretion (49).

A study by Jonker et al. (51) of 13 subjects (8 male and 5 female) investigated the effects of low doses of casein hydrolysate (6 or 12 g) coingested with 50 g carbohydrates vs. a 50 g carbohydrate control, to determine if low casein doses could influence glucose and insulin responses. The researchers reported that a 12 g dose significantly increased postchallenge peak insulin concentrations compared with the control, and also decreased the glucose response over time. No significant effects were seen for the 12 g dose on the total AUCs for glucose and insulin, nor for any measure relating to the 6 g dose. Geerts et al. (50) investigated the effects of higher casein doses in 36 subjects (27 male and 9 female). The researchers monitored the 4 h postprandial effects of a single meal replacement (35 g carbohydrates and 5 g fat), and either 15 g unhydrolyzed casein, 15 g hydrolyzed casein, or 15 g hydrolyzed casein + 5 g leucine. Interestingly, the unhydrolyzed casein increased insulin concentrations (36.0% above placebo) more than the hydrolyzed casein (26.1% above placebo) but less than the hydrolyzed casein with leucine (51.8% above placebo), once again showing that leucine is a potent stimulator of insulin secretion. However, the unhydrolyzed casein did not affect glucose concentrations compared with the carbohydrate and fat control, whereas the hydrolyzed casein with or without leucine similarly lowered glucose by 4.7% ($P < 0.005$). These results suggest that some other factor besides total insulin secretion may be affecting glucose concentrations in this population. The 4-h postprandial glucagon concentrations were similar between all protein intervention groups, increasing by ~14% above the placebo in this study. The evidence that the hydrolyzed casein lowered glycemic response despite a higher caloric load shows great promise for the glucose-lowering potential of casein supplementation for individuals with T2DM.

Whey protein. Seven of the 16 clinical publications on whey and/or casein ingestion in subjects with T2DM reported on the insulin- and glucose-related effects of whey protein consumption in subjects with T2DM (24, 25, 52, 54–56, 62). The first of these publications was by Frid et al. in 2005 (25). They investigated the effects of 18 g whey protein or lean ham + lactose added to both a high-glycemic breakfast (white wheat bread) and lunch meal (instant mashed potatoes and meatballs) in 14 subjects (8 male and 6 female) aged 27–69 y. After the breakfast meal, 3 h AUC insulin secretion was reported to be 31% higher with whey protein intake than ham intake, but there was no difference in glucose concentrations between groups. However, after the lunch meal, whey protein led to a 57% higher 3 h AUC insulin secretion, while also significantly reducing 3 h AUC glucose concentrations by ~21%. Additionally, whey protein led to higher GIP concentrations after both meals than did ham + lactose, but no differences were seen with glucagon-like peptide 1 (GLP-1) response. The lower insulin response

after breakfast may be due to several factors such as increased insulin resistance in the morning or the different quality of macronutrients between the breakfast and lunch meals. Although this was an acute study, it provided important evidence that the timing of whey protein ingestion during the day may affect its abilities to moderate postprandial insulin and glucose concentrations or its effects at the next meal. A study by Ma et al. (52) further investigated the effects of timing on whey protein ingestion and insulin response in 8 subjects (7 male and 1 female). The researchers tested the effects of consuming 55 g whey protein 30 min before a high-glycemic meal vs. consuming the protein with the high-glycemic meal vs. the high glycemic control meal alone. The researchers reported that, compared with the control meal, insulin, GLP-1, and GIP iAUC were all higher when subjects consumed whey protein before the meal ($P < 0.05$), and also when they consumed it with the meal ($P < 0.005$). However, GLP-1 was also significantly higher through the 90 min postprandial mark when the whey protein was consumed 30 min before the meal than it was when it was consumed with a meal ($P < 0.0001$). Interestingly, gastric emptying was also the slowest when whey protein was consumed 30 min before the meal than it was when whey was consumed with a meal or not consumed at all. Overall, postprandial blood glucose concentrations were significantly lower in both whey protein meals than when no whey was consumed ($P < 0.005$ for both).

Mortensen et al. (55) tested the effects of 45 g of 4 different varieties of whey protein (whey isolate, whey hydrolysate, α -lactalbumin-enhanced whey, and caseinoglycomacropeptide-enhanced whey) in conjunction with a fat- and carbohydrate-rich meal in 12 subjects (5 male and 7 female). The researchers collected data over an 8 h postprandial period, and reported that the initial insulin response in the first 30 min was significantly higher after the whey hydrolysate was added to a meal than it was with the 3 other whey protein groups ($P < 0.001$). Additionally, both the whey hydrolysate and the whey isolate produced significantly higher 8 h iAUC insulin responses than the other 2 “peptide-enhanced” whey protein supplements ($P < 0.001$). However, somewhat counter-intuitively, the iAUC for glucose through the 2 h mark was significantly higher in the whey hydrolysate group (i.e., the highest insulin secreting group) than in the caseinoglycomacropeptide-enhanced whey protein group (i.e., the lowest insulin-secreting group) ($P < 0.035$). The whey hydrolysate group also had the lowest initial GIP response through 60 min and the highest GLP-1 through the first 30 min of testing, showing important yet divergent effects of different whey protein preparations on insulin, glucose, and incretins when added to a high-fat, high-carbohydrate meal in subjects with T2DM.

Most recently, Jakubowicz et al. (62) performed a study on 15 subjects (9 male and 6 female) investigating the postprandial effects of ingesting 50 g whey protein concentrate or a noncalorically matched water control 30 min before consuming a 353 calorie high-glycemic breakfast. The results showed that consuming whey protein before a high-glycemic

meal significantly increased early insulin release by 52% over consuming the same meal with a placebo preload. Over the course of 3 h, plasma total insulin concentrations in the whey protein preload group were also significantly higher than after the placebo. Additionally, despite taking in ~200 kcal more before their meal, the whey protein supplement group had a reduced glucose excursion over the course of testing and a 28% reduction in postprandial glucose concentrations over the course of 3 h. In this study, whey protein supplementation also led to higher GLP-1 concentrations throughout the testing period, with the most profound effects in the first 30 min after the meal was consumed. Both GLP-1 and insulin are known appetite-suppressing hormones (63, 64). Although this study did not use a calorie-equivalent control group, it did show that whey protein, when used as an additional supplement to a meal instead of a replacement for part of a meal, can help manage postprandial blood sugar and improve the secretion of multiple anorectic hormones. These are both key concepts for the management of T2DM in free-living populations. It shows that a dose of premeal whey protein could potentially reduce dependency on insulin therapy and also prolong appetite suppression, thereby reducing the potential for energy intake from other less nutritious calorie sources.

Casein vs. whey protein. Very few of the studies of dairy proteins and T2DM compared casein to whey protein, and none of them were long-term or dose-response studies. In 2007, Tessari et al. (24) performed a challenge study with the use of 12 subjects (5 female and 7 male) that investigated the effects of a mixed meal (6 kcal/kg BW) with an additional 0.7 g protein/kg BW of the following: 1) whey isolate; 2) micellar casein; or 3) a free amino acid control meal. The protein dose of 0.7 g protein/kg BW was on average roughly equivalent to 40–55 g protein per meal. The results over the 3 hr postprandial period showed significantly higher ($P < 0.0001$) essential amino acid (EAA) and BCAA concentrations with whey protein consumption than with casein or the amino acid control. The whey protein group also tended to have higher concentrations of insulin and GLP-1 and similar concentrations of circulating GIP and glucose than did the casein group. The similar concentrations of glucose between the whey and casein groups are of interest here, because they show that, despite the improved β cell function with whey, the cells responsible for glucose uptake may still not be able to compensate for the extra insulin secreted. A separate study by Mortensen et al. (54, 56) involving 12 subjects (7 female and 5 male) compared the effects of a fat- and carbohydrate-rich meal with 45 g of either whey, casein, gluten, or cod protein. In contrast with the study by Tessari et al. (24), the glucose response was lower after the whey challenge than after casein, wheat, or cod protein despite the fact that there were no significant differences between insulin, glucagon, and incretin responses. The differences in these findings may be because of the length of postprandial data collection between the 2 studies, which differed by several hours, with Mortensen et al. (54) extending their

testing to the 8 h mark. Additionally, the composition of the mixed meals in the studies by Tessari et al. and Mortensen et al. differed considerably in fat content, which could have altered gastric emptying rates and therefore circulating amino acid concentrations and their insulin signaling abilities. Interestingly, the study by Mortensen et al. (54) did show that, compared with other proteins, adding whey to a high-fat meal also reduced fat-induced postprandial lipemia, which could have beneficial implications for subjects with T2DM.

The clinical research on whey protein in subjects with T2DM has been more promising than the clinical work on casein for the modulation of several chronic disease risk factors. The specific effects of whey on T2DM are likely due to multiple factors: 1) its relatively fast digestion and absorption; 2) its particular amino acid profile, which is rich in BCAAs; and 3) its unique complement of bioactive proteins and peptides. Evidence for the insulinogenic potency of these peptides has been provided by studies showing that hydrolyzing whey proteins, and thereby producing more bioactive peptide fragments, can lead to a significantly greater insulin response than consuming fully intact whey protein (65). We have discussed the direct mechanisms, such as improvements in islet secretion and glycemic control, in detail. However, indirect mechanisms, most likely from long-term dairy protein supplementation, may also mitigate several symptoms of T2DM and necessitate further study. For example, the potential effects of improved weight loss (i.e., fat loss and lean-mass retention) with whey protein supplementation; increased satiety signaling and therefore reduced or more controlled eating patterns with whey protein supplementation; and the consistent thermogenic effects from regular whey protein intake could all additively benefit glycemic control and overall health (66).

Previously, researchers have suggested that the acute effects of whey protein consumed with or before a meal have effects that are comparable to other insulin medications such as sulfonylureas for the management of hyperglycemia in patients with T2DM (16, 52, 62). So far, these promising results have only been shown in acute studies, but not in long-term clinical studies. Although most clinical studies have shown the beneficial effects of whey protein while testing dosages of 25–50 g/d, the data are not sufficient to make any final recommendations in regard to a specific whey protein dosage or duration of supplementation. So far, the short-term clinical evidence and the epidemiologic evidence tend to agree that dairy proteins are beneficial for T2DM, but long-term clinical studies are necessary to confirm the proper dosing, safety, and efficacy of consistent dairy protein supplement consumption.

Conclusions

The current body of epidemiologic research on dairy foods and T2DM has shown promise for the increased use of dairy foods in reducing the risk of T2DM (16, 67–69). There have only been a few long-term clinical studies on dairy intake and T2DM. These studies primarily have focused on a

type of Middle Eastern yogurt drink called doogh, which contains both whey and casein and also has undergone a fermentation process. The general results from the doogh studies revealed that daily fortified yogurt supplementation could improve glycemic status in adults with T2DM, and that many of the beneficial effects on glycemic control appeared to be dependent on factors such as vitamin D fortification and the addition of certain probiotic strains (40, 44). The effects of the specific dairy proteins in the yogurt were not clear, because they could not be singled out from the food as a whole.

In regard to the dairy proteins casein and whey, limited clinical evidence shows the most promise from the use of ~25–50 g whey protein/d in the management of T2DM. However, the clinical studies on dairy protein and T2DM are all short-term studies and have used mixed populations containing subjects with controlled and uncontrolled T2DM with different degrees of insulin resistance, β cell function, and body fat. These studies have been mostly descriptive and have not been focused on important T2DM endpoints, such as the prevention, management, or treatment of T2DM. The effects of long-term dairy protein supplementation on T2DM are unknown and there is need for research in this area.

Currently, there are 2 clinical studies investigating the effects of long-term whey protein supplementation in the management of T2DM (70, 71). One of these studies is a randomized, double-blind, 3-mo-long intervention trial being performed in the United States at the University of California, Davis Medical Center by Karakas (70). The other study is also a 3-mo intervention trial. It is being performed in Israel at Tel Aviv University by Jakubowicz (71). Both of these studies should contribute greatly to the body of knowledge regarding long-term whey protein supplementation and management of glycemic control in adults with T2DM.

It is important to understand that the proteins, peptides, and amino acids in dairy products are just some of the many components that make up nature's most complex food, milk. But of all of the innately occurring components in dairy foods, the protein fractions shows the most promise for beneficially modulating the metabolic health of human adults, whereas the fat and carbohydrate contents appear to be less influential. These "innately occurring components," however, do not include the probiotics or bioactive end-products in cultured dairy products such as yogurt, doogh, and kefir; these probiotic strains are not considered to be "innate," because they are added to milk after the initial production stage. The addition of specific probiotic strains and the resulting fermentation process has shown promise for modulating inflammation, metabolism, and glycemic control in individuals with T2DM. Clinical evidence suggests that cultured dairy foods may not evoke as large an insulin or incretin response as isolated or concentrated dairy proteins, but nonetheless may greatly improve glycemic status.

Although dairy foods (i.e., milk, yogurt, and cheese) and dairy proteins (i.e., casein and whey) share many functional properties and physiologic effects, it is likely that they differ

in their metabolic effects primarily because of differences in their absorption kinetics, micronutrient content, and concentration of bioactive components. The benefits of dairy foods on insulin secretion and glycemic control appear to come primarily from the following: 1) an amino acid profile rich in EAAs; 2) specific combinations of macronutrients and micronutrients; and 3) unique probiotic strains and fermentation end-products found in cultured products such as cheese and yogurt. However, the specific insulinogenic and glycemic effects from the consumption of the dairy proteins in the whey fraction of milk primarily come from the following: 1) a unique amino acid profile rich in EAAs and BCAAs; 2) a fast digestion and absorption rate; and 3) a relatively concentrated bioactive peptide profile compared with whole dairy foods.

The consistent consumption of protein-rich dairy foods, cultured dairy foods, and/or dairy protein supplements may likely work to improve the glycemic health of many individuals with T2DM, with the caveat that different disease states would require different and individualized doses. T2DM is a heterogeneous disease with multiple pathophysiologies, so there is no reason to believe that one food, supplement, or medicine is going to work for everyone. For example, regularly increasing insulin secretion through whey protein consumption may be contraindicated in chronically hyperinsulinemic individuals, or in inactive and obese populations with T2DM. On the other hand, improving insulin and incretin secretion through whey ingestion directly before a meal may be the best therapy for active and/or nonobese individuals with impaired β cell sensing and signaling functions, whether they have T2DM or not. Given cultured dairy products' long history of safe use, and whey protein's overall efficacy in clinical studies so far, these dairy products appear to have great potential to assist with the management of T2DM in millions of people worldwide, in an inexpensive and easily implementable manner.

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