Effect of Dairy Proteins on Appetite, Energy Expenditure, Body Weight, and Composition: a Review of the Evidence from Controlled Clinical Trials[1]

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ABSTRACT

Evidence supports that a high proportion of calories from protein increases weight loss and prevents weight (re)gain. Proteins are known to induce satiety, increase secretion of gastrointestinal hormones, and increase diet-induced thermogenesis, but less is known about whether various types of proteins exert different metabolic effects. In the Western world, dairy protein, which consists of 80% casein and 20% whey, is a large contributor to our daily protein intake. Casein and whey differ in absorption and digestion rates, with casein being a "slow" protein and whey being a "fast" protein. In addition, they differ in amino acid composition. This review examines whether casein, whey, and other protein sources exert different metabolic effects and targets to clarify the underlying mechanisms. Data indicate that whey is more satiating in the short term, whereas casein is more satiating in the long term. In addition, some studies indicate that whey stimulates the secretion of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide more than other proteins. However, for the satiety (cholecystokinin and peptide YY) and hunger-stimulating (ghrelin) hormones, no clear evidence exists that 1 protein source has a greater stimulating effect compared with others. Likewise, no clear evidence exists that 1 protein source results in higher diet-induced thermogenesis and promotes more beneficial changes in body weight and composition compared with other protein sources. However, data indicate that amino acid composition, rate of absorption, and protein/food texture may be important factors for protein-stimulated metabolic effects. *Adv. Nutr. 4: 418–438, 2013.*

Introduction

With the increasing prevalence of obesity and metabolic disorders, much effort has been placed in the study of the obesogenic and metabolic effects of specific micro- and macronutrients. Dietary proteins, in particular, have been studied extensively during recent years, and accumulating evidence supports that a high proportion of dietary energy from protein increases weight loss and prevents weight (re)gain (1–3). The beneficial effect of a high-protein intake seems to be due to increased diet-induced thermogenesis (DIT)[4] (4), increased satiety (3,5) and decreased hunger (2), which is suggested to be mediated through gastrointestinal (GI) hormones. Proteins have unique characteristics related to its source, content of amino acids, and absorption kinetics. It is therefore speculated that proteins from different sources have diverse metabolic effects (6), and some evidence exists that different protein sources differ in their satiating capacity (7–9). In the Western world, dairy products are a major source of dietary protein, and some studies have shown promising effects of dairy consumption on body weight and composition (10,11). However, results are conflicting, and evidence from 2 recent meta-analyses (12,13) indicates that dairy intake combined with energy restriction, but not combined with ad libitum diets, may favor weight loss.

Dairy protein is made up of 2 major classes of proteins: casein (80%) and whey (20%). Bovine casein consists of α_{s1}- (~37%), α_{s2}- (~10%), β- (~35%), and κ-caseins (~12%). Caseins are phosphoproteins that precipitate from raw milk by acidification. The phosphoproteins are dispersed in milk in the form of micelles that are stabilized

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[4] Abbreviations used: αlac, α-lactalbumin; BCAA, branched-chain amino acids; CCK, cholecystokinin; DIT, diet-induced thermogenesis; E%, energy percent; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GMP, glycomacropeptide; PYY, peptide YY; RQ, respiratory quotient; VAS, visual analogue scale.

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by κ-caseins. The casein micelle granules are maintained as a colloidal suspension in milk. In contrast, whey proteins are the proteins that remain soluble after precipitation of casein and consist of ~50% β-lactoglobulin, 20% α-lactalbumin (αlac), 10% albumin, and lactoferrin with lactoperoxidase making up the rest (14–16). Casein and whey are both complete proteins containing all essential amino acids, but they differ in the way in which they are digested and absorbed. The concept of "slow" and "fast" proteins was introduced by Boirie et al. (17) in 1997. Casein, unlike whey, coagulates in the acidic environment in the stomach, which delays its gastric emptying and induces a slow postprandial increase in plasma amino acids. Whey, on the contrary, induces a fast, high, and transient increase in plasma amino acids (17). Some studies have suggested that whey is more satiating than casein (7,18). Furthermore, it is suggested that whey and casein may affect DIT and body weight to different extents (9,19).

The aim of this review is to examine the existing evidence from controlled clinical trials investigating the effects of consumption of dairy protein (total dairy protein, whey, and/or casein) and other protein sources on appetite regulation, energy expenditure, body weight, and body composition. Furthermore, the review aims to elucidate the potential mechanisms underlying the protein-specific effects.

Studies eligible for inclusion in this review were identified by searching 6 electronic databases (PubMed, Web of Sciences, MEDLINE, EMBASE, Cab Abstracts, and Cochrane Library) for controlled clinical trials examining the effects of dairy proteins, whey, and/or casein on appetite, GI hormones, energy expenditure, body weight, and body composition in healthy humans. Included studies are presented in **Table 1** (appetite), **Table 2** (energy expenditure), and **Table 3** (body weight and composition).

Appetite

Protein is more satiating than fat and carbohydrate (5,20–27), but the effect may be source dependent. Several studies have examined the appetite-regulating effect of proteins (Table 1). No clear evidence exists that 1 protein source is more satiating than others. However, discrepant results may be explained by different study designs, including timing of measurements, protein structure, and food texture. Whey consumption has shown promising effects in several health aspects, such as obesity and type 2 diabetes (28), and it could be speculated that part of this effect is due to the satiating effect of whey. The satiating effect of whey has been examined and compared with that of casein and other protein sources in several studies using a visual analogue scale (VAS), ad libitum energy intake, and measurement of postprandial GI hormone responses (Table 1).

Protein quality

The most important factor determining protein quality is its amino acid composition. Whey has a high content of essential and branched-chain amino acids (BCAAs), which is likely the reason that it is highly effective at promoting protein synthesis (29). In addition, whey contains the bioactive components glycomacropeptide (GMP), αlac, and other minor abundant components such as lactoferrin and lactoperoxidase. GMP is a carbohydrate-containing peptide derived from κ-casein during cheese making and extracted into the whey fraction. It has a high content of BCAAs and is potentially an effective secretagogue of cholecystokinin (CCK), which is secreted in the gut in response to food intake and acts as a satiety signal (30). In accordance, Veldhorst et al. (31) demonstrated an increased energy intake after consumption of a GMP-depleted whey supplement compared with consumption of whey alone. However, most data on subjective feelings of appetite indicate that GMP is not critical for whey-induced satiety (30–34) or for whey induced decreases in energy intake (30,32,33).

The fraction of αlac makes up ~20% of whey (14) and 3.4% of total protein in bovine milk (35). It has been hypothesized that αlac has a beneficial effect on satiety owing to a high content of essential amino acids such as leucine, lysine, and tryptophan (35–37). Tryptophan is a precursor of the neurotransmitter serotonin, which acts as an anorexigenic signal in the brain stimulating satiety. Leucine and lysine are ketogenic amino acids, and it has been shown that appetite decreases under ketogenic conditions (21). In support, data on αlac indicate a satiating effect beyond that of whey when appetite measures are obtained by VAS (34,36) and ad libitum energy intake 180 min after protein consumption (34). However, only a few studies have been conducted, and it is still not clear whether the effect persists over time.

Furthermore, whey has been found to increase satiety compared with protein from tuna, turkey (8), and egg (8,38) when measured by VAS or ad libitum energy intake. In addition to whey, casein is also a complete protein. Moreover, soy is often classified as a complete protein, despite a much lower content of essential amino acids than the dairy proteins (39). As shown in Table 1, data from several studies indicate no difference in satiety between these 3 proteins in both acute and long-term settings (34,40–47). However, Veldhorst et al. (18) studied the appetite-regulating effects of whey, casein, and soy at 10 energy percent (E%) and 25 E% from protein given as custards at breakfast. They found whey to decrease hunger compared with casein and soy at the low dose, but they observed no difference at the high dose. Moreover, there was no difference between casein and soy at both doses, and ad libitum energy intake did not differ between any of the proteins. Veldhorst et al. (18) propose that the concentration of certain amino acids needs to be above a particular threshold to promote a relatively stronger hunger suppression or greater satiety. Their results suggest that certain proteins will reach these threshold concentrations at lower concentrations than other sources of proteins. At high protein concentrations, it may not be possible to discriminate between complete proteins because the amino acid concentrations are above the threshold for all protein sources. In most of the studies comparing whey, casein, and soy, the protein concentration is >10 E% (Table 1),

Table 1. Controlled clinical trials with appetite ratings, energy intake and/or GI hormone response as outcome[1]

		Intervention			Outcome[2]	
Reference	Popopulation	Design	Diet	EI	Appetite (VAS)	GI hormones
Acheson et al. 2011 (9) (Switzerland)	23 lean men and women	Randomized, double-blind, crossover (MT)[3]	Meals (shakes), energy density 1 kcal/g (459 kcal): whey, casein, soy (all 50 E% P) or CHO (isocaloric)	—	330 min (AUC): Desire to eat, hunger, and prospective food consumption: whey > casein ($P < 0.005$), whey > soy ($P < 0.01$), casein = soy Fullness: casein > whey ($P < 0.005$), soy > whey ($P < 0.01$), casein = soy	—
Akhavan et al. 2010 (60) (Canada)	Study I: 16 men Study II: 22 men and women	2 randomized, crossover studies (MT)	300-mL liquid preloads (~50 kcal): Study I: whey (10, 20, 30, or 40 g) or water Study II: whey (5, 10, 20 g), WPH (10 g) or water	Ad libitum meal after 30 min (study I): 10 g whey = 20 g whey = 30 g whey = 40 g whey	95 min (study I) and 170 min (study II): Appetite: study I: 10 g whey = 20 g whey = 30 g whey = 40 g whey; study II: 5 g whey = 10 g whey = 20 g whey = 40 g whey; study II: 10 g whey = 10 g WPH	—
Alfenas et al. 2010 (42) (Brazil)	26 normal-weight men and women 24 completed the first 3 sessions, only 10 completed the soy session	Randomized, crossover (7 d)	Served as breakfast shakes on 7 consecutive days, 0.5 g P/kg BW (~265 kcal): whey, casein, soy (~25 g P), or control (~8.5 g P)	Whey = soy 24-h EI: Whey > casein ($P = 0.02$) Casein = soy	120 min: Whey = casein = soy	—
Anderson et al. 2004 (38) (Canada)	Study I: 13 young men Study II: 22 young men Study III: 10 young men	4 crossover studies (3 of which are relevant for the aim of this review) (MT)	400-mL preloads (833 kJ): Study I: whey, soy, egg albumen, sucrose (all 0.65 g/kg BW), or water Study II: whey, egg albumen (both 50 g P), or water Study III: intact whey, WPH (both 50 g P), or water	Ad libitum meal after 60 min: Study I: whey = soy, whey < egg albumin ($P < 0.05$) Study II: whey < egg albumin ($P < 0.05$) Ad libitum meal after 120 min (study III): whey = WPH	—	—
Baer et al., 2011 (43) (USA)	90 overweight and obese men and women 73 completers	Randomized, double-blind, parallel (23 wk)	Supplements, 2 packets/d (1670 kJ/d) included in usual diet: whey, soy (both ~28 g P/packet), or CHO (isocaloric)	24-h dietary records (every 10th day): Whey = soy	Before evening meal at wk 23: Hunger, desire to eat, prospective food consumption and fullness: whey = soy	Ghrelin (0, 12, 16, 20, 23 wk): Whey < soy ($P = 0.04$)
Bowen et al., 2006 (41) (Australia)	72 normal-weight and obese men	Randomized, crossover (MT)	Liquid preloads (~1.1 MJ): whey, soy, gluten (all 71 E% P), or glucose (isocaloric)	Ad libitum meal after 180 min: Whey = soy = gluten	180 min: Whey = soy = gluten	GLP-1, CCK and ghrelin: Whey = soy = gluten

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Table 1. (*Continued*)

Reference	Popopulation	Intervention		EI	Outcome[2]	
		Design	Diet		Appetite (VAS)	GI hormones
Bowen et al., 2006 (40) (Australia)	19 overweight and obese men	Randomized, crossover (MT)	Liquid preloads (∼1 MJ): whey, casein (both ∼52 g P), lactose, or glucose (both isocaloric)	Ad libitum lunch after 180 min: Whey = casein	Appetite during 180 min: Whey = casein	CCK (AUC 180 min): Whey = casein Ghrelin (at 180 min): Whey = casein
Burton-Freeman, 2008 (30) (USA)	20 normal-weight men and women	Randomized, double-blind, crossover (MT)	300 mL semisolid preloads (∼1 MJ): whey, whey w/o GMP (both 44 E% P), GMP (3 E% P), or CHO (isocaloric)	Ad libitum lunch after 75 min: Whey = whey w/o GMP = control = GMP	75 min after preload consumption (prelunch): Women: Hunger, desire to eat, and prospective consumption: whey and whey w/o GMP < GMP ($P < 0.05$) Fullness: whey and whey w/o GMP > GMP and control ($P < 0.05$) Men: Appetite: whey = whey w/o GMP = GMP 105 min after preload consumption (postlunch): Women: Fullness and prospective consumption: whey = whey w/o GMP = GMP Hunger and desire to eat: whey and whey w/o GMP < GMP ($P < 0.05$) Men: Hunger, prospective food consumption and desire to eat: GMP < whey, whey w/o GMP ($P < 0.05$) Fullness: GMP > whey w/o GMP ($P < 0.05$), whey = GMP, whey = whey w/o GMP	CCK: 75 min after preload consumption (prelunch): Women: Whey and whey w/o GMP > GMP ($P < 0.05$) Men: Whey w/o GMP > whey ($P < 0.05$), *GMP ($P = 0.07$)* 105 min post preload consumption (post lunch): Men: Whey = whey w/o GMP = GMP Women: GMP > whey w/o GMP ($P < 0.05$) Whey = GMP, whey = GMP w/o GMP

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Table 1. (*Continued*)

Reference	Popopulation	Intervention		EI	Outcome[2]	
		Design	Diet		Appetite (VAS)	GI hormones
Calbet and Holst, 2004 (58) (Denmark)	6 healthy men	Crossover (MT)	Liquid preloads (600 mL, ~1000 kJ/L): intact whey, intact casein, WPH, or hydrolyzed casein (all 60 g P/L)	—	—	GLP-1 and PYY: Intact whey = intact casein = WPH = hydrolyzed casein GIP: 20 min: WPH + hydrolyzed casein > intact whey + intact casein (*P* value NA) 60 min: WPH + hydrolyzed casein < intact whey + intact casein (*P* value NA) All time: whey = casein
Diepvens et al., 2008 (67) (The Netherlands)	39 overweight men and women	2 randomized, single-blind, crossover studies (MT)	Study I+II: preloads as shakes (1024 kJ): whey, pea protein hydrolysate, whey + pea protein hydrolysate and milk (all 25 E% P)	Ad libitum lunch after 180 min (study II): whey = pea = whey+pea = milk	Study I: Hunger: 240 min (AUC): pea < whey and whey+pea (*P* < 0.05) 90 min: pea < milk (*P* < 0.05) Satiety, fullness, and desire to eat: whey = pea = whey+pea = milk Study II: Hunger: whey = pea = whey +pea = milk Satiety and fullness: 30, 90 min: whey > milk and whey+pea (*P* < 0.05) 30,60,180 min: pea > milk and whey+pea (*P* < 0.05)	GLP-1 (AUC 120 min): Pea < milk (*P* < 0.05), whey = pea = whey+pea CCK (AUC 120 min): Milk > pea, whey, and whey +pea (*P* < 0.05), whey = pea = whey+pea PYY (AUC 120 min): Pea = whey = whey+pea = milk Ghrelin (AUC 120 min): Pea = whey = whey+pea = milk
Hall et al., 2003 (7) (United Kingdom)	Study I: 16 healthy men and women Study II: 9 healthy men and women	2 randomized, crossover studies (MT)	Liquid preloads (~1700 kJ): whey or casein (both 48 g P)	Ad libitum lunch after 180 min (study I): Casein > whey (*P* < 0.05)	180 min (study II): Desire to eat: whey < casein (*P* < 0.005) Hunger: whey < casein (*P* = 0.061) Fullness: whey > casein (*P* < 0.05)	GLP-1 (0–180 min): Whey > casein (*P* < 0.05) GIP (0–180 min): Whey > casein (*P* < 0.005) CCK (0–180 min): Whey > casein (*P* < 0.01)

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Reference	Popopulation	Intervention		EI	Outcome[2]	
		Design	Diet		Appetite (VAS)	GI hormones
Hermansen et al., 2005 (88) (Denmark)	100 hypercholesteroleamic men and women 89 completers	Randomized, double-blind (24 wk)	Protein supplements included in usual diet (2 sachets/d): soy or casein (both 30 g P/d)	24-h records (0, 24 wk): Casein = soy	—	GLP-1 (iAUC 8 h): Change after 24 wk: soy = casein GIP (iAUC 8 h): Increase after 24 wk: soy > casein ($P < 0.05$)
Hochstenbach-Waelen et al., 2009 (48) (The Netherlands)	23 healthy men and women	Randomized, single-blind, crossover (MT)	Protein custards (10 E%/25 E%): casein or gelatin	—	24 h: Hunger (AAC): 10 E% gelatin > 10 E% casein ($P < 0.05$), 25 E% gelatin = 25 E% casein Fullness (AUC): 10+25 E% gelatin = 10+25 E% casein	GLP-1: Dinner: 10 E% gelatin > 10 E % casein ($P < 0.05$) Lunch: 25 E% gelatin > 25 E% casein ($P < 0.0001$) PYY: 10+25 E% gelatin = 10+25 E% casein Ghrelin: 10 E% gelatin = 10 E% casein 25 E% gelatin < 25 E% casein ($P < 0.05$)
Hochstenbach-Waelen et al., 2010 (52) (The Netherlands)	81 overweight and obese men and women 72 completed weight loss period, whereas 65 also completed weight maintenance period	Randomized, single-blind, parallel (24 wk) Phase 1: 8-wk weight loss period (33% of ER), phase 2: 16-wk maintenance period: wk 9–16: complete diet was provided, wk 17–24: 50% of the diet was provided, 50% ad libitum	Medium milk (wk 9–16: 15 E% P, wk 17–24: 30 E% P) High milk (wk 9–16: 30 E% P, wk 17–24: 60 E% P) Gelatin (50/50% milk protein/gelatin; wk 9–16: 30 E% P, wk 17–24: 60 E% P)	—	VAS appetite rating in the morning after an overnight fast: Satiety, fullness, hunger, and desire to eat: medium milk = high milk = gelatin	GLP-1 and PYY (change from wk 8–16): Medium milk = high milk = gelatin
Hochstenbach-Waelen et al., 2011 (51) (The Netherlands)	81 overweight and obese men and women 72 completers	Randomized, single-blind, parallel (8 wk) Phase 1: wk 1–4 100% of ER, Phase 2: wk 5–8 33% of ER	Medium milk (phase 1: 10 E% P, phase 2: 30 E% P) High milk (phase 1: 20 E% P, phase 2: 60 E% P) Gelatin (50/50% milk protein/gelatin, phase 1: 20 E% P, phase 2: 60 E% P)	—	VAS appetite rating in the morning after an overnight fast: Satiety, fullness, hunger, and desire to eat: medium milk = high milk = gelatin	GLP-1 and PYY (change from wk 0–8): Medium milk = high milk = gelatin

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Table 1. (*Continued*)

Reference	Popopulation	Intervention		EI	Outcome[2]	
		Design	Diet		Appetite (VAS)	GI hormones
Holmer-Jensen et al., 2012 (65) (Denmark)	11 obese men and women	Randomized, controlled, crossover (MT)	Milkshakes containing: whey, WPH, αlac, or GMP (all 45 g/19 E% P)	—	—	GLP-1, GIP, CCK and ghrelin: Whey = WPH = αlac = GMP
Hursel et al., 2010 (36) (The Netherlands)	35 healthy men and women	Randomized, single-blind, crossover (MT)	Breakfast yogurt drinks (15% of ER): whey, αlac (both 41 E% P), or milk (15 E% P)	—	240 min: Hunger (AAC): αlac < whey ($P < 0.05$) Desire to eat (AAC): αlac < whey ($P < 0.01$) Fullness and appetite suppression: αlac = whey	—
Juvonen et al., 2011 (54) (Finland)	8 normal-weight young men	Randomized, crossover (MT)	400-mL preloads (2.4 kJ/g): viscous casein, casein-TG, or whey (all ~92 E% P)	—	240 min: Fullness: 15, 30, 120 min: casein-TG > whey ($P < 0.05$) 30 min: casein-TG > casein ($P < 0.05$) All time: whey = casein Hunger, desire to eat, and satiety: whey = casein = casein-TG	GLP-1: 15 min: whey > casein-TG ($P = 0.074$) 30 min: casein > casein-TG ($P = 0.074$) Whey = casein CCK: 15 min: whey and casein > casein-TG ($P < 0.001$) 30 min casein > whey and casein-TG ($P < 0.05$) PYY: Whey = casein = casein-TG
Keogh et al., 2010 (32) (Australia)	20 overweight and obese men	Randomized, double-blind, crossover (MT)	895-kJ preloads containing 50 g of min. GMP, high GMP, whey w/o GMP, or glucose	Ad libitum lunch after 180 min: Min. GMP = high GMP = whey w/o GMP	180 min: Min. GMP = high GMP = whey w/o GMP	CCK: Min. GMP = high GMP = whey w/o GMP
Lam et al., 2009 (33) (New Zealand)	50 healthy men and women	Randomized, single-blind, crossover (MT)	Liquid preloads as milkshakes (~1300 kJ): whey w/o GMP, whey including 21% GMP, whey including 21% GMP+GMP (~45 g P), or CHO (isocaloric)	Ad libitum lunch after 30 min: Whey w/o GMP = whey including 21% GMP = whey including 21% GMP+GMP	90 min: Whey w/o GMP = whey including 21% GMP = whey including 21% GMP+GMP Fullness before ad libitum lunch: whey including 21% GMP > whey w/o GMP, whey including 21% GMP +GMP ($P < 0.05$)	—
Lang et al., 1998 (44) (France)	12 healthy normal-weight men	Nonrandomized, crossover (MT)	Test meals (~5.2 MJ): casein, egg albumin, gelatin, soy, pea, or wheat gluten (all ~70 g P)	24-h EI: Casein = egg albumin = gelatin = soy = pea = gluten	Appetite during 480 min: Casein = egg albumin = gelatin = soy = pea = gluten	—

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Table 1. (*Continued*)

Reference	Popopulation	Intervention		EI	Outcome[2]	
		Design	Diet		Appetite (VAS)	GI hormones
Lang et al., 1999 (45) (France)	9 healthy normal-weight men	Nonrandomized, crossover (MT)	Test meals (∼1.8 or 3.6 MJ, 23 E% P): casein, gelatin, orsoy (25, 50 g)	24-h EI: Casein = gelatin = soy	Appetite during 480 min: Casein = gelatin = soy	—
Lorenzen et al., 2012 (46) (Denmark)	22 overweight men 17 completers	Randomized, blinded, cross-over (MT)	Served as shakes with break-fast (3 MJ): casein, whey, or milk (all ∼34 g P)	Ad libitum lunch after 240 min: Milk < casein and whey, (P = 0.03), casein = whey	240 min: Whey = casein = milk	—
Nieuwenhuizen et al., 2009 (53) (The Netherlands)	24 healthy men and women	Randomized, single-blind, crossover (MT)	Breakfast custards (20% of ER ≈2.54 ± 0.06 MJ, 10 E% P): αlac, gelatin, or gelatin +TRP	Ad libitum lunch after 180 min: αlac = gelatin = gelatin+TRP	240 min: Hunger AUC: αlac = gelatin = gelatin+TRP At 240 min: αlac < gelatin ($P < 0.01$) and gelatin+TRP ($P < 0.05$)	GLP-1 and ghrelin (AUC 180 min): αlac = gelatin = gelatin+TRP
Nilsson et al., 2004 (63) (Sweden)	12 healthy men and women	Randomized, controlled, crossover (MT)	Breakfasts: white wheat bread, gluten-low (both 2.8 g P), gluten-high, cod, milk, whey, or cheese (casein) (all 18.2 g P)	—	—	GLP-1 (iAUC 45 min): Whey = cod = milk = cheese (casein) = white wheat bread (gluten NA) GIP (iAUC 45 min): Whey > cod, milk, cheese (casein) and white wheat bread ($P < 0.05$) (gluten NA)
Nilsson et al., 2007 (64) (Sweden)	12 healthy men and women	Randomized, crossover (MT)	Breakfast liquid meals (250 mL): glucose (25 g CHO), whey, AA2,[4] AA3,[4] or AA5[4] (18 g P)	—	—	GLP-1 (iAUC 90 min): Whey = AA2 = AA3 = AA5 GIP (iAUC 90 min): Whey > AA2, AA3, AA5 ($P < 0.05$)
Pal and Ellis, 2010 (8) (Australia)	22 healthy lean men	Randomized, single-blind, crossover (MT)	Liquid preloads (∼1.2 MJ): whey, tuna, turkey, or egg albumin (all 71 E% P)	Ad libitum EI after 240 min: whey < tuna, egg, and turkey ($P < 0.01$)	240 min (iAUC): Hunger and prospective consumption: whey < tuna ($P < 0.03$), turkey ($P < 0.01$), and egg ($P < 0.001$) Fullness: whey and tuna > turkey ($P < 0.03$) and egg ($P < 0.001$)	—
Potier et al., 2009 (47) (France)	20 normal-weight women	Randomized, crossover (5 d)	Solid cheese preloads (∼1000 kJ/100 g): casein, whey+casein (1:2) (both 22 g P), or no preload	Ad libitum lunch after 60 min and 24-h EI: casein = whey +casein	Appetite before lunch and rest of day: Casein = whey/casein	—

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Table 1. (*Continued*)

Reference	Popopulation	Intervention		EI	Outcome[2]	
		Design	Diet		Appetite (VAS)	GI hormones
Veldhorst et al., 2009 (18) (The Netherlands)	25 healthy men and women	Randomized, single-blind, crossover (MT)	Breakfast meal custards (20% of ER, 10 E%/25 E% P): whey, casein, or soy	Ad libitum meal after 180 min: casein = whey+casein	240 min (AUC): Hunger: 10 E%: whey < casein ($P < 0.05$), casein = soy, whey = soy 25 E%: whey = casein = soy	GLP-1 (AUC 180 min): 10 E%: whey = casein = soy 25 E%: whey > casein ($P < 0.05$), whey = soy, casein = soy Ghrelin (AAC 180 min): 10 E%+25 E%: whey = casein 10 E%: casein < soy ($P < 0.05$)
Veldhorst et al., 2009 (31) (The Netherlands)	25 healthy men and women	Randomized, single-blind, crossover (MT)	Breakfast custards (20% of ER, 10 E%/25 E%): whey or whey w/o GMP	Ad libitum meal after 180 min: Whey < whey w/o GMP ($P < 0.05$)	240 min: Satiety: 10 E% > 25 E% ($P < 0.05$) Whey = whey w/o GMP	GLP-1: 25 E% > 10 E% ($P < 0.05$) Whey = whey w/o GMP Ghrelin: 25E% < 10E% ($P < 0.01$) Whey = whey w/o GMP
Veldhorst et al., 2009 (34) (The Netherlands)	24 healthy men and women	Randomized, single-blind, crossover (MT)	Breakfast custards (20% of ER, 10 E%/25 E% P): casein, soy, whey, whey w/o GMP, αlac, gelatin, or gelatin +TRP	Ad libitum meal after 180 min: 10 E%+25 E%: αlac, gelatin, and gelatin+TRP < casein, soy, and whey w/o GMP ($P < 0.05$), 25 E%: αlac and gelatin+TRP < whey ($P < 0.05$)	180 min: Satiety: 10 E%+25 E%: αlac, gelatin, and gelatin+TRP > casein, soy, whey, and whey w/o GMP ($P < 0.05$)	GLP-1: 10 E%: casein = soy = whey = whey w/o GMP = αlac = gelatin = gelatin+TRP 25 E%: gelatin+TRP > casein and soy ($P < 0.05$) Ghrelin: 10 E%+25 E%: casein = soy = whey = whey w/o GMP = αlac = gelatin = gelatin +TRP

[1] AAC, area above the curve; αlac, α-lactalbumin; AUC, area under the curve; BW, body weight; casein-TG gel, casein cross-linked by transglutaminase; CCK, cholecystokinin; CHO, carbohydrate; E%, energy percent; EI, energy intake; ER, daily energy requirement; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GMP, glycomacropeptide; high GMP, glycosylated GMP; iAUC, incremental AUC; min. GMP, minimally glycosylated GMP; NA, not applicable; P, protein; PYY, peptide YY; TRP, tryptophan; VAS, visual analogue scales; WPH, whey protein hydrolysate; w/o, without.

[2] Selected outcomes; for all outcomes, see original papers.

[3] MT includes both preload and meal test studies.

[4] AA2, 1.6 g lysine, 1.4 g threonine; AA3, 2.2 g leucine, 1.1 g isoleucine, 1.1 g valine; AA5, 2.2 g leucine, 1.1 g isoleucine, 1.1 g, valine, 1.6 g lysine, 1.4 g threonine.

Table 2. Controlled clinical trials with energy expenditure as outcome[1]

Reference	Population	Intervention		TEE	Outcome[2]	
		Design	Diet/supplement		DIT	Substrate balances
Acheson et al., 2011 (9) (Switzerland)	23 lean men and women	Randomized, double-blind, crossover Duration: 330 min	Meals (shakes) – energy density 1 kcal/g (459 kcal): whey, casein, soy (all 50 E% P), or CHO (isocaloric)		Whey > casein ($P = 0.002$) Whey > soy ($P = 0.001$) Whey = casein	Fat oxidation: casein = whey, casein = soy, whey > soy *($P = 0.098$)*
Alfenas et al., 2010 (42) (Brazil)	26 normal weight men and women 24 completed the first 3 sessions, only 10 completed the soy session	Randomized, crossover Duration: 7 d (DIT: 60 min)	Served as breakfast on 7 consecutive days, 0.5 g P/kg BW (∼265 kcal): whey, casein, soy (∼25 g P), or control (∼8.5 g P)	—	Whey = casein Soy > whey (day 7, $P = 0.024$)	RQ: whey = casein, whey < soy, (day 7, $P < 0.05$)
Hochstenbach-Waelen et al., 2009 (48) (The Netherlands)	23 healthy men and women	Randomized, single -blind, crossover Duration: 36 h (DIT: 24 h)	Served as breakfast custards (20% of ER, 10 E%/25 E%): casein or gelatin	10 E% + 25 E%: casein = gelatin	10 E% + 25 E%: casein = gelatin	Protein balance: 10 E% (negative): casein < gelatin ($P < 0.05$), 25 E% (positive): casein > gelatin ($P < 0.0001$) Protein oxidation: casein < gelatin (10 E%, $P < 0.05$, 25 E%, $P < 0.0001$) RQ: 10+25 E%: casein = gelatin
Hursel et al., 2010 (36) (The Netherlands)	35 healthy men and women	Randomized, single-blind, crossover Duration: 240 min	Breakfast yogurt drinks (15% of ER): whey, αlac (both 41 E% P) or milk (15 E% P)		Whey = αlac	Protein balance: whey = αlac RQ: whey = αlac
Karst et al., 1984 (71) (Germany)	Study I: 5 healthy normal weight men	Crossover Duration: 360 min	Served as shakes: egg, gelatin, casein, or starch (all 1 MJ)	—	Casein > gelatin and starch ($P < 0.01$) Casein = egg	—
Lorenzen et al., 2012 (46) (Denmark)	22 overweight men 17 completers	Randomized, blinded, crossover Duration: 240 min	Served as shakes with breakfast (3 MJ): casein, whey, or milk (all ∼34 g P)	—	Whey = casein = milk protein	Fat oxidation: Casein > whey ($P = 0.015$) casein = milk whey = milk

[1] αlac, α-lactalbumin; BW, body weight; CHO, carbohydrate; DIT, diet-induced thermogenesis; E%, energy percent; ER, daily energy requirements; P, protein; RQ, respiratory quotient; TEE, total energy expenditure.
[2] Selected outcomes; for all outcomes, see original papers.

Table 3. Controlled clinical trials with body weight or body composition as outcome[1]

Reference	Population	Intervention		Outcome[2]		
		Design	Diet/supplement	BW	FM/ %FM	FFM/%FFM/lean mass
Exercise programs						
Colker et al., 2000 (75) (USA)	16 athletic men All completers	Randomized, double-blind (10 wk) Resistance training program (3 times/wk)	Protein from food could not exceed 1.6 g/kg/d. In addition, supplements were added: whey (whey concentrate 30 g/d + whey isolate 10 g/d), or whey +BCAA+glutamine (whey concentrate 30 g/d and whey isolate 10 g/d, L-glutamine 5 g/d, BCAA (leucine 1.5 g/d, isoleucine 0.75 g/d, valine 0.75 g/d))	Greater increase for whey +BCAA+glutamine group than whey ($P < 0.05$)	%FM: significant decrease in both groups NS between groups	FFM: tendency for greater increase for whey+BCAA +glutamine than whey ($P = 0.09$)
Cribb et al., 2006 (74) (Australia)	19 men 13 completers	Randomized, double-blind parallel (10 wk) Resistance training program (3 times/wk)	Supplements added to usual diet (1.5 g supplement · $kg^{-1} \cdot d^{-1}$): WPH or intact casein (~90 g P)	—	FM: greater decrease for whey than casein, NS (P value NA)	Lean mass: greater increase for whey than casein ($P < 0.01$)
Demling and DeSanti, 2000 (19) (United Kingdom)	38 overweight men 32 completers	Randomized, parallel (12 wk) Resistance training program (4 times/wk)	Hypocaloric diet (80% of estimated food intake): hydrolyzed casein, WPH (both resistance training + 70–75 g P/d), or control (all hypocaloric diet)	Significant decrease for both whey and casein NS between groups	FM: greater decrease for casein than whey ($P < 0.05$)	FFM: greater increase for casein than whey ($P < 0.05$)
Kerksick et al., 2006 (76) (USA)	36 healthy men Completers uncertain	Randomized, double-blind (10 wk) Resistance training program (4 times/wk)	Supplements added to usual diet: whey+BCAA+glutamine (40 g/d+3 g/d+5 g/d), whey+casein (40 g/d+8 g/d), or CHO (48 g/d CHO)	Significant increase in whey +casein group NS between groups	FM: no significant change in any groups NS between groups	FFM + lean mass: greater increase for whey+casein than whey+BCAA +glutamine ($P < 0.05$)
Lollo et al., 2011 (78) (Brazil)	24 young professional soccer players (men)	Double-blind, parallel Average work load: 1–2 games/wk and 6–8 training session/wk of 2.5 h (8 wk)	Subjects were housed and fed under the same condition. Protein supplement 1 g/kg/d after the daily training session: whey, WPH (degree of hydrolysis: 10.5%), or casein (all ~90% P)	No significant change in any groups	%FM: decreased in WPH ($P < 0.05$) No change in the whey and casein groups.	FFM: increased in casein group ($P < 0.05$) No change in the whey and WPH groups
Energy-restricted diets						
Anderson et al., 2005 (80) (USA)	90 obese men and women 52 completers	Randomized, parallel (12 wk)	Energy-reduced diet (1200 kcal/d): milk (13 g P) or soy (18 g P)	Significant decrease in both groups NS between groups	—	—
Anderson et al., 2007 (81) (USA)	43 obese women 35 completers	Randomized, single-blind, parallel (16 wk)	Energy-reduced diet (4.5–5.0 MJ/d): soy+isoflavones or casein (both ~20 g P)	Significant decrease in both groups NS between groups	FM: significant decreased in both groups NS between groups	Lean mass: significant increase in both groups NS between groups

(Continued)

Table 3. (*Continued*)

Reference	Population	Intervention		Outcome[2]		
		Design	Diet/supplement	BW	FM/ %FM	FFM/%FFM/lean mass
Faghih et al., 2011 (11) (Iran)	100 overweight and obese women 85 completers	Randomized (8 wk)	Energy-reduced diet (500 kcal/d energy deficit): control (500–600 mg Ca/d), calcium (800 mg Ca/d), milk (3 × 220 mL milk/d including 1200–1300 mg Ca/d), or soy (3 × 220 mL soy milk/d fortified with 1200–1300 mg Ca/d)	Greater decrease for milk than soy milk ($P < 0.05$), calcium ($P < 0.01$), and control ($P < 0.01$)	%FM: significant decrease in all groups NS between groups	—
Hochstenbach-Waelen et al., 2011 (51) (The Netherlands)	81 overweight and obese men and women 72 completers	Randomized, single-blind, parallel (8 wk) Phase 1: wk 1–4, 100% of ER, phase 2: wk 5–8, 33% of ER	Medium milk (phase 1: 10 E% P, phase 2: 30 E% P) High milk (phase 1: 20 E% P, phase 2: 60 E% P) Gelatin (50/50% milk protein/ gelatin, phase 1: 20 E% P, phase 2: 60 E% P)	Phase 1+2: significant decrease in all groups NS between groups	FM and %FM: phase 1+2: significant decrease in all groups NS between groups	FFM: phase 1+2: Significant decrease in all groups NS between groups FFM as % BW: phases 1+2: significant increase in all groups NS between group
Keogh and Clifton, 2008 (84) (Australia)	127 overweight and obese men and women 72 completers	Randomized, double-blind, parallel (12 mo) Phase 1: 2 shakes/d, 6 mo, phase 2: 1 shake/d, 6 mo	Energy-reduced diet (exact energy intake NA): 90% GMP or milk (both 15 g P)	Significant decrease in both groups NS between groups	FM: significant decrease in both groups NS between groups	Lean mass: significant decrease in both groups NS between groups
Soenen et al., 2010 (82) (The Netherlands)	87 overweight and obese men and women 72 completers	Randomized, parallel (6 mo) Phase 1: 1 mo, 100% EI as meal replacement; phase 2: 1 mo, 33% of EI as meal replacement; phase 3: 2 mo, 67% EI as meal replacement; phase 4: 2 mo, 33% EI as meal replacement + 33% EI ad libitum	αlac (50/50 mix of αlac and milk protein; phase 1: 20 E % P, phase 2: 60 E% P, phase 3: 30 E% P) High milk (phase 1: 20 E% P, phase 2: 60 E% P, phase 3: 30 E% P) Medium milk (phase 1: 10 E% P, phase 2: 30 E% P, phase 3: 15 E% P)	Significant decrease in all groups NS between groups	FM: significant decrease in all groups NS between groups	FFM: decreased only in medium milk group ($P < 0.05$) NS between groups

(*Continued*)

Table 3. (*Continued*)

Reference	Population	Intervention		BW	Outcome[2]	
		Design	Diet/supplement		FM/ %FM	FFM/%FFM/lean mass
Weight maintenance						
Baer et al., 2011 (43) (USA)	90 overweight and obese men and women 73 completers	Randomized, double-blind (23 wk)	Supplements, 2 packets/d (1670 kJ/d) included in usual diet: whey, soy (both ~28 g P/packet), or CHO (isocaloric)	No significant change in any groups, but greater decrease with whey than CHO ($P < 0.006$) NS between whey and soy	FM: greater decrease for whey than CHO ($P < 0.005$) NS between whey and soy	Lean mass: no significant change in any groups NS between groups
Claessens et al., 2009 (86) (The Netherlands)	60 overweight and obese men and women 48 completers	Randomized, parallel (blinded to the type of protein) (17 wk) Phase 1: 5-wk liquid diet (500 kcal/d) Phase 2: 12-wk weight maintenance, ad libitum EI	Phase 2: weight maintenance: whey, casein, or CHO (50 g/d)	Phase 2: greater decrease for whey and casein than CHO ($P = 0.04$) NS between whey and casein	FM: phase 2: greater decrease for whey and casein than CHO ($P = 0.02$) NS between whey and casein	FFM: phase 2: trend for greater increase for whey than casein ($P = 0.09$)
Hochstenbach-Waelen et al., 2010 (52) (The Netherlands)	81 overweight and obese men and women 72 completed weight-loss period, whereas 65 also completed weight maintenance period	Randomized, single-blind, parallel (24 wk) Phase 1: 8 wk, weight-loss period (33% of EI), phase 2: 16-wk maintenance period: wk 9–16: complete diet was provided, wk 17–24: 50% of the diet was provided, 50% ad libitum	Medium milk (wk 9–16: 15 E% P; wk 17–24: 30 E% P) High milk (wk 9–16: 30 E% P; wk 17–24: 60 E% P) Gelatin (50/50% milk protein/gelatin; wk 9–16: 30 E% P, wk 17–24: 60 E% P)	Phases 1+2: significantly decreased in all groups during weight loss and sustained during weight maintenance NS between groups	FM: phase 2: no significant change in any groups NS between groups	FFM: phase 2: no significant change in any group NS between groups
Takahira et al., 2011 (87) (Japan)	48 men and women with visceral fat area > 100 cm^2 43 completers	Randomized, double-blind, parallel (20 wk)	Usual diet: milk (21.9 g/d) or soy (12 g soy+9.25 g milk/d)	20 wk: decreased only in milk group ($P < 0.01$)	Visceral fat area: greater decrease for milk than soy (P value NA)	—

[1] αlac, α-lactalbumin; BCAA, branch-chained amino acids; BW, body weight; Ca, calcium; CHO, carbohydrate; E%, energy percent; EI, energy intake; ER, daily energy requirement; FFM, fat free mass; FM, fat mass; GMP, glycomacropeptide; NA, not applicable; NS, nonsignificant; P, protein; WPH, whey protein hydrolysate.

[2] Selected outcomes; for all outcomes, see original papers.

which may partly explain why no differences in satiety measures are observed.

In contrast, it has been suggested that incomplete proteins may be more satiating than complete proteins in the acute setting (48). According to that hypothesis, consumption of diets low in essential amino acids will induce a decrease in plasma concentration of these amino acids, which in rodents is found to be detected in the brain and lead to a behavioral response rejecting consumption of imbalanced diets and consequently a suppression of hunger (49,50). The satiating effect of whey, casein, and soy has been compared with the incomplete protein gelatin in a few studies (Table 1) (34,44,45,48). Two studies by Lang et al. (44,45) observed no difference in appetite between proteins in the acute settings, but, in contrast, Hochstenbach-Waelen et al. (48) demonstrated a hunger-suppressing effect of gelatin compared with casein at a low (10 E%) protein dose, and Veldhorst et al. (34) found gelatin to increase satiety compared with casein and whey, independent of protein dose. A limitation of the studies by Lang et al. (44,45) is that protein meals were not completely identical in macronutrient and energy composition. Moreover, proteins were not consumed as supplements, but as mixed meals with varying fiber content, which may have blunted the potential differences between different protein sources (44). In addition, only 12 (44) and 9 (45) subjects were included. The decreased hunger feelings with consumption of gelatin observed by Hochtenbach-Waelen et al. (48) may have been understood as an anorexigenic effect of intake of food lacking essential amino acids. After consumption of the 10 E% gelatin breakfast, the plasma concentrations of the essential amino acids histidine, valine, methionine, isoleucine, phenylalanine, tryptophan, and leucine decreased and were lower than after casein consumption. Under the 25 E% conditions, only the plasma concentration of tryptophan decreased and was lower after consumption of the gelatin compared with the casein breakfast (34,48). This does not, however, seem to play a role in the long term. When appetite was recorded over several weeks, there was no difference in appetite regulation between gelatin and milk (51,52). Furthermore, data from Nieuwenhuizen et al. (53) indicate that tryptophan alone may not play a very important role in appetite regulation as no difference in subjective feelings of satiety and ad libitum energy intake was observed between gelatin and gelatin with added tryptophan. However, tryptophan may be important in combination with other essential amino acids.

Digestion and absorption rate

Besides differences in amino acid composition, proteins differ in digestion and absorption rates, which may be important with regard to appetite regulation. It is well-known that whey and casein differ in absorption rate, with whey being absorbed rapidly and casein slowly as it coagulates in the acidic environment in the stomach (17). The satiating effect of the 2 proteins have been compared in few studies, most of which were acute studies (7,9,18,40,42,46,47,54) (Table 1) showing no clear evidence that 1 protein is more satiating than the other.

Hall et al. (7) showed that whey was more satiating when subjective appetite sensations were recorded for 180 min, and, in accordance, whey was more efficient at decreasing energy intake at an ad libitum lunch buffet served 90 min after preload consumption compared with casein. In contrast, casein has been shown to be more satiating than whey when subjective appetite measures were continued for 330 min (9). These results suggest that timing of appetite measures may be important and that the effects of casein may not be fully developed when appetite measures are obtained shortly (90–180 min) after preload consumption. Additionally, when appetite measures are obtained several hours (330 min) after protein consumption, as in the Acheson study (9), the concentration of amino acids after whey consumption may have reached baseline. Previous studies support this (17,55). It has been shown that plasma amino acid concentrations were higher after whey compared with casein 100 min after protein ingestion and vice versa 300 min after protein ingestion (17). Likewise, Dangin et al. (55) showed that a free amino acid mixture matched to casein (fast digestion rate) and whey induced a fast and transient increase in amino acids, whereas intact casein and whey given in small boluses to mimic a slow digestion rate gave rise to prolonged and maintained plasma amino acid concentrations. Moreover, Dangin et al. (55) showed that a slower digestion rate favors greater whole-body protein balance, at least over rapidly digested proteins. The meals were matched for nitrogen and leucine content, and the results therefore support that digestion rate is an independent factor regulating protein kinetics (55).

Therefore, all of these data could indicate that the "fast" protein whey is more satiating than the "slow" protein casein in the short term and vice versa in the long term, which may partly be explained by the difference in the rate of amino acid appearance in the blood and the postprandial secretion of GI hormones. Alfenas et al. (42) support the finding that casein is more satiating than whey in the long term. Casein was found to reduce daily energy intake compared with whey during a 7-d supplementation period. Additionally, casein supplementation induced a lower energy intake on day 7 compared with day 1.

Addition of energy from carbohydrate and fat

In studies with focus on appetite, proteins are rarely served free of energy from carbohydrate and fat. This may mask the difference in protein kinetics observed for casein and whey and thereby partly explain why a difference in the satiating effect of whey and casein has not been observed in all studies.

Dangin et al. (56) showed that in young adults, the differences in the rate of amino acid appearance in the blood were less pronounced when whey and casein were consumed with added energy from carbohydrate and fat. This was mostly due to a slower absorption of whey when carbohydrate and fat were added. However, the increase in plasma amino acids was still faster for whey than casein (56). Moreover, the more beneficial effect of casein compared with whey on

protein balance when given alone (17) was reserved when energy from carbohydrate and fat was added (56). Protein synthesis was not affected, but protein breakdown was highly decreased after whey consumption and slightly decreased after casein consumption (no difference between proteins) (56). The less pronounced decrease with casein may be explained by its already present depression of protein breakdown when consumed alone (17), which may be explained by prolonged hyperaminoacidemia. However, other factors such as protein structure and secretion of GI hormones most likely also play a role in protein-induced satiety.

Protein structure

Protein structure may influence the absorption rate and thereby play an important role in a protein's ability to stimulate satiety. Proteins can be broken down into smaller peptide fractions and free amino acids by exogenous hydrolysis, which thereby potentially induces an increased digestion and absorption rate of the protein (57). Calbet and Holst (58) demonstrated that hydrolyzed casein was absorbed more rapidly than intact casein and that the absorption rate of hydrolyzed casein approached the rate of whey. In contrast, they observed similar intestinal absorption rates of intact whey and its hydrolysate. This is, however, not a consistent finding (59). Moreover, when examining the effects on appetite regulation, hydrolysis of whey seems to be of less importance (38,60). This may be explained by the fast absorption and digestion of intact whey protein. Mahé et al. (61) showed that β-lactoglobulin, a main component of whey, was rapidly recovered in the upper intestine mostly in the form of intact protein that needs to be further degraded to be absorbed more distally. In contrast, casein was slowly recovered in the jejunum, mainly in the form of degraded peptides efficiently absorbed in the upper part of the intestine (61). These differences in absorption kinetics may be explained by the different structure of the 2 proteins. As previously described, casein exists as micelles, which, in addition to casein, contains water and salts. The caseins are hydrophobic, but κ-casein contains the hydrophilic component GMP, which stabilizes the micelle. In contrast, whey proteins are soluble and remain soluble in the stomach, which is why they reach the upper intestine more rapidly than casein (61). The impact of protein hydrolysis on satiety may consequently be different for casein, but this has to our knowledge not yet been investigated.

Another aspect, which should be taken into consideration when measuring appetite sensations, is that the initiation of an eating episode does not wholly rely on hunger sensations. The sensory properties of a food item can stimulate food intake even when satiety signals are present (7). Hall et al. (7) proposed that if protein preloads are administered as a liquid meal rather than a more customary solid meal, the cognitive and sensory stimuli that normally inhibit the desire to eat will be repressed until the consumption of a more familiar solid meal, such as the standard lunch buffet.

This was supported by Juvonen et al. (54), who recently showed that gelation of casein by cross-linking with transglutaminase resulted in increased subjective feelings of fullness compared with viscous casein and liquid whey. However, no treatment effects were observed in hunger, the desire to eat, and satiety (Table 1). Moreover, it should be noted that the palatability of the test meals was much lower for the gel-based casein than for casein and whey. It could therefore be speculated that the increased fullness observed with the casein gel was associated with the poor palatability and not only the texture of the protein. However, it is known that an increase in the viscosity or firmness of a food item delays gastric emptying (54). Future studies are needed to determine the effect of food texture and protein structure when comparing the satiating effects of different proteins.

GI hormones

Hormones are secreted in response to food intake from specialized enteroendocrine cells throughout the GI tract. The overall function of the GI hormones is to regulate food intake, either by inducing hunger (ghrelin) or satiety [CCK, glucagon-like peptide 1 (GLP-1), peptide YY (PYY)] and/or to stabilize postprandial glucose excursions [the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP)] (62). Thus, the effects of ingested macronutrients on appetite may in part be mediated by postprandial GI hormone responses.

In some, but not all, studies, whey has been found to stimulate 1 or both of the incretin hormones to a greater extent than other protein sources, such as casein, milk, cod (7,18,63), and specific combinations of the essential amino acids: leucine, isoleucine, lysine, valine, and threonine (64). However, in other studies, no difference was observed between whey and casein (34,58). Additionally, Holmer-Jensen et al. (65) found no difference in plasma levels of GLP-1 and GIP between whey and specific whey components (hydrolyzed whey, αlac, and GMP).

In accordance with a more satiating effect of whey compared with casein, Hall et al. (7) demonstrated a larger increase in GLP-1, GIP, and CCK after whey consumption, suggesting that the satiating effect of whey at least in part was mediated through GI hormones. In addition, the secretion profiles over time (0–180 min) were somewhat different for the 3 hormones. This possibly mirrors the different localizations of the different endocrine cell types (66) but may also suggest differences in the mechanisms behind the observed effects. Contrary, postprandial hormone responses do not always translate into satiety. In the study by Juvonen et al. (54), the effect on fullness (Table 1) was unlikely to be caused by alterations in the secretion of satiating hormones. Postprandial CCK response was significantly greater after liquid whey and viscous casein consumption compared with the gel-based casein, whereas fullness was greater after consumption of the gel-based casein compared with whey and casein. Likewise, a similar trend ($P = 0.074$) was observed for GLP-1. Veldhorst et al. (18) support the finding that the secretion of GI hormones does not always translate into a more satiating effect of a given protein. In their study,

they observed no difference in postprandial GLP-1 response after intake of whey and casein given at 10 E%, but at 25 E% from protein, postprandial GLP-1 response was greater after whey consumption compared with casein. This is in contrast to the findings on appetite, where it was only possible to detect a difference at the low protein dose. For ghrelin and PYY secretion, no clear evidence exists that 1 protein source induces higher postprandial responses than other protein sources (34,40,41,48,54,58,67) (Table 1).

Few studies have looked at the effect of protein hydrolysis. Holmer-Jensen et al. (65) demonstrated similar concentrations of GLP-1, GIP, CCK, and ghrelin after consumption of whey protein isolate and hydrolyzed whey. In the study by Calbet and Holst (58), whey, casein, and their hydrolysates elicited a similar concentration of GLP-1 and PYY. GIP secretion was greater for the hydrolysates than for the intact proteins during the first 20 min and less after 60 min (58). None of these studies examined the association with appetite regulation, but for whey and its hydrolysate, the findings are in accord with findings on appetite in other studies (38,60).

In summary, no clear evidence exists that 1 protein source is more satiating than others. However, the "fast" protein whey seems to be more satiating than the "slow" protein casein in the short term and vice versa in the long term. Additionally, data indicate that protein quality and protein kinetics may be important factors in appetite regulation. Finally, there is no clear evidence that secretion of GI hormones is directly translated into greater satiety, and no clear evidence that 1 protein source elicit greater postprandial GI responses than others.

Energy expenditure

Diet-induced thermogenesis

In addition to the satiating effect of protein, it is well documented that DIT is greater for protein (20–35% of ingested energy) than carbohydrate (5–15% of ingested energy) and fat (0–3% of ingested energy) (4,68,69). DIT is the increase in energy expenditure above baseline after food consumption, which represents the energy required primarily for digestion, absorption, and disposal of ingested nutrients (68). The high thermogenesis of protein may be explained by the lack of storage capacity in the body, the high ATP cost of protein synthesis, and the metabolic costs of urea synthesis (70). Because proteins vary in amino acids and their effect on protein synthesis, it can be speculated that protein from different sources have different effects on DIT, but only sparse information is available (Table 2) (4). Few studies have examined the effects of whey and casein on DIT. Acheson et al. (9) found whey to increase DIT to a greater extent than casein. They propose that the difference in the rate of body protein synthesis after whey or casein consumption may explain the observed difference in DIT. Boirie et al. (17) showed that protein synthesis was 2-fold more rapid, measured 40–140 min, after consumption of whey compared with casein. In contrast, others have not been able to show any difference in DIT between whey and casein (28,31). However, a small study supports the finding that DIT depends on protein source (71). Karst et al. (71) demonstrated a higher DIT after casein consumption compared with consumption of isocaloric shakes of egg protein and gelatin. In contrast, Hochstenbach-Waelen et al. (48) observed no difference in DIT after casein or gelatin consumption, and Hursel et al. (36) were not able to show a difference in DIT between whey and αlac. Furthermore, the findings on DIT are not always in accord with the findings on appetite. Acheson et al. (9) found that casein was more satiating than whey, but that whey stimulated DIT to a greater extent than casein, whereas Hursel et al. (36) found αlac to suppress hunger more than whey, whereas they observed no difference in DIT. This may indicate that different mechanisms come into play when examining appetite regulation and energy expenditure.

Lipid oxidation

In addition to the effects on DIT, protein-induced lipid oxidation was also examined by Lorenzen et al. (46) and Acheson et al. (9). Lorenzen et al. (46) observed a small increase in lipid oxidation after casein consumption compared with whey, but, in contrast, Acheson et al. (9) observed no difference between the 2 proteins. However, they observed a tendency for whey to stimulate a greater lipid oxidation than soy. To our knowledge, these are the first studies to investigate lipid oxidation induced differences between casein and whey. In addition, 1 study has examined the effects on the respiratory quotient (RQ), an indicator of lipid oxidation (42). It supports that whey and casein have a similar RQ and that the RQ is lower after whey consumption compared with soy (42). The increased lipid oxidation after consumption of casein compared with whey observed by Lorenzen et al. (46) may be due to differences in postprandial insulin response, but this was not measured. Insulin is known to suppress lipid oxidation why a lower postprandial increase in insulin would be expected to induce a higher postprandial lipid oxidation. However, the study by Acheson et al. (9) does not support this notion. Although, Acheson et al. (9) did not observe any difference in lipid oxidation between casein and whey, they observed a lower postprandial insulin response after casein consumption compared with whey. Also, postprandial insulin responses were similar between whey and soy, despite a tendency for a greater lipid oxidation after whey consumption. Other mechanisms must therefore be involved, and this needs further investigation in future studies.

Body weight and composition

Increased satiety and energy expenditure observed with consumption of high-protein diets may translate into beneficial effects on body weight and composition over time. A recent review examined the hypothesis that different protein sources affect body weight and composition to different extents (6). They concluded that there was no clear evidence that 1 protein source was preferable over other sources, but that animal protein, especially from dairy, was better at promoting protein synthesis than plant proteins. This may be

because amino acids from dairy products are used to a lesser extent for splanchnic catabolic activity and to a greater extent for peripheral anabolic activity than plant proteins (72). Because of protein's anabolic activities, caused by increased muscle protein synthesis, bodybuilders and athletes often consume protein supplements with the purpose of increasing lean body mass. Moreover, proteins are found to be beneficial in weight-reducing programs because they help preserve lean body mass (73).

Exercise programs

As described previously, proteins high in BCAA and other essential amino acids are proteins of high quality, which are more effective at promoting protein synthesis than proteins low in essential amino acids (29). In addition to protein quality, the results obtained from resistance training combined with protein supplementation may depend on the rates of absorption and unique hormonal responses, such as secretion of insulin (74). Colker et al. (75) demonstrated a greater increase in body weight ($P < 0.05$) and lean body mass ($P = 0.09$) (Table 3) when adding BCAA and glutamine to whey compared with whey alone. Moreover, Kerksick et al. (76) showed a superior effect of whey and casein compared with whey, BCAA, and glutamine, which support that supplementation with proteins of higher quality promotes protein synthesis and thereby increases lean body mass. Consumption of whey primarily stimulates protein synthesis, whereas consumption of casein primarily inhibits protein breakdown (17,39). This may explain the beneficial effects on lean body mass observed when the 2 proteins are combined.

Casein appears to produce a greater protein balance than whey (17). However, when whey and casein are consumed with other sources of energy, whey appears to stimulate a greater protein balance than casein (56). The latter is important because athletes rarely consume protein supplements free of other energy sources. Likewise, it has been shown that muscle protein synthesis is higher at rest and after exercise after consumption of hydrolyzed whey compared with micellar casein (77), possibly because of the difference in protein kinetics or because whey induced a higher plasma concentration of leucine than casein (77). Cribb et al. (74) support this because they found a whey protein hydrolysate to reduce fat mass (NS) and increase lean body mass to a greater extent than casein (Table 3). In contrast, Demling and DeSanti (19) found hydrolyzed casein to decrease body fat mass and increase lean body mass to a greater extent than hydrolyzed whey. Moreover, they observed a tendency toward a greater loss of body weight with casein compared with whey supplementation. This supports the finding by Calbet and Holst (58) that hydrolysis affects casein kinetics and thereby potentially the results on body weight and body composition. However, a recent study by Lollo et al. (78) showed that intact casein was superior to both intact and hydrolyzed whey in increasing muscle mass in professional soccer players (Table 3).

Energy-restricted diets

Proteins are found to inhibit loss of lean body mass during energy restriction (73,79), presumably due to a positive protein balance. Moreover, proteins are found to induce greater weight and fat mass loss than carbohydrates (73). As casein and whey differ in their effect on protein balance, it could be speculated that dissimilar effects will be found when proteins are added to weight loss programs. Unfortunately, we are not aware of any human studies comparing the weight loss–inducing effects of whey and casein during energy restriction, but few studies have investigated the body weight–reducing effects of milk or dairy protein (combination of casein and whey) compared with other protein sources (Table 3). Faghih et al. (11) found milk to induce a greater reduction in body weight and central obesity than soy milk fortified with calcium during an 8-wk period. In contrast, Anderson and Hoie (80) observed no difference in body weight loss between soy and milk supplementation during 12 wk of energy restriction. In this study, it should, however, be noted that the soy protein was consumed more often than the dairy protein, which resulted in a higher dose of soy protein (Table 3). Data might have been different if the supplements had been isocaloric and if the subjects had consumed the same daily quantity of protein. Furthermore, in a study by Hochstenbach-Waelen et al. (48), gelatin was found to suppress hunger, but when gelatin was added to milk and compared with milk alone, no body weight–reducing difference was observed (51). The anorexigenic effect of gelatin did therefore not seem to translate into a beneficial effect on body weight when mixed with dairy protein compared with dairy protein alone.

In another study, Anderson et al. (81) examined the effects of casein and soy combined with energy restriction on body weight and composition (Table 3). Both proteins resulted in similar reductions in body weight and fat mass and similar increases in lean body mass. The result that soy and casein induce similar long-term effects on body weight is in line with the acute findings on appetite by Lang et al. (44,45).

With regard to studies on appetite regulation, the whey components αlac and GMP are suggested to have beneficial effects on body weight. Few short-term studies have found αlac to be more satiating than whey (34,36). To our knowledge, the long-term effects of αlac on body weight in humans have only been examined in 1 study, which did not find αlac to be superior to milk with regard to effects on body weight and composition (82) (Table 3). However, energy intake was highly regulated, and a potential effect of αlac on appetite regulation was probably not possible to detect, which might explain the missing effect on body weight and composition. Pilvi et al. (83) found that during energy restriction, αlac reduced body fat mass to a greater extent than whey in obese mice. Because αlac has beneficial short-term effects on appetite and animal studies indicate a beneficial effect on body fat mass, more human studies to elucidate the long-term effects on body weight and composition are needed.

Keogh and Clifton (84) examined the effects on body composition of isocaloric shakes of GMP or skimmed milk (Table 3). They observed no difference in loss of

body weight or fat mass or gain in lean body mass between groups. The observation that GMP adds no extra effect to milk is in line with the overall findings observed when looking at acute responses on energy intake or subjective sensations of appetite (30–32,34). On the other hand, results from a study in rats indicated a beneficial effect of GMP when looking at the effects on body fat accumulation (85). However, when examining the effect on body weight, whey seemed to be more beneficial than GMP. The GMP dose used in the rat study was much greater than that used in the human study, and it could be speculated that a higher dose of GMP might also be beneficial for humans.

Weight maintenance

Data published from the Diet Obesity and Genes (DiOGenes) study showed that a high protein/low glycemic index diet was beneficial in maintaining body weight after weight loss (1). However, the effects of protein from different sources were not examined. A study by Claessens et al. (86) investigated the effects of consumption of whey, casein, and carbohydrate on body weight and body composition during weight maintenance after 5 wk of energy restriction. During a 12-wk period, both protein groups showed significantly better weight maintenance after weight loss than the carbohydrate group (Table 3). Proteins induced a greater decrease in body fat mass than carbohydrate, but no difference was found between proteins. In addition, all supplements induced an increase in lean body mass, and they observed a tendency ($P = 0.09$) for whey to increase lean body mass compared with casein. They thereby support the finding by Cribb et al. (74), who found whey to increase lean body mass to a greater extent than casein during a 10-wk resistance training program. However, they do not agree with the findings by Demling and DeSanti (19) that casein is more beneficial than whey in sparing lean body mass during energy restriction. This may, however, partly be ascribed to the structure of the proteins examined as hydrolyzed casein was studied by Demling and DeSanti (19), whereas intact casein was studied by Claessens et al. (86) and Cribb et al. (74).

Few studies have compared the effects of dairy protein and soy. Baer et al. (43) observed no difference between proteins when looking at body weight, fat mass, and lean body mass. However, they observed that whey was superior to carbohydrate in reducing body weight and fat mass, whereas no difference was observed between soy and carbohydrate. In contrast, Takahira et al. (87) found milk to be superior to soy in reducing body weight and visceral adiposity. In this study, the milk formula contained a larger amount of calcium than the soy formula, and because calcium has shown beneficial effects on body weight (10), part of the effect may also be ascribed to this mineral.

Finally, Hochstenbach-Waelen et al. (52) supported the findings of gelatin on body weight during energy restriction. Both gelatin and milk resulted in a successful weight maintenance period with no weight regain, but no significant differences were observed between proteins (Table 3).

In summary, data provide no clear evidence that whey is better at inducing weight loss or maintaining body weight than casein or vice versa. However, data indicate that protein structure, intact versus hydrolyzed protein, may be of importance, especially when examining the effects of casein because data indicate that the absorption and digestion rates of casein are increased by exogenous hydrolysis. In future studies, as for studies on appetite regulation and energy expenditure, it could therefore be interesting to examine the effects of hydrolyzed casein versus intact casein with regard to changes in body weight and composition.

Conclusion

Despite good evidence to support that protein is beneficial in increasing and maintaining weight loss due to effects on appetite regulation and energy expenditure, data are inconclusive with regard to the effects of various protein types. However, there is some evidence indicating that whey is more satiating than casein in the short term, whereas casein is more satiating in the long term. This may be explained by the differences in protein kinetics between the 2 dairy proteins. When examining the effects on GI hormones, some studies propose whey to be superior to other proteins, especially when studying the effects on GIP, but data are inconsistent, and more studies are needed. Likewise, no consistent data exist on DIT where only very few studies have compared casein and whey. Finally, when interpreting data on appetite and body weight regulation, studies indicate that the structure of the protein seems to be very important, especially when examining the effects of casein.

Based on the studies included in this review, the timing of protein supplementation and measures of appetite and energy expenditure, as well as protein structure, seem to be key elements in the design of future studies. In addition, most studies examining the effects on appetite and energy expenditure only study the acute effects, and in future studies, it would therefore be interesting to study the long-term effects with regard to these parameters.

Acknowledgments

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