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REVIEW

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Can dietary proteins selectively reduce either the visceral or subcutaneous adipose tissues?

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Summary

There is a considerable appeal for interventions that can selectively reduce either the visceral or subcutaneous white adipose tissues in humans and other species because of their associated impact on outcomes related to metabolic health. Here, we reviewed the data related to the specificity of five interventions to affect the two depots in humans and rodents. The interventions relate to the use of dietary proteins, monounsaturated fatty acids, polyunsaturated fatty acids, calorie restriction, or bariatric surgery. The available data show that calorie restriction and bariatric surgery reduce both visceral and subcutaneous tissues, whereas there is no consistency in the effect of monounsaturated or polyunsaturated fatty acids. Dietary proteins, more specifically, whey proteins show efficacy to reduce one or both depots based on how the proteins interact with other macronutrients in the diet. We provide evidence that this specificity is related to changes in the composition and the functional potential of the gut microbiota and the resulting metabolites produced by these microorganisms. The effect of the sex of the host is also discussed. This knowledge may help to develop nutritional approaches to deplete either the visceral or subcutaneous adipose tissues and improve metabolic health in humans and other species.

KEYWORDS
energy balance, gut microbiota, metabolites, nutrition

1 | INTRODUCTION

All mammals attempt to regulate calorie (energy) intake and usage (in tissues), so that at any given time, there is no energy excess or deficit. However, this is hard to achieve because of the energetic challenges faced by organisms on a daily basis. The imbalances in energy are counteracted by the ability of the adipose tissue to store the excess energy as lipids and mobilize these at times of energy deficit to sustain functions of tissues. This role is assigned to the white adipose tissues (WATs), which can be broadly categorized as visceral WAT (vWAT) or subcutaneous WAT (sWAT).[1] Interestingly, it is widely recognized that excess lipid accumulation in the vWAT increases the risk of metabolic syndrome, while storage in the sWAT, in particular in the thigh, has reduced risk of this negative health outcome,[1,2] albeit evidence also suggests that the deep sWAT in the abdominal area could be an exception.[3] Thus, interventions that can selectively reduce the vWAT or the specific tissues associated with sWAT, can provide significant health benefits. Additionally, and beyond the health implications, there is a societal burden to maintain specific body shape for males and females that store dietary fat differently.[4] Of note, males tend to store excess lipids in the vWAT while deposition in the females is mainly targeted toward the sWAT.[4] Furthermore, although there is on average a higher calorie intake in males than females, females have a greater overall body fat.[4,5] Thus, for both health and

TABLE 1 Impact of protein source on the visceral and subcutaneous adipose tissues in humans. Colored rows indicate efficacy on one or both tissues.

Protein source and F/C in the serving	Dose length	Pre-intervention subjects				Post-intervention impact on adiposity							
		Age	Sex M/F	Diet	BMI	Control	BW	Fat	vWAT	sWAT	Method	EI	Ref
Milk protein 22 g/d in serving with 3× energy CHO versus FAT	20 W	54 ± 13	Both 6/18	Free living	29 ± 0.8	Base line	↓ ~ 2.6%	?	↓ ~ 15%	↓ ~ 5%	CT	?	6
Whey 60 g/d in water	16 W	50 ± 2	Both 7/11	Free living	28 ± 1	Base line	↓ ~ 2.2%	↓ ~ 0.6%	↔	↓ ~ 6%	DXA	↔	7
Whey 56 g/d in serving with 4× energy CHO versus FAT	23 W	49 ± 9	Both 10/13	Free living	31 ± 2.2	CHO	↓2%	↓ ~ 6%	?	↓(?)	Air-displacement plethysmography	↔	8
Whey 56 g/d in serving with 4× energy CHO versus FAT	23 W	49 ± 9	Both 10/13	Free living	31 ± 2.2	Soy	↔	↔	?	↓(?)	Air-displacement plethysmography	↔	8
E-Lf 300 mg/d tablet	8 W	42 ± 10	Both 5/8	Free living	30 ± 4.8	Placebo	↓ ~ 1.9%	↔	↓ ~ 12%	↔	CT	↔	9
Whey 40 g/d in serving with 2× energy CHO versus FAT	8 W	37 ± 2.9	F 17	Free living	31 ± 1	Collagen	↔	↔	↓ ~ 3%	↔	DXA	↔	10
Whey −40 g/d in serving with 2× energy CHO versus FAT	8 W	37 ± 2.9	F 17	Free living	31 ± 1	Base line	↔	↔	↓ ~ 6%	↔	DXA	↔	10
CAS −0.63 g/d in serving with 4× energy CHO versus FAT	20 W	44 ± 1	Both 25/25	Free living	27 ± 0.3	Base line	↔	↔	↑ ~ 4%	↔	CT	↔	11
CAS −20 g/d in serving with 2.8× energy CHO versus FAT	12 W	55 ± 5	F 15	Free living	30 ± 3.1	Base line	?	↔	↔	↑ ~ 22.9 cm^2	DXA	?	12
Lactic fermented egg white −8 g/d in serving with 48× energy CHO versus FAT	8 W	53 ± 3.1	M6	Free living	28 ± 1.5	Base line	↔	↔	↓ ~ 9%	↔	CT	↔	13
Conglycinin −0.63 g/d in serving with 4× energy CHO versus FAT	20 W	43 ± 2	Both 22/23	Free living	27 ± 0.3	Base line	↓ ~ 0.8%	↓ ~ 2.5%	↔	↔	CT	↔	11
Soy −20 g/d in serving of 2.8× energy CHO versus FAT	12 W	55 ± 5	F15	Free living	30 ± 3.1	Base line	?	↓50 cm^2	↔	↓ ~ 14.73 cm^2	DXA	?	12

Note: Error shown as standard deviation, except data from references 9 and 12, which are shown as standard deviations.

Abbreviations: BMI, body mass index; BW, body weight; CAS; casein; CHO, carbohydrate, CT; Computed Tomography; DXA; dual energy X-ray absorptiometry, E-Lf, enteric coated lactoferrin; F, female; F/C, fat to carbohydrate ratio M; male; vWAT; visceral white adipose tissue; sWAT subcutaneous white adipose tissue; EI, energy intake; W, weeks; ↓ decrease; ↔ no change; ↑ increase; ?, not reported.

TABLE 2 Impact of dietary proteins from animal and plant sources and the associates amino acids on the visceral and subcutaneous adipose tissues in rodents. Colored rows indicate efficacy.

Protein/dose	Control/dose	F/C ratio	Length	BW	Body fat
Whey 32%	Whey 8%	High (1.3× energy FAT versus CHO)	9 W	↔	?
Whey 30%	CAS 30%	High (3.6× energy FAT versus CHO)	12 W	↓ ~ 14%	?
Whey 20%	CAS 20%	High (1.3× energy FAT versus CHO)	5 W	↓ ~ 8%	?
BSA 20%	CAS 20%	High (1.3× energy FAT versus CHO)	13 W	↓ ~ 37%	↓ ~ 27%
Whey 20%	CAS 20%	Low (7× energy CHO versus FAT)	17 W	↓ ~ 30%	?
Whey 20%	CAS 20%	Low (7× energy CHO versus FAT) to High (1.3× energy FAT versus CHO)	10 W	↔	?
Whey 20% + ABX	Whey 20%	High (1.3× energy FAT versus CHO)	10 W	?	?
CAS 20%	Chicken 20%	High (3× energy FAT versus CHO)	14 W	↔	?
CAS 20%	Chicken 20%	Low (7× energy CHO versus FAT)	14 W	↔	?
CAS 20% + ABX	CAS 20%	High (1.3× energy FAT versus CHO)	10 W	?	?
CAS 16/32% Hydrolyed	CAS 16 32%	Low (1.4× energy CHO versus FAT)	8 W	↓ ~ 50%	?
Kangaroo muscle 32%	Kangaroo muscle 8%	High (1.3× energy FAT versus CHO)	9 W	↔	?
Egg white 20%	CAS 20%	Low (1.4× energy CHO versus FAT)	4 W	↔	?
Cod/Scallop 15%	Chicken 15%	High (3.7× energy FAT versus CHO)	6 W	?	?
Soy 17%	CAS 17%	High (1.2× energy FAT versus CHO)	6 W	↔	?
Soy 17%	CAS 17%	Low (3.7× energy CHO versus FAT)	6 W	↔	?
EAA 20% Suppl.	CAS 20%	High (1.3× energy FAT versus CHO)	80 W	↓ ~ 63%	↓ ~ 31%
BCAA-Rest. 18%	Un- Rest 18%	High (3× energy FAT versus CHO)	16 W	↓ ~ 27%	↓ ~ 55%
BCAA-Phe Rest. 18%	Un-Rest 18%	High (3× energy FAT versus CHO)	16 W	?	↓ ~ 20%
BCAA-Rest 20%	Unrest 20%	Low (3.2× energy CHO versus FAT)	10 W	?	?
Leu-Rest 20%	Unrest 20%	Low (3.2× energy CHO versus FAT)	10 W	?	?

Abbreviations: ABX, antibiotics; ATND, adipose tisue not distinguished; BCAAs; branch chain amino acids; BSA; bovine serum albumin; BW, body weight; CAS, casein; CHO, carbohydrate, EAA, essential amino acids; eWAT; epididymal white adipose tissue; EI, energy intake; F, female; F/C, fat to carbohydrate ratio; M; male; iWAT, inguinal white adipose tissue; Leu, leucine; pWAT, perirenal white adipose tissue, Rest, restricted; mWAT, mesenteric white adipose tissue; rWAT, retroperitoneal white adipose tissue; Phe; phenylalanine; vWAT; visceral white adipose tissue; sWAT subcutaneous white adipose tissue; ↓ decrease; ↔ no change; ↑ increase; ?, not reported.

TABLE 2 (Continued)

Protein/dose	vWAT type	sWAT type	EI	Species	Sex	Ref
Whey 32%	↓ ~ 27% eWAT ↓ ~ 38% pWAT	↓ ~ 32% ND	↓ 19%	Rat	M	[14]
Whey 30%	↓ ~ 20% eWAT ↓ ~ 40% mWAT ↓ ~ 28% rWAT	↓ ~ 22% ND	↔	Mouse	M	[15]
Whey 20%	↓ ~ 39% eWAT	↓ ~ 32% ND	↑ ~ 10%	Mouse	M	[16]
BSA 20%	↔eWAT	↓ ~ 39% ND	↑ ~ 16%	Mouse	M	[17]

TABLE 2 (Continued)

Protein/dose	vWAT type	sWAT type	EI	Species	Sex	Ref
Whey 20%	↓ ~ 32% eWAT	↔ND	↑ ~ 14%	Mouse	M	
Whey 20%	↔ eWAT	↓ ~ 27% ND	↑ ~ 12%	Mouse	M	16
Whey 20% + ABX	↓ ~ 76% eWAT ↓ ~ 83% rWAT ↓ ~ 96% mWAT	↓ ~ 74% ND	?	Mouse	M	19
CAS 20%	↓ ~ 20% eWAT ↔ pWAT	?	↔	Mouse	M	20
CAS 20%	↔ eWAT ↔ pWAT	?	↔	Mouse	M	20
CAS 20% + ABX	↓ ~ 42% eWAT ↓ ~ 39% rWAT ↓ ~ 33% mWAT	↓ ~ 50% ND	?	Mouse	M	19
CAS 16/32% Hydrolyed	↓ ~ 69% eWAT	↓ ~ 68% iWAT	↔	Mouse	M	21
Kangaroo muscle 32%	↓ ~ 21% eWAT + mWAT+ pWAT	↓ ~ 32% ND	↓19%	Rat	M	14
Egg white 20%	↓ ~ 12% eWAT+mWAT+pWAT_rWAT	↓ ~ 20% ND	↔	Rat	M	22
Cod/Scallop 15%	↓ ~ 52% eWAT ↓ ~ 56% p/rWAT	↓ ~ 50% iWAT	↔	Mouse	M	23
Soy 17%	↓ ~ 23% eWAT	?	?	Rat	M	24
Soy 17%	↓ ~ 14% eWAT	?	?	Rat	M	24
EAA 20% Suppl.	?	?	↔	Mouse	M	25
BCAA-Rest. 18%	↓ ~ 67% eWAT	↓ ~ 74% iWAT	?	Mouse	M	26
BCAA-Phe Rest. 18%	↔eWAT	↓ ~ 55% iWAT	?	Mouse	M	25
BCAA-Rest 20%	↔eWAT	↔iWAT	↑ ~ 27%	Mouse	M	27
Leu-Rest 20%	↑ ~ 84% eWAT	↔iWAT	↔	Mouse	M	27

Abbreviations: ABX, antibiotics; ATND, adipose tisue not distinguished; BCAAs; branch chain amino acids; BSA; bovine serum albumin; BW, body weight; CAS, casein; CHO, carbohydrate, EAA, essential amino acids; eWAT; epididymal white adipose tissue; EI, energy intake; F, female; F/C, fat to carbohydrate ratio; M; male; iWAT, inguinal white adipose tissue; Leu, leucine; pWAT, perirenal white adipose tissue, Rest, restricted; mWAT, mesenteric white adipose tissue; rWAT, retroperitoneal white adipose tissue; Phe; phenylalanine; vWAT; visceral white adipose tissue; sWAT subcutaneous white adipose tissue; ↓ decrease; ↔ no change; ↑ increase; ?, not reported.

cosmetic reasons, there is a demand for safe and cost effective interventions. Here, we reviewed evidence for types of interventions that can selectively reduce the vWAT or the sWAT. The interventions are consumption of dietary proteins (Tables 1 and 2), monounsaturated fatty acids (MUFAs),[28–32] or polyunsaturated fatty acids (PUFAs)[32–41] (Table S1). We also assessed the effect of calorie restriction (CR)[42–51] and bariatric surgery (Rou-en-Y gastric bypass; RYGB),[52–57] (Table S1). Of note, we highlight the mechanisms that are likely to mediate effects of dietary proteins on the vWAT and the sWAT (Tables 1 and 2).

1.1 | Adipose tissues differ in location and function

Adipocytes exist as white, brown, and/or beige.[58,59] While mammals differ in the size and location of the adipose tissues, their overall functionality appears to be preserved across the Animal Kingdom. Notably, the WAT functions to regulate energy balance, whereas the brown adipose tissue (BAT), which is located in several regions including the interscapular region and around the kidneys, is involved in non-shivering thermogenesis.[60,61] While the existence of WAT and BAT have been known for some time, the beige (or brown in white) is a more recent discovery, presumably because these cells are found interspersed within the WAT, and can be induced to achieve a thermogenic potential similar to BAT by external stimuli such as exposure to cold, exercise, or tissue injury.[58]

The vWAT is located throughout the body and can be further subcategorized ascardiac WAT (epi-, peri-, and para-cardial), omental WAT (oWAT), mesenteric WAT (mWAT), retroperitoneal WAT (rWAT), perirenal WAT (pWAT), periaortic, or the gonadal WAT, which in males, is the epididymal WAT (eWAT) and in females, the periovarian.[62] The sWAT compartment is located under the skin, which exists as anterior (suprascapular and interscapular) or posterior, the latter as dorsolumbar, inguinal (iWAT) or the gluteal.[62,63] While this classification is based on studies conducted in rodents, there are some similarities (e.g., mWAT and rWAT) and differences with corresponding tissues in humans. Of note, the humans do not have the perigonadal fat that rodents have, and the sWAT in humans is located in the abdomen and the gluteofemoral regions, whereas in rodents, the sWAT can be found in the anterior and posterior regions as detailed above.[64] Interestingly, and in contrast, the BAT and beige show remarkable topological similarity between humans and rodents.[65] The comparison between species is further complicated by the fact that there is no formal definition as to which tissues constitute vWAT and sWAT. Accordingly to one classification, the vWAT drain blood into the hepatic portal vein, while sWAT drain blood systemically into the vena cava. According to this classification, rWAT is sometimes excluded as vWAT and yet its metabolic activity is more similar to vWAT than sWAT.[62]

Twin studies suggest a substantial (>75%) genetic contribution to the variance in body mass index (BMI) in humans.[66,67] Indeed, we know that distinct genetic programs determine the differences in functionality and location of the adipose tissues,[68–71] which show diverse neuronal innervation.[72–74] These differences allow the adipose tissues to have distinct hyperplastic potential,[75] respond differently to nutrient quantity and quality,[76–78] via their access through the surrounding vasculature,[79] leading to increased cell number by cellular proliferation and differentiation (hyperplasia), and/or cell expansion because of excess storage (hypertrophy).[75] For the sWAT, the tissue expansion occurs by hyperplasia and hypertophy, while the vWAT grows by cellular hypertrophy.[62] Additionally, the sex of the individual, puberty, and the composition of the gut microbiota all contribute to the differences in functionality of adipose tissues, as discussed below. Thus, alteration in the mechanisms that link these different components can provide a route to selectively alter the mass of the sWAT or the vWAT.

1.2 | Selectivity of dietary proteins with respect to affecting either the vWAT or sWAT

It is generally believed that the obesity crisis has arisen, at least in part, from the increased intake of calories, mainly from dietary fat,[80–83] rather than due to a declined energy expenditure.[84] In contrast, intake of dietary proteins has remained largely stable in humans, roughly around 15% of total intake.[80,83] This suggests that intake of dietary protein is largely regulated in humans and accordingly, the protein leverage hypothesis was formulated based on the data that intake of diets low (5%) in proteins caused a higher energy intake compared to intake of diets high (30%) in proteins.[85,86] However, data also exist that contradict this hypothesis with some studies showing no effect on energy intake (Tables 1 and 2). Thus, there is a renewed focus on assessing if protein quality, within the range that humans consume this macronutrient, affects satiety,[87–90] energy expenditure,[90,91] and/or feed efficiency,[8,15,92,93] as this in turn would affect energy balance and adiposity. When assessing the effects of different proteins, it is important to note that dietary proteins differ substantially in terms of their amino acid composition including branch chain amino acids (BCAAs),[94,95] and how they are released upon digestion and how they are absorbed into the blood stream.[96] Of note, whey proteins derived from milk have high levels of BCAA compared to casein proteins, derived also from the same source, as well as compared to many plant proteins.[94] Additionally, whey proteins are digested quickly and the amino acids are absorbed much more rapidly than most other dietary proteins.[96] Thus, while excess availability of BCAA has been shown to cause detrimental metabolic health effects,[97,98] intake of dietary proteins rich in BCAA (e.g., whey proteins) provide many health benefits including improved body composition.[15,16,91,99,100] Here, we highlight how variation in protein quality and associated amino acids can selectively affect either the vWAT or sWAT and how interactions with other macronutrients in the diet (dietary fat to carbohydrate [F/C] ratio) can further modify this effect.

1.2.1 | Human studies

The impact of protein quality on vWAT and sWAT have been investigated using different doses (0.63 up to 60 g/d), over a range of durations (8–20 weeks), using both or one sex (only females), and in

individuals of different ages who are either overweight or obese and with different BMIs (Table 1). In these studies, the effects of the tested dietary protein were compared to baseline measurements or to a different control protein, where the magnitude of the effect on the vWAT and/or the sWAT was calculated using a wide variety of techniques (Table 1). Despite these differences, a pattern emerges highlighting an effect of protein quality on the two depots. Notably, while milk proteins (22 g/d), which are a mixture of whey and casein proteins,[101] reduced both vWAT and sWAT in individuals who were obese after 20 weeks of intake compared to baseline measurements,[6] intake of a higher quantity of whey (60 g/d) alone reduced sWAT without affecting vWAT[7] (Table 1). In comparison to intake of soy protein or carbohydrates, a similar dose of whey proteins reduced waist circumference,[8] suggesting an effect on the sWAT because of the stronger correlation between waist circumference and the sWAT than vWAT[102,103] (Table 1). Switching the protein quality to one of the nine individual proteins that constitute whey, notably lactoferrin (Lf),[101] and using the enteric-coated form of the protein (E-Lf) to protect it from digestion in the upper digestive tract, also switched the effect, which reduced vWAT,[9] similar to intake of fermented egg white,[13] whereas intake of soy proteins reduced only the sWAT[12] (Table 1). The specificity of soy proteins to affect one depot was not seen using the peptide β-conglycin, derived from soy protein.[11] Ultimately, these data suggest an effect of dietary protein quality on the vWAT and/or sWAT. These observations are in contrast with intake of MUFA,[28–32] PUFA,[32–41] CR,[42–51] or bariatric surgery (RYGB),[52–57] which affect both depots (CR and RYGB), or show no consistency in their effects on either depot (MUFA and PUFA) (Table S1).

1.2.2 | Rodent studies

Extending the findings from humans, the effects of protein quality have been investigated in rodents in specific tissues associated with the two depots, although it should be noted that the majority of these studies focused on the vWAT (Table 2). Furthermore, there was a bias toward using males (Table 2). However, these studies benefited from being able to have greater control over the ingredients that can be added into the diets to investigate the interaction between protein quality and F/C ratio. While studies conducted in human show that whey proteins specifically reduced sWAT in males and females who are obese, when tested together as a group, or reduced vWAT in females (Table 1), data from rats show that 32% (energy) protein either as whey or the muscle from Kangaroo, were able to reduce both vWAT and sWAT when compared to intake of 8% (energy) protein[14] (Table 2). Interestingly, whey reduced both eWAT and pWAT, whereas the meat from the Kangaroo significantly reduced the combine weight of eWAT, rWAT and pWAT (Table 2). Similar data were obtained when we compared consumption of 30% or 20% energy from whey proteins to intake of casein in mice[15,16] (Table 2). Since the various studies referred above focused on the collective proteins within whey and assessed effects at high F/C ratios, we then investigated the effects of individual whey proteins on the two depots. In the first series of investigations, using the same high F/C ratio, 20% energy from bovine serum albumin (BSA), associated with whey, reduced sWAT without affecting the eWAT compared to intake of casein in mice,[17] which contrasts with the impact of the collective whey proteins, which affected both depots[16] (Table 2). Interestingly, this specificity was not seen with some other whey proteins, namely Lf[104] or lactalbumin,[105,106] regardless of the control protein used in mice. Other proteins have also been studied. Casein has been shown to be more efficacious than chicken proteins, reducing eWAT but not pWAT.[20] Cod/scallop reduced eWAT, and pWAT/rWAT tissues and with an added reduction in iWAT approximately by 50%.[23] Collectively, these data from studies conducted in rodents provide further evidence that the quality of the protein in a diet enriched with high F/C ratio affects the adipose tissue.

Extending the above line of investigation into the interaction between whey proteins and F/C ratio, the same protein combination as part of diet enriched with low F/C ratio reduced the eWAT without affecting the sWAT in mice.[18] Interestingly, in the latter case, re-switching the animals fed a diet enriched in whey proteins from a low to high F/C changed the specificity from eWAT to sWAT,[16] but did not regain the specificity to affect both depots, seen as part of intake of whey proteins with high F/C ratio[16] (Table 2). Similarly, the ability of casein to reduce eWAT relative to the impact brought about by the intake of chicken can be abolished by switching the diet from a high to low F/C[20] (Table 2). There was no difference in the ability of soy proteins to reduce eWAT in rats fed diets with either high or low F/C ratio[24] (Table 2). These data suggested that the effects of some dietary proteins, and in particular whey, can be tailored to affect the vWAT or sWAT by varying the F/C ratio. Extending this work, and within the same high F/C diet, mice that drank water supplemented with antibiotics and ingested whey had a greater loss of tissues compared to mice that drank water without antibiotics, whereas the effect was less for the same comparison in mice-fed casein[19] (Table 2). This further suggest that the related effects involve the gut microbiota, which are impacted by the consumption of dietary proteins (see below). Indeed, it may be that the microbial utilization of the digested dietary proteins reduced (and modify) the direct impact of the digested components on the host tissues.

In searching for the bioactivity associated with the effect of dietary proteins, data have emerged highlighting the importance of dietary amino acids. Of note, mice that ate hydrolysed casein in diets high in F/C ratio reduced both depots relative to the impact of intake of casein that was unhydrolysed.[21] It has also been shown that supplementing essential amino acids (EAAs) in place of casein in diets high in F/C ratio reduced body weight and body fat in mice, although the affected adipose tissues were not reported in this study[25] (Table 2). Further studies have narrowed the impact to a specific reduction of BCAA in the diet, which reduced both depots in mice fed diets high in F/C ratio.[26] Moreover, the specificity can be altered such as to only reduce the iWAT in the subcutaneous depot by reducing the BCAA in the diet in combination with phenylalanine.[26] Interestingly, this effect is lost when switched to diets low in F/C ratio,[27] or

can be reversed to cause a gain in weight (for the eWAT) if a low F/C ratio is combined with a diet restricted in leucine[27] (Table 2).

Given that whey proteins contain a high BCAA content,[94] we wondered how whey proteins can specifically affect the vWAT or sWAT tissues, when reducing the BCAA in diets had a similar impact on the two tissues.[26,27] Some clues that might explain this paradox came from analysis of the metabolite content in the caecal samples collected from mice-fed whey proteins.[15] The data show that ingestion of whey proteins relative to casein as part of a diet with a high F/C ratio decreased levels of BCAA, in particular valine, in the caecum in mice and that this change in the BCAA content was associated with the reduction in body weight gain and fat mass.[15] We have now established that the gut microbiota are the primary cause of the reduced BCAA seen with intake of whey (see below).

1.3 | Potential mechanisms

1.3.1 | Calorie intake

There is evidence supporting the protein leverage hypothesis,[85,86,107–109] where the effects relate, at least in part, to the production of satiety related hormones.[89,110–113] However, there is also accumulating evidence that dispute the protein leverage hypothesis. As detailed above, there are studies showing that dietary proteins have no effect on energy intake or that it increases intake, and yet, the effects on vWAT or the sWAT are still sustained (Tables 1 and 2). For instance, enteric coated Lf reduced vWAT[9] and intake of whey reduced sWAT[7] without changing intake in humans (Table 1). Similarly, the hydrolysed form of casein[21] or intake of fish (cod/scallop),[114] reduced both vWAT and sWAT via a mechanism that did not change energy intake in mice (Table 2). In some instances, specificity to affect tissues was seen even during increased intake of energy,[16–18] albeit this was not consistently reported.[105,115] These data suggest that the effects of dietary proteins to impact on either or both depots, are not dependent on energy intake. In fact, subjecting animals of different species to an imposed reduction in calorie intake reduced both v- and sWAT simultaneously[42–51] (Table S1), whereas intake of dietary proteins retained specificity to affect one or both tissues, based on the interaction with other macronutrients.

1.3.2 | Gut microbiota

The importance of the gut microbiota for energy harvest was demonstrated by the finding that germ-free mice consume more food despite a reduced body weight gain and body fat.[116] Further evaluation of the relationship between diet, the gut microbiota and energy balance has shown that dietary fat is the main cause of changes in the composition of the gut microbiota in humans and mice[15,117] but, in addition, in humans, there is a measurable effect of protein quality when the source of dietary fat is separated into high and low saturated forms.[117] Similar effects were notable in mice when fed whey proteins in diets with a high[15,16] or low F/C ratio.[18] Focusing on whey proteins, and within diets high in F/C ratios, the impact that reduced both vWAT and sWAT also altered the beta diversity in the gut microbiota compared to intake of casein, with some difference in alpha diversity.[16] Mice-fed whey or casein that were administered antibiotics, supplemented in water, had a depleted gut microbiota and had reduced adipose tissues, with the impact been greater in mice consuming whey (Table 2), suggesting a potential role for the gut microbiota in modifying the effects of source of protein on specific depots.[19] Further evidence in support of this hypothesis came from our work with diets enriched with whey or casein and with a low F/C ratio. In this experimental setup, whey proteins reduced only the eWAT and not the sWAT, and the impact on the gut microbiota now included changes in both alpha and beta diversities.[18] A switch from low to high F/C ratio that also switched the specificity of whey proteins onto the sWAT, resulted in the low impact on alpha and beta diversities.[16] Of note, the abundance of *Lactobacillus murinus* and its functional pathways were associated with the effect of whey in diets high in F/C ratio but not in animals that had a previous history of consuming a diet with a low F/C ratio,[16] which we know to affect the sWAT.[18] These data generated from mice from adolescent to adulthood (15 weeks old), were further extended by feeding the proteins at a much older age (20 weeks). In these older mice, increasing the F/C ratio with a much higher protein quantity (30% whey proteins), altered the bacterial species, with increased abundance of *Bacteroides uniformis* and *Akkermansia muciniphila*[15] and increased the pathways associated with degradation of proteinogenic amino acids as well as synthesis of lipids in the gut microbiota.[15] This effect was reflected in the caecal metabolome, which differed between mice-fed whey or casein.[15] Of note, and consistent with the metabolism of amino acids by the gut microbiota, the concentration of caecal BCAA, specifically, valine, decreased in the group-fed whey, as detailed above.[15] Furthermore, and consistent with the increased activity of the pathways in microbiota related to lipid biosynthesis, the caecal availability of medium and long chain fatty acids increased.[15] This metabolite profile has been shown to reduce both vWAT and sWAT in humans[118] (Table S1), where the effect is accentuated by intake of whey,[92] likely due to changes in the gut microbiota.[15] In fact, transfer of microbiota from mice-fed whey to mice-fed casein, reduced weight gain among the recipients by 90%.[15] The data highlight the importance of the gut bacteria and its functional pathways in mediating the effects of whey proteins, although data are lacking for how these microorganisms mediate other protein effects particularly related to humans.[117]

1.3.3 | Sex

There is a striking difference in the body composition between males and females, with females having a higher percentage of body fat than males.[4,119,120] Yet, males consume more energy,[5] whereas females have greater clearance of free fatty acids[121] and glucose metabolism, which could explain why males tend to have a higher prevalence of type 2 diabetes.[119,122] This suggests the existence of mechanisms that

partition energy differently in males and females. These mechanisms include genetic contributions[119,123,124] and sex hormones,[119] which are further modified by the diet.[78,122] Of note, feeding a diet high in fat to males and females differentially affected genes involved in glucose and fatty acid transport,[125] lipid accumulation and synthesis, as do fasting and refeeding.[126] Extending the effect of diet, there is now growing evidence that the composition of the gut microbiota also segregate according to sex.[127–129] The sex specificity in the gut microbiota is further highlighted by the finding that the transfer of fecal matter from a 32-year woman to male and female rats that were germ-free resulted in clustering of microbiota according to the sex of the host animal.[130] Interestingly, it has been shown that effects that are independent of sex predispose the gut microbiota to differences that are specific to the sex.[131]

There is limited data on how the sex modifies the effects of dietary proteins on the vWAT and sWAT as majority of the studies have been undertaken in groups that included both sexes in humans and in males only in different rodent species (Tables 1 and 2). Of note, only six studies tested the effects of dietary proteins on both sexes (together) in humans, whereas three undertook similar work only recruiting females and one with only males (Table 1). In rodents, only two studies used females but, in both cases, there were no effects of the tested protein (glycomacropeptide and salmon) on the two depots.[115,132] Despite this, there are some interesting observations that need to be highlighted. For instance, while above studies show that whey proteins reduce sWAT in both male and female subjects that were obese when tested together as a group, studies undertaken with only females show that whey proteins reduced only the vWAT (Table 1).[10] Similarly, effects of casein were confined to the vWAT in both sexes when tested together,[11] but when only females were used, the effect was seen only in the sWAT[12] (Table 1). In the latter instance, it is uncertain if the effect on the sWAT relates to the life stage of the females (postmenopausal). Regardless, and in contrast to all other proteins mentioned above, intake of dietary casein increased the size of the adipose tissues in humans (Table 1). These data suggest that the effects of dietary protein on the vWAT and sWAT can further be modified by the sex of the individual, which may be related to the difference in energy and macronutrient intake exhibited by females as compared to males.[5] Indeed, the effects of whey proteins on energy intake, gastric emptying, and the production of gut hormones are influenced by the sex of the individual.[133] In trying to untangle these different possibilities of interactions between protein quality and sex, and to determine the associated mechanisms of action, we showed that microbiota associated with intake of casein in mice, as part of diets high in F/C ratio, do in fact increase weight gain in males in the same species.[15] To explore the effect of sex, we investigated for metabolites that are specific to each sex. In this unpublished study, we fed male and female mice that are of adolescent age, 20% (energy) casein for 4 weeks and analyzed the caecal contents by metabolomics approach as detailed previously.[15] Data show the presence of a unique molecule, which was more abundant in females than in males (Figure S1A). Moreover, in virgin females, the abundance of this molecule can be further increased by feeding whey proteins (Figure S1B), where the effect was sustained at lactating females that had reduced eWAT and rWAT, based on the effect of protein quality and the energetic demand of lactation (Figure S1C). The data provide the incentive to search for other metabolites with the view to determining if these have functional links with the vWAT or sWAT.

1.3.4 | Future studies

Based on data presented for humans in Table 1, there is a need to focus attention on males and females separately, and to assess the effect of protein quality on the two depots in humans consuming diets high or low in F/C ratio as free living individuals. Similarly, in studies related to rodents, the bias toward using males need to be addressed (Table 2). In both species, more work is needed to determine if the sensory aspects of protein quality affect energy partitioning in the two depots. Moreover, and exploiting the similarities and differences in the gut microbiota between humans and rodents,[134,135] which are reflected in the caecal and plasma profiles between species,[136,137] it might be then possible to understand how cross species transfer of microbiota (from the humans to rodents in each sex) could modify vWAT and/or the sWAT compared to the effects seen within the species.

2 | CONCLUSION

Based on the limited studies in humans and the more extensive work undertaken in rodents, evidence suggest that dietary proteins, in particular whey proteins, can selectively reduce either the vWAT or sWAT. Studies undertaken in rodents further show that dietary proteins interact with other macronutrients in the diet, and change the above outcomes, where the effects are likely to be mediated by the associated gut microbiota and the metabolites produced by these microorganisms, and accordingly to the sex of the host. The data provide direction to further investigate and develop dietary approaches to improve metabolic health in humans and in other species in a way that has not been achieved to date.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

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