A word of caution against excessive protein intake

Bettina Mittendorfer, Samuel Klein and Luigi Fontana

Abstract | Dietary protein is crucial for human health because it provides essential amino acids for protein synthesis. In addition, dietary protein is more satiating than carbohydrate and fat. Accordingly, many people consider the protein content when purchasing food and beverages and report 'trying to eat more protein'. The global market for protein ingredients is projected to reach approximately US$90 billion by 2021, largely driven by the growing demand for protein-fortified food products. This Perspective serves as a caution against the trend of protein-enriched diets and provides an evidence-based counterpoint that underscores the potential adverse public health consequences of high protein intake.

Dietary protein is a critical macronutrient component of our diet that provides essential amino acids (BOX 1) needed to synthesize proteins that constitute the skeletomuscular system, enable the function of vital organs and immune cells, and act as regulatory and transporter molecules. Adequate essential amino acid consumption is therefore required for optimal physical and physiological function. During times of inadequate protein consumption or illness, amino acids stored in muscle are released to support protein synthesis and essential physiological functions in vital organs. In addition, dietary protein is more satiating than carbohydrate and fat, which could be beneficial in lifestyle interventions aimed at preventing or treating obesity[1–3]. For these reasons, a high dietary protein intake has been recommended by medical organizations, international expert groups and health-care professionals to increase muscle mass and strength and facilitate weight management[1,4–8]. However, incorporating excessive amounts of protein into the diet could have adverse effects on insulin action and increase the risk of developing type 2 diabetes mellitus (T2DM)[9–16]. Therefore, it is important to understand the complex balance between the potential beneficial effects of high protein intake on muscle mass and function and the potential adverse effects of high protein intake on metabolic function.

In this Perspectives, we discuss protein intake requirements, recommendations and consumption. Furthermore, we discuss the relationship between protein intake and muscle protein turnover, total lean mass and muscle mass and physical function. We also highlight the relationship between protein intake and plasma glucose homeostasis (FIG. 1). We do not cover the adverse effects of inadequate protein intake and protein insufficiency, protein needs during illness or the therapeutic use of a high-protein diet in conjunction with low-carbohydrate and low-energy intake in people with obesity and T2DM[1,6,8,17–21].

Protein intake recommendations

The Institute of Medicine (IOM), a non-profit organization affiliated with the National Academy of Sciences that is devoted to providing leadership on health care, determined that the average requirement of protein for adults is 0.6 g/kg per day and proposed that the recommended daily intake (RDI) for protein needed to avoid loss of body nitrogen (that is, muscle wasting) in 97.5% of adults is 0.8 g/kg per day[22]. Furthermore, an expert consultation by the Food and Agriculture Organization of the United Nations, the WHO and United Nations University set a population reference intake (PRI) of 0.83 g/kg per day, which is considered adequate for all adults[23]. The IOM has also proposed that protein should comprise 10–35% of total daily energy intake[22] even though protein intake ≥15% of daily energy intake exceeds the RDI and PRI[22,23] (BOX 2).

International expert groups (European Society for Parenteral and Enteral Nutrition and PROT–AGE Study) recommend a protein intake of 1.0–1.2 g/kg per day, which is greater than the RDI and PRI, for older adults (>65 years old) to prevent age-associated declines in muscle mass[4,5]. High protein intake (defined in this Perspectives as more than the RDI of 0.8 g/kg per day) is also commonly recommended to help people maintain or lose body weight because protein is more satiating than carbohydrate and fat and has a greater thermic effect of feeding (that is, the increase in metabolic rate due to digestion, absorption and metabolism of ingested nutrients) than carbohydrate and fat[1–3]. The perception that high protein intake improves muscle mass, muscle function and body weight has led the general public to believe that a high protein intake from consuming naturally protein-rich and protein-enriched foods is 'healthy'[24,25]. For example, ~65% of adults in the USA consider the protein content when buying food or beverages and report 'trying to eat more protein'[25,26]. The global market for protein ingredients is projected to reach approximately US$90 billion by 2021, predominantly driven by the growing demand for protein-fortified food products[7,27–29].

Protein consumption

Most adults in the USA and other developed countries consume substantially more protein than the RDI and PRI[22,23], and some consume even more than the amount recommended for older adults[4,5]. For example, data from the Framingham Third Generation Study[30], conducted in the USA, showed that 82% of the study population consumed at least the RDI for protein and that the median intakes in the first, second, third and fourth quartiles of protein intake were 0.8, 1.1, 1.3 and 1.8 g/kg per day, respectively. Furthermore, the 2001–2014 National Health and Nutrition Examination Survey[31], conducted in the USA, found that 85% of the study population consumed at least the RDI for protein. In this study[31], the average protein intake was greater in men than in women and greater in young adults than in older adults; average intakes ranged

from 1.5 g/kg per day in men 18–30 years old to 1.0 g/kg per day in women ≥80 years old[31]. Generally, protein intake is proportional to energy intake and accounts for ~15% (interquartile range: 10–22%) of total energy intake. Carbohydrates account for ~50% and fat for ~35% of total energy intake across all ages and BMI values[31–33]. Accordingly, high protein intake (>0.8 g/kg per day) often occurs when dietary energy, carbohydrate and/or fat intakes are not restricted.

Muscle protein turnover

In the post-absorptive (fasting) state, net muscle protein balance is negative (that is, muscle protein is lost) because the rate of muscle protein breakdown exceeds the rate of muscle protein synthesis[34]. Ingestion of protein or a mixed macronutrient meal stimulates muscle protein synthesis[34–36]. This effect is mediated by the postprandial increase in the concentrations of amino acids in plasma, which activate anabolic signalling pathways to increase amino acid incorporation into muscle proteins[34,37]. In addition, protein or mixed meal ingestion also inhibits muscle protein breakdown by stimulating insulin secretion. Insulin has potent anti-proteolytic effects[34,38] and the plasma concentration of insulin necessary to achieve maximal suppression of muscle protein breakdown is ~15–30 μU/ml, which is achieved or even exceeded after consuming a small (~250 kcal) mixed meal[34,36,38–40]. The stimulatory effect of protein ingestion on muscle protein synthesis and the inhibitory effect of insulin on muscle protein breakdown cause net muscle protein deposition after meals. Consequently, increases in muscle mass occur when the postprandial net gain in muscle protein exceeds the post-absorptive net loss, whereas muscle mass decreases when the postprandial net gain in muscle protein is insufficient to compensate for the post-absorptive net loss.

The ability of muscle to convert ingested protein and its constituent amino acids into myofibrillar and other intramyocellular proteins is tightly regulated (FIG. 2). The relationship between protein intake and the postprandial muscle protein synthesis rate is saturable, reaching a maximum muscle protein synthesis rate at 0.25 g/kg and 0.40 g/kg in young (aged 18–37 years) and middle-aged and older (aged ≥55 years) adults, respectively[35,41,42]. On average, this intake corresponds to ~18 g protein consumed in one sitting by a young adult and ~28 g in an older adult. Amino acids from protein consumed in excess of this amount are oxidized[35]. Therefore, researchers have recommended that a maximal stimulatory amount of protein (~30 g) is consumed with every meal[43]. In addition, muscle protein synthesis is refractory to sustained hyperaminoacidaemia and the protein synthesis rate returns to basal values after ~2.5 h, even when amino acid availability in the plasma is still elevated or further increased by additional amino acid consumption[44–46]. These physiological factors make it difficult to augment muscle protein accretion by increasing the amount and frequency of protein consumption.

Box 1 | **Amino acids and their daily requirements for adults**

Essential amino acids are those that cannot be synthesized by humans and must therefore be consumed in the form of dietary protein. By contrast, conditionally essential amino acids are only required by the body during specific circumstances, for example, during periods of illness. The data in this box are derived from Institute of Medicine 2005 Dietary Reference Intakes[116].

Essential amino acids

- Histidine: 14 mg/kg per day
- Isoleucine: 19 mg/kg per day
- Leucine: 42 mg/kg per day
- Lysine: 38 mg/kg per day
- Methionine[a]: 19 mg/kg per day
- Phenylalanine[b]: 33 mg/kg per day
- Threonine: 20 mg/kg per day
- Tryptophan: 5 mg/kg per day
- Valine: 24 mg/kg per day

Conditionally essential amino acids

- Arginine
- Cysteine
- Glutamine
- Glycine
- Proline
- Tyrosine

Non-essential amino acids

- Alanine
- Aspartic acid
- Asparagine
- Glutamic acid
- Serine
- Selenocysteine

[a]Sum of methionine and cysteine, which can be converted to methionine. [b]Sum of phenylalanine and tyrosine, which can be converted to phenylalanine.

Protein intake and lean mass

The effects of high protein intake on total body mass, lean mass and muscle mass have been evaluated in both population studies and randomized controlled trials. The randomized controlled trials included weight maintenance, high-calorie feeding and diet-induced weight-loss studies. The population studies included both cross-sectional and longitudinal studies. Total lean mass was measured by various methods, including DXA, bioimpedance, air displacement plethysmography, hydrostatic weighing or deuterium oxide dilution. Muscle mass was estimated as appendicular lean mass measured using DXA.

Population studies. One cross-sectional cohort study, conducted in the USA, found that BMI and waist circumference were inversely associated with protein intake (expressed as grams per kilogram of body weight per day)[47]. However, another study, conducted in the UK, found that protein intake (expressed as percentage total energy intake) was directly related to BMI and waist circumference[33]. Moreover, both weight gain and obesity risk were directly related to dietary protein intake (expressed as percentage of total energy intake) in several longitudinal cohort studies that were conducted in Europe[48,49]. Total lean body mass and muscle mass were also directly related to protein intake in some population studies conducted in the USA and the UK[30,50–52], suggesting that some of the protein-associated increases in body mass seen in other studies[33,48,49] were due to increased lean mass. However, the effects of high protein intake on lean mass and muscle mass were often very small and the associations between protein intake and lean mass and muscle mass were not statistically significant after adjusting for important confounding influences, such as total body and fat mass[30,50–52].

In the Framingham Third Generation Study, conducted in the USA[30], people who consumed the lowest quartile of protein intake, which included inadequate intakes of <0.8 g/kg per day because the median intake of this quartile was 0.8 g/kg per day, had a lower appendicular lean mass than those who consumed more protein. However, appendicular lean body mass did not differ among people in the second through fourth quartiles of protein intake, with median intakes ranging from 1.1 to 1.8 g/kg per day[30]. In the prospective Health ABC study[9], conducted in the USA, men and women 70–79 years old who consumed <0.8 g/kg per day of protein lost statistically significantly more total and appendicular lean mass

over 3 years of follow up than those who consumed ≥0.8 g/kg per day. However, the protective effect of high protein intake on lean mass loss was limited to only men and women who lost weight during the study; high protein intake did not prevent or blunt the normal age-associated loss of lean mass and muscle mass in those who maintained their body weight[9].

Randomized controlled trials during weight maintenance. The results from several randomized controlled trials demonstrate that increasing protein intake by 30–56 g per day through protein supplementation for 12 weeks to 2 years did not affect body weight or increase lean mass in people with overweight or obesity. Moreover, the high-protein interventions did not help maintain muscle mass (assessed as appendicular lean mass using DXA or myofibre cross-sectional area using histology) in older (aged ≥65 years) adults who consumed adequate amounts of protein at baseline[53–56]. The data from several systematic reviews and meta-analyses also show little or no effect of increased protein intake (up to twice the RDI) and supplemental amino acid intake on exercise training-induced muscle hypertrophy in middle-aged (aged >45 years) and older (aged ≥65 years) adults[56–62]. However, increasing protein intake above the RDI increases exercise training-induced muscle hypertrophy in young (aged <45 years) adults[58].

Randomized controlled high-calorie diet studies. One randomized controlled study evaluated the effects of high-calorie weight-gaining diets that contained ~40% more energy than necessary to maintain body weight (an additional ~1,000 kcal per day) and varying amounts of protein on body weight and lean body mass[63]. In this study, people who consumed a low-protein high-calorie diet (<0.7 g/kg per day) gained less lean mass than those who consumed higher protein high-calorie diets[63]. However, when protein intake was adequate (≥0.8 g/kg per day), higher protein intake did not lead to greater increases in lean body mass; as such, the increase in lean body mass was not different in people who consumed 25% of energy from protein compared with those who consumed 15% of energy from protein[63]. Moreover, individuals who consumed the low-protein diet (5% of energy as protein; that is, <0.7 g/kg per day of protein) gained less total body weight than those who consumed the higher protein diets (15% and 25% of total energy or ≥0.8 g/kg per day of protein). In addition, total weight gain was not different in individuals who consumed 25% of energy from protein and those who consumed 15% of energy from protein[63]. Another randomized controlled study evaluated the effect on lean mass of supplementing an energy and protein-rich (2.0 g/kg per day of protein) weight-regaining diet after short-term severe negative energy balance during military training in US Marines with an additional 84–133 g of protein per day[64]. The study found that the additional protein consumed did not improve the regain of lean mass[64].

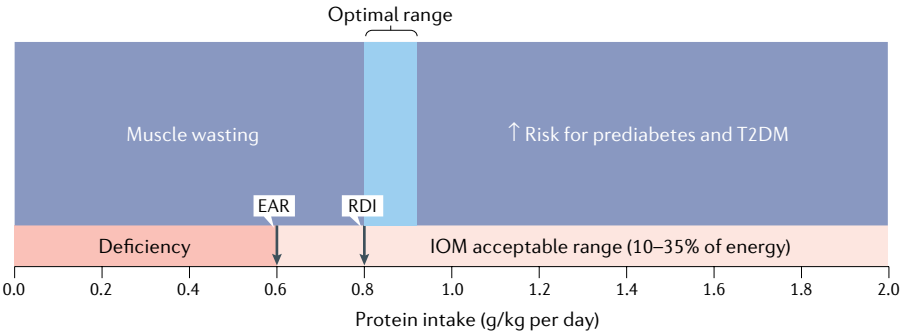

Fig. 1 | **Relationship between protein intake and health.** Both insufficient protein intake and protein overconsumption can have adverse health consequences. Inadequate consumption of essential amino acids can cause amino acid deficiencies and muscle wasting. Protein overconsumption can cause insulin resistance, prediabetes and type 2 diabetes mellitus (T2DM). The Institute of Medicine (IOM) has proposed values for estimated average requirements (EAR) and a recommended daily intake (RDI) of dietary protein. The RDI represents the amount of protein that ensures protein intake sufficient to prevent loss of body nitrogen is met by 97.5% of the population. We propose an optimal range of protein intake, which we based on the results from studies reviewed in this Perspective. The optimal intake range represents amounts of protein that are not associated with adverse health outcomes due to either underconsumption or overconsumption.

Randomized controlled weight-loss studies. The effect of high-protein diets on body weight loss has been evaluated in several systematic reviews and meta-analyses[6,17,65–67]. The authors of these papers found a beneficial effect of a high-protein diet (≥0.8 g/kg per day) on body weight loss in short-term (<12 weeks) studies and in longer studies that either combined high protein intake with low carbohydrate intake in the intervention arm or those in which the control group consumed a low-protein (<0.7 g/kg per day) diet. However, in studies longer than 12 weeks, study groups with high protein consumption without substantial carbohydrate restriction did not have increased weight loss compared with groups that consumed the RDI of protein (0.8 g/kg per day).

Weight loss causes a decrease in total body mass due to a decrease in both fat mass and lean mass. Consuming a high-protein diet during weight loss diminishes the weight loss-induced reduction of lean mass and muscle mass compared with consuming the RDI of protein. The results of several systematic reviews and meta-analyses[65,68] demonstrate that high (here defined as >1.0 g/kg per day) compared with normal (0.8 g/kg per day) protein intake prevents a loss of lean mass of 0.5–1.0 kg during moderate weight loss (5–10% of weight at baseline). In a randomized controlled weight-loss intervention study, in which all food was provided to participants, we found that a 50% increase in daily protein consumption (1.2 g/kg per day compared with 0.8 g/kg per day) during 10% diet-induced weight loss (~26 weeks) decreased the losses of lean mass by ~0.7 kg (REF.[69]) and of bilateral thigh muscle mass (evaluated using MRI) by ~0.05 kg (REF.[70]).

The pattern of protein consumption does not alter the effect of high protein intake on lean mass and muscle mass during weight loss. For example, consuming a high-protein (1.1 g/kg per day) low-calorie diet in which the protein was evenly distributed within each meal to maximize postprandial muscle protein synthesis was not associated with increased retention of lean mass during weight loss compared with varying the protein content of each meal[71]. In addition, providing a diet that contained 1.2 g/kg per day of protein through continuous 24-h enteral tube feeding instead of four meals per day during 1 week of bed rest did not alter the short-term bedrest-induced loss of lean mass and muscle mass in healthy men[72].

Summary. Although high protein intake (>0.8 g/kg per day) can increase muscle mass during resistance exercise training in young adults and blunt the small weight loss-induced decreases in lean mass and muscle mass in people with obesity, data from randomized controlled studies do not

Box 2 | **Acceptable dietary protein intake**

The data in this box represent dietary protein intake in grams per kilogram of body weight per day based on dietary protein content as a percentage of total daily energy intake for a sedentary 70 kg man consuming a weight-maintaining diet of 2,200 kcal per day.

- 10% of total daily energy: 0.77 g/kg per day of protein
- 15% of total daily energy: 1.15 g/kg per day of protein
- 20% of total daily energy: 1.53 g/kg per day of protein
- 22% of total daily energy: 1.92 g/kg per day of protein
- 35% of total daily energy: 2.86 g/kg per day of protein

support a beneficial effect of high protein intake on total lean mass or muscle mass during weight maintenance or weight gain.

Protein intake and physical function

The effect of high protein intake on physical function (including muscle strength and activities of daily living) has been evaluated in both cross-sectional and longitudinal population studies and in randomized controlled trials.

Population studies. Muscle strength and overall physical function, including activities of daily living, were directly related to protein intake in several population studies[50–52,73–77]. However, this association was not consistently observed and was often due to the adverse effect of low (<0.8 g/kg per day) protein intake rather than a beneficial effect of high (>0.8 g/kg per day) protein intake or was no longer statistically significant after adjusting for important confounding influences, such as body adiposity[50–52,73–77]. Moreover, high protein intake did not prevent or blunt the age-associated decline in muscle strength, assessed as grip strength, and in overall physical function, assessed using the timed up-and-go test[73,75].

Randomized controlled studies. The data from most randomized controlled studies during weight maintenance or diet-induced weight loss show that increasing protein intake above the RDI for up to 2 years does not have beneficial effects on muscle strength or overall physical function[53,55–62,70,78,79]. By contrast, the data from some randomized controlled studies, including two pilot studies, show a statistically, but probably not clinically, significant beneficial effect of high protein intake for 10–24 weeks on selected measures of strength and physical function[80–83].

Summary. Data from both population studies and randomized controlled studies do not support a clinically meaningful beneficial effect of high protein intake (defined as more than the RDI of 0.8 g/kg per day) on muscle strength and overall physical function.

Glucose homeostasis

The plasma concentration of glucose is maintained by the balance between hepatic and renal glucose production, the appearance of ingested glucose in the systemic circulation and the rate of tissue glucose uptake. Insulin is a major regulator of endogenous glucose production and tissue glucose uptake[84]. Insulin suppresses endogenous glucose production by acting directly on hepatocytes and indirectly by inhibiting glucagon production and inhibiting free fatty acid release from lipolysis of stored triglycerides in adipose tissue. Both endogenous glucose production and lipolysis are very sensitive to the inhibitory effect of insulin and very small increases in plasma concentrations of insulin above basal values cause maximal suppression of endogenous glucose production and the lipolytic rate[85]. In addition, insulin stimulates tissue (predominantly muscle) glucose uptake in a dose-dependent manner and the maximal stimulatory effect of insulin on glucose uptake far exceeds the normal postprandial rise in plasma concentrations of insulin[85,86].

Individuals with prediabetes or T2DM have increased plasma concentrations of glucose, a condition that is referred to as hyperglycaemia. Several mechanisms contribute to this pathogenic phenotype[84,87]. First, hepatic glucose production is increased because of hyperglucagonaemia. Furthermore, multi-organ (liver, adipose tissue and muscle) insulin resistance occurs, which is characterized by impaired insulin-mediated suppression of hepatic glucose production, decreased insulin-mediated inhibition of adipose tissue lipolysis and impaired insulin-mediated stimulation of tissue glucose uptake. When these effects are combined with insufficient compensatory increases in insulin secretion and decreases in insulin clearance, glucose homeostasis is disturbed, leading to hyperglycaemia.

Protein intake and glucose metabolism. Protein consumption and the subsequent increase in plasma concentrations of amino acids have potent effects on glucose metabolism. Protein ingestion and amino acids stimulate both glucagon and insulin secretion in a dose-dependent manner[88–90]. In addition, both increasing plasma concentrations of amino acids by infusing complete or essential amino acid solutions and protein ingestion impair insulin action (assessed using the hyperinsulinaemic–euglycaemic clamp procedure) in healthy people[91–93]. Glucagon secretion in response to protein ingestion is a normal physiological response that helps to dispose of excess amino acids and nitrogen in the plasma via glucagon-stimulated amino acid catabolism and ureagenesis[94]. In addition, the stimulation of glucagon secretion and hepatic glucose production[95] and the inhibition of insulin-stimulated glucose disposal[93] helps prevent insulin-mediated hypoglycaemia. However, the insulin-to-glucose ratio is often greater after protein ingestion compared with fasting and also often greater after combined protein and carbohydrate ingestion compared with carbohydrate ingestion alone. This observation occurs because plasma concentrations of insulin, but not glucose, increase after protein ingestion alone and plasma concentrations of insulin are often greater after combined protein and carbohydrate ingestion compared with carbohydrate ingestion alone[89,95–100].

The type of protein consumed can affect the rate of protein digestion and the rate of amino acid appearance into the circulation. For example, a more rapid and pronounced increase in plasma concentration of insulin was observed after whey ingestion compared with casein ingestion[100,101]. Dietary protein type is therefore a potentially important determinant of the metabolic response to protein ingestion.

Protein intake and insulin sensitivity and glycaemic control. The insulinotropic effect of protein ingestion can help control blood glucose concentration in people with T2DM. For example, a protein 'preload' before consuming carbohydrates or protein co-ingestion with carbohydrates helps to ameliorate the defect in glucose-stimulated insulin secretion and reduce the postprandial increase in plasma concentrations of glucose in people with T2DM[99,102]. In people without T2DM, however, the insulinogenic effect of protein ingestion could be involved in the pathogenesis of insulin resistance.

This is evidenced by studies showing that even small experimentally induced increases in plasma concentrations of insulin in healthy people can cause insulin resistance within a few days, presumably by downregulating insulin receptor expression and by causing post-receptor defects in insulin signalling[103–105].

The effects of chronic high protein intake on insulin sensitivity and blood concentrations of glucose in healthy individuals and those with obesity and T2DM are unclear. The authors of several systematic reviews and meta-analyses of randomized controlled trials concluded that it is not possible to determine the effect of high protein intake on insulin sensitivity and glycaemic control, owing to potential confounding influences of food selection and overall diet composition, differences between participant characteristics in the intervention and control groups, as well as differences in the methods used to evaluate insulin sensitivity[106–108]. A study of individuals with overweight or obesity that used the hyperinsulinaemic–euglycaemic clamp procedure in conjunction with stable isotopically labelled glucose tracer infusion found that consuming a weight-maintaining high-protein diet for 6–18 weeks caused a small, but statistically significant, increase in basal hepatic glucose production and a decrease in insulin-mediated glucose disposal after 6 weeks[109]. At 18 weeks, the difference was not statistically significant but adherence with the diet prescription after 6 weeks was poor, which confounded the results.

Protein intake during diet-induced weight loss and glucose metabolism. Increasing dietary protein intake in conjunction with a marked decrease in dietary carbohydrate intake facilitates weight loss and decreases 24-h plasma concentrations of glucose and HbA_{1c} in people with obesity and T2DM, even with minimal (<5%) weight loss[8,110]. However, increasing dietary protein intake without a considerable decrease in dietary carbohydrate intake could blunt the beneficial effect of weight loss on glucose metabolism. We found that increasing protein intake from 0.8 to 1.2 g/kg per day by adding whey protein to a low-calorie macronutrient-balanced diet (49% of energy as carbohydrate, 29% as fat and 22% as protein versus 43% of energy as carbohydrate, 26% as fat and 31% as protein) completely prevented the beneficial effect of 10% weight loss on insulin-mediated glucose disposal, assessed using the hyperinsulinaemic–euglycaemic clamp procedure[69]. The adverse metabolic effect of a protein-enriched low-calorie diet (50% of energy as carbohydrate, 25% as fat and 25% as protein versus 50% of energy as carbohydrate, 30% as fat and 20% as protein) on weight loss-induced insulin sensitivity has been confirmed by other investigators, who assessed insulin sensitivity using the intravenous glucose tolerance test in 18–65 years old women with overweight or obesity[111]. However, weight loss decreased fasting plasma concentrations of insulin and the basal glucose production rate (expressed as micromoles of glucose per minute) in both the high-protein and standard-protein low-calorie diet groups[69,111].

A small ($n=6$ per group) study conducted in people with T2DM found that a low-calorie, high-protein diet (43% of energy as carbohydrate, 32% as fat and 27% as protein) for 8 weeks prevented the improvement in fasting plasma glucose concentration and insulin sensitivity (assessed using the hyperinsulinaemic–euglycaemic clamp) observed in the control group that consumed a standard-protein (50% of energy as carbohydrate, 30% as fat and 20% as protein) low-calorie diet[112]. In addition, the weight loss-induced decrease in HbA_{1c} was statistically significant in the standard-protein group but did not reach statistical significance in the high-protein group[112].

Summary. These data show that a single protein meal or adding protein to a carbohydrate meal stimulates glucagon and insulin secretion, which helps metabolize amino acids. Protein ingestion also impairs insulin action, which prevents insulin-induced hypoglycaemia. Moreover, high protein intake during weight-loss therapy blunts the beneficial effects of weight loss on glucose metabolism in healthy people and in people with T2DM. These data suggest that the therapeutic effect of high-protein diets on glycaemic control observed in people with T2DM[8,110] is most likely related to weight loss and the reduction in carbohydrate intake[18,113].

Protein intake and risk of T2DM

The data from a series of large population studies, including the Health ABC[9], Rotterdam[10], Nurses' Health II and Health Professionals Follow-up[11], Melbourne Collaborative Cohort[12], MASALA[13], Women's Health Initiative[14], EPIC[15] and ATBC[16] studies, have shown that high protein intake was associated with an increased prevalence and risk of developing prediabetes and T2DM. The risk of developing T2DM increased by 20–40% for every 10 g of protein consumed in excess of 64 g per day and the risk of developing

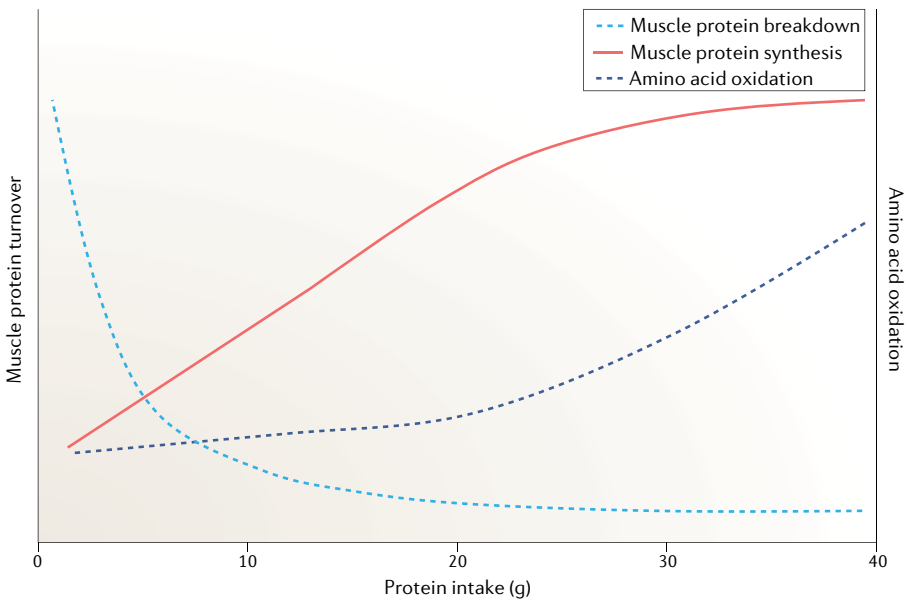

Fig. 2 | **Effect of protein intake on muscle protein turnover and amino acid oxidation.** Protein or mixed meal ingestion inhibits muscle protein breakdown and increases the muscle protein synthesis rate because it stimulates insulin secretion and activates anabolic signalling pathways that stimulate amino acid incorporation into muscle proteins. The plasma concentration of insulin necessary to achieve maximal suppression of muscle protein breakdown is achieved or even exceeded after consuming a small amount of protein or a small mixed meal. The relationship between protein intake and the postprandial muscle protein synthesis rate is saturable, reaching a maximum at ~30 g of protein. Amino acids from protein consumed in excess of this amount are degraded and oxidized. Postprandial net muscle protein accretion can therefore not be increased by eating more protein.

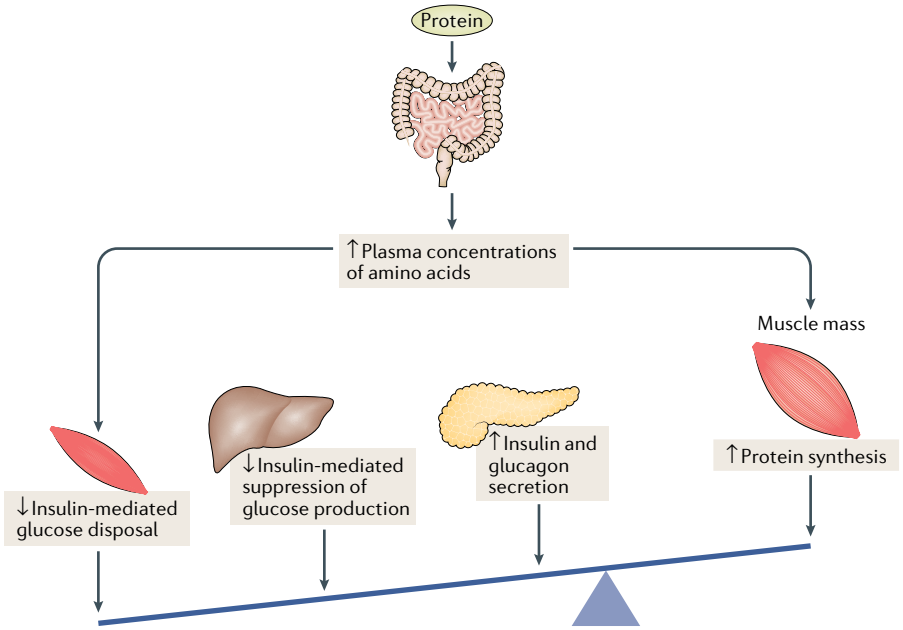

Fig. 3 | **Effect of protein ingestion on muscle protein synthesis and glucose metabolism.** Protein ingestion increases muscle protein synthesis and decreases muscle protein breakdown but the relationship between protein ingestion and net protein balance reaches a plateau at ~20–30 g per meal. Protein ingestion also stimulates insulin and glucagon secretion and impairs insulin action, which enables amino acid metabolism and prevents hypoglycaemia, but also provides a potential mechanistic link for the increased risk of type 2 diabetes mellitus that is associated with high protein intake in population studies.

T2DM in people in the highest quartile of protein consumption was nearly twice that of people in the lowest quartile[13–15]. In some, but not all, of these studies, the association between high protein intake and the risk of developing prediabetes and T2DM was related to the source of protein. In three studies[10,12,15], high intake of animal protein, but not of plant protein, was associated with an increased risk of T2DM. In a fourth study[11], it was estimated that substituting 5% of energy intake from vegetable protein in place of animal protein decreases the risk of T2DM by about 25%. However, the authors of another study[16] estimated that replacing 2% of dietary energy obtained from protein with carbohydrate was associated with a decreased risk of developing T2DM, independent of whether animal or plant proteins were replaced.

Whether the discrepancy in the effects of animal-derived and plant-derived proteins on metabolic health observed in the aforementioned studies is due to differences in statistical power (fewer people consume high amounts of plant proteins), the type of proteins themselves or bioactive substances that accompany animal and plant protein intake is unclear. In a study that evaluated plasma concentrations of glucose and glucoregulatory hormones after ingestion of meals high in animal proteins and high in plant proteins, the postprandial plasma metabolic profile was substantially different but more favourable after the high animal protein meal than the high plant protein meal. Consuming the high plant protein compared with the high animal protein meal was characterized by greater increases in plasma concentrations of glucagon, insulin and glucose[114].

Conclusions

The results from both population and randomized experimental diet intervention studies conducted in people do not support the popular trend in the general population of increasing dietary protein intake beyond the RDI to increase muscle mass, overall physical function and glucose homeostasis. Although high dietary protein intake can increase muscle mass during resistance exercise training in young adults, a high-protein diet does not have clinically meaningful effects on lean mass or muscle mass during weight maintenance, weight gain or weight loss. Moreover, increasing protein intake is not without risk and can have adverse effects on metabolic function (FIG. 3).

The stimulation of glucagon and insulin secretion and impairment of insulin action that occurs immediately after protein ingestion provides a potential mechanistic link between high protein intake and the increased risk of prediabetes and T2DM observed in population studies. In addition, in people with overweight and obesity, high protein intake without a concomitant substantial decrease in carbohydrate intake attenuates the therapeutic effect of diet-induced weight loss on whole-body insulin sensitivity. However, increased protein intake and consequent glucagon secretion could be beneficial in people with obesity and T2DM by facilitating weight loss and improving glycaemic control through an increase in satiety and the thermic effect of feeding, slower gastric emptying, decreased and slower glucose appearance in plasma and enhanced insulin secretion[1–3,99,102,115].

Bettina Mittendorfer[1]*, *Samuel Klein*[1] *and Luigi Fontana*[1,2]

[1]*Center for Human Nutrition, Washington University School of Medicine, St Louis, MO, USA.*

[2]*Charles Perkins Center, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia.*

**e-mail: mittendb@wustl.edu*

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