Clinical Science (2020) **134** 389–401
https://doi.org/10.1042/CS20190583

PORTLAND PRESS

Review Article

Obesity and adiposity: the culprit of dietary protein efficacy

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Obesity and increased body adiposity have been alarmingly increasing over the past decades and have been linked to a rise in food intake. Many dietary restrictive approaches aiming at reducing weight have resulted in contradictory results. Additionally, some policies to reduce sugar or fat intake were not able to decrease the surge of obesity. This suggests that food intake is controlled by a physiological mechanism and that any behavioural change only leads to a short-term success. Several hypotheses have been postulated, and many of them have been rejected due to some limitations and exceptions. The present review aims at presenting a new theory behind the regulation of energy intake, therefore providing an eye-opening field for energy balance and a potential strategy for obesity management.

Obesity worldwide

Obesity, or increased adiposity, has become one of the most widespread public health problems. The prevalence of obesity is still continuously growing and is alarming in numerous countries. Although genes play a crucial role in the onset of obesity, the interplay between genetic and epigenetic factors [1] determines the final outcome; and this what makes obesity a complex equation that is not easy to solve. The rise in the number and size of adipocytes among obese people is known to increase the risk of chronic diseases, morbidity, and mortality [2].

Many underlying factors have been described in the causative pathway for excess body weight. The aetiology of the epidemic of obesity has been questioned and has been for long attributed to an imbalance in energy. Both epidemiological and interventional studies were used to comprehend the relation between diet and energy balance.

Energy in, energy out

For a long time, weight maintenance has been described to be the balance between energy intake and expenditure. Consequently, weight gain and obesity were attributed to an energy imbalance, and thus most approaches back then, aiming at weight loss, have been focusing on reducing caloric consumption (food and beverage) and increasing physical activity. Any failure was attributed to the absence of behaviour changes and lack of compliance of the subjects, though the mechanisms behind the failure were not fully addressed.

It has been shown that energy balance is a dynamic process that involves factors that are beyond calorie counting. In fact, food restriction is not always the optimal solution for weight loss [3], as it is accompanied by compensatory mechanisms that lower energy expenditure and stores mobilization [4]. Additionally, energy intake is shown to be highly affected by the composition rather than the energy content of the diet [5].

As a result, the inconsistent findings of the effect of diet manipulation on weight have raised the question of whether a calorie is just a calorie [6]. Nevertheless, the majority of studies focused on the impact of macronutrients (carbohydrate, fat, and protein), since they are the main source of energy.

Received: 25 September 2019
Revised: 24 January 2020
Accepted: 10 February 2020

Version of Record published:
17 February 2020

Clinical Science (2020) **134** 389–401
https://doi.org/10.1042/CS20190583

The macronutrient focus

In almost all countries, the trends in the consumption of all of the three macronutrients were reported to change over the years [7]. For instance, in the U.S.A., between 1971 and 2006, the obesity rate and total energy intake increased in both men and women [8]. This was accompanied by an increment of the percentage of energy from carbohydrates (from 44% to around 49%) and a decrease of the percentage of energy from fat and proteins (from 37% to 34% for fat and from 17% to 16% for protein) [8].

Carbohydrate

Over the past decades and despite the inter-individual variability, trends of populations' intakes have revealed that the increased total energy intake since 1971 was highly attributed to that of the percentage of energy consumed from carbohydrate [9–11]; thus implicating carbohydrate in the development of obesity [12,13]. The nutrition transition has led to more westernized diets characterized by a rise in the contribution of refined carbohydrate [13] and sugars [14] and a drop in complex carbohydrates and fibres [13]. The implication of carbohydrate in the development of obesity is believed to be mediated through its capacity to alter postprandial glycaemia [15]. This was further supported by studies in which high quantities of high glycaemic index carbohydrates have been associated with several chronic conditions, including insulin resistance and Type 2 diabetes [16], cancer [17–19], cardiovascular diseases, and mortality [20]. On the other hand, low glycaemic index carbohydrates (unprocessed grains that are rich in minerals and vitamins), which consumption was reduced over the years, were shown to support weight loss [21] and reduce risks of metabolic diseases [22].

Additionally, excess consumption of sugary drinks was proposed to be a major cause of increased obesity and adiposity. In fact, sugar-sweetened beverage (SBB) consumption has been shown to be positively correlated with obesity prevalence in many places [23–27]. This correlation can be attributed to the palatable taste, which stimulates energy intake, and to its affordable price [28]. In support, the price of carbonated beverages (that are SSB) has a compelling inverse relationship with obesity prevalence among youth between 1999 and 2009 [23], which makes it an additional argument supporting the causative role of SSB in the aetiology of obesity [29]. Added to the price, another major carbohydrate-related factor that induces food intake is palatability. A study conducted on rats strongly supported that the palatability of drinks has a significant role in inducing overeating [30]. A vicious cycle best describes the relationship between palatable foods (such as high sugar) and obesity. This associative model was portrayed through a cognitive decline related to hippocampus changes that inhibit satiety signals [31]. In line, the hippocampus of children with obesity was reported to be smaller with some alterations in its activation in response to taste [31]. Many authors have emphasized the potency of the hedonic drives in the control of appetite [32] by down-regulating the expression of satiety signals and up-regulating the ones of hunger [33]. As a result, in the past few decades, many countries developed and implemented policies for reducing sugar intake, including the ones of SSB [34].

However, the reduction in the consumption of carbohydrate and sugar since 2000 [35] failed to halt obesity [36], and this raises a question on whether carbohydrate intake or metabolism is involved in the obesity epidemic. Sartorius et al., in their systematic review and meta-analysis that assessed high and low carbohydrate diets, concluded that patterns rich in carbohydrates (in terms of percent of total energy) could not alone increase the odds of obesity [37]. This was in line with a recent review that evaluated non-communicable diseases in relationship with sugar and postulated that the detrimental effect is attributed to an excess amount of calories consumed as sugar and not as sugar per se [38].

Moreover, the inverse relationship between adiposity and the consumption of fruits and vegetables (which are significant sources of carbohydrates) [39], as well as whole grains [40] is believed to be the outcome of improvement in carbohydrate metabolism mediated by components associated with their intake (e.g. vitamins, minerals, fibre). The role of fibre in this process is alleged to be of minor importance since it is not known to influence postprandial glycaemia significantly [41,42]. Given that, the detrimental impact of carbohydrate consumption may not relate to carbohydrate per se, but rather to factors related to its proper metabolism.

Fat

Fat consumption has been blamed for being the most significant contributor to increased adiposity and obesity, mainly due to its high energy density and palatability. In the U.S.A., the fat contribution to total energy intake increased from 27% to 30% between 1991 and 2008 [43]. In Europe, data from 24 European countries revealed that fat contribution to total energy intake ranged from 29 to 46%, exceeding the total fat recommendations (20–35%) in nine countries [44].

However, the relation between dietary fat intake and adiposity remains controversial. Ad libitum dietary interventions showed a weight loss among the group having reduced-fat diets as compared with control [45]. In contrast,

low-fat diets were reported to have the same impact as other weight-reducing diets with no significant additional value [46], and thus high-fat diets are not thought to be the leading cause of excess body adiposity [47]. Inline, epidemiological studies failed to show an association between the percentage of energy consumed from fat and obesity rate [48]. For example, the high fat intake in France, consisting of up to 39% of total energy intake per day [49], was associated with a low obesity rate (∼17% of adults) [50]. This French paradox highlighted the involvement of other components in the French diet like dairy products [51], ethanol [52], polyphenols [53] of wine, or others [50] that have the potential to protect against cardiovascular diseases and perhaps obesity.

On another note, the paralleled reduction in the percentage energy from fat with annual per capita national income [54] is not compatible with the fact that obesity is more common among people of low socioeconomic status (SES) [55,56].

Recently, the percentage of energy from fat, including saturated, monounsaturated, and polyunsaturated fatty acids, was reported to be inversely associated with the risk of major cardiovascular diseases and total mortality [20]. While, the adoption of the Mediterranean diet was found to yield a better weight reduction and lipid biomarker outcomes as compared with a low-fat diet [57], and this was thought to relate to its increased intake of olive oil, nuts, seeds, and dairy products [58]. These observations raise a question on whether health outcomes are related to the type or quantity of fat ingested or to factors associated with fat ingestion.

Indeed, high-fat dairy consumption is known to be inversely related to obesity [59,60], cardiovascular and metabolic diseases [59], and has demonstrated improvement in postprandial glycaemia [61,62]. Hence, it remains to be understood whether the dairy product (French and Mediterranean diets etc.) effects are attributable to the fat content or associated nutrients, especially since dairy products (except butter) are considered rich sources of protein and micronutrients.

The fact that carbohydrate and fat are the primary sources of energy intake prompted scientists to focus on their role in the regulation of energy balance. Consequently, many public health recommendations were developed to guide their consumption, but unfortunately, these had resulted in controversial findings and had a limited impact on curbing obesity. For this reason, there is a crucial need to understand the reasons behind these limitations and to broaden our approach and address protein metabolism and energy balance regulation.

Protein

In contrast with fat and carbohydrate, population data over the past few decades have revealed minimal variation in the percentage of energy consumed from protein [63]. In the USA, the percentage of energy from protein varied between 15.2 and 16.5% [9]. Both protein quantity and quality were discussed in relation to health outcomes, not to exclude weight management and energy balance.

Most studies have shown that increased protein consumption (quantity) favours energy balance through alterations of both energy intake and expenditure [64]. Protein metabolism (synthesis, breakdown, and oxidation) is a costly energy-requiring process, and thus protein has the highest postprandial thermogenesis among other macronutrients [65], and this is thought to be behind its greater satiating power [66]. Therefore, high protein diets became a top hit in dietetics and sports nutrition for their effect on promoting fullness [67], reducing weight [64], and improving body composition [68].

On the other hand, prolonged low protein diets were shown to trigger food intake, facilitate positive energy balance and increase weight and adiposity [69] due to lack of essential and/or sufficient load of amino acid, the building blocks of proteins, needed for *de novo* synthesis of proteins. This further confirms the need for exogenous proteins to support body proteins, the lean body mass. At a population level, total energy percentage (%) from protein has been described to fluctuate slightly within the SES and the annual per capita national income [54]. However, protein quality or the ratio between animal and vegetable protein increases among higher income people [54]. This fact comes in line with the higher obesity prevalence among lower SES populations who strongly depend on vegetable proteins and carbohydrate in their diets [55,56].

The involvement of the protein in energy metabolism and weight management incited several trials to understand the mechanism/s by which protein regulates food intake. The protein leverage hypothesis was proposed, suggesting that the body requires a specific percentage of energy from protein (∼14%). If that amount is not met, a physiological regulatory mechanism is activated to increase energy intake in an attempt to meet the protein requirements [70,71]. In support, the percentage energy intake from protein (10% *E* and above) was reported to be negatively associated with energy intake irrespective of whether fats or carbohydrates were the diluents of protein [72]. Nevertheless, the relationship between protein and energy intake (*E*%) was not found to be linear under varied conditions of protein intake. In rodents, energy intake was reported to increase when maintained on a diet below 15% energy from protein

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https://doi.org/10.1042/CS20190583

[73], yet it decreases when levels go below 5% or beyond 20% [74–76]. Therefore, diets with very low protein content (5% percent of total energy (%*E*) and below) do not abide by the protein leverage theory [77]. This fact highlights the involvement of other factors, like protein quality in this process.

Food intake was found to increase when the quality of protein was moderately reduced (a restriction of at least one amino acid) [78–80], while to depress under conditions of severe amino acid limitation [81]. This implicates protein quality in energy balance and necessitates the understanding of its interaction with protein quantity. However, the reduction in food intake under severe protein quantity reduction [81] or quality diminishing [81] may be adaptive to avoid the toxicity of amino acid accumulation due to reduced capacity to metabolise protein. At some point in a study by Sanahuja et al. (1962), rats were able to switch from protein-imbalanced diets to protein-free diets to limit amino acids that cannot support protein metabolism from accumulating [82]. This phenomenon is also shown when other crucial components of protein metabolism are missing. Indeed, food intake was shown to decrease among rats having low-protein low-phosphorus diets as compared with higher phosphorus diets despite having the same dietary protein quality and content [83]. This would be attributed to the reduced ATP availability that is dependent on exogenous phosphorus supply. Consequently, under the condition of energy deficit, protein synthesis is restricted, and food intake is limited to prevent the accumulation of unprocessed amino acids in the circulation.

When looking at energy metabolism, a U-shaped relationship exists between protein (%*E*) and energy expenditure as well as energy efficiency (cost of weight gain). At the intake of approximately 15–20% *E*, both energy expenditure and cost of weight gain (the lowest the amount of protein that is capable of supporting growth and maintenance at the lowest energy cost) were the lowest [84,85] signifying optimal protein efficacy. The ability of moderate reduction in both protein quality and quantity to stimulate energy intake is believed to be an adaptive mechanism to increase protein intake, though this would be expected to reduce protein efficacy and to augment adipogenesis due to increased energy intake.

Overall, it is reasonable and logical to postulate that survival instinct necessitates the need for nutrients to support vital processes (e.g. the body's metabolically active compartment, including lean body mass) at the lowest cost. Inline, the strong dependence of energy intake on lean body mass, the primary determinant of basal metabolic rate [86], infers the presence of a dynamic interaction between protein metabolism and energy intake. Accordingly, dietary factors involved in the control of protein metabolism become the prime candidates for the control of energy metabolism.

Regulation of energy intake

Many factors have been proposed to influence food initiation, quantity, frequency, and choice. Some determinants are physiological (palatability, hunger, and appetite), psychological (stress and mood), social (culture, religious, media, accessibility, and availability), educational (knowledge and attitude), economic, etc. Apart from the above-mentioned factors, several biological theories have been postulated to explain the phenomenon behind food intake [87]; however, most of them failed to provide full explanations. Most of the theories revolve around the energy status of the body, whether "energy production" or "energy need".

Energy-related theories

The "energy production" theories stipulate that food intake is regulated by the variation of body temperature (heat production) and that its manipulation aims to sustain body temperature at 37°C. The *thermostatic theory* implies that the food intake is controlled by body temperature, and both external (cold or hot weather) [88] and internal (thermogenesis) temperatures play pivotal roles. This highlights the effect of proteins in controlling food intake since they are known to have high thermogenic activity [89].

The "energy need" theories include the *glucostatic* [90], *lipostatic* [91,92], and *glycogen theories* [93]. They all postulate that food intake is increased when energy substrates are depleted. The *glucostatic* and *glycogen theories* rely on supporting glycaemia, at the central level through arteriovenous regulation and systemic level through glycogenolysis. These theories were rejected for holding many exceptions, such as not explaining hyperphagia in diabetes [94]. Additionally, the involvement of fat in the control of food intake and weight holds many commercial biases [95] and fails to support the dynamic phase of obesity when subjects keep on increasing their weights.

In fact, both concepts (energy need and energy production) are interrelated. The needs for energy trigger the body to assure the availability of substrates (induce food intake) which in turn produces heat that controls intake (inhibition food intake). Consequently, carbohydrates and fats serve only to provide energy but not to work dynamically on metabolism.

Protein-related theories

Alternative theories propose that food intake is controlled by the body urge to maintain its protein status; among these theories, we state the *protein leverage theory*, the *aminostatic theory*, and the *set-point theory*. The mechanism behind the *aminostatic theory* concept focuses on having a particular concentration of circulating amino acids. The serum level of amino acids is shown to be inversely associated with appetite [96]. This is in line with the findings favouring high protein foods when studying satiety and satiation [97,98]. The field has witnessed lots of work on the satiety and satiation effect of different types of proteins. Whey protein, also known as "fast" protein, results in a fast increment of circulating amino acids and appetite hormones [99,100]. This was shown to favour fullness acutely in the post-absorptive phase, when compared with a slower protein, the casein [100,101]. In harmony with the *aminostatic theory*, the *protein leverage hypothesis* suggests that the needs for proteins drive energy intake. In other terms, in order to assure the required amino acid concentration, a specific protein percentage from total energy intake is desired. In a study by Hall et al., dogs and cats were offered feeds of the same taste but different macronutrient composition to rule out the palatability effect of food choice [102]. The study showed that animals opt for constant protein intake (for each animal a different percentage). Whenever diets differ in taste, food palatability takes over; however, when the taste effect is attenuated, optimal protein is taken to support protein metabolism ideally.

Under the same umbrella, the *set-point theory* or the *organismic set-point* brought the idea of having a "privileged" body weight that regulates energy intake by stimulating over or underfeeding [103]. Unlike in the *lipostatic hypothesis*, body composition is relatively maintained. In a study on rats, ad libitum feeding had followed overfeeding, underfeeding or starvation of rats in different groups and body composition was assessed [104]. The findings revealed that starved rats were hyperphagic during refeeding, and they regained protein faster than fat. Another study on animals showed that dogs with high-fat mass favoured diets rich in proteins [102], and this strongly supports that food intake aims at balancing body composition and preserving lean body mass.

Our "protein efficacy" theory

Taken together, the protein leverage theory [77] with the findings that lean body mass is the main predictor of energy intake [86], it can be claimed that dietary protein intake is there to cater for the need of lean body mass. Therefore, the better the capacity of dietary protein to support the integrity of lean body mass, the less is the need for energy intake. Consequently, we hypothesize that dietary protein efficacy (the capacity of the protein to support growth and maintenance at the lowest energy cost) is the major predictor or determinant of energy intake. In turn, protein efficacy depends on the availability of essential amino acids and sufficient energy (ATP) to support their metabolism and wire protein synthesis. Such energy, the ATP, is highly governed by exogenous phosphorus supply. As discussed above, and in line with our hypothesis, both protein quantity and quality influence food intake. When looking at protein metabolism, it is clear that protein synthesis is an expensive energy-requiring process, in which 4 ATP equivalents are required for the formation of 1 peptide bond, or the equivalent of 0.67 kcal per one gram of protein synthesized [105]. In support, several observations indicate that this process is highly dependent on phosphorus availability [106–108].

ATP

Mitochondrial ATP production requires several micronutrients including phosphorus, niacin (NADH), and riboflavin ($FADH_2$). Most countries (including those with high rates of obesity) are known to have active B-vitamin fortification programs, and consequently, these vitamins would not be limiting factors for ATP synthesis. The fact that cells contain small quantities of phosphorus [109] makes many metabolic processes dependent on extracellular inorganic phosphate availability that is highly governed by exogenous phosphorus supply. Hence, ATP production that is highly dependent on phosphorus availability [110,111] would be affected by phosphorus intake. In support, the "phosphate-sequestering" capacity of fructose was reported to alter ATP status [112,113] negatively [110,113–115]. Moreover, the need for phosphorus for the phosphorylation of many compounds (e.g. metabolites, proteins, etc.) is thought to create a competition for phosphorus between the varied metabolic reactions, which can ultimately compromise the activity of some. It has been previously shown that the administration of 75 g of glucose via the oral glucose tolerance test (OGTT) decreased serum phosphate levels [116].

On the other hand, the dependence of protein synthesis on ATP made it difficult to dissect the impact of ATP from that of protein synthesis on food intake. Nonetheless, the physiological regulation of food intake, which acts principally at the central level, was reported to be partially governed by signals originating from ATP production [113,117–121]. Moreover, obese humans and animals were shown to have abnormalities in ATP status (mainly hepatic ATP) [115,122–124]. At the same time, ATP production was reported to modulate the activity of adenosine

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https://doi.org/10.1042/CS20190583

monophosphate-activated protein kinase (AMPK), which is involved in the regulation of several processes, including protein metabolism, appetite, and food intake [125]. On the other side, the high phosphorus content of proteins may partially explain the synergistic relationship between protein intake and energy balance [126,127], especially since phosphorus was reported to increase resting metabolic rate [128,129] and postprandial energy expenditure [130,131], and to suppress food intake [132]. Indeed, high phosphorus diets were shown to suppress fatty acid synthesis [133,134] and decrease visceral fat, increase fat oxidation of white adipose tissue [130,135], and improve insulin sensitivity [116]. However, phosphorus depletion was reported to reduce energy production [109] and cause skeletal muscle dysfunction due to defects in ATP synthesis [108]. Therefore, phosphorus manipulation has likely pertinent effects on energy metabolism and body composition. Moreover, the high phosphorus content of dairy products may have contributed to the inverse association between dairy product intake and body weight, given that calcium has failed to explain such an association [136–138].

Phosphorus content of several major raw (unrefined) food commodities is about 1 mg/kcal. Hence, daily consumption of 2500 kcal from unrefined food, which is comparable to the diet of our ancestors, would provide around 2.5 g of phosphorus, while the current intake is about half the amount (∼1.4 g/day or 0.5 mg/Kcal) [139]. Both ancestral and current intakes are higher than the recommended dietary allowance (RDA) of 0.7 g/day but lower than the upper intake limit of 4 g/day [140]. At the same time, the actual phosphorus intake is lower than that recommended for animals [141], and this questions the accuracy of the RDA for phosphorus [142] and raises the voice for revisions of the recommendations.

In the past few decades, the major changes in dietary habits that paralleled the rise in obesity prevalence were related to the dramatic increase in the intake of refined food (cereals, sweeteners, sugar, high-fructose corn syrup, oils, etc.) which are low or free of phosphorus. In most countries, approximately 60% of the energy supply comes from refined foods [7]. In fact, the rise in the obesity rate in the United States between 1971 and 2006 [8] might be attributed to the 5% increase in "micronutrient deficient" carbohydrate, which hinders proper protein metabolism, which was further coupled with a 1% decrease in protein intake. Additionally, approximately 70% of protein intake of most Middle Eastern countries is derived from plant sources (low quality), in contrast with western countries in which approximately 60% of protein intake (North America and Western Europe) originate from animal products (high-quality protein) [7]. Interestingly, obesity was reported to be widespread among people of low SES [55,56], who are known to consume a high proportion of refined food and plant proteins (low quality) due to their low cost [143]. This dietary pattern compromises phosphorus (quantity and bioavailability) and protein (quality) that are needed for ATP synthesis and protein metabolism, respectively.

We have recently shown that phosphorus supplementation mitigated the growth measures (including body protein content) of rats fed low protein diets [83]. Egg white was used as a protein source in this study. Interestingly, despite the complete amino acid profile and the high-quality of the egg white protein [144], the rats' growths were blunted [83]. Besides, this work demonstrated that dietary phosphorus was inversely related to plasma urea nitrogen, reflecting less protein catabolism. The study boldly affirmed that protein synthesis and growth are not dependent on the quality of the protein and the presence of essential amino acids. In another study, phosphorus reintroduction to the phosphate-restricted diet (via potassium phosphate water) was able to reverse partially the detrimental effect on growth; and this was conceived by a drop in plasma and cerebrospinal fluid phosphate levels, leading to a behavioural response to increasing phosphorus intake [145]. Likewise, phosphorus addition to a gluten protein diet was able to improve lean body mass when supplemented with lysine [146]. In both studies, phosphorus was able to increase body protein content significantly. In humans, weight gain under phosphorus-deficient diet was reported to be attributed mainly to an increase in adipose tissue, while nitrogen retention was impaired [147], and this seems to mimic the effect of a low-protein, low-phosphorus diet [148]. Moreover, the ability of phosphorus to mitigate growth measures of rats maintained on low protein diets (10%*E*) or to improve protein efficacy may be of significant consequence since maternal protein restriction predisposes offspring to chronic diseases [149,150].

Amino acids

The choice of quality of protein intake has been referred to in animals as euphagic selection [151]. Several trials showed food preferences related to optimal protein consumption. In support of the association between low-quality protein translated into poor protein metabolism and weight gain, a recent review has suggested an alteration in glycine (an amino acid) metabolism in obesity [152]. Glycine requirements in obesity increase due to an alteration in absorption, a drop in synthesis, and/or an increase in excretion, making it a conditionally essential amino acid. Due to poor

glycine availability, the metabolism would continuously request this substrate and aim at providing it through an increase in random food intake. This review suggests increasing glycine availability/intake to curb the progression of obesity and its associated metabolic abnormalities [152].

Additionally, a meta-analysis showed considerable alterations of amino acid profiles of obese people as compared to healthy ones. The authors concluded that obesity was associated with the most changes in circulating amino acid as compared with other chronic conditions like metabolic syndrome and Type 2 diabetes [153]. The analysis also showed a drop in glycine levels in addition to citrulline, serine, and glutamine. The potential alteration of certain amino acid transporters has been discussed. Also, it has been shown that knocking out SLC6A15, a gene that encodes a leucine transporter, in mice, attenuates the leucine capacity to reduce food intake [154].

Furthermore, many food modifications can have disadvantageous effects on the quality of the proteins and alter some amino acids. Processed meats, for instance, are mostly derived from animal products and are theoretically not deficient in essential amino acids. However, it has been shown that some meat processing techniques (such as carbonylation, hydroxylation, nitration, nitrosylation, sulfoxidation, chlorination, etc.) reduce the quality of proteins by either compromising their availability or changing their metabolic activities [155]. For example, lysine and threonine in bread were shown to be decreased upon baking [156].

Consequently, assuring a proper amino acid balance from high-quality proteins has to be in the driver's seat. In the same context, many studies reported high-energy and low-nutrient density diets among obese people [157,158], which also reflect pooper micronutrient status as compared with control subjects. This phenomenon is known as micronutrient-specific hunger that stimulates food intake in order to feed up processes and pathways that require specific nutrients [159].

The proposed mechanism

Our hypothesis postulates that optimal protein metabolism to support skeletal muscle integrity is essential for the control of energy intake. In turn, protein metabolism is contingent on dietary protein efficacy that is reliant on the co-availability of ATP (dependent on precursor availability) and adequate amino acids (quantity and quality). Each component of dietary protein efficacy (ATP and amino acids) was reported to affect energy intake. To our knowledge, they were not addressed together, although part of their mechanistic effect seems to interact.

In brief, weight loss in high protein diets was reported to be attributed to reduced energy intake that is induced through the activation of a mammalian target of rapamycin complex 1 (mTORC1)-dependent pathway in the muscles and brain [160–162]. In the hypothalamus, mTOR suppresses AMP-activated protein kinase (AMPK) phosphorylation and increases the expression of anorexigenic neuropeptides [161]. At the same time, ATP that is stimulated by the availability of dietary phosphorus [110] lowers ADP to ATP ratio that consequently deactivates AMPK and stimulates the mTOR signaling pathway [163].

The fact that, most protein sources are rich in phosphorus confounds the segregation of the impact of ATP from that of amino acids on energy intake. Therefore, we hypothesize that exogenous phosphorus enhances protein efficacy by boosting ATP availability using the mTOR and AMPK interplay. Further work is needed to reveal the mechanisms of action behind our hypothesis.

Conclusion

Obesity and increased energy intake have accompanied a dramatic change in macro and micronutrients intake, with a preference for high energy, high carbohydrate, and low nutrients foods. Previously, all attention was given to the macronutrient effect on health and diseases. Not too far ago, scientists have shifted their interest to micronutrients and have described micronutrient deficiencies as global health silent epidemics. Surprisingly, this epidemic did not spare people with obesity, known to have high energy intake. Many hypotheses have failed to adequately explain mechanisms behind energy metabolism leading to excess food intake and weight gain. We hypothesize that dietary protein efficacy, in terms of quantity and quality of protein and phosphorus support of energy required for protein metabolism, is a strong determinant of energy balance. The enhancement of protein metabolism by both phosphorus (for ATP) and limiting amino acids would favour the regulation of body weight. Future research should focus on factors to enhance ATP production and affect protein quality, such factors are defects in amino acids, their transporters, and absorption under varied conditions.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Clinical Science (2020) **134** 389–401
https://doi.org/10.1042/CS20190583

Funding
The authors declare that there are no sources of funding to be acknowledged.

Author Contribution
The manuscript was written by C.E.M. and O.O.

Abbreviations
%E, percent of total energy; RDA, recommended dietary allowance; ATP, adenosine triphosphate; SES, socioeconomic status; SSB, sugar-sweetened beverages.

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