The challenges associated with a low protein diet (Review)

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Abstract. Low-protein diet regimes, not necessarily focused on coeliac disease management, as individuals with this condition can consume alternative non-gluten protein sources, but for individuals carrying in-born errors of metabolism gene defects, such as phenylketonuria and certain kidney/liver diseases, are challenging. Protein provides texture in foods, setting aside its critical role in nutrition, which is difficult to replicate using other molecular systems. In fact, it is impossible to do so in reality. However, a number of low-protein products have been developed for individuals with the low protein need and many have proven to be acceptable, better than the metered consumption of specific amino acid blends alone. Although critical in the diet, these amino acid blends are not only monotonous with a generally unattractive taste, but they also never replace the eating experience as both a pleasurable personal activity and social activity. The present mini-review considers the challenges and potential management options of low-protein foods and diets.

Contents

1. Introduction

General. Proteins (and hence enzymes) are commonly composed of ~20 different amino acid structures in the natural world. For human adults, nine of these are 'essential' or 'indispensable' and must be obtained from the diet: Histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. For children, arginine, cysteine, glutamine, glycine, proline and tyrosine are also considered to be essential amino acids and are referred to thus as 'conditionally' essential. The reference nutrient intake of protein for adults is 0.75 g protein per kg body weight per day equivalent to 56 g per day, and 45 g per day for males and females of average body weights, respectively (1,2). The dietary intake of 1.0, 1.3 and 1.6 g protein per kg body weight per day is recommended for minimal, moderate and intense physical activity (1). Chronic relatively high protein intake in excess of 2 g per kg body weight per day for adults may be detrimental, resulting in for example, digestive, renal and vascular abnormalities (1).

Nitrogen balance. Nitrogen balance is critical for optimal health, where nitrogen intake from the diet should equal nitrogen excretion (in its different forms). Protein deficiency will lead to the progressive deterioration of the body, and ultimately, to mortality if the situation is chronic and severe, whilst protein excess can also be detrimental to health (1), as discussed below. It is interesting that longevity is supported by a relatively low protein-high carbohydrate diet (3,4), which appears counter intuitive. The benefit of this relatively low-protein intake diet is particularly relevant when reducing animal-derived protein intake (3). Certain amino acids, particularly branched chain amino acids (isoleucine, leucine and valine) together with (and particularly) methionine, are negatively associated with longevity through multiple mechanisms, where the restriction of their intake is potentially beneficial (3). It is believed that cancers can be regulated by managing (specific) amino acid availability, although this is not yet fully understood (5,6).

Extreme protein deficiency and excess

Deficiency. Acute protein/energy malnutrition may be described as 'primary' (insufficient food intake) or 'secondary' (due to disease, excess energy usage or decreased consumption linked usually to another ailment) as discussed in the study by Dipasquale *et al* (7). Moderate acute malnutrition anatomical indices include a mid-upper arm circumference ≥115 mm and <125 mm with a weight for height Z score of <-2 but >-3, whilst severe acute malnutrition includes a mid-upper arm circumference of <115 mm and a weight for height Z score of <-3 (7). Classically, two low protein/energy disease states are often described: i) Marasmus, where there is a negative dietary energy balance that results in severe

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wasting; ii) Kwashiorkor, which is of uncertain cause, but includes a range of physiological manifestations, mainly fatty liver disease, skin problems, glutathione depletion and most evidently, oedema (7,8). Sometimes, the combination disease state Marasmic-Kwashiorkor is described in the literature. Dietary protein deficiency causes a decrease in the capacity of the body to undertake protein synthesis with the increased proteolysis of skeletal muscle and proteins across the whole body; this is associated with numerous other impacts as the deficiency endures (1). For critically ill patients, enteral or parenteral feeding is a crucial element of care although overfeeding calories leads to an increased risk of infection, morbidity, and mortality (9).

Excess. A long-term excess of dietary protein/animal protein consumption (>0.8 g protein per kg body weight per day) can lead to: i) Bone and calcium homeostasis disorders; ii) kidney (renal function) disorders; iii) an increased risk of developing cancer; (d) liver function disorders; and (e) coronary heart disease progression (10).

2. The need for a low-protein diet

The mechanism by which low-protein diets 'work' has been discussed in detail by Pezeshki and Chelikani (4), where they state that 'Dietary protein restriction results in reduced concentration of most essential amino acids in the circulation, which play a role in metabolic adaptations to protein deficient diets'. This approach limits the amount of one or more amino acids entering and being metabolised by the body.

Low-protein diets and physical disease states. The human diet is shifting to a lower protein consumption, where what used to be defined as 'moderately restricted' low-protein diets of 0.8 g protein/kg/day are now considered to be normal, where 1.0 to 1.2 g protein/kg/day has become 'high protein' (11). Low-protein diets are used for kidney disease in particular, where there are established variants of the low-protein diet approach (11,12) as follows: i) Traditional moderate protein restriction to 0.6 g mixed origin protein/kg/day; ii) vegan protein restriction to 0.6 g vegetable origin protein/kg/day; iii) vegan protein restriction supplemented with keto and amino acids, 0.6 g vegetable origin protein/kg/day; iv) low-protein diet with 'protein-free' mixed origin food, 0.6 g protein/kg/day; and v) very low protein diet of 0.3 g vegetable origin protein/kg/day. Liver disease states (especially hepatic encephalopathy) may also be managed in part by careful applications of low-protein diets (13).

According to Piccoli and Cupisti (14), low-protein diets represent a method of increasing energy loading without an additional nitrogen load. They consider that there are numerous positive attributes of low-protein diets: i) Feasible to live on; ii) safe and may be followed with good adherence iii) adaptable to different settings and may be designed with different menus; iv) not necessarily boring; v) not restricted to any geographic location or alimentary habit; vi) potentially delicious.

Low-protein diets and mental health. The role of amino acids in mental health issues are complex, as they form protein structures and in addition, can function as neurotransmitters (15). In terms of mental health, Sheikhi *et al* (16) indicated that consuming a diet rich in animal protein predisposes women to mental illness, a finding which is essentially in contrast to the view presented in the study by Li *et al* (17) regarding the benefits of dairy derived protein intake. Increasing dietary calories from protein sources overall reduces the prevalence of depression according to Oh *et al* (18). This has been supported by studies with athletes (19).

In-born errors of metabolism. In-born errors of metabolism reflect genetic defects responsible for the formation of specific enzymes, and they consequently affect the utilisation of different nutrients,including amino acids. These diseases have been discussed extensively in the literature (20-27). Enzyme replacement therapy has been useful for managing some disorders (e.g., the lack of certain digestive enzymes) although not possible for the vast majority of intracellular enzyme deficiencies. Whilst gene therapy has been proposed as a treatment for genetic defects reflecting metabolism of different nutrients, that approach does appear to be many years away before medical implementation. To a large extent today, genetic disorders are managed by clinical nutrition approaches, which may include nutrient exclusion as for example phenylalanine for phenylketonuria (PKU). Metabolic defects have the following concept: A single gene defect → a single enzyme dysfunction → build-up of substrate → intoxication by substrate and deficiency of product(s). The impacts of single-enzyme dysfunction then resonate throughout the body.

Microbial aspects. Although the present review is not focused on gut microbiology, researchers such as Hsu *et al* (28) have reviewed the impacts of the low-protein diet on gut microbiology. Their overall conclusion was that the effects on the gut microbiota were observed predominantly at microbial families and species levels, but minimally on their 'diversity or richness', where the species-level changes appeared to them to be insufficient to alter metabolic or clinical outputs. Other authors have a different overall perspective with respect to dietary protein impact on gut microflora.

According to Yao *et al* (29), in general, dietary manipulation to minimise the potentially harmful effects of protein fermentation in the gut should focus on the modification of total protein and the type of amino acids consumed (together with increasing delivery of fermentable carbohydrates) to shift bacterial activity away from protein fermentation.

Singh *et al* (30) discussed in their review the impact of protein source and intake on the diet in some detail. Overall, they reported that for the majority of the studies they considered, protein consumption was positively associated with overall colonic microbial diversity.

According to Bartlett and Kleiner (31) dietary protein markedly affects the intestinal microbiota composition and function; where the protein-microbiota interactions can have 'critical impacts' on host health. In addition, they discussed how protein sources may influence microbiota functionality, in particular on the differences in metabolites produced by both protein hydrolysis and amino acid fermentation.

In the review by Wu *et al* (32), it was indicated that: i) Several factors, such as protein source, protein content, dietary composition, glycation of protein, processing factors and

Table I. Protein quality parameters.

Parameter	Description	Calculation
Amino acid score (AAS) and protein digestibility corrected amino acid score (PDCAAS)	Expressed as the amount of the first limiting essential amino acid of the test protein as a percentage of the amount of the same amino acid in a reference pattern of essential amino acids (FAO/WHO, 1990). When corrected for the true digestibility of the test protein the value is referred to as the protein digestibility corrected amino acid score. Egg for example scores 1 (100 percent).	The mg/g nitrogen x100 Corresponding values in mg/g nitrogen listed for the optimal reference (FAO/WHO) pattern
Biological value (BV)	How efficient the body uses a selected dietary protein. A high BV reflects a protein rich in essential amino acids. Animal protein tends to have a higher BVs than plant. Egg, for example, scores 100%.	Nitrogen retained x100 / Nitrogen absorbed
Digestibility (D)	Digestibility reflects the amount consumed less the amount retained in the faeces.	Nitrogen absorbed x100 / Nitrogen ingested
Net protein utilisation (NPU)	A direct measure of the retention of absorbed nitrogen. Note that the BV is calculated from nitrogen *absorbed*, but NPU from nitrogen ingested. Egg, for example, scores ~94%	Nitrogen retained x100 / Nitrogen ingested
Protein efficiency ratio (PER)	The PER reflects the growth induced effectiveness of a consumed protein compared to a standard value of 2.5 (casein). Egg for example scores 3.9.	Weight gain (g) / Protein intake (g)

For further details, please see FAO/WHO (77), and the studies by Schaafsma (78), and Hoffman and Falvo (79).

Table II. Protein alternatives sourced from plants.

Protein analogue type	Comment
Meat and fish	Various - soya, other legumes, seeds, grains (particularly wheat gluten), nuts, fruit (e.g. jackfruit although relatively low in protein), mushrooms, microorganisms (e.g., *Fusarium venenatum*-previously misidentified as *Fusarium graminearum*)
Dairy	Soya, other legumes, cereal, nut, coconut, potato, hemp
Egg	Plant proteins (soya and/or other beans and pulses, cereal) blended sometimes with gums (sometimes starches/gums used without protein creating a low protein format)
Gluten (wheat)	Used to structure many food products. Main ingredient in seitan.

protein oxidation all affect the digestibility and bioavailability of dietary proteins. These factors in turn can then influence protein fermentation, absorption, and functional properties in the gut with an impact upon the composition of gut microbiota and associated human health. ii) Since the gut microbiota can release metabolites that can affect the host physiology (positively or negatively), dietary protein quality and food processing conditions are important with respect to creating a positive effect on gut microbiota and human health.

3. The roles of protein in foods

Providing food structure. Apart from nutritional roles and quality aspects (Table I), dietary proteins play a critical role in structuring food, both plant and animal origin proteins (33-38). Without the presence of proteins, it is often very difficult to create a relevant desirable texture. In numerous meat analogue products (such as vegan variants), polysaccharides (and fats) are employed to try to replicate the native protein-like structure. Creating a desirable texture is a considerable challenge to deal with in low protein foods. This experience is also linked to aroma and taste experiences.

Animal protein-like food structures, occurring naturally and man-made, can be built from sensorially attractive analogues which are usually vegan or vegetarian in design; using different types of proteins, carbohydrates and lipids (Table II). Where plant proteins are incorporated into analogues, the overall protein load may not decrease and the approach is hence limited in application for low protein foods. On the other hand, polysaccharide-and lipid-based structures reduce the protein content effectively. Vegan ‘cheese’ (based on coconut or cashew nut fat in combination with polysaccharides

most often) is a good example. There is considerable consumer and commercial interest in this area for vegetarian and vegan markets especially (37-43).

For low-protein diets, the issues are not focused primarily most often on the origin of the protein, but on the necessity to control/restrict all protein (and hence amino acid) content in the diet. This is in the most part due to specific amino acids, which need to be controlled for in-born errors of metabolism, although allergies/intolerances will also require the exclusion of specific protein types. The issues then arise as to what can be used in the place of protein in a low-protein product to provide texture. Setting aside food ingredients that do not need to carry 'E-numbers' but contain structuring agents/thickeners, ingredients that can contribute to product structure, that are not proteins, are essentially starch or non-starch polysaccharides (Table III). The relative safety of E-numbers has been discussed by The European Food Safety Authority (EFSA, Anon) (44) which is due to be updated in 2025.

Himashree *et al* (45) reviewed the thickeners used in foods and drinks in terms of origins, structures and functionality (viscosity and rheology especially). In addition, Himashree *et al* (45) reported that hydrocolloids (such as food thickeners) have additional health benefits in that they may lower the risk of cardiovascular disease, blood cholesterol concentration and boost immune activity. Thickeners may be digestible (such as pre-gelatinised starch) or carried to the colon largely intact (as gums). They are considered generally to be safe to use, although there may be potential issues with usage in particular situations.

For clinical use, thickeners are not consumed by choice, but due to their impact on the safety of swallowing, where they are employed therapeutically by clinicians due to their efficacy, low cost and ease of implementation, as discussed by Hadde *et al* (46). In the context of gastroesophageal reflux and oropharyngeal dysphagia, in particular in infants and children, Duncan *et al* (47) discussed the potential benefits, mechanisms of effect and optimisation of thickener usage. They recognised potential risks of usage which include exposure to heavy metals such as arsenic, necrotising enterocolitis, dehydration, decreased intake nutrient intake and constipation. According to Duncan *et al* (47), these concerns may limit their use in clinical practice.

Yang *et al* (48), in their review of thickener usage, focused on dysphagic patients and warned that there were risks of using thickeners which include the following: i) The bioavailability of medication can be impaired by viscous substances; ii) as the viscosity of any liquids increase, the feelings of thirst and satiety will increase; iii) the flavour of the thickened product will deteriorate regardless of the thickening agent; iv) thickened liquids are considered less palatable than the un-thickened counterparts; v) for pre-gelatinised starch-based thickeners, salivary amylase may depolymerise the thickener and reduce its viscosity-hence starch or pre-gelatinised starch are considered potentially unsafe options; vi) there are limited clinical data available on the long-term effects of thickeners on dysphagic patients where more high-quality clinical trials are required.

Providing functionality. Polysaccharide functionality in food depends on a number of factors-not only the molecular species but size, linearity, substitution, charge, concentration,

Table III. Ingredients that may be used as structuring ingredients in food (UK and Europe) to contribute to structure with associated 'E-Numbers' (80).

E-Number	Name
E400	Alginic acid
E401	Sodium alginate
E402	Potassium alginate
E403	Ammonium alginate
E404	Calcium alginate
E405	Propane-1,2-diol alginate
E406	Agar
E407	Carrageenan
E407a	Processed eucheuma seaweed
E410	Locust bean gum; carob gum
E412	Guar gum
E413	Tragacanth
E414	Acacia gum; gum arabic
E415	Xanthan gum
E416	Karaya gum
E417	Tara gum
E418	Gellan gum
E425	Konjac
E426	Soybean hemicellulose
E427	Cassia gum
E440	Pectins
E460	Cellulose
E461	Methyl cellulose
E462	Ethyl cellulose
E463	Hydroxypropyl cellulose
E464	Hydroxypropyl methyl cellulose
E465	Ethyl methyl cellulose
E466	Carboxy methyl cellulose
E468	Crosslinked sodium carboxy methyl cellulose
E469	Enzymatically hydrolysed carboxy methyl cellulose
E423	Octenyl succinic acid modified gum Arabic
E1200	Polydextrose
E1204	Pullulan
E1404	Oxidised starch
E1410	Monostarch phosphate
E1412	Distarch phosphate
E1413	Phosphated distarch phosphate
E1414	Acetylated distarch phosphate
E1420	Acetylated starch
E1422	Acetylated distarch adipate
E1440	Hydroxyl propyl starch
E1442	Hydroxy propyl distarch phosphate
E1450	Starch sodium octenyl succinate
E1451	Acetylated oxidised starch
E1452	Starch aluminium Octenyl succinate

Note where thickening products are part of an ingredient naturally (and historically)-for example starch in flour or alginate in seaweed-no approval is required. Some are employed typically as thickeners-some not.

Table IV. Examples of egg alternatives based on carbohydrates.

Brand	Composition (ingredients)
Crackd (https://www.crackd.com/the-no-egg-products/the-no-egg-egg)	Water, Pea Protein (3%), Corn Oil, Thickener (methyl cellulose), Pea Starch, Gelling Agent (Gellan Gum), Flavourings, Firming Agent (Calcium Lactate), Dried Inactive Yeast, Acid (Lactic Acid), Black Salt, Acidity Regulator (Potassium Bitartrate), Colour (Beta Carotene), Stabilisers (Calcium Carbonate, Guar Gum, Cellulose Gum), Vitamins (D and B12), Dextrose.
Free and Easy Egg Replacer (https://www.baldwins.co.uk/free-easy-egg-replacer-135g)	Potato Flour, Tapioca Flour, Cream of Tartar, Xanthan Gum, Methylcellulose
Just Egg (https://www.ju.st/eat/just-egg)	Water, Mung Bean Protein Isolate, Expeller-Pressed Canola Oil, Sugars (Tapioca Syrup Solids, Sugar), Soy Lecithin, Tetrasodium Pyrophosphate, Salt, Gellan Gum, Potassium Citrate, Carotene, Nisin, Transglutaminase, Maltodextrin, Natural Flavours, Dehydrated Onion, Turmeric.
Oggs Vegan Aquafaba Egg Substitute (https://www.loveoggs.com/product/product-oggs-aquafaba-egg-alternative/)	Liquid Chickpea Extract
Orgran Health Gluten Free No Egg, Egg Replacer (https://orgran.com/product/orgran-no-egg-egg-replacer-mix/)	Potato Starch, Tapioca Starch, Raising Agent: Calcium Carbonate, Acidity Regulator: Citric Acid, Vegetable Gum (Stabiliser): Methylcellulose
Scrambled Oggs Plant Based Eggs Alternative (https://www.loveoggs.com/)	Water, Sunflower Oil, Chickpea Protein, Maize Starch, Thickener: Methyl Cellulose, Nutritional Yeast (Dried Inactive Yeast), Emulsifier: Sunflower Lecithin, Acid (Lactic Acid), Firming Agent: (Calcium Lactate, Calcium Carbonate), Sugar, Gelling Agent: Gellan Gum, Acidity Regulator: Sodium Citrate, Natural Flavouring, Black Pepper, Maltodextrin, Black Salt, Colour: Beta-Carotene
Simply Eggless (https://trysimplyeggless.com/index.html#eggless)	Water, Lupin Protein Concentrate, High Oleic Sunflower Oil, Gluten Free Beta Glucan, Natural Flavours, Calcium Lactate (Vegan Source), Vegan Enzyme, Tetrasodium Pyrophosphate, Agar, Xanthan Gum, Natural Extractives Of Turmeric, Natural Extractives Of Carrot, Nisin (a Natural Preservative)
Tesco Egg Alternative (https://www.tesco.com/)	Haricot Bean Flour (60%), Pea Fibre (18%), Potato Starch, Maltodextrin, Rice Flour, Tapioca Starch, Foaming Agent (Hydroxypropyl Methyl Cellulose).
The Vegg (https://thevegg.com/nutritional-facts/)	Pea Protein, Nutritional Yeast (fortified with Folic Acid, B-12 and Iron), Xanthan and Guar Gum, Black Sea Salt
Vegan Egg (https://followyourheart.com)	Organic Soymilk Powder (Organic Soybeans), Modified Cellulose, Gellan Gum, Cellulose, Calcium Lactate, Carrageenan, Black Salt (Black Salt, Herbs), Nutritional Yeast, Natural Flavours, Beta Carotene for Colour.

temperature, water availability, rheological properties, gelling properties, syneresis, presence of (other) ions and/or molecules, local environment, etc. (49-52). To replace the exact properties of proteins with polysaccharides is not (as discussed above) possible. However, a number of protein substitutes have been created-initially driven by vegan needs perhaps-which have desirable features. A good example is egg alternatives (Table IV, where some examples are provided with their ingredient profile). Gluten replacement by alternative crops other than wheat (e.g. oats) with/without hydrocolloids has been driven by a number of factors-including the demand for coeliac suitable baked goods alternatives. For low protein diets, however, coeliac friendly products which are not low protein, are not suitable. Low protein 'breads' are usually starch based with added gums (improvers, e.g. guar gum) to cause adherence and additional structure. The use of hydrocolloids as improvers have been discussed elsewhere (53), as has more extensive discussion regarding the replacement of protein with hydrocolloids (54,55). Setting aside product structure management for protein alternatives, there are several other issues to consider:

i) Aroma: Although not necessarily due directly to the protein or protein hydrolysate, proteins from different sources are associated with a particular aroma(s) before/during/after cooking. The aroma of boiled eggs for example is very distinctive-due to ferrous sulphide produced at the interface of the yolk and albumen (56). This adds to the eating experience anticipation. Amino acids, peptides and proteins are not themselves volatile. Sohail *et al* (57) described the aroma

from cooked meat as follows: a) 332 which included, b) 157 compounds from lipid degradation, c) 98 from Maillard reactions, d) 18 from interactions of lipid degradation and the Maillard reactions, and e) 59 compounds from other sources.

ii) Colour: Proteins and amino acids contribute to food colour through non-enzymatic (Maillard) browning reactions during processing (which also contributes to the aroma and texture with an associated reduction in nutritional quality). Previous studies have reviewed the complexities of non-enzymatic browning mechanisms in food (58,59) and the impact on sensory and health related properties.

iii) Energy: The energy value of food macronutrients is presented in Table V. Note that non-starch polysaccharides (as dietary fibre) have half the calories of protein and approximately half the calories of potentially digestible carbohydrates. Some of the apparently digestible carbohydrate as starch will actually resist digestion ('resistant starch') and in effect function as dietary fibre. Further information about starch digestibility can be found elsewhere (60-62).

iv) Co-nutrients: These are associated with proteins in foods although mostly as separate molecules/entities (unlike glyco-proteins and lipo-proteins in the body). v) Digestibility: Apart from digestive enzyme inhibitors in foods, which are prevalent in plant tissues in particular, research on cooked and uncooked proteins from different sources has compared how native and cooked plant and animal proteins are digested. Examples include the following: a) The assimilation of cooked egg is incomplete; however, ileal digestibility is enhanced by heat-pre-treatment (63); b) milk protein denaturation (through cooking) does not affect overall digestibility (64); c) not specifically on the protein molecules per se, cooking improves plant protein quality (65); d) although discussing cereal proteins in the most part, Joye (66) indicated generally that the digestibility of proteins benefits from (thermal) denaturation-supporting this view by citing *in vitro* study of Swaisgood and Catignani (67). It is difficult to draw a firm conclusion about processing impacts on proteins in foods in terms of digestibility. This is due to the relative effects on the proteins themselves and other molecules/structures that could modify digestibility in the native *versus* processed product. This is in contrast with free amino acids when added to foods-used as the major source of amino acids in many diets built for in born error of metabolism management-which are absorbed more rapidly with greater postprandial plasma amino acid availability than for an equivalent amount of intact milk protein (68).

v) Satiation and satiety: Proteins are effective satiating components of the diet (69). In low-protein products, the satiation/satiety 'deficiency' is compounded by the fact that it is usually replaced by carbohydrates which may (particularly sugars) stimulate the desire to eat. The replacement will also impact on lipid consumption-increased too due to the relative depletion of dietary protein. This enhancement of lipid and carbohydrate consumption is an important aspect to consider to avoid calorie loading when consuming low protein diets.

Table V. Relative macronutrient calorie density.

Nutrient	Energy in kcal/g	Energy in kJ/g
Fat	9	37
Alcohol	7	29
Protein	4	17
Carbohydrate	3.75	16
Dietary fibre	2	8

One kilocalorie (1 kcal) is equivalent to 4.18 kilojoules (4.18 kJ).

4. Challenges associated with a low-protein diet

Consumption. In Table VI, aspects of the low-protein diet on food consumption patterns are highlighted. It is a non-natural physiological state to consume amino acid powders and restrict food intake more generally to avoid exposure to potentially toxic amino acids (phenyl alanine as an example in phenylketonuria). The nutritional impacts are not only associated with protein restriction, but in addition, the consumption of excess volume/calories from carbohydrates and lipids. This switch inevitable when protein is restricted. This can often, as a consequence of restricted protein intake with a switch to carbohydrate and lipid, lead to weight gain.

The longer-term impact of eating low protein foods has both physiological and psychological dimensions. These range from an appreciation of the appearance, smell, taste, texture and satiety as a consequence of digestive processing and physical utilisation through to psychological appreciation. These psychological elements are on both a personal (controlled and restricted eating regime) and social (limiting severely meal experiences with others) basis. The low-protein diet is thus a very different experience than consuming a 'normal' diet. This, a permanent issue for the patient to manage.

Protein exchanges and low protein food classification. Protein exchanges have similarities with carbohydrate exchanges in diabetes (where one carbohydrate exchange is equivalent to 15 g carbohydrate). This system allows patients to match their carbohydrate food choices, while staying within their carbohydrate allocation for any given meal. For PKU-focused protein exchanges, one exchange is taken to be equivalent to 50 mg phenylalanine with is taken to be ~1 g protein (although proteins vary in phenylalanine content). There is a traffic light system which is used to classify food acceptability for PKU diets where: i) Red=avoid, high protein; ii) amber=contains a significant amount of protein-consume according to protein exchanges; iii) green=very little protein which can be consumed without restriction.

Low-protein diets (particularly for PKU) have been discussed in detail by MacDonald *et al* (70) and in this context, low-protein foods that can be eaten without restriction on a PKU diet. These represent for example: i) Drinks not containing phenylalanine in the form of aspartame; ii) fats and lipids <1 g protein/100 g without reference to exchanges; iii) fruits and vegetables (excluding potatoes, calculated per protein exchange) containing <75 mg protein/100 g; iv) starches <0.5 g protein/100 g; v) sugar sources <0.5 g protein/100 g; vi) vegan cheese substitutes <0.5 g protein/100 g; vii) vegan milk substitutes <0.1 g protein/100 g. The intake restrictions focus on amounts likely to be consumed (although the protein

Table VI. The impact of a low-protein diet on overall consumption profiles.

The consequence of a low-protein diet	
Increase	Decrease
Increased consumption of carbohydrate and lipid - potentially more calories with impact on body weight, diabetic tendency etc.	Reduction in protein mediated satiety.
Fat contains more calories than protein.	Care required for micronutrient consumption due to dietary restriction.
Fibre consumption may be increased.	Sensory properties of food diminished where amino acid powders for example are consumed in place of protein.
Increased exposure to sugar may impact on tooth decay.	Social impact of restricted food choice.

phenylalanine content is very pertinent in this context, but harder to manage for patients).

Food production. Producing low-protein foods for special nutritional needs is very challenging. Ironically, the rise in the awareness and demand for vegan foods has made certain low protein products very much more available serendipitously. Vegan 'cheeses' made from coconut oil, for example, are typically <0.5-1.5% protein by weight (unlike cheddar cheese, for example, which comprises ~25% protein). In terms of baked goods, it is more difficult to make good low-protein products in view of the structuring role of the plant protein (particularly wheat gluten). However, companies such as Firstplay Dietary Foods Limited (Stockport, UK) and Taranis (part of Lactalis Nutrition Santé, Torcé, France) do make a range of baked and biscuit type products that are low protein.

Low-protein medical diets are most often underpinned by the consumption of powdered amino acid blends which are hydrated and drank. Gels are available for the same purpose. Generally amino acids are not used (added into) in food formats that are heated-e.g., bread analogues-in part due to the sensory properties of the products that are formed and in addition, the 'loss' of the amino acid during processing-e.g., through browning reactions.

Terminology. In the context of low-protein diets for kidney disease, De Mauri *et al* (71) highlighted the contemporary medical terminology applied to condition management (through diet) where: i) Adherence describes where the patient matches the clinician's recommendations; ii) compliance relates to where the patient complies with the recommendations; and iii) concordance relates to the 'therapeutic alliance' between the patient and clinician. There are a number of personal and social factors which challenge adherence, compliance and concordance-perhaps mostly adherence due to modern lifestyles.

Adherence to low-protein diets. Low-protein diets do inevitably restrict food choice and dining experiences, which can be very challenging. In the context of PKU specifically, Yagudina *et al* (72) captured these dietary adherence challenges (which will apply more generally beyond PKU) within four main groups: Family-related (including social interactions etc.); patient-specific (personal commitment etc.); environmental (factors impacting on lifestyle etc.) and; therapy-related (dietary format etc.). It is evident that compliance with a low-protein diet requires a large amount of commitment from the individual and support from those around the individual. In the modern world information and opportunities are more accessible as are lifestyle options, which may lead to less focus on professional clinical advice and perhaps less authoritative disease management options.

Pegvaliase and related therapies. To help manage the challenges of a PKU diet, therapies such as pegvaliase have been introduced. Pegyaliase is a pegylated form of the recombinant enzyme phenylalanine ammonia lyase, which is administered subcutaneously and converts phenylalanine to ammonia and trans-cinnamic acid (73). This type of contemporary approach to condition management may well have applications in numerous fields, including some conditions managed with low protein diets.

5. Low-protein products

Tinned, frozen and chilled low-protein foods can be obtained in different formats. Non-starch and starch polymers are invariably used to generate structure but do not have the properties of normal products that general consumers would be familiar with. High-fat products are an option for low protein diets but tend to be difficult to consume sometimes and fats provide more than double the calories of protein. Sources of information regarding low-protein foods can be obtained through healthcare professionals. A list of low protein food options prescribed in the UK for example, has been published by Wood *et al* (74). This includes a broad range of different food types and associated costs to the National Health Service. Of note, low-protein crispbread-type crackers, Xpots (low protein pot noodle) and liquid milk replacements had the highest price differential than the regular comparator; at 1,117 to 1,143% more expensive. This reflects a number of price pressures placed on the products, which include ingredient costs, small-scale processing cost base, specialist processing conditions required, specialist sales and marketing structures (outside supermarket supply chains in the most part as the products tend to be prescribed), product registration costs, dietetic support, competition etc.

Baked goods can be constructed without flour using typically starch and gums. Again, this comes with a price

premium. Taking the cracker market alone, according to Wood *et al* (74), there is currently a 259% difference between available products and regular competitors. This based around Nutricia Loprofin crackers and Vitaflo mini crackers. These two products have similar structure (different shapes) with a comparable ingredients list. They are designed to imitate conventional (cream) crackers although the mouth feel and taste is not the same. New products coming to the market in this sector include the Glycologic Limited (GLY-LOW) crackers which have a different format and thus sensory experience. They are also designed uniquely to release energy in a slow and sustained fashion [with parallels to other cracker types they have developed (75)].

There are a number of opportunities to make acceptable low protein products, where carbohydrates and fat are required to compensate for the protein in the most part. The overall in born error of metabolism market for food products is perhaps surprisingly large and anticipated to reach in the region of $5,768.79 million by 2027 from $2,507.80 million in 2019 with a growth rate of 11.2% during this period (76). The need for products is obviously a driver although where more product choice becomes available to prescribers and non-prescribers, sensory profiles will become far more important in the overall selection of products.

6. Conclusions and future perspectives

In the early days of clinical nutrition product manufacture, the overall aim was to get the nutrition profile 'right' with less focus on the sensory properties of the products. This led, undoubtedly, to many patients not conforming with the dietary regime-although critical for their health. These days there is much more emphasis-rightly so-on the eating experience for the patients too. This brings with it considerable challenges. However, with time, investment and processing skills huge strides can be made to provide nutritional support with sensory enjoyment. This does not necessarily require novel ingredients but an understanding of the chemistry of how ingredients interact during processing to create desirable and functional products. This offers benefits to manufacturers but undoubtedly and especially for patients. It may well not be possible to expand the low protein offering to the restaurant sector due to supply and demand issues primarily.

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RT was involved in the writing and preparation of the original draft of the manuscript. XQ was involved in the writing, reviewing and editing of the manuscript. Both authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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