Review

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Effect of nutritional intervention on nutritional status among children with disorders of amino acid and nitrogen metabolism (AANMDs): A scoping review

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SUMMARY Disorders of amino acid and nitrogen metabolism (AANMDs) occur due to an enzyme deficiency in a normal biochemical pathway. Nutritional intervention is recognized as the mainstay of treatment for children diagnosed with AANMD. Hence, this scoping review aimed to identify the nutritional interventions available in managing AANMD disorders and their effects on nutritional status. A systematic search using PRISMA Extension for Scoping Reviews (PRISMA-ScR) method was conducted across 4 databases: PubMed, ScienceDirect (Elsevier), EBSCOhost and Cochrane Central Register of Controlled Trials (CENTRAL). Inclusion criteria for the study to be selected are: subjects aged less than 18-year-old, article published in English, utilized an experimental design and published within the past 20 years. A total of 22 articles were included in this review. The majority of the subjects are boys (55.6%) and employed a randomized controlled trial (RCT) study design (45.4%). Nutritional interventions were categorized into 4 categories which are: "protein substitute" (n = 5), "protein substitute with modified composition" (n = 6), "nutrient supplementation (n=8)", and "distribution and dosage of protein substitute (n = 3)". The most frequently assessed outcomes were biochemical parameters that gauge the effectiveness of metabolic control (68.2%). Overall, "protein substitute enriched with inhibitive amino acids", "long-chain polyunsaturated fatty acids supplementation", and "evenly distributed protein substitute" demonstrated beneficial effects towards the nutritional status, especially in terms of biochemical parameters. In summary, nutritional intervention plays a significant role in improving the nutritional status of AANMD patients. Further investigations of nutritional intervention among AANMD children using a meta-analysis approach are necessary for better comprehension of their impact in management of AANMD disorders.

Keywords nutrition therapy, amino acid metabolism, inborn errors, nutritional status

1. Introduction

The prevalence of amino acid and nitrogen metabolism disorders (AANMDs) at birth is 26.31 per 100,000 live births worldwide (*1*). AANMDs are a group of rare, heterogeneous genetic diseases that arise due to the deficiency of an enzyme, its co-factors, or a transporter that results in the disruption of an amino acid in a metabolic pathway (*2*). When the body is unable to break down a particular amino acid, toxic metabolites begin to accumulate in the blood, urine, body tissues as well as the brain (*3*). When these toxic molecules accumulate in the brain, they harm neurons leading to neuronal damage, neuronal death as well as impaired synaptic plasticity and excitability. This often manifests as learning, behavioural, and emotional difficulties. This accumulation also inhibits energy production within neuron cells resulting in cell swelling and acute encephalopathy (*4*). Other common neurological symptoms of AANMDs include seizures, progressive mental retardation, psychomotor retardation, ataxia, as well as changes in episodic consciousness (*5*). These clinical signs and symptoms

are often precipitated by fasting, catabolism, pyrexia, intercurrent illness, injury, and the overconsumption of intact proteins (*6*).

Nutritional therapy has remained the cornerstone of treating AANMDs since it was first used to successfully treat phenylketonuria (PKU; MIM ID #261600); the "poster child" of metabolic diseases; in 1951 (*7*). The primary goal of dietetic management is to reduce toxic metabolite production and accumulation as well as maintain blood amino acid indices within a non-neurotoxic range (*8*). Furthermore, it is prudent to maintain good nutrition in order to support normal physiological protein synthesis and prevent catabolism (*9*). Dietetic interventions primarily include restricting the intake of naturally-occurring proteins (*10*), introducing protein substitutes that are free of precursor amino acids, and the intake of adequate amounts of low protein food to meet energy requirements (*11*). Medical nutrition therapy (MNT) has been found to favourably affect the nutritional indices of AANMD patients. In this study, patients were thought the importance of metabolic control, provided with low protein recipes and low protein products as well as regularly followed-up at metabolic clinics (*12*).

A literature review revealed that most existing studies only summarise the types of nutritional interventions available for AANMD patients. However, none have thoroughly investigated the effects that these nutritional interventions have on nutritional indices (*11*). Furthermore, instead of consolidating all nutritional interventions into one article, only a handful of studies have examined the nutritional impact of supplementing PKU patients with specific nutrients (*13-15*). Therefore, a scoping review was performed to identify and map the available data on the impact of nutritional intervention on the nutritional indices of AANMD patients (*16*). A scoping review was employed to identify the types of nutritional interventions available as well as investigate their impact on the nutritional indices of children and adolescent with AANMDs.

2. Materials and Methods

2.1. Study design

PRISMA-ScR (PRISMA extension for Scoping Reviews) was used to draft the protocol that was used in this scoping review (*17*). For the purposes of this scoping review, nutritional interventions were defined as the prescription of natural food, medical food or formula, and dietary supplements (*8*). Studies were selected for inclusion only if the participants were below the age of 18 and had been diagnosed with AANMD. One justification for only including patients from this age group was the high prevalence of failure to thrive (FTT) among children with AANMD. Apart from that, studies that had been published between 2001 to 2021 in full text and in English were included in this scoping review. Studies that had been published 20 years ago instead of 5-10 years ago were included in this scoping review in view of the scarcity of research in this field.

Additionally, only studies that tracked and reported changes in nutritional indices; such as anthropometry measurements, biochemical parameters, clinical outcomes, or dietary intake; were included in this scoping review. Lastly, the design of these studies had to be experimental. This included randomised controlled trials (RCT), pre- and post-studies as well as quasi-experimental studies. Only studies with the types of the study designs outlined in the published literature were selected for inclusion (*18*). This was because an experimental study design is commonly used to evaluate research questions on therapeutic agents. This is like our scoping review which aims to assess the effects of nutritional interventions. Therefore, only studies that met all the above-mentioned criteria were included in this scoping review regardless of the length of the intervention or the sample size.

2.2. Search strategy

This scoping review utilised the bibliographic research methodology for the literature search. The relevant studies were searched on electronic bibliographic databases, such as PubMed®/MEDLINE (National Library of Medicine), ScienceDirect® (Elsevier), EBSCOhost, and Cochrane Central Register of Controlled Trials (CENTRAL). A literature search was also performed on an additional resource; the Journal of Inherited Metabolic Disorders (JIMD), to ensure that the search for AANMD-related studies would be extensive. Furthermore, the reference lists of the included studies as well as AANMD-related systematic reviews and clinical guidelines were also reviewed and screened. The first author drafted search strategies which was then cross-checked by the second author to ensure that important keywords had not been omitted from the search. The completed search results were then exported into Mendeley (version 1.19.8), a citation management software. The keywords used in the search were divided into two categories: *i*) synonyms for "nutritional intervention", such as "nutritional management"; and *ii*) the names of all AANMDs. A list of AANMDs was retrieved from Nutrition Support Protocols: The Ross Metabolic Formula System (2005) (19). The Boolean operator "AND" was used to combine keywords from both categories while "OR" was used to combine phrases within each category. Table 1 presents a list of all the keywords that were used during the search.

2.3. Study selection

The studies that were exported to Mendeley (version

Table 1. Key search term in the scoping review

Nutritional Treatment	Disorders of Amino Acid and Nitrogen Metabolism (AANMDs)
Nutritional Intervention	Phenylketonuria
Nutritional Approach	Tyrosinemia
Nutritional Strategies	Maple Syrup Urine Disease
Nutritional Management	Isovaleric Acidaemia OR 3-Methylcrotonylglycinuria OR 3-Methylglutaconic Aciduria OR 3-Hydroxy-3-Methylglutaric Aciduria
Nutritional Education	Homocystinuria
Dietary Treatment	Glutaric Aciduria OR 2-Ketoadipic Aciduria
Dietary Intervention	Propionic Acidaemia OR Methylmalonic Acidaemia
Dietary Approach	Urea Cycle Defects OR Urea Cycle Disorders
Dietary Strategies	Nonketotic Hyperglycinemia
Dietary Management	
Dietary Education	

1.19.8) were first screened for duplication after which duplicate studies were removed from the folder. The title of each study was then read, one-by-one, to determine its relevance to the research questions after which irrelevant studies were removed from the folder. The abstract of each study was then read to determine if it answered the research questions. Finally, the full text of each study was read to confirm its eligibility as some of the population characteristics were not reported in the abstract. The studies selected by the first author were then checked by the second author to ensure that every study met the eligibility criteria of this scoping review.

2.4. Data charting

Data from the eligible studies was charted in a standardised table that presented six important components: *i*) study characteristics (authors, year of publication, country, study design, and type of AANMD diagnosed), *ii*) intervention features, *iii*) intervention length, *iv*) study outcome, *v*) study results, and *vi*) summary. The outcome of each study was further divided into four main categories: *i*) anthropometry measurements, *ii*) biochemical parameters, *iii*) clinical parameters, and *iv*) dietary intake. In the end, three types of tables were presented in this scoping review as multiple study designs were included. This made it difficult to coherently present all the data in a single table. The charted table was reviewed by the second author to ensure that it was comprehensible.

3. Results

3.1. Study selection and characteristics

A total of 1,755 studies were identified from the electronic databases. After removing duplicate studies, 1,679 study titles remained to be screened. At this stage, 65 studies were retrieved and assessed for eligibility by reading the abstracts of each study. Of the remaining 35 full-text studies, 13 studies were excluded as the participants were above the age of 18 (n = 5), six were excluded as they did not meet the study design criterion (n = 7), and one was excluded because it did not report nutritional indices as the outcome (n = 1). Therefore, a total of 22 studies were selected for inclusion in this scoping review (Supplemental Tables S1-3, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=84*). The selection process is outlined in Figure 1.

In terms of study characteristics, the selected studies comprised of 652 participants (range: 7 to 109 participants). 55.6% of the participants were male and 44.4% were female. However, three of the selected studies did not provide gender characteristics (*20-22*). Most of the studies recruited participants that had been diagnosed with PKU (n = 17, 73.7%) (*22-37*). This was followed by glutaric aciduria type 1 (GAT1; MIM ID #231670) (n = 2, 10.5%) (*38,39*). Only single studies investigated patients with maple syrup urine disease (MSUD; MIM ID #248600) (*21*), methylmalonic aciduria (MMA; MIM ID #251000) or propionic aciduria (PA; MIM ID #606054) (*40*), and urea cycle disorders (CPS1D, OTCD, ASSD, ASLD, ARG1D, and NAGSD with MIM IDs #237300, #311250, #215700, #207900, #207800, #237310; respectively) (*20*). Eight (36.4%) of the studies were published in the United Kingdom (UK) (*23-25,32,34,35,37,41*), followed by Germany (n = 5) (*22,26,27,36,39*), the United States of America (US) (n = 4) (*20,21,38,40*), Italy (n = 3) (*28-30*), and Egypt (n = 1) (*33*). Only one study was performed in multiple countries; namely France and the UK (*31*). In terms of study design, five studies (22.7%) used a pre-post design without control arms (*20,21,23,33,40*) while seven studies (31.8%) used a non-randomised prospective interventional design with one or more control arms (*26,34,36-39,41*). Four out of six studies had only one control group while the other two studies had more than one treatment group. The remaining ten studies (45.4%) used a randomised controlled trial (RCT) design (*22,24,25,27-32,35*). Of the ten studies, four were a double-blind RCT (*22,27-29*) and four were a crossover RCT (*24,25,32,35*).

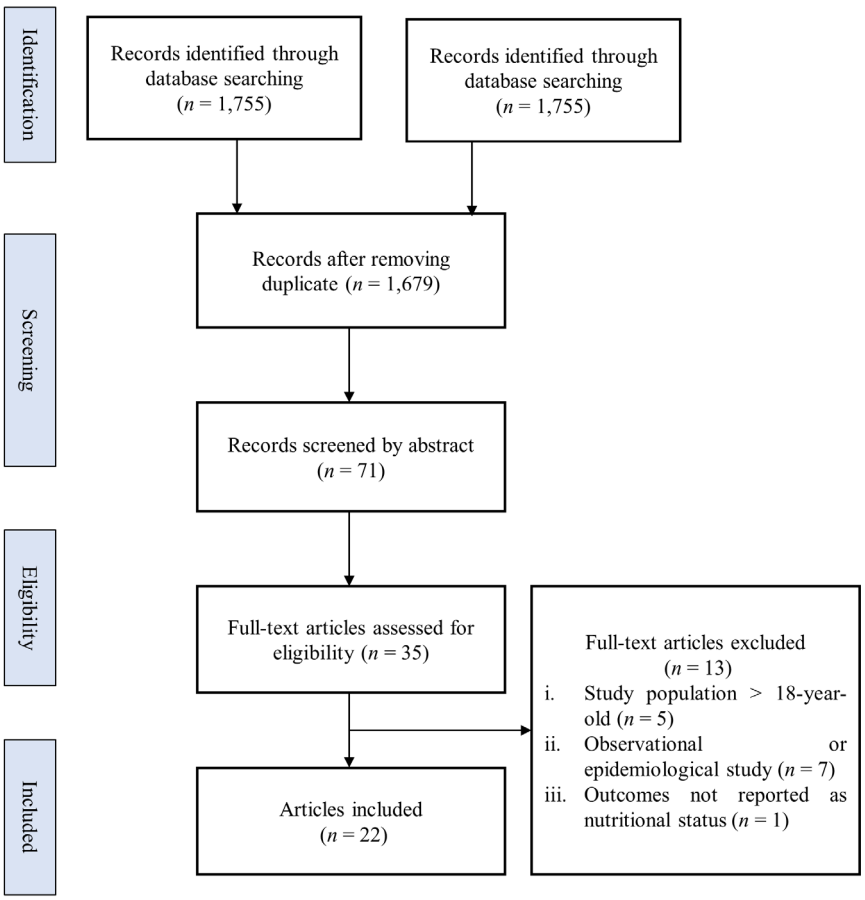

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting the literature search and study selection process.

3.2. Nutritional interventions and outcomes

For the purposes of this scoping review, nutritional interventions were classified into four main categories: *i*) "protein substitute", *ii*) "protein substitute with modified composition", *iii*) "nutrient supplementation", and *iv*) "distribution and dosage of protein substitute". Table 2 depicts a summary of each category of nutritional intervention and outcome measurements.

3.2.1. Medical formula/protein substitute

In this scoping review, the terms "medical formula" and "protein substitute" are interchangeable. Four protein substitutes that had been customised for different types of AANMDs were identified. Two out of five studies revealed an improvement in anthropometric parameters; such as weight and height; as well as biochemical parameters; such as of plasma amino acid concentrations, protein indices, and vitamin indices; in UCD and MMA or PA patients that had been supplemented with medical formulas that were free of essential amino acid and free of methionine and valine, respectively (*20,40*). Apart from that, two studies that utilised a formula enriched with a group of amino acids that compete with lysine and BCAA uptake into the brain demonstrated a significant increment in the uptake of inhibitive amino acid substrate among GAT1 and MSUD patients, indicating the neuroprotective properties of the protein substitute in question. Metabolic control was also found to be significantly improved (*21*). On the other hand, two studies found that GAT1 patients supplemented with a lysine-free, tryptophan-reduced, and arginine-fortified formula had significantly higher total arginine intake than the control group (*38,39*).

3.2.2. Protein substitute with modified nutritional composition

Six studies employed the use of protein substitutes that had modified nutritional compositions as part of their nutritional interventions. The term "modified nutritional composition" was defined as a protein substitute with a different amino acid profile and macronutrient content other than a conventional protein substitute". Of the six studies, five studied the effect that casein glycomacropeptide (CGMP)-based protein substitutes with conventional amino-acid-based protein substitutes had on the weight, metabolic control,

Table 2. Summary of nutritional strategies and outcomes measures

Nutritional strategies	Descriptions
Protein substitute/Medical formula (*n* = 5)	- Formula free of non-essential amino-acid (*20*) - Formula enriched with selenium, zinc, alpha-linolenic acid, and a group of amino acids that compete with BCAA for uptake into the brain (*21*) - Formula free of methionine and valine (*40*) - Medical formula with low lysine (0 mg) and fortified with arginine (90 mg), reduced tryptophan (5mg) (*38,39*)
Protein substitute with modified nutritional composition (*n* = 6)	- Low CHO protein substitute with a CHO/Protein-equivalent ratio 0.5:1 (*35*) - Casein glycomacropeptide (CGMP) based protein substitute (*32-34,37,41*)
Distribution and dosage of protein substitute (*n* = 3)	- Prolonged-release phenylalanine free protein substitute (*30*) - Administration of protein substitute evenly (shorter time gap) throughout the day (*25*) - Higher dosage of protein substitute compared with an alternative dose (*24*)
Nutrient supplementation (*n* = 8)	- Infant protein substitute supplemented with prebiotics (*42*) - LC-PUFA-supplementation (*22,26,28,36*) - EFA-supplemented phenylalanine free formula (*27,29,31*)
Outcomes	**Parameters**
Anthropometric measurements (*n* = 7)	- Body weight (*20,40*) - Body length/height (*19,38,40*) - Body mass index (*20,34,35,37,38,40,41*) - Head circumference (*19,38,40*)
Biochemical parameters (*n* = 15)	- Markers that gauge the effectiveness of metabolic control (*etc*: Phe, Leu, Gly) (*21,23-26,30,32-35,37-41*) - Indices of protein status (*20,21,30,33,40*) - Micronutrients' status (*21,33,40,41*) - Liver and kidney profile (*33*)
Clinical outcomes (*n* = 7)	- Neurological functions (*22,29*) - Cognitive function (*22,26,29,39*) - Rates of cerebral uptake for amino acid substrates (*21,38*) - Gastrointestinal tolerance (*23*)
Dietary Intake (*n* = 10)	- Total energy and macronutrient intake (*21,24,27,31,34,35,37*) - Specific amino acid intake (*25,38,39*) - Essential fatty acid intake (*27,31*)

BCAA: Branched chain amino acid; CHO: Carbohydrate; LC-PUFA: Long-chain polyunsaturated fatty acids; EFA: Essential fatty acids; Phe: Phenylalanine; Leu: Leucine; Gly: Glycine.

and total macronutrient intake of PKU patients (*32-34,37,41*). With the exception of Zaki *et al.* (2016) (*33*), the other three studies concluded that CGMP-based protein substitutes led to a significantly higher blood phenylalanine level (*32,34,41*). Furthermore, it was also found to stabilise phenylalanine concentrations with less fluctuations (*32*). One of the three studies concluded that CGMP-based protein substitutes significantly improved whole blood and plasma selenium levels in comparison to amino-acid-based protein substitutes (*41*). However, some studies did not observe any changes in anthropometric parameters (*34,37,41*). Another study compared the effect of a protein substitute with a lower carbohydrate/protein (CHO/PRO) ratio of 0.5:1 and a traditional protein substitute with a CHO/PRO ratio of 1:1 and found no significant differences in plasma phenylalanine concentrations and weight changes, indicating the feasibility of this protein substitute (*35*).

3.2.3. Nutrient supplementation

Of the 22 studies, the most common nutritional strategy was supplementation with a specific nutrient. Long-chain polyunsaturated fatty acid (LC-PUFA) was the most common nutrient supplement for PKU patients (*n* = 7). It was either added in the phenylalanine-free protein substitute (*27,29,31*) or given as a sole supplement (*22,26,28,36*). LC-PUFA was administered in the form of precursor essential fatty acids (EFA); particularly linoleic acid (LA) and α-linolenic acid (ALA) or their eicosanoids derivatives; such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA). These seven studies demonstrated favourable outcomes in terms of plasma LCPUFA. In terms of physiological outcomes, three studies used visual evoked potentials (VEPs) as an indicator of neurological (visual) function (*22,29*) while four studies assessed motor development and mental

or cognitive performance (*22,26,29,39*). One study found a significant improvement in visual function; as evidenced by a shortening in the VEPs (*36*); while another study reported a significant improvement in the motor development index (*26*). Additionally, one pilot intervention study that examined the tolerability and efficacy of a protein substitute supplemented with prebiotics revealed a significant reduction in median stool pH among PKU patients (*42*).

3.2.4. Distribution and dosage of protein substitute intake

Two studies investigated the effects of protein substitute distribution on blood phenylalanine control. A direct and traditional method is to manipulate the timing of the protein substitute by increasing the frequency of administration throughout a more extended period in a day (*25*). The other method is to prolong the release or duration of action of a conventional protein substitute to mimic the effect of frequent protein substitute administrations by adding a chemical substance known as sodium alginate (*30*). Both studies showed a significant improvement in blood phenylalanine control; as evidenced by lower phenylalanine values and smaller fluctuations in 24-hour plasma phenylalanine. Apart from achieving better metabolic control, better protein indices were also reported. In terms of dosage, one study found that participants on the higher doses of protein substitutes had a significant decrease in median plasma phenylalanine concentrations (*24*).

4. Discussion

By adopting the review protocol described in PRISMA-ScR (PRISMA extension for Scoping Reviews), this scoping review successfully addressed and detailed the evolution of nutritional interventions for AANMDs by reviewing literature published over the past 20 years. Unlike existing studies that only address the historical evolution, dosage, and distribution of protein substitutes among PKU patients (*43,44*), this scoping review contributes to existing knowledge by exploring multiple nutritional interventions and their impact on the nutritional indices of different types of AANMDs instead of a single disorder.

This scoping review demonstrated that most nutritional interventions incorporate a medical formula or protein substitute of different properties and characteristics as a treatment plan. Apart from that, it also found that most of the selected studies involved participants that had been diagnosed with PKU. One possible explanation for these two findings is the successful nutritional intervention of PKU; the paradigm AANMD; using a low-protein or phenylalanine-free formula back in the 1960s (*45*). Since the successful treatment of PKU, medical formula has emerged as a cornerstone in AANMD management. The primary treatment mechanism of medical formulas lies in their nutritional compositions which omit substrates that are associated with neurotoxicity, hence preventing neurological damage and metabolic crisis (*46*). As seen in the studies included in this scoping review, the medical formulas of the early 2000s supplied patients with complete and balanced macronutrients as well as additional vitamins and minerals to meet the recommended nutrient intake and improve growth and overall protein indices (*20,40*). As one of the medical ethical principles of healthcare research is non-maleficence, it is not feasible to conduct a randomised controlled trial (RCT) to assess the efficacy of medical formulas by excluding medical formula from the normal diet of some participants as it will endanger their health (*47*). As such, a pre-test post-test interventional study is the best study design with which to investigate the effect of supplementing AANMD patients with medical formulas.

Over the past two decades, significant advances in the clinical neurological research of metabolic diseases have facilitated the creation of improved medical formulas. Prior to a study by Strauss *et al.* (2010) (*21*), the principle of competitive inhibition in the dietary treatment of amino acid disorders was largely unknown. Thanks to this neuroimaging study, it is now well known that large neutral amino acids; such as phenylalanine, tryptophan, leucine, methionine, isoleucine, tyrosine, histidine, valine, and threonine; as well as cationic amino acids; such as lysine and arginine; are transported across the blood-brain barrier (BBB) *via* the common transporters; L1-neutral amino acid transporter (LAT1) and cationic transporter (y^+ system); respectively (*48,49*). This principle has been played a critical role in the formulation of a new medical formula as the theory posits that a high concentration of a single acid or a group of amino acids will inhibit the uptake of another offensive amino acid as they share a common transporter thereby reducing exposure to cerebral toxins. Unlike the traditional formula which only omits the offending amino acids, the improved medical formula is enriched with amino acids that compete with leucine or lysine for brain uptake thereby increasing the potential of improving metabolic control.

Dietary supplementation is another treatment modality for AANMD patients. Studies have established that patients diagnosed with PKU, MSUD, and other AANMDs have significantly lower concentrations of plasma, erythrocyte docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) primarily due to a vegan-like diet which excludes DHA-rich food; such as fish and other whole animal food (*50-52*). Given the pivotal role that DHA plays in visual and neurological development, PKU patients are supplemented with long-chain polyunsaturated fatty acids (LCPUFA) to improve plasma fatty acid indices. The role of LCPUFA supplementation in improving plasma DHA indices

has sparked considerable research into supplementing medical formulas with either precursor essential fatty acids or their eicosanoids derivatives; such as DHA and/or AA; to address fatty acid deficiencies among children with AANMDs. While it has been assumed that the conversion of ALA to EPA to DHA is limited in humans (*53,54*), the studies presented thus far demonstrate that both types of supplementation lead to significant improvements in plasma DHA indices as well as total essential fatty acid intake. This suggests that ALA sources; such as safflower or canola oil; can be used as an alternative but it can be incorporated into protein substitutes to improve palatability. Nevertheless, there is mixed evidence on the ability of LCPUFA supplementation to improve neurological function among PKU patients. However, the different outcomes might be due differences in the testing instruments that were used to assess cognitive and mental development.

It has been hypothesised that patients of metabolic diseases are at higher risk of an imbalance in the microbiome due to the nature of their disease requires them to adhere to a strict dietary regime. To reduce the risk of accumulating toxic compounds, such dietary regimes always lack elements or nutrients that the patient is unable to metabolise (*55*). For instance, a breastfeeding-restricted infant will lack the oligosaccharides normally present in breast milk. This renewed interest in introducing a phenylalanine-free infant formula that contains a specific mixture of prebiotic oligosaccharides for PKU children. The results of a small-scale pilot study showed a significant reduction in stool pH while maintaining *bifidobacteria* levels, which reduces the risk of infection (*23*). However, due to small sample size, the findings of this study cannot be extrapolated to the whole PKU population. Therefore, a larger sample size should be gathered prior to conducting future studies on prebiotics in infant protein substitute to fully evaluate the health benefits.

There has been an increase in the number of studies investigating alternative sources of protein substitutes in recent years. Due to its unique physiological properties, casein glycomacropeptide (CGMP), a whey protein derived from cheese production, has attracted considerable interest as a potential substitute for phenylalanine-free amino acid-based formulas. CGMP had been proven to promote satiety (*56*), decrease the rate of amino acid absorption, thereby reducing fluctuations in plasma phenylalanine (*57,58*); and improve taste acceptability and palatability of the medical food and formula, thereby improving dietary compliance (*59*). However, although this whey protein derivative demonstrated some physiological benefits in adult participants, it contains residual phenylalanine (equivalent of ~1.8 mg/g cGMP protein) which might adversely affect metabolic control in PKU patients (*60*). Based on the included studies, children and adolescents who were given CGMP-AA, a mixture of CGMP and essential and conditional amino acids, had significantly higher levels of plasma phenylalanine in comparison to those given a phenylalanine-free formula. However, these findings differ from a meta-analysis (*61*) and few clinical trials which only found a negligible difference in phenylalanine concentrations between the two groups (*58,62,63*). Participant age could explain the disparity of the findings as the only participants included in this scoping review were children and adolescents while the other studies included adults. As studies have shown that phenylalanine concentrations in PKU patients increase with age, it may mask the significant increase in phenylalanine concentrations among adult participants prescribed with CGMP (*64*). Furthermore, children are more susceptible to fever and recurrent infections which may further increase phenylalanine fluctuations (*61*). Nevertheless, the introduction of CGMP as a replacement for traditional phenylalanine-free protein substitutes has successfully improved acceptability in terms of taste, mouthfeel, texture, and smell among PKU children (*34*). It has been suggested that adjusting the amount of dietary phenylalanine from natural food among PKU patients receiving CGMP-AA protein substitute can significantly lower phenylalanine concentrations (*32*). Furthermore, studies have acknowledged the critical role that large neutral amino acid (LNAA) play in decreasing blood phenylalanine concentrations by inhibiting and competing with phenylalanine in the gastrointestinal tract and across the blood-brain-barrier (*65*). Studies involving adult participants reported some benefits of supplementing PKU patients with LNAA among which was decreased phenylalanine concentrations (*66*), increased tyrosine concentrations, which is always lower than reference value among PKU patients (*67*); and improving cognitive performance (*68*). Nevertheless, there is no direct comparison between the effects of increased LNAA in CGMP-AA protein substitute on metabolic control and a CGMP-AA formula to meet the minimum safe amino acid intake levels. Hence, we recommend that future studies attempt to identify an optimum amino acid profile of CGMP-AA protein substitute for safe metabolic control and taste acceptability among PKU children given the physiological benefits of CGMP-AA protein substitute.

The rapid absorption kinetics of the free AA in protein substitutes is known to affect the plasma phenylalanine concentrations of PKU patients over time (*69*). This has led to new technology in the dietary approach of PKU treatment, more specifically a "prolonged release" amino acid formula capable of mimicking the physiological protein absorption kinetics of healthy children (*65*). Although benefits were observed in terms of metabolic control and protein indices (*30*), the general lack of research on this type of protein substitute warrants more studies in this emerging field in order for PKU children to reap the most nutritional benefits. Furthermore, more

large-scale and multicentre studies of PKU patients need to be conducted to determine the optimum dosage of protein substitute required to support normal growth and control phenylalanine indices.

The key strength of this scoping review is the inclusion of nutritional indices; such as anthropometry, biochemical, clinical, and diet; as it helps paint a clearer picture of the clinical effects of a particular nutritional treatment which leaves ample room for discussion. However, this scoping review is not without its limitations. Firstly, although this scoping review was only limited to interventional or experimental study designs, most of the studies did not utilise RCT; the gold standard of measuring the efficacy of a new intervention or treatment (*70*). Some studies utilised a quasi-experimental design, where the intervention and control groups were not selected at random; while some studies did not even have a control group. Therefore, it was impossible to conclusively deduce if changes in nutritional indices and metabolic control were due entirely to the intervention in question (*18*). Secondly, the sources of information used to search for relevant studies were limited to online electronic databases and hand-searching reference lists of past systematic and integrative studies. Furthermore, the exclusion of grey literature, such as unpublished thesis, technical reports, conferences, and proceedings may have resulted in fewer studies being included in this scoping review. As such, the efficacy of each nutritional intervention could not be determined due to the small number of studies on each intervention. Lastly, a statistical analysis was not carried out to pool the effect of each nutritional intervention and its study outcome.

5. Conclusion

In conclusion, the prescription of protein substitutes remains at the core of dietary treatment for AANMDs. Major advances in nutrition and dietetics research have facilitated the development of protein substitutes with modified nutritional properties and components; such as CGMP-based protein substitutes, prolonged-released protein substitutes, and protein substitute fortified with specific nutrients or certain amino acids; that have a neuroprotective effect. This scoping review showed that formula supplemented with LC-PUFA has a positive impact on plasma DHA and EPA indices as well as dietary fatty acid intake. Similarly, fortifying protein substitutes with specific amino acids holds great promise according to the neurological concept proposed in this scoping review. At the same time, there is a great potential of administering prolonged release protein substitutes in improving metabolic control. Nevertheless, the safety and efficacy of CGMP-AA protein substitute in the treatment of PKU children remain unclear. In the future, efforts should be increased to study the effects of prebiotic supplementation and a protein substitute with a lower carbohydrate (CHO) content as only a handful of studies have been conducted. Furthermore, due to the negligible number of studies on non-PKU-related AANMDs, we urge that more research on novel nutritional strategies, be it new protein substitute formulations, nutrient supplementation, or innovations in nutritional education; such as using mobile technology; be carried to cater to the nutritional needs of patients with other AANMDs.

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