PKU sphere™

The introduction and use of **PKU sphere™,** a Glycomacropeptide (GMP) based medical food, **in children and adults with PKU**

Disclaimer

These guidelines should be **read in conjunction with local guidelines** for the dietary management of Phenylketonuria (PKU). They are based on the most recent scientific evidence available on the use of GMP based medical food in PKU. PKU sphere is a medical food consisting of a blend of GMP and free amino acids **(GMP-AA)** for use in the dietary management of individuals 6 years of age through adulthood.

These guidelines are **for use by health care professionals** working with children and adults diagnosed with PKU.

They are **not for use by parents/caregivers** of children or adults with PKU.

They are for general information only and must not be used as a substitute for professional medical advice.

Any product information contained in these guidelines, although accurate at the time of publication, is subject to change.

The most current product information may be obtained by referring to product labels.

PKU sphere is a medical food intended for use under medical supervision.

PKU sphere is not suitable as a sole source of nutrition and is designed to supplement a low phenylalanine (Phe)/protein diet. A low Phe/protein diet should provide essential Phe requirements, energy, adequate fluid and general nutritional requirements.

PKU sphere contains Phe - 36 mg per 20 g PE; this must be taken into consideration when introducing PKU sphere into the dietary management of PKU. Introduction detailed in section 5A is based on data from a clinical trial (publication pending) where natural protein/exchanges remained the same throughout introduction of PKU sphere. A gradual and systematic approach allows monitoring of metabolic control and discussion with patient/caregiver at each step. Health care professionals should use clinical judgment to determine what is an appropriate introduction plan for individual patients.

Allergies/intolerances

As GMP is the dominant protein source in PKU sphere and it is derived from cow's milk there may be a risk of a reaction for those with cow's milk protein allergy.

Collaborators

Vitaflo® dietitians in collaboration with:

Professor Anita MacDonald PhD, BSc, OBE (Consultant Dietitian, Birmingham Children's Hospital, UK)
Anne Daly MSc, RD (Senior metabolic dietitian, Birmingham Children's Hospital, UK)

Contents

Abbreviations

AA	Amino acids.
GMP	Glycomacropeptide.
GMP-AA	Medical food based on GMP supplemented with the limiting free amino acids +/- micronutrients and essential fatty acids. May vary in format - powder, liquid or bar.
HCP	Health care professional.
L-AA supplement	Phenylalanine free medical food based on synthetic amino acids +/- micronutrients and essential fatty acids. May be powder, liquid, bar or tablet.
LNAAs	Large neutral amino acids.
PE	Protein equivalent.
Phe	Phenylalanine.
MF	Medical Food.
Unmodified GMP	Glycomacropeptide as a raw material isolated from cheese whey.

Forward

Dietary treatment of PKU is multifaceted, challenging and lifelong[1-3]. Key dietary behaviors associated with optimal control of blood Phe levels include the avoidance of high protein foods plus evenly distributed consumption of the L-AA supplements throughout the day[2-4]. PKU is a chronic condition, and although it is not unusual for adherence to be poor[5] particularly in teenagers and adults, it is essential that treatment is lifelong in order to achieve optimal neuropsychological functioning. Common issues with medical food (MF) adherence in patients of all ages is their palatability, smell, taste, texture and aftertaste[1, 6, 7].

Glycomacropeptide (GMP) is a well-researched protein that offers an alternative approach to MF provision in PKU. GMP is a natural protein that is produced as a by-product of the cheese making process (see Appendix A & B for further information on how GMP is produced and why it can be classed as a whole protein). Unmodified, it has an incomplete amino acid profile; it is not only low in Phe, but it is also low in other important amino acids in PKU such as tyrosine, leucine and tryptophan[8-10]. Thereby, GMP requires measured and appropriate supplementation of these amino acids (apart from Phe) in order to aid attainment of satisfactory blood Phe levels as well as have potential to correct some large neutral amino acid (LNAAs) deficiencies in the brain[11]. GMP combined with these limiting essential amino acids (GMP-AA) and additional micronutrients ensure its suitability as an alternative to L-AA supplements[12-14]. Due to its structure, GMP may also have other potential health benefits (see Appendix C). The vast majority of evidence is from animal studies, however short-term cohort studies and case studies have been reported[12, 14, 15].

Vitaflo has carefully developed and researched a new GMP-AA (PKU sphere) suitable for PKU. We now have over 2 years' experience of using this product in children and teenagers with PKU in the UK; we have assessed its acceptability and tolerance plus its effects on plasma amino acid profiles, micronutrient levels and growth when compared with conventional L-AA supplements (See Appendix D for further information on the safety of GMP).

Vitaflo has developed guidelines on the use and introduction of PKU sphere in children over the age of 6 years and adults. Like any GMP-AA, it does contain some Phe (36 mg/20g protein equivalent), so it is essential that every patient with PKU is assessed individually taking into account their current adherence to MF and diet, Phe tolerance, metabolic control and this residual amount of Phe within PKU sphere. Following the suggested step wise system for introducing PKU sphere will aid its successful introduction without loss of metabolic control. Some patients may be able to fully or partially replace their conventional L-AA supplement with this new MF.

Anita MacDonald

PKU sphere is a blend of isolated unmodified GMP and free amino acids with added micronutrients and DHA.

Isolated unmodified

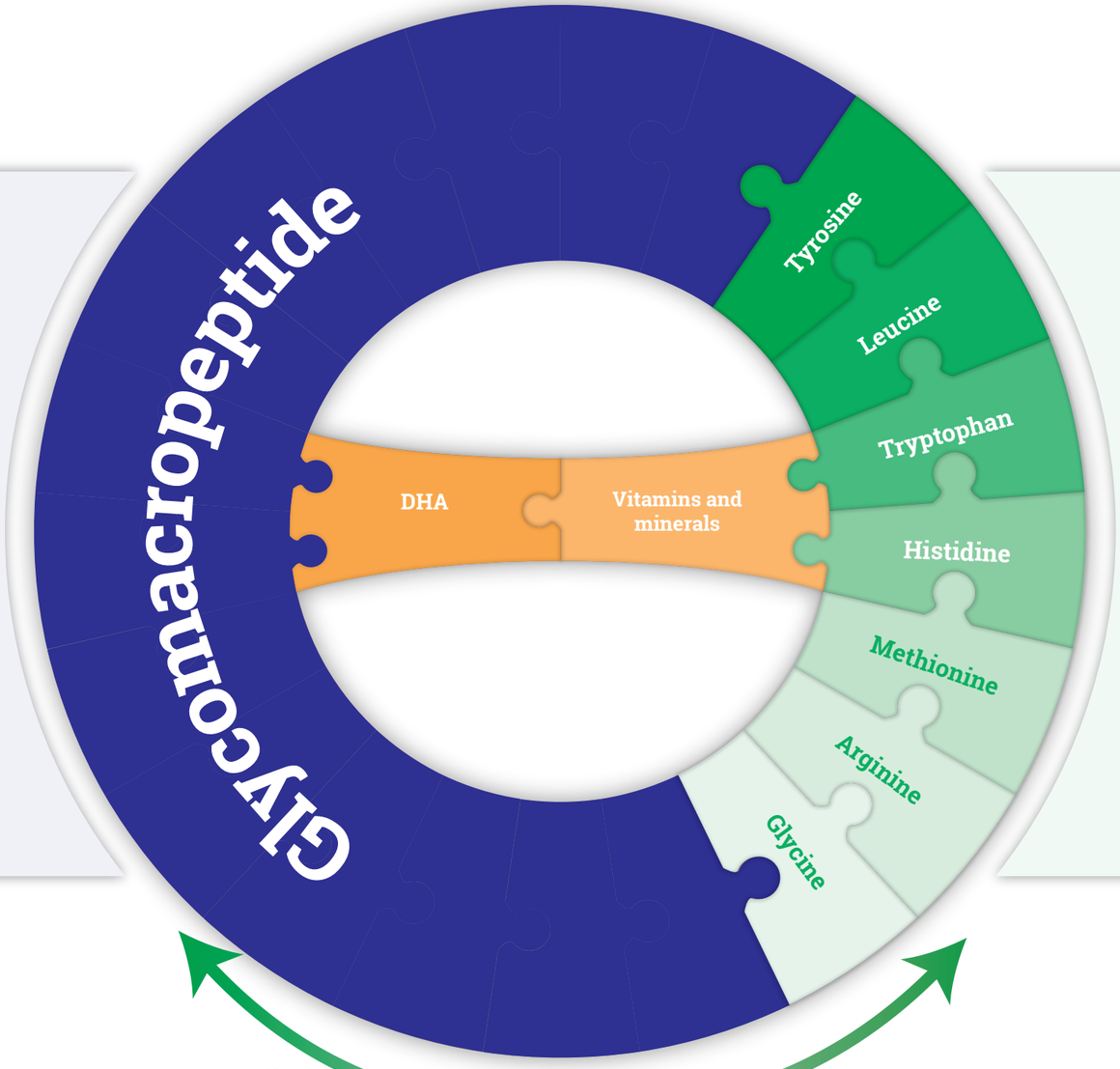
GMP

Palatable source of natural protein.

Low in Phe.

Naturally high in the LNAAs threonine, isoleucine and valine.

Low in a number of essential amino acids.



AA

Added amino acids to complement GMP.

Ensures overall good quality protein* for growth, repair and development.

Prevents essential amino acid deficiencies which would be rate limiting for protein synthesis.

Achieves an overall balanced amino acid profile to optimize blood Phe control.

* When coupled with tolerated Phe allowance.

2 Features of PKU sphere

Optimal nutritional profile

Amino acid profile - PKU sphere is formulated using the latest nutritional science to ensure the combination of the added LNAAs and GMP are in balance to optimize blood Phe control.

The added LNAAs in PKU sphere may compete with Phe both at the blood brain barrier and in the gut.

Contains DHA

Comprehensive micronutrient profile

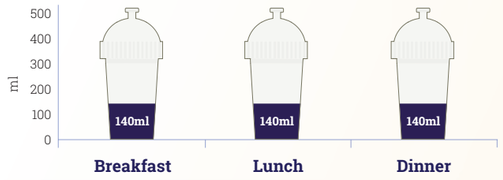
Low volume

PKU sphere has been designed to deliver a set protein equivalent in a low volume to help aid adherence.

High volumes of medical food can be difficult to manage especially in addition to maintaining a healthy food intake.

Low volume of PKU sphere allows it to fit easily into a '3-a-day' medical food approach.

Volume per packet PKU sphere20 x 3/day - 60g PE



= 420ml per day

1 packet PKU sphere20 + 120ml water= 140ml

Low in energy and sugar

PKU sphere has been designed to be low in calories and sugar.

PKU sphere contains 120 calories per 20g PE and is similar in energy content to L-AA supplements such as PKU express and PKU cooler.

PKU sphere **PKU cooler20**

Obesity is a global issue. The calorie content and overall nutritional intake should be monitored closely in PKU with encouragement and advice on how to maintain a healthy weight, an important aspect of dietary care, particularly in teenage and adult patients. It is expected that most of the energy requirements will be met by low Phe food.

PKU sphere™

Palatable

PKU sphere offers an alternative tasting product to L-AA supplements.

PKU sphere is available in 2 different flavors: Vanilla and Red berry.

Due to its palatability, PKU sphere could improve adherence in a patient group where it may waver.

Interchangeable

PKU sphere has been developed in line with the **micronutrient profile** of other PKU products in Vitaflo's portfolio.

Provided blood Phe control is maintained, PKU sphere is interchangeable with an equivalent amount of PE from these L-AA supplements:

1 packet of PKU express20 or
1 pouch of PKU cooler20

Convenient

PKU sphere is presented in a convenient pre-measured packet which can be made up accurately, quickly and easily.

3 Who may benefit from PKU Sphere?

PKU sphere:

Is suitable from 6 years of age through adulthood.

Offers an alternative tasting product to L-AA supplements for individuals experiencing taste fatigue or struggling with adherence.

Is a palatable option for those returning to diet.

May be appealing to those interested in the potential health benefits of GMP-AA.

Considerations

Pregnancy

Excellent blood Phe control prenatally and during pregnancy is crucial to minimize risk of birth defects especially microcephaly and congenital heart disease[16].

It is common for natural protein/exchange tolerance to be extremely low prenatally and particularly in the first trimester of pregnancy. There are no published data of GMP-AA use in pregnancy. A few cases have been reported in the USA, however all 4 cases were taking sapropterin with higher natural protein/exchange tolerance[17].

For those individuals struggling to adhere to L-AA supplements during pregnancy, PKU sphere may be an alternative choice given under careful supervision.

If PKU sphere is introduced, the 36mg Phe per 20g PE should be accounted for and introduction carried out according to the clinical judgment of the managing HCP. It should be noted, that the use of GMP-AA may not be appropriate in some cases of maternal PKU.

Young children

The micronutrient profile of PKU sphere is suitable from 3 years of age, however as yet there is no published evidence of use in young children under the age of 6 years. Research is ongoing in children from the age of 6 years, with preliminary results suggestive of the need for a gradual systematic introduction of PKU sphere for those with good metabolic control, particularly for those with low phe tolerance. (See Section 5A).

Long term data is required to enable evidence based guidelines to be written for the use of GMP-AA in the younger population under the age of 6 years.

4 Managing Phe intake and blood levels

The **potential impact the extra Phe** from PKU sphere will have on blood Phe levels will likely **be less in an individual with a higher natural protein/exchange tolerance.**

If an individual is taking 60g of protein equivalent from PKU sphere (108mg Phe) and adhering to their low protein diet, the percentage extra he or she receives will depend on their natural protein/exchange tolerance:

Phe tolerance/day	Approximate extra phe from PKU sphere
200mg	50%
500mg	20%
1000mg	10%

Therefore the Phe content of PKU sphere **may** have an impact in patients:

With good metabolic control + Adhering to low a protein diet + Have a **low natural protein/Phe tolerance**

When first introducing PKU sphere (e.g. 1 x 20g PE sachet) the natural protein intake should not need to be adjusted. As PKU sphere is increased to meet target volume, a reduction of natural protein/exchanges can be considered if blood Phe levels have increased above target treatment range with no other explanation suspected.

However, a reduction in the amount of natural protein intake can reduce variety, quality and adherence of the diet. A recent publication reported that although individuals were advised to reduce the Phe in the diet to compensate for the Phe in the GMP-based products they did not do so[15].

Introducing PKU sphere gradually, in a systematic way, can allow monitoring of metabolic control and discussion with patient/caregiver at each step. This approach can also allow for adjustments based on individual Phe tolerance, preference and circumstance. For example, an individual may continue to increase PKU Sphere, remain on a combination of PKU Sphere and L-AA supplements, or reduce natural protein/exchanges to meet target volume of PKU sphere.

All individuals who want to try PKU sphere need to be assessed on an individual basis. Introduction and progression with PKU sphere will depend on metabolic control, adherence to the low protein diet and the clinical judgement of the managing HCP.

The following section (5) gives an example of how to introduce PKU sphere to (A) an individual with good metabolic control and (B) an individual on a relaxed or non-adherent diet.

5 How to introduce PKU Sphere

A. For an individual with good metabolic control

Note: The suggested guideline of introducing and transitioning to PKU sphere from an L-AA supplement, is based on data from a clinical trial (publication pending). The managing healthcare professionals are encouraged to use their clinical judgment to determine what is appropriate for the individual patient.

Assuming a daily intake of 60g PE from MF, taken as 3 x 20g PE throughout the day.

Start

20g PE | 20g PE | 20g PE

Taking 3 x L-AA supplements with good blood Phe control

- Discuss PKU sphere as an alternative MF and the pros and cons of GMP.
- Consider starting transition to PKU sphere.

- Advise on keeping the natural protein/exchanges intake the same throughout introduction of PKU sphere.

Stage 1

20g PE | 20g PE | 20g PE

Replace 1 dose of L-AA supplement with 1 packet of PKU sphere

- Monitor fasting blood Phe levels weekly/ every two weeks
- Once managing HCP satisfied with metabolic control - Progress to stage 2.

Note: 1 packet of PKU sphere is unlikely to have any impact on blood Phe levels.

Stage 2

20g PE | 20g PE | 20g PE

Replace another dose of L-AA supplement with 1 packet of PKU sphere

- Monitor fasting blood Phe levels weekly/ every two weeks.
- Once managing HCP satisfied with metabolic control - Progress to stage 3.

Encourage adherence with L-AA supplement during this transition stage.

Stage 3

20g PE | 20g PE | 20g PE

Replace last dose of L-AA supplement with 1 packet of PKU sphere

- Once managing HCP satisfied with metabolic control continue on PKU sphere.

Continue to monitor fasting blood Phe levels as per local/ national policy.

Note:

Take into consideration any significant calorie difference between current L-AA supplement and PKU sphere; advise on nutritional intake accordingly.

If blood Phe level is high

Check all other reasons or causes for high levels.

If no other cause suspected, consider reducing PKU sphere by 1 packet and replace with L-AA supplement.

Monitor blood Phe levels and once there are satisfactory results within target treatment range increase again by 1 packet and continue transition.

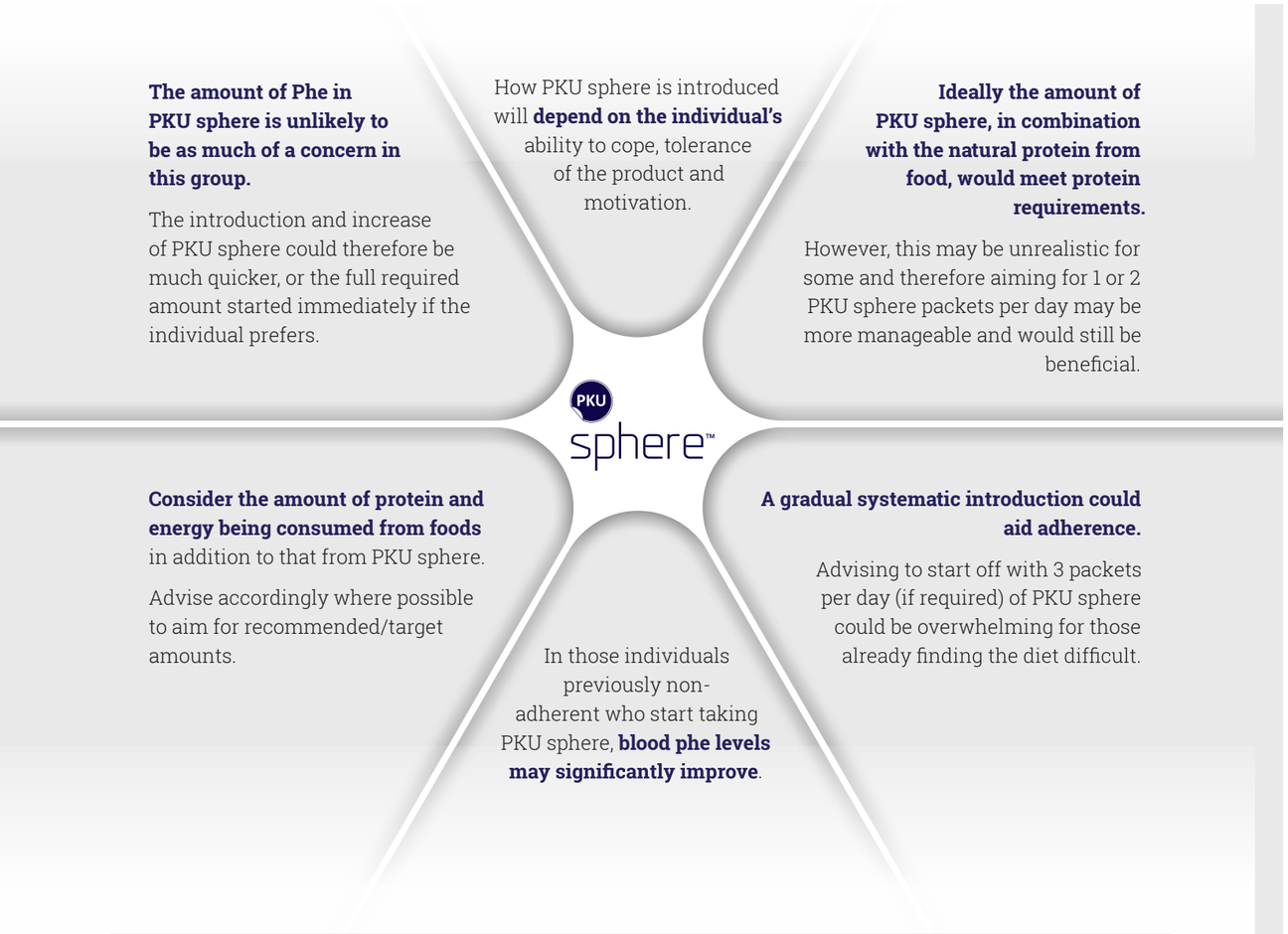
If blood Phe levels have increased and no other cause detected - some indiviuals with a higher Phe/ natural protein tolerance may prefer to reduce natural protein in the diet rather than reduce PKU sphere.

5 How to introduce PKU Sphere

B. For an individual on a relaxed or non-adherent diet

Individuals struggling to take their recommended amount of L-AA supplements or adults on a more relaxed diet may find a GMP-AA easier and more manageable to take. Discuss PKU sphere as an alternative MF, the pros and cons and potential health benefits of GMP-AA .

PKU sphere may help individuals to return to diet and/or regain control of blood Phe levels. Consider introducing PKU sphere taking into account the below points.



Published studies reveal patients may prefer GMP-AA, are able to take it frequently spread throughout the day and in many cases do not want to switch back to L-AA supplements[12,15].

8 Guideline references

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13. LaClair CE, Ney DM, MacLeod EL, Etzel MR. Purification and use of glycomacropeptide for nutritional management of phenylketonuria. J Food Sci.2009;74(4):E199-E206.

8 Guideline references

14. van Calcar SC, MacLeod EL, Gleason ST, Etzel MR, Clayton MK, Wolff JA, et al. Improved nutritional management of phenylketonuria by using a diet containing glycomacropeptide compared with amino acids. Am J Clin Nutr. 2009;89(4):1068-77.

15. Ney DM, Stroup BM, Clayton MK, Murali SG, Rice GM, Rohr F, et al. Glycomacropeptide for nutritional management of phenylketonuria: a randomized, controlled, crossover trial. Am J Clin Nutr. 2016;104(2):334-45.

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17. Bausell H, Aspan A, Arduini K, Paras A, Burton BK. Review of maternal phenylketonuria treatment methods including sapropterin and glycomacropeptide. 2016. Poster presented at National Phenylketonuria Alliance (NPKUA) conference, Indianapolis, USA.

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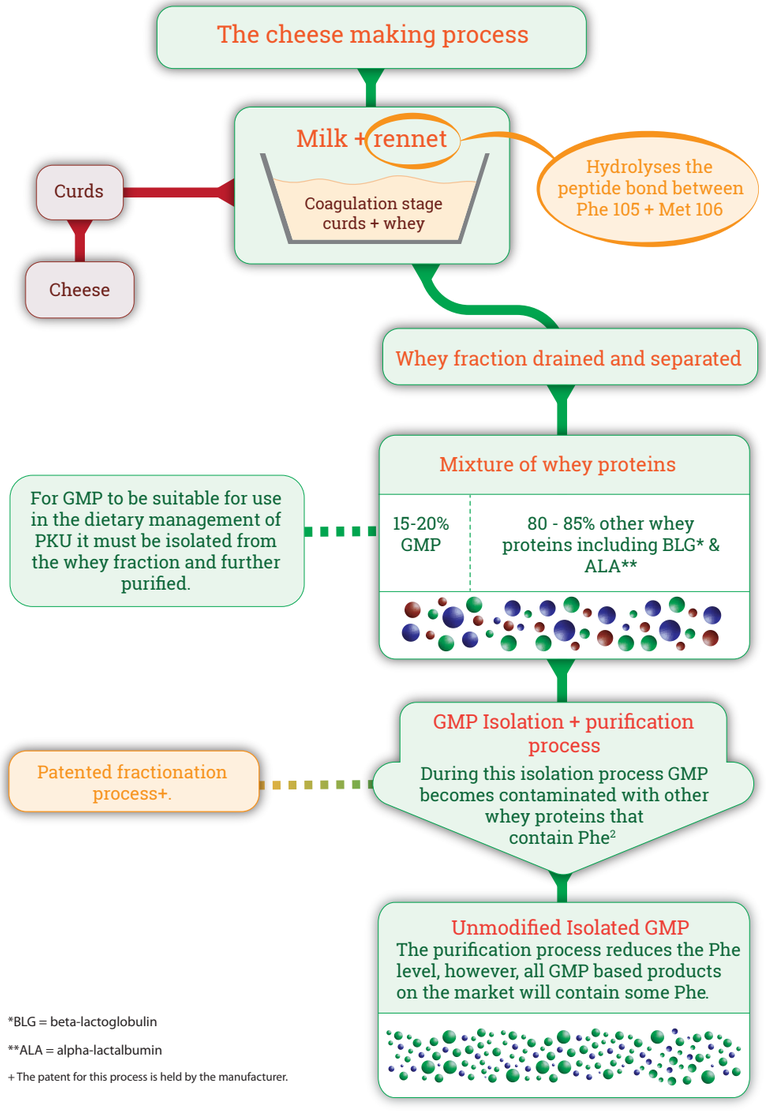
A Appendix | What is GMP and how is it produced?

Glycomacropeptide (GMP) is a 64 amino acid (AA) glycophospho-peptide produced as a by-product during the cheese making process. GMP is formed at the coagulation stage when rennet (a complex of enzymes) is added to the milk, to produce a mixture of curds and whey. An enzyme in rennet specifically hydrolyses kappa (k)-casein (a protein in milk) at the peptide bond between the Phe 105 and methionine 106 amino acid residues. It therefore splits into para-k-casein containing Phe, which remains in the cheese curd, and GMP which drains off with all the whey proteins forming the whey fraction[1] (see figure 1.).

Figure 1. illustrates how GMP is formed and isolated through the cheese making process.

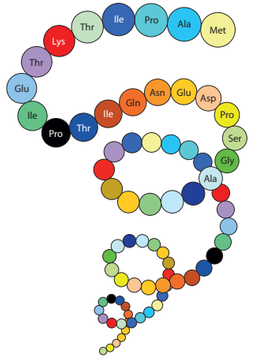


Amino acid profile of isolated, unmodified GMP

Isolated, unmodified GMP has an unusual amino acid profile. It contains low levels of Phe and other aromatic amino acids and has two to three times the amount of the LNAAs threonine and isoleucine compared to other proteins[2, 3].

Unmodified GMP

High levels of LNAAs:
Threonine
Isoleucine
Valine



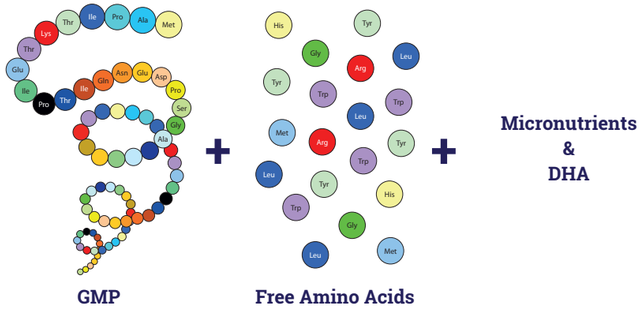
Low levels of the following amino acids:
Histidine
Leucine
Tryptophan
Methionine
Phenylalanine
Tyrosine
Cysteine
Arginine

Addition of free amino acids

Isolated, unmodified GMP must be supplemented with the limiting indispensable amino acids (apart from Phe) to ensure it is a viable alternative to L-AA supplements in PKU.

GMP-AA

GMP supplemented with the limiting essential amino acids provides a **low-Phe 'protein*'** for individuals with PKU. The inclusion of micronutrients and DHA in GMP-AA provides a more nutritionally comprehensive product.



GMP + **Free Amino Acids** + **Micronutrients & DHA**

All commercial GMP-AA contain Phe and therefore partial or full replacement of the L-AA supplements will depend on an individual's blood Phe control.

References

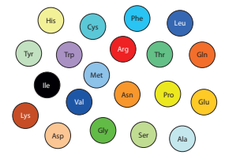
1. Doultani S, Turhan K, Etzel M. Whey Protein Isolate and Glyco-macropeptide recovery from whey using ion exchange chromatography. J Food Sci. 2003;68(4):1389-95.
2. LaClair CE, Ney DM, MacLeod EL, Etzel MR. Purification and use of glycomacropeptide for nutritional management of phenylketonuria. J Food Sci.2009;74(4):E199-E206.
3. Etzel MR. Manufacture and use of dairy protein fractions. J Nutr. 2004;134(4):996s-1002s.

B Appendix | Why can GMP be classed as a protein?

Protein is a macronutrient which is an essential component of everyday nutritional requirements. It is essential for growth, tissue repair and many biological pathways within the body.

A low phenylalanine diet, the principal treatment in PKU, is prescribed to reduce intake of Phe to a safe tolerated level. This together with evenly-distributed consumption of the medical food over the day are key dietary components associated with optimal control of blood Phe levels[1].

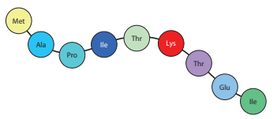
Amino acids



Amino acids are the building blocks of protein. There are 20 different amino acids, 9 of which cannot be made by the body and are therefore essential. When amino acids are not linked together in a chain they are termed 'free amino acids'. Phe is not added to L-AA supplements for PKU making them 'Phe free'.

Conventional medical food for PKU are based on free amino acids.

Peptides



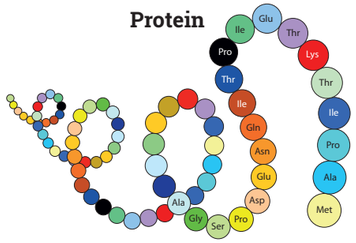
Peptides are short chains of amino acids joined together by peptide bonds. Peptides can be as small as 2 amino acids (building blocks) joined by a peptide bond, up to around 50 amino acids all linked together building a long chain peptide.

Protein substitutes were first developed in the 1950's using protein hydrolysates (containing peptides) passed through charcoal to remove Phe and tyrosine.

GMP is a 'macropeptide' consisting of 64 amino acids linked together in a chain. With this number of amino acids it can be classified as a protein.

It has a unique amino acid profile which is naturally low in Phe.

Protein



Proteins are generally made up of hundreds or thousands of amino acid building blocks attached to each other in long chains. The sequence of the 20 amino acids determines each protein's unique 3-dimensional structure and its specific function.

In PKU, Phe is provided from whole protein food sources.

References

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C Appendix | Summary of references related to GMP potential benefits

GMP scientific evidence summary

GMP has a unique chemical structure. It is highly polar with a strong negative charge and is a rich source of sialic acid (also known as N-acetylneuraminic acid (NANA)), a carbohydrate moiety attached to the threonine sites of the protein. Many of the biological properties of GMP are attributed to this unique structure. Since the 1970's GMP has been of interest for its potential benefits in many population groups and conditions.

Specific investigations into GMP for use in the management of PKU first arose because of the natural low levels of Phe. Further potential benefits of GMP have been proposed and reported, mainly in relation to bone and gut health, but also its impact on overall nitrogen metabolism. The following is a summary of evidence listing the potential benefits of GMP. References marked in bold font denote research directly linked to GMP whereas references marked in non-bold font denote research that, while not directly linked to GMP, is of relevance to the highlighted issue.

Potential GMP benefits directly related to PKU

The vast majority of evidence is from animal studies, however short-term cohort studies and case studies have been reported.

Reduction of phe in the brain

Ney et al 2008[1], Pietz et al 1999[2], Sanjuro et al 2003[3], van Spronson et al 2010[4]

Increased efficacy of protein utilization / improved nitrogen retention

Ney et al 2014[5], van Calcar et al 2009[6]

Improved long term bone health

Solverson et al 2012[7]

Better palatability

Lim et al 2007[8], van Calcar et al 2009[6], Ney et al 2016[9]

Oral hygiene

White et al 2010[10], Aimutis 2004[11], Brody 2000[12]

Other potential GMP related benefits

Prebiotic effect

Brody 2000[12], Chen et al 2012[13], Sawin et al 2015[14]

Anti-inflammatory effect

Jia et al 2011[15], Sprong et al 2010[16], Requena et al 2008[17], Wang et al 2012[18], Daddaoua et al 2005[19], Hvas et al 2016[20], Solverson et al 2012[21]

Binds to enterotoxins & inhibits bacterial and viral adhesion

Kawasaki et al 1992[22], Nakajima et al 2005[23], Hermes et al 2013[24], Dziuba et al 1996[25]

Improved satiety

Burton-Freeman et al 2008[26], Macleod et al 2010[27]

Role in weight management

Xu et al 2013[28], Royle et al 2008[29]

Improvement of zinc absorption

Kelleher et al 2003[30]

Stimulation of brain development

Wang et al 2007[31]

D Appendix | Safety of GMP

GMP has an excellent safety record and is already incorporated into foods, including infant formula[1]. The use of GMP in the dietary management of PKU was first reported in a paper in 2008[1]. The investigators set out to assess if the ingestion of GMP could support the growth of mice with PKU. They also measured both brain and plasma amino acid levels. They found that PKU mice fed a diet of GMP supplemented with essential amino acids (GMP-AA) had a 20% decrease in their cerebellar Phe concentrations compared to mice fed conventional L-AA supplements. They also observed similar levels of growth when mice were fed a GMP-AA based diet compared with those fed a L-AA supplement.

Another preclinical study investigated the body composition of PKU mice fed a predominately GMP based diet compared to an L-amino acid diet. They found that diet had a significant effect on body composition[2] and mice fed a mainly GMP based diet showed a significantly lower percentage of body fat compared to mice fed an amino acid based diet, despite similar lean mass and gain in body weight in the 2 groups. The findings supported their hypothesis that a GMP based diet provides a more physiological source of protein compared to amino acids in mice but that further work in humans was required.

The first report of GMP in an adult patient with PKU was a case study published in 2009[3]. The study lasted a total of 15 weeks with the first 3 and last 2 weeks requiring the patient to take his usual amino acid based medical food (MF). During the middle 10 weeks GMP based MF replaced his usual amino acid MF. The patient achieved a 10% reduction in blood Phe levels when taking a GMP-AA compared to a L-AA supplement.

The first trial conducted in patients with PKU was published in 2009[4]. Although this was a small, short term, study investigating 11 patients over two 4-day periods, it compared patients taking both a GMP-AA and a L-AA supplement. It investigated the safety of GMP, plasma amino acid levels and acceptability. There were no physical concerns detected on examination or expressed by any subjects to indicate GMP-AA had a negative effect on health and at the end of the study 6 of the 7 adult patients expressed a strong preference to continue with the GMP-AA. A second larger scale trial was published by the same center in 2016[5], again looking at efficacy, acceptability and safety of using GMP-AA compared with L-AA supplements. This was a two stage, randomized crossover trial including 30 early treated PKU subjects aged 15 – 49 years. The period of treatment on GMP-AA was 3 weeks compared with 3 weeks on L-AA supplements. A 3 week washout period separated the 2 blocks of treatment. The most important finding of the study was that there was again no significant difference in the post prandial plasma Phe levels over time when subjects took GMP-AA compared to a L-AA supplement.

In summary over the last 8 years, GMP products have been studied with respect to providing an alternative protein source within the management of PKU. GMP must be supplemented with limiting indispensable amino acids to be an appropriate alternative to some or all of a phenylalanine free L-amino acid medical food. It has proved to be safe in preclinical animal models, small scale human trials and case studies. It may have additional health benefits for the PKU individual of which further long term research is required.

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