Safety of Glycomacropeptide (GMP) in the nutrition management of phenylketonuria (PKU)

GMP has an excellent safety profile and is incorporated into foods, including standard infant formula used in general nutrition[1, 2]. GMP-based medical foods (GMP-MF) were commercialized for the dietary management of PKU in North America in 2010[3]. This scientific evidence summary includes the published research on the safety of GMP-MF in the nutrition management of PKU.

Key points:

- GMP must be supplemented with the limiting amino acids to ensure it is nutritionally suitable as a primary low phenylalanine (Phe) protein source for the nutrition management of PKU. In addition to meeting requirements, the blend of amino acids used to supplement GMP significantly impacts metabolic control in children with PKU[4].
- GMP-MFs have been shown to be safe and suitable in relation to metabolic control and micronutrient status in adults with PKU[3, 5].
- GMP-MFs have been shown to maintain metabolic control in children when introduced systematically, as well as, support growth and nutritional status[6, 7].
- The Phe content of GMP-MF does not significantly impact the blood Phe control of *adults* with PKU[3, 8-9].
- The Phe content of GMP-MF may impact blood Phe levels in well-controlled children[5, 6, 8]. In a clinical trial[6], target blood Phe levels were maintained, without dietary Phe adjustment, when GMP-MF were introduced systematically, with nearly half of children tolerating a complete transition. For some children, adjustment of dietary Phe to account for Phe provided by the GMP-MF might support a more consistent blood Phe profile within the target range[7].
- Published evidence on the safety and use of GMP-MF in infancy and young children below the age of 5 years is lacking.

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Supporting education in the dietary management of rare diseases

Ney *et al.*

Study:
Case report of an individual taking a GMP-MF with run-in and wash-out period taking AA-MF.

Duration:
15 weeks, 10 weeks taking GMP-MF.

Subjects:
1 PKU adult patient.

Results:
Blood Phe levels were 10% lower while taking GMP-MF[11].

van Calcar *et al.*

Study:
Clinical trial comparing intakes of AA-MF and GMP-MF.

Duration:
8 days (Two 4-day study periods).

Subjects:
11 PKU patients (aged 11–31 years).

Results:
There was no significant difference observed in the post prandial plasma Phe levels. No adverse reactions and no significant difference in blood Phe concentrations were detected. Concluded that GMP-MF are a safe and suitable alternative to AA-MF[12].

Ney *et al.*

Study:
A two stage, randomized crossover trial.

Duration:
9 weeks: 3 weeks taking each GMP-MF and AA-MF separated with a 3-week wash-out.

Subjects:
30 early treated PKU subjects (aged 15–49 years).

Results:
There was no significant difference observed in the post prandial plasma Phe levels over time[8].

Pinto *et al.*

Study:
Retrospective review of annual clinical assessments.

Subjects:
11 patients (mean age 27 +/- 10 years) who consumed AA-MF at baseline and then consumed GMP-MF.

Results:
Average time on GMP-MF was 13 +/- 5 months and mean intake provided 57% (27 to 100%) of medical food intake. Nutritional intake, anthropometry, body composition, blood pressure and blood biochemistry measures were similar in both groups (except HbA1C which significantly decreased with GMP-MF). Median blood Phe levels did not change (p=0.594) and tyrosine levels significantly (p=0.033) increased. Study concluded that although GMP-MF contain some Phe, they can contribute partially to total medical food intake without any negative effects on the nutritional status of PKU patients[3].

Ahring *et al.*

Study:
Randomized, cross-over, short-term trial comparing 4 different formulations of medical foods (2 GMP-MF and 2 AA-MF) to assess absorption and short-term effects on plasma AA, biomarkers related to food intake, taste and satiety.

Duration:
4 hours on 4 separate days.

Subjects:
8 PKU patients (aged 15–48 years).

Results:
All patients received each medical food formulation and intake was followed by blood sampling at 15, 30, 60, 120 and 240 minutes. Residual Phe in the GMP-MF did not significantly influence short-term plasma Phe levels when compared to an identical formulation of Phe-free AA-MF. Differences in the scores for satiety and taste were not statistically significant[9].

Daly *et al.*

Study:
Prospective, longitudinal, parallel, controlled trial.

Duration:
12-months.

Subjects:
48 children with PKU (aged 5–16 years, 29 taking GMP-MF and 19 taking AA-MF).

Results:
With a systematic introduction, and no adjustment of dietary Phe almost 50% of children were able to transition to GMP-MF in full to provide 100% of their daily medical food requirement without compromising metabolic control. On average the subjects could take 75% of their daily medical food requirement as GMP-MF also without compromising metabolic control.

The intake of GMP-MF maintained adequate nutritional status and growth in children compared to amino acid-based medical foods[6].

2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

Ney *et al.*

Study:
Series of 3 animal studies were conducted to compare how diets with either GMP, amino acids or casein affect growth and concentrations of amino acids in plasma and brains of PKU compared to wild type (WT) mice.

Duration:
Experiment 1: 42 days.
Experiment 2: 21 days.
Experiment 3: 47 days.

Subjects:
Experiment 1: 10 male WT mice.
Experiment 2: 10 male and female PKU mice.
Experiment 3: 15 WT and 21 PKU male and female mice.
Aged 4–10 weeks.

Results:
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 amino acid-based supplements. Similar levels of growth were reported in both groups[2].

Solverson *et al.*

Study:
Animal study comparing growth, body composition, and energy balance in PKU and WT mice fed low-Phe GMP, low-Phe AA, or high-Phe casein diets from time of weaning.

Duration:
20 weeks.

Subjects:
41 WT and 43 PKU mice studied from the ages of 3–23 weeks.

Results:
PKU mice showed growth and lean mass similar to WT littermates fed the GMP or amino acid based diets. PKU mice fed the GMP diet had significantly reduced energy expenditure and food intake. Both GMP and PKU mice fed a GMP-based diet showed a significantly lower % body fat compared to mice fed an amino acid-based diet despite similar lean mass and weight gain[10].

Daly *et al.*

Study:
Prospective, longitudinal, parallel pilot study.

Duration:
6 months.

Subjects:
PKU subjects (aged 5–16 years), 12 taking GMP-MF and 9 taking AA-MF.

Results:
The AA-MF group took 100% of their protein equivalent from AA-MF. In the GMP group median intake of protein equivalent was 50% from GMP-MF and 50% from AA-MF after 6 months. Median blood Phe concentrations of the GMP-MF group rose significantly but were maintained within the target range. The amount of protein equivalent from GMP-MF was reduced to avoid median Phe concentrations exceeding the target range in 7 subjects.

The blend of amino acids added to GMP-MF significantly impacts Phe-control in children with PKU[4].

Pena *et al.*

Study:
Systematic review and meta-analysis of dietary management of PKU with GMP-MF.

Subjects:
Systematic review: 8 studies out of 274 eligible for inclusion. 139 PKU subjects.

Meta-analysis: 2 randomized, controlled trials (RCT) included with adequate comparable methodology. 36 PKU subjects.

Results:
The meta-analysis pooled results showed GMP-MF were well accepted and no significant effect was found for all outcome measures, including blood Phe and tyrosine, blood urea nitrogen and glucose levels.

Despite the different approaches used to measure acceptability in 6 of the included studies[4, 8, 9, 12–15], GMP products were well accepted by patients.

It should be noted there were many variables between studies, including baseline metabolic control and Phenotypic presentation. More research is warranted to understand in depth the safety and health benefits of GMP in the context of PKU[5].

Daly *et al.*

Study:
Randomized controlled cross over study to examine 24-hour blood Phe variability in well controlled children using 3 diet regimens: R1, GMP-MF and usual dietary Phe; R2, GMP-MF minus Phe content of GMP-MF from usual diet; and R3, AA-MF and usual dietary Phe.

Duration:
6 weeks.

Subjects:
16 children with PKU (aged 6–16 years).

Results:
GMP-MF and usual dietary Phe was associated with increased blood Phe concentrations in well controlled children, however median Phe remained within treatment range. GMP-MF appear to give less blood Phe variability compared to AA-MF, but the authors suggest this effect may be masked by the increased blood Phe concentrations. Reducing dietary Phe intake to compensate for GMP-MF Phe content may be considered for some children[7].

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