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Glycomacropeptide for PKU:
Sifting through the Science

Sandy van Calcar PhD, RD, LD
Dept. of Molecular & Medical Genetics
Graduate Programs in Human Nutrition
Oregon Health & Science University
Portland, Oregon

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Disclosures

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- Honorarium from Nutricia for presenting today
- Presentations with honoraria for other medical food manufacturers and Metabolic University
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None pose any conflict of interest for this presentation

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

Learning Objectives

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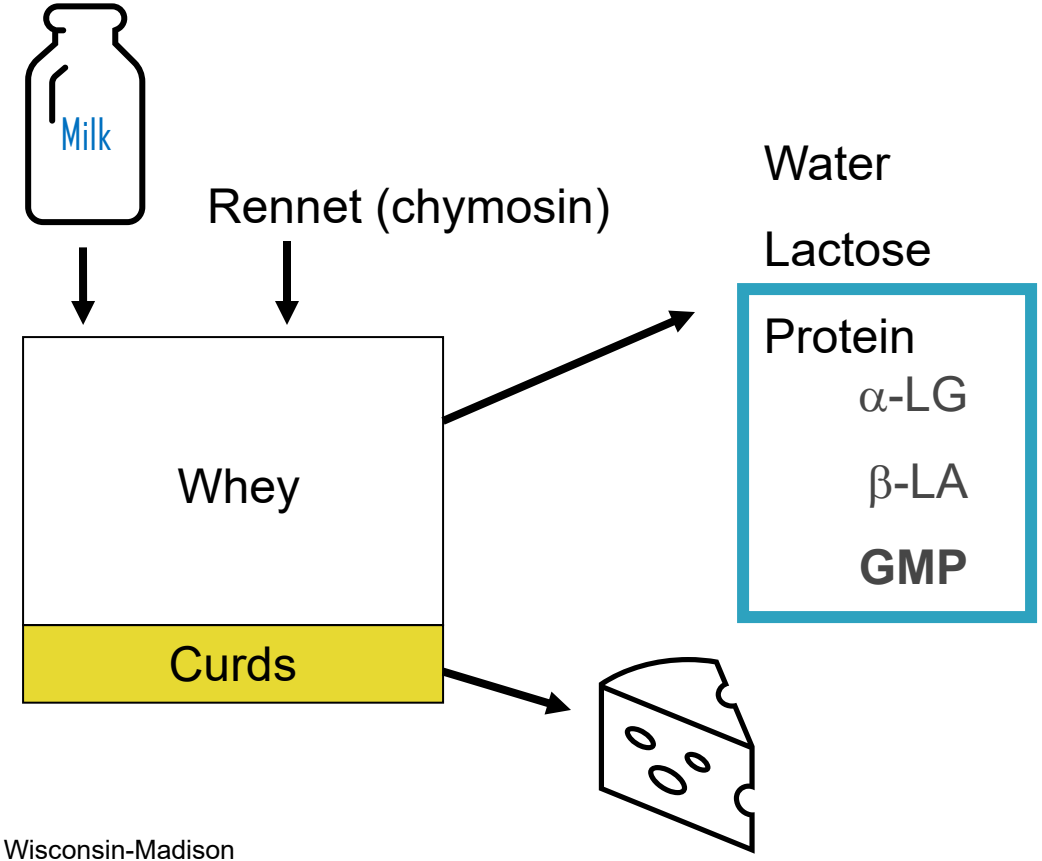
- Participants in this activity will learn to:
  - Explain what glycomacropeptide is and how it's utilized in PKU formulas
  - Summarize the considerations and benefits of GMP for PKU as evidenced by current research
  - Assess the bearing of clinical research findings on one's own clinical practice

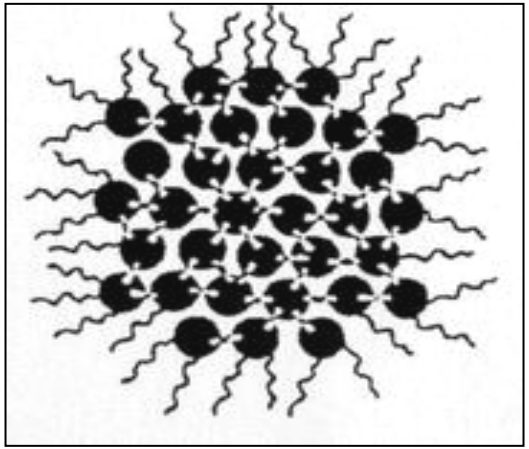
What is glycomacropeptide (GMP)?

GMP is derived from cheese production



Slide courtesy of D. Ney, University of Wisconsin-Madison

GMP- a part of k-casein from the casein micelle



Casein micelle

α- casein

β- casein

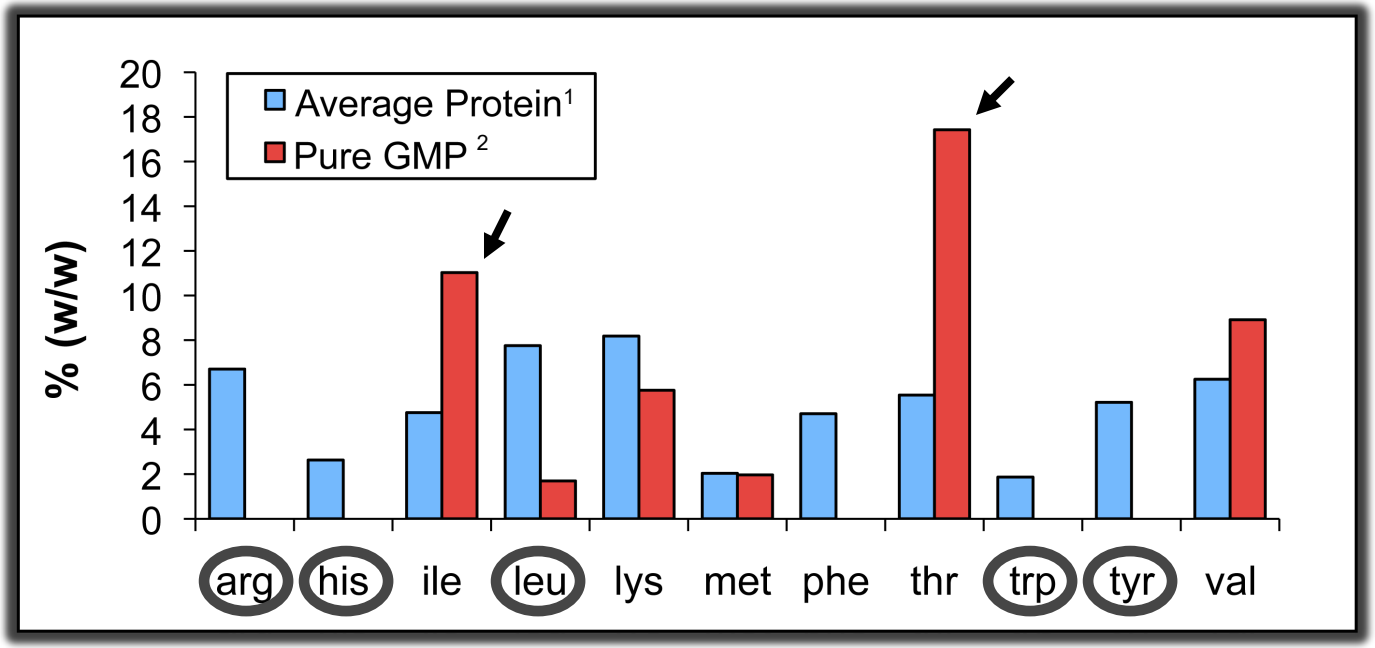
κ-casein —chymosin→ GMP

- 64 amino acid glycophosphopeptide
- GMP = 15-25% of total protein in sweet whey
- Pure GMP contains no phe, but commercial GMP: ~ 1.5 mg phe/g protein

Slide courtesy of D. Ney, University of Wisconsin-Madison

Essential AA Profile of GMP

Differs from average protein profile



Slide courtesy of D. Ney, University of Wisconsin-Madison

1) Klapper MH. *Biochem Biophys Res Commun.* 1977;78:1018-24. 2) Etzel MR. *J Nutr.* 2004;134:996S-1002S.

A Variety of GMP-Based PKU Medical Foods (MF) are Available in the U.S.

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- 3 manufacturers of GMP-MF
- Various formats
  - Powder (can or pouch), liquid, bars
- Varying grams of protein equivalent (PE) per serving
  - 5 – 20 g PE/unit
- Slight variation in phenylalanine (Phe) content
  - 1.0 – 2.1 mg Phe per g PE

GMP studies we'll keep coming back to….

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- University of Wisconsin-Madison (2004-2018). PI = Denise Ney
  - Short term, inpatient study to compare diets containing either an AA-based medical food (AA-MF) or GMP-based medical food (GMP-MF)
    - 11 subjects, Ages 11-31 yr
    - Both diets matched in calories, total protein, mg Phe
  - Outpatient study
    - 30 subjects, Ages 15-49 yr
    - Cross-over design, 21 days on each diet, matched in protein equivalents
- Birmingham Women's & Children's Hospital (2017-2021). PI = Anita MacDonald
  - Outpatient study with up to 3 years follow-up
    - 50 subjects, Ages 5–16 yr
    - Subjects self-selected AA-MF or GMP-MF

What is the effect of GMP-MF on plasma PHE levels compared to AA-MF?

No Significant Change in Postprandial Plasma Phe Concentration with GMP-MF Compared to the AA-MF in Wisconsin studies

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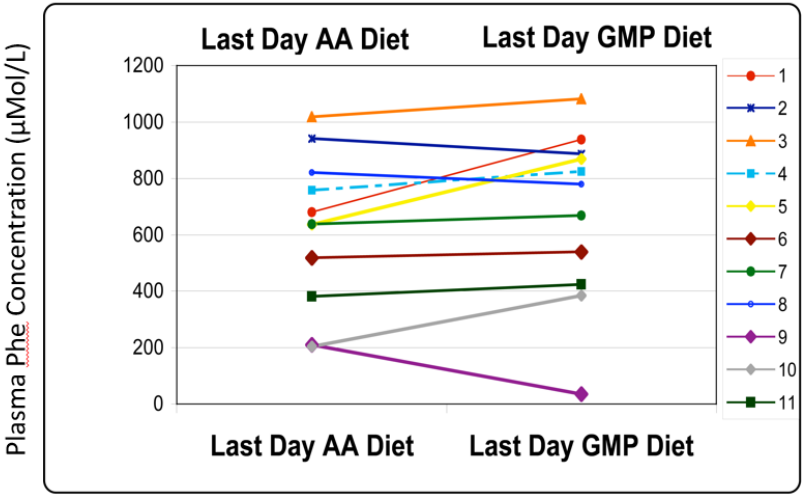
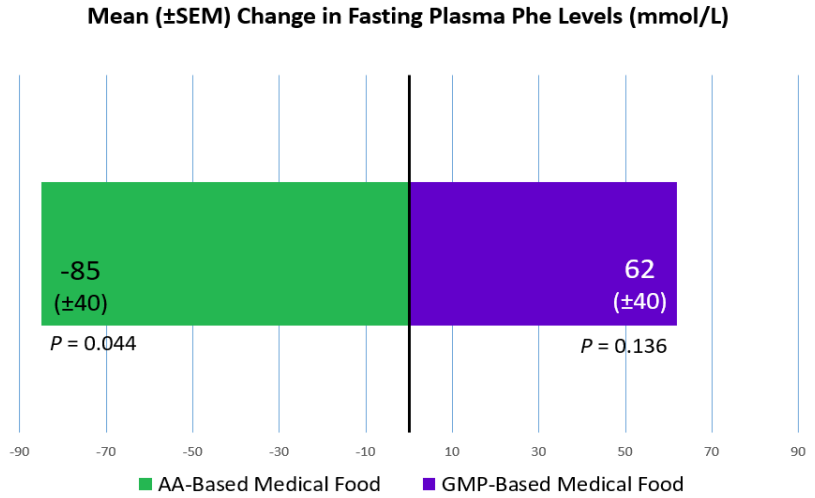
Inpatient study (N=11)



Mean change, Day 4 vs. Day 8: +57±52 µmol/L
p=0.20

Based on Van Calcar SC, et al. *Am J Clin Nutr.* 2009;89:1068-77.

Outpatient study (N=30)



21 days on each diet; 8 samples/diet
Increase in Phe on GMP diet not significant

±SEM = Standard Error of the Mean

Based on Ney DM, et al. *Am J Clin Nutr.* 2016;104:334-45.

Other studies comparing plasma phe of AA vs. GMP-based diets confirm finding

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Study	Patient info	Results
Pena, 2021	N=11; Ages 15-43 yr Time on GMP: ~ 29 mo.	**No significant change in blood phe with GMP** AA: 885 mg intake; Mean phe 562 ± 289 µmol/L GMP: 978 mg intake; Mean phe 628 ± 317
Pinto, 2017	N=11; Ages 27 ± 10 yr Time on GMP: ~13 mo Partial GMP with AA	**No significant change in blood phe** Partial GMP provided additional 34 mg phe/d
Zaki, 2016	N=10; Ages 4-16 yr “GMP Cheese”	**No significant change in blood phe** On 50% AA/50% GMP: Mean phe = 376 µmol/L On 100% GMP: Mean phe = 490 µmol/L

1) Pena MJ, et al. *Orphanet J Rare Dis.* 2021;16:84. 2) Pinto A, et al. *Eur J Clin Nutr*. 2017;71:1230-4. 3) Zaki OK, et al. *J Nutr Metab*, 2016:2453027.

No significant difference in plasma PHE in children consuming AA-MF or GMP-MF

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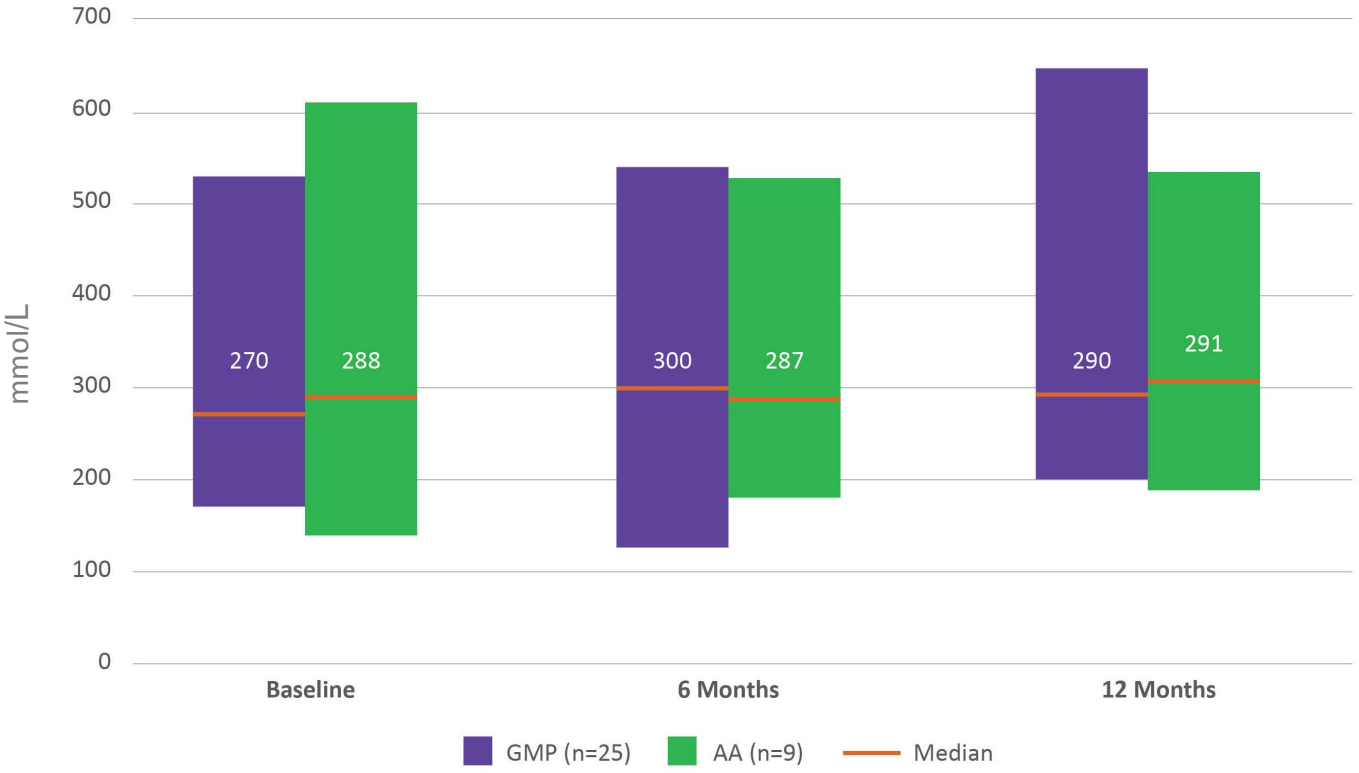
But reintroduction of some AA-MF to GMP-MF required to maintain metabolic control

- Ages 5 – 16 years
- Self-selected AA-MF (n=19) or change to GMP-MF (n= 31)
- If phe levels increased above treatment range, then some AA-MF was titrated back into GMP-MF to help maintain optimal Phe levels
  - 52% of subjects on GMP-MF required some combination of AA-MF and GMP-MF
- The median amount of medical food provided by GMP that could be tolerated without affecting blood Phe = 75% of total amount
  - Range of GMP intake: 30% to 100%

1) Daly A, et al. *Orphanet J Rare Dis.* 2019;14:44.

Range of Blood Phe Levels in Patients on GMP-MF vs. AA-MF at Baseline, after 6 Months and after 12 months



Based on Daly A, et al. *Orphanet J Rare Dis.* 2019;14:44.

Conclusions:

GMP-MF may increase plasma phe concentrations.

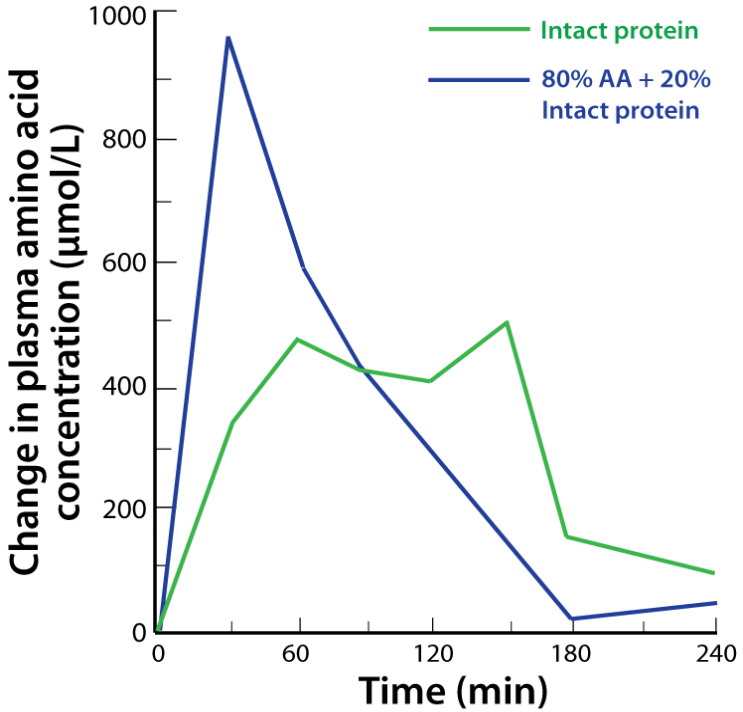
Significance of the increase depends primarily on a patient's age and degree of metabolic control.

What is the effect of GMP-MF on amino acid/protein metabolism compared to AA-MF?

What are some markers of amino acid/protein metabolism investigated in these studies?

- **Total plasma amino acids**

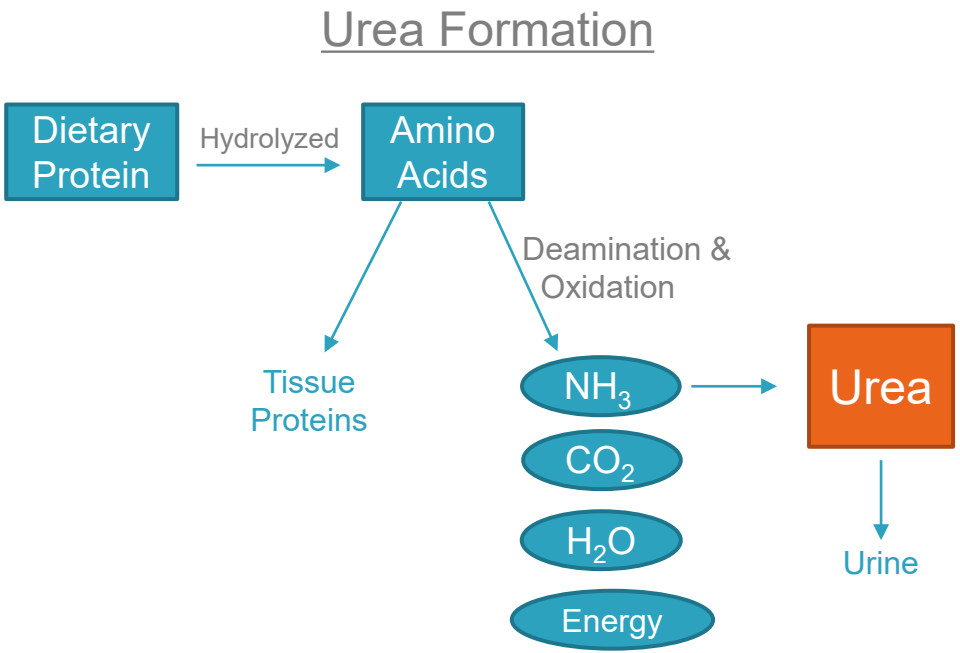
  Improved amino acid utilization with prolonged maintenance of higher amino acid concentrations



Based on Gropper SS, Acosta PB. *JPEN*. 1991;15:48-53.

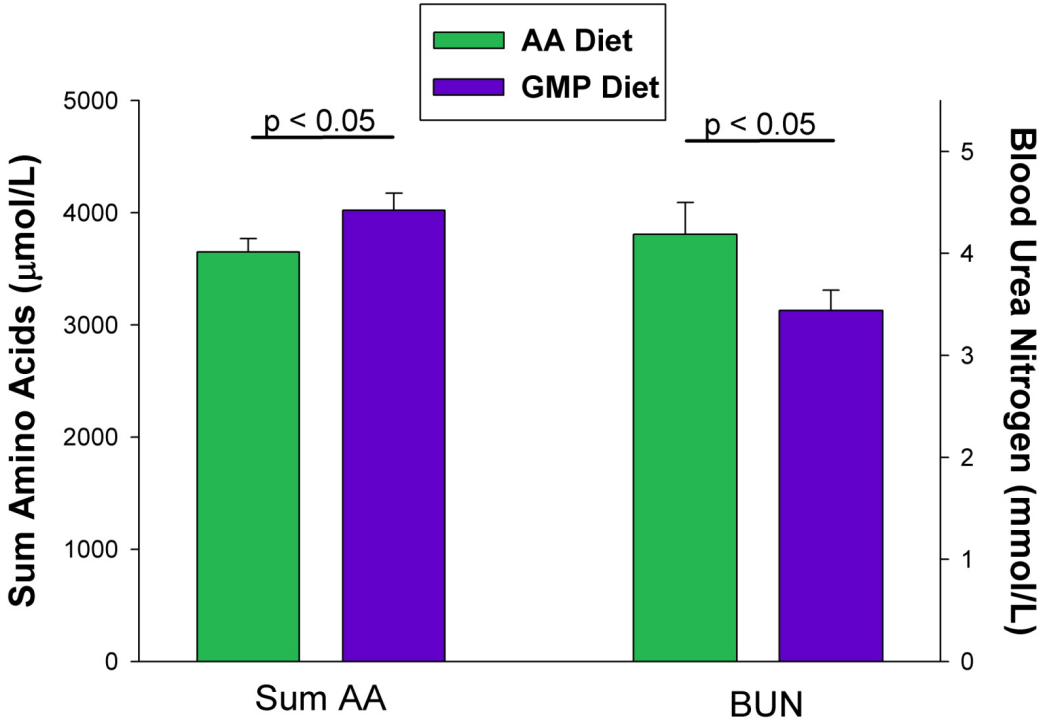
What are some markers of amino acid/protein metabolism investigated in these studies?

- Total plasma amino acids
- **Blood Urea Nitrogen (BUN)**
  - BUN reflects plasma amino acid catabolism
  - Nitrogen balance is primarily regulated by urea production



1) Young VR, et al. *J Nutr.* 2000;130:761-6.

Higher post-prandial AA and lower BUN after eating GMP compared with AA at breakfast in inpatient study



Both total amino acids and BUN were not significantly different in outpatient study comparing GMP-MF and AA-MF

Based on Van Calcar SC, et al. *Am J Clin Nutr.* 2009;89:1068-77.

Ney DM, et al. *Am J Clin Nutr.* 2016;104:334-45.

Are similar results found in other studies?

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- Ahring (2018) measured AAs in subjects who consumed 4 test MF (2 GMP-based and 2 AA-based) in a standard meal
  - Blood collected at 0, 15, 30, 60, 120 and 240 min
  - Plasma AAs reflected different AA profile of each diet
  - **No sig. differences found in <u>total</u> amino acids collected on different diets**
- In children (Daly et al, 2020) consuming either AA or GMP-based MF x 11 mo, plasma collected fasting and post-prandial (120 min)
  - Plasma AAs reflected different amino acid profile of AA-MF or GMP-MF
  - **No sig. differences between the two groups for <u>total</u> AAs and <u>total</u> essential AAs.**
- BUN was not measured in these studies

1) Ahring KK, et al. *J Nutr Metab.* 2018:6352919. 2) Daly A, et al. *Nutrients.* 2020;12:2443.

What are some markers of amino acid/protein metabolism investigated in these studies?

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- Plasma amino acids
- Blood Urea Nitrogen (BUN)
- **Variability of blood Phe over time**

Molecular Genetics and Metabolism

Volume 95, Issue 1-2, Sep-Oct 2008, pages 17-20

Elsevier

Stability of blood phenylalanine levels and IQ in children with phenylketonuria

Vera Anastasoaie [a], Laura Kurzius [a], Peter Forbes [a], Susan Waisbren [a, b]

[a] Children's Hospital Boston, Department of genetics, 1 Autumn street, Room 525, Boston, MA 02115, USA
[b] Harvard Medical School, Boston, MA, USA

Received 1 May 2008, Revised 24 June 2008, Accepted 25 June 2008, Available online 13 August 2008.

https://doi.org/10.1016/j.ymgme.2008.06.014

Despite higher median phe level with GMP-MF, less variability in phe values over 24 hours than AA-MF

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- 18 children (ages 6-16 yr) randomized to consume 3 diets for 14 days each.
- Final day of each diet, the test MF divided in 3 servings in 24 hr
  - collect plasma q 4 hrs
- 3 medical food/diet options
  - **GMP-MF + Phe**: Consume usual phe allowance without accounting for additional phe from GMP
  - **GMP-MF – Phe**: Consume usual phe allowance, but reduce diet phe to account for additional phe in GMP
  - **AA-MF**: Consume usual phe allowance with AA-based MF

1) Daly A, et al. *Nutrients.* 2019;11:520.

Variation in Plasma Phe Levels (µmol/L) with 3 Dietary Regimens over 8 Hour Time Periods

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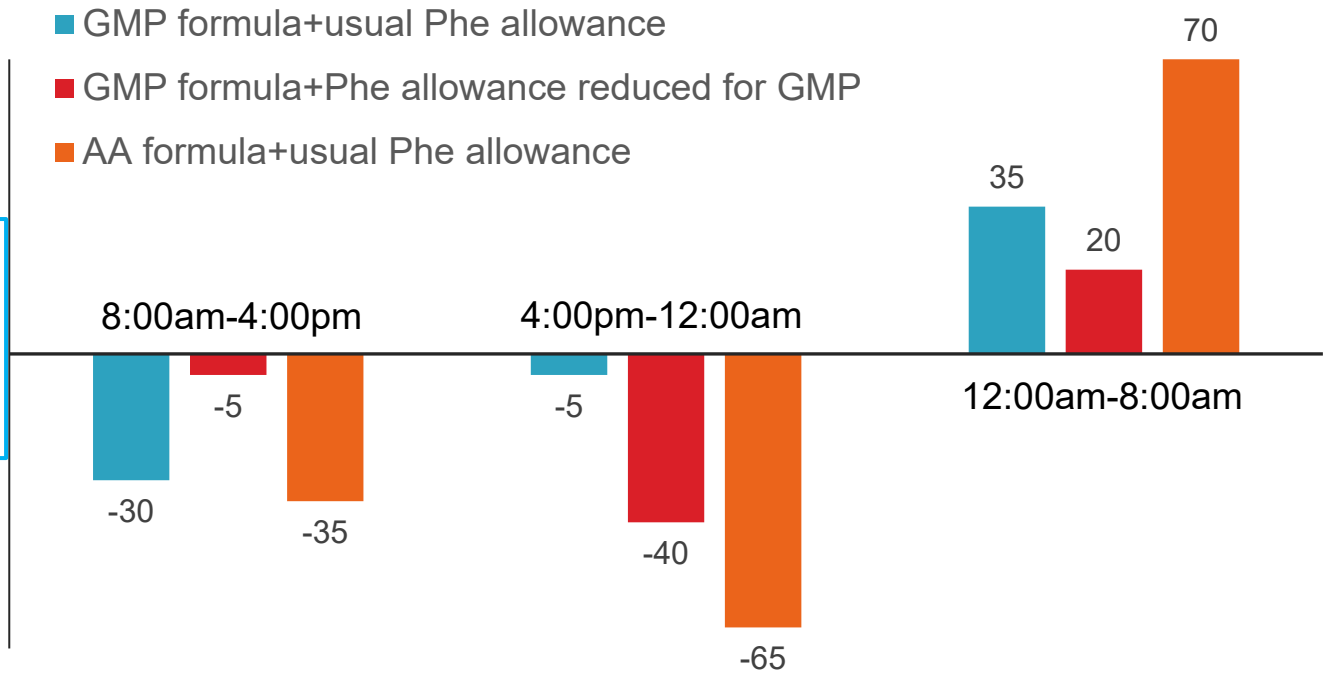
Overall Variability*
GMP + Phe = 35 µmol/L
GMP – Phe = 45
AA-MF = 95



*Variability determined by subtracting lowest Phe level from highest Phe level collected over 24 hours

Based on Daly A, et al. *Nutrients.* 2019;11:520.

Conclusion:

Markers of protein/amino acid metabolism improved on GMP-MF compared with AA-MF in inpatient study, but less evident in outpatient studies.

Does a GMP-based medical food improve satiety?

“How much food do you think you could eat?”

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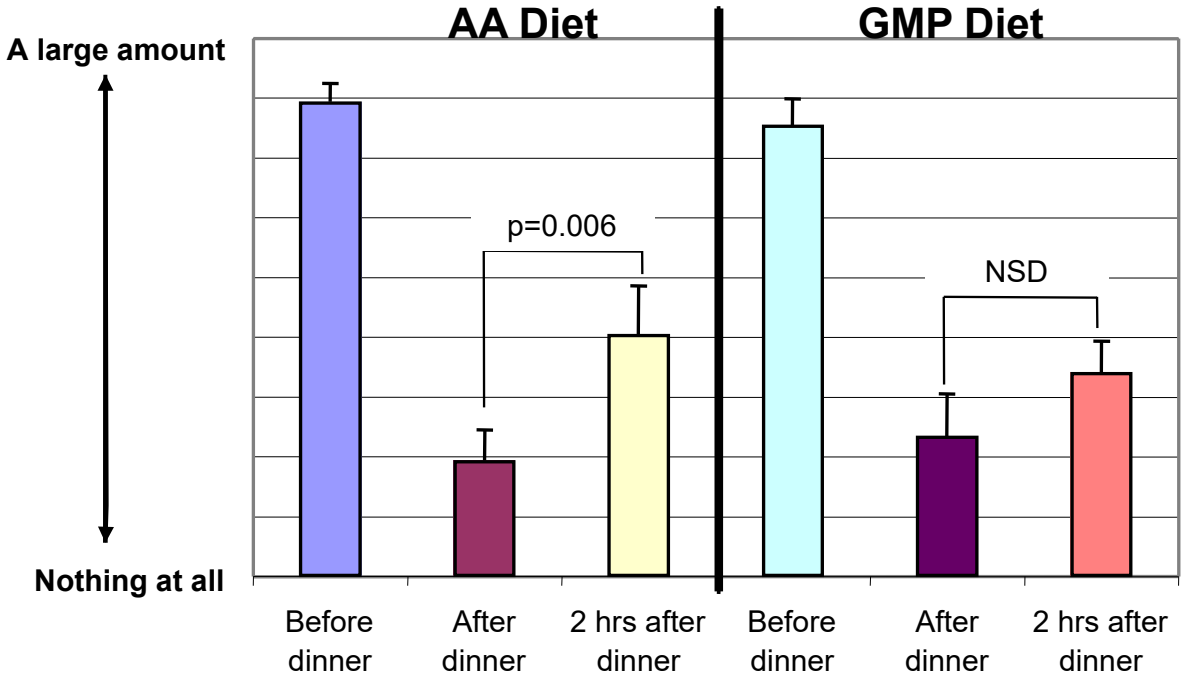
Visual Analog Scale scores 0 to 100



Based on MacLeod EL, et al. *Mol Genet Metab* 2010;100:303-8.

Other studies assessing "feeling fuller" with GMP vs AA-based MF

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Study	Subjects, Diets	Results
Daly 2020	N=28; Ages 6-16 yr Consume either GMP-MF or AA-MF x 3 yrs	**No difference in total energy intake, weight, BMI, incidence of overweight or obesity** No evidence to suggest difference in intake with GMP vs AA
Ahring 2018	N=8; Age > 15 yr Randomized standardized test meals with GMP or AA-MF. Collect plasma at 0, 15,30, 60, 120, 140 min	VAS subjective questionnaire **No significant differences in responses between 4 test meals**

1) Daly A, et al. *Nutrients.* 2020;12:2704. 2) Ahring K, et al. *J Nutr Metab.* 2018;6352919.

Regulation of Satiety

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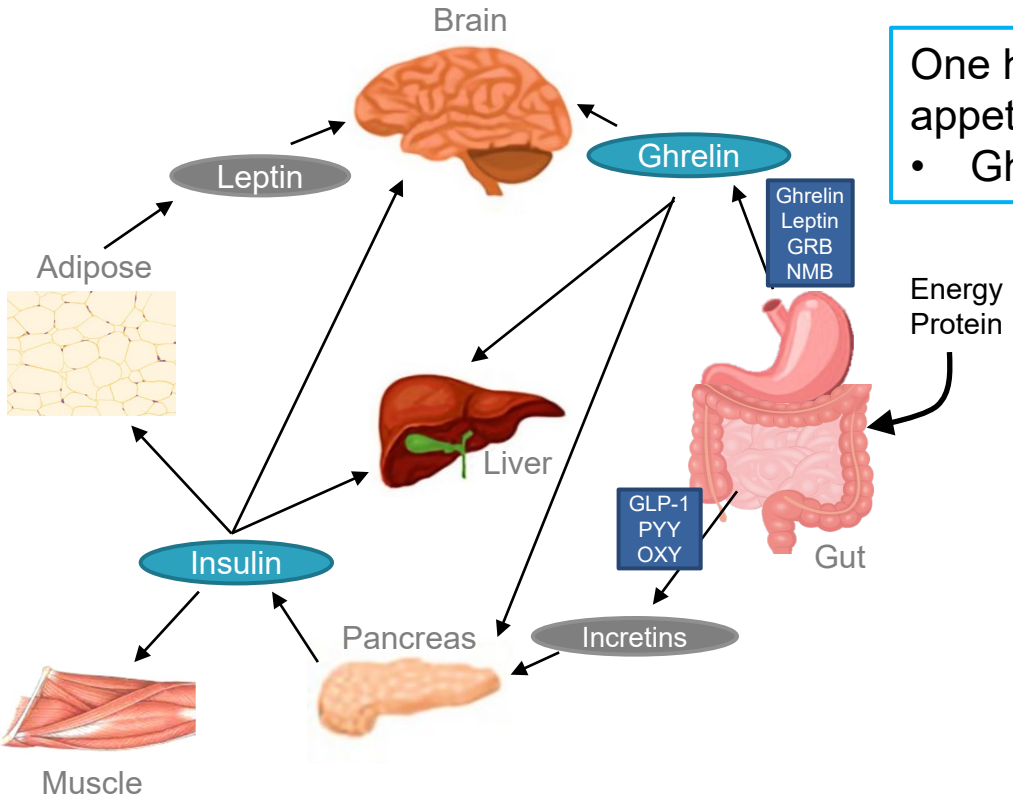
Hormones that signal ↓ appetite and/or food intake:
- Insulin
- GLP-1
- PYY
- CCK



One hormone signals ↑ appetite and food intake:
- Ghrelin

Hormones signaling hunger/satiety via hypothalamus “satiety center”

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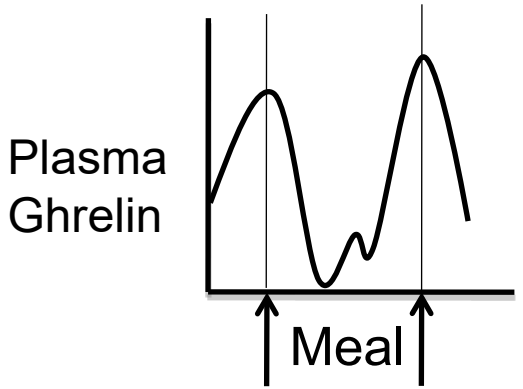
- With increased plasma AAs, greater stimulation of GI hormones:
- **Ghrelin** stimulates appetite; it is high just before a meal and decreases after a meal.



- **Insulin** is transported via BBB receptors to signal hypothalamus satiety center to decrease food intake

1) Lv Y, et al. *Biosci Rep.* 2018;38:BSR20181061. 2) Mitchell CS, Begg DP. *J Neuroendocrinol.* 2021;33:e12952.

MacLeod et al: Labs suggest improved satiety following a meal with GMP-MF vs. AA-MF

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- Inpatient study; hormone levels measured immediately after & 120 min after breakfast
- Following the meal with GMP-MF:
  - **Postprandial Ghrelin was significantly lower** (p=0.004)
    - Suggests a more robust signal to maintain reduced appetite following a GMP-MF compared to an AA-MF
  - **Postprandial Insulin was significantly higher** (p=0.053)
    - Suggests a more robust signal to reduce food intake following a GMP-MF compared to an AA-MF

1) MacLeod EL, et al. *Mol Genet Metab.* 2010;100:303-8.

Ahring et al: No significant differences in ghrelin and other hunger/satiety markers after meals with AA-MF or GMP-MF

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Ghrelin

Change in Ghrelin Concentration After a Test Meal		
Time (minutes)	**GMP (% relative to time 0)**	**AA (% relative to time 0)**
0	100	100
15	90	75
30	78	80
60	80	75
120	75	74
240	105	100

Other markers

- Insulin
- GLP-1
- PYY
- CCK
- Glucose
- Visual Analog Scale

Based on Ahring K, *et al. J Nutr Metab*. 2018:6352919.

Conclusions:

Subjective assessment of satiety often better with a GMP-MF. Other factors may also contribute to satiety.

Hormones associated with satiety support this finding in an inpatient study, but not an outpatient study.

Is there a positive effect of GMP-MF on bone health?

Is skeletal fragility a complication for individuals with PKU?

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- **Lower BMD, but only small subset of clinical concern**
  - Meta- Analysis[1] found that spine BMD was 0.100 g/cm^2 lower in 67 subjects with PKU, compared to 161 controls ($p<0.001$)
    - 3 studies, only one corrected BMD for reduced height of subjects
  - In 183 adults with PKU[2], BMD was significantly lower than general population, but frequency of a significant clinical decrease (Z score < -2) was 1.6 – 5.5%

- **Rates of fracture**
  - Meta-analysis[1] of 6 studies, 20% of children with PKU (53 of 263 subjects) experienced fractures
    - Only 1 study compared to healthy controls (siblings)
  - Fractures in ~16% of adults[2] was lower than age-standardized fracture prevalence of England

- Meta-analysis[1] found **no association between BMD and blood phe level** over 12 studies in 412 subjects

- In 15 participants in Wisconsin Outpatient study[3], mean total body BMD (Z-score ±SE):
  - Males: -0.9 ±0.4 and Females 0.2 ±0.3

1) Hansen KE, Ney DM. *J Inherit Metab Dis.* 2014;37:875-80; 2) Lubot C, et al. *J Inherit Metab Dis.* 2020;43:251; 3) Stroup B, et al. *MGM Rep.* 2018;15:30-5.

GMP increases bone size & mass in PKU- and wild-type mice

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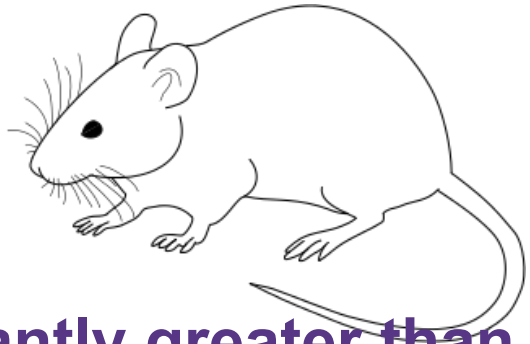
- PKU mice were fed a GMP-based diet or an AA-based diet
- For the mice on the GMP-based diet:
  - **Bone size & bone mass were significantly greater than a AA-based diet**
    - Measurements were similar to wild-type mice fed a casein-based diet
    - Suggest that a GMP-based diet given to PKU mice can improve measures of bone strength to be similar to measures in mice *without* PKU



1) Solverson P, et al. *PLoS One.* 2012;7:e45165.

No significant difference in bone density by DXA scan in 15 children consuming either GMP or AA-MF for 3 years

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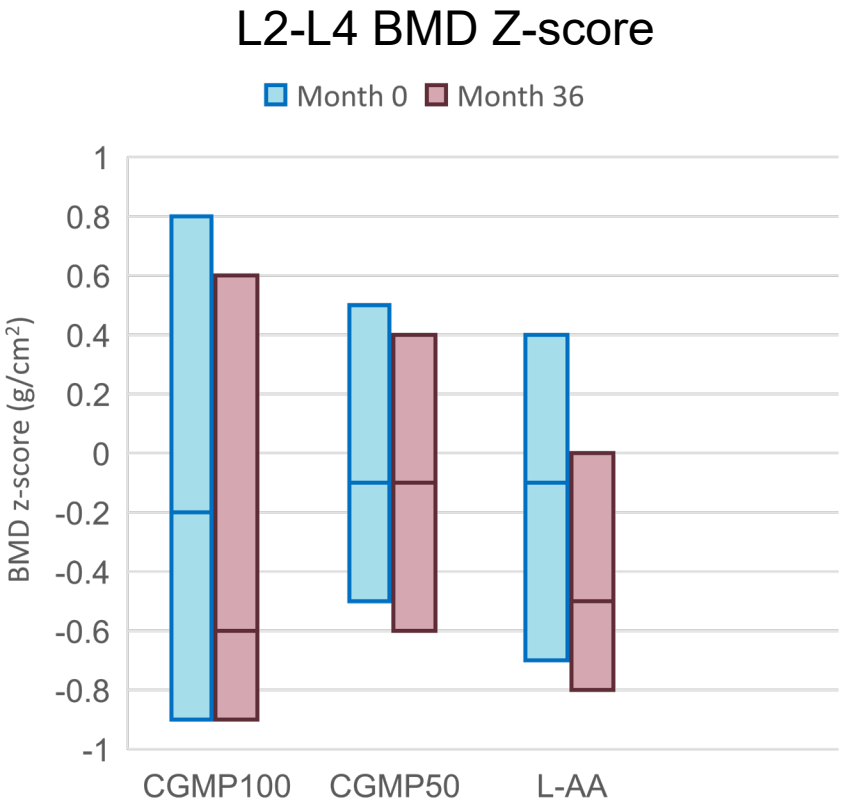
Bone density at all time points clinically normal, but median Z-score < population mean scores

No significant differences in various bone turnover markers (blood & urine) measured at baseline, 6 mo, 12 mo, 36 mo.

Author's conclusion: No advantage of GMP on bone density, bone mass, bone geometry or bone turnover markers



Based on Daly A, et al. *Nutrients.* 2021;13:2075.

Conclusions:

In those with PKU, may see lower BMD, but appears to be of clinical significance in only a small subset.

Greater size and mass of bones are measured in PKU mice fed a GMP-based diet.

No evidence of benefit of GMP to bone health in clinical trials.

Is there a concern for renal health in those consuming AA-MF vs. GMP-MF?

Stroup et al (2017): AA-MF may provide a higher dietary acid load with increased renal net acid and mineral excretion in urine

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- Stroup et al (2017) measured markers of renal status in 24-hr urine in subjects on GMP-MF and AA-MF
- PRAL = Potential Renal Acid Load
  - PRAL equation includes excretion of amino acids (Met, Cys), electrolytes and minerals
  - AA-MF have a 1.5–2.5x higher PRAL score than GMP-MF
- Significantly higher in patients consuming AA-MF:
  - Renal net acid excretion
  - Ammonium (NH_{4+})
  - Excretion of chloride, calcium, magnesium and phosphate
    - Calcium excretion ~ 40% lower on GMP-MF

Note: The PKU diet when rich in fruits and vegetables, counterbalances the medical food resulting in a comparatively low PRAL for the PKU diet overall.

1) Stroup BM, et al. *J Nutr Metab.* 2017:1909101.

Conclusion:

One preliminary study suggests that renal health may be impacted in individuals with PKU.

Potential mechanisms of actions are unclear and controversial. More evidence is needed before any recommendations for clinical care can be made.

What about overall acceptability of GMP-MF vs. AA-MF?

Subjective assessment of acceptability often positive for GMP-MF compared to usual AA-MF

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In outpatient study (Ney et al, Am J Clin Nutr, 2016)

1. Recorded daily frequency of MF intake > GMP than AA (p = 0.001)
2. Subjective questionnaire at end of each diet: 4 of 6 questions were significantly more positive for GMP diet

Question:
How much do you like your AA-MF vs. GMP products?
How easy is it to stay on your PKU diet when using AA-MF vs. GMP products?
How comfortable are you eating AA-MF vs. GMP products in social situations?
Overall, how convenient is it to take and consume AA-MF vs. GMP products away from home?

Other studies with similar subjective questionnaire results: Daly et al 2017, Zaki et al 2016

1) Ney DM, et al. *Am J Clin Nutr.* 2016;104:334-45. 2) Daly A, et al. *J Hum Nutr Diet.* 2017;30:515-23. 3) Zaki OK, et al. *J Nutr Metab.* 2016:2453027.

Conclusion:

Improved measures of diet acceptance frequently noted in inpatient and outpatient studies for patients consuming GMP-MF.

Take-Aways

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- **MOST IMPORTANT:** Finding a medical food that is acceptable for each patient whether it is AA-based or GMP-based
- Additional phenylalanine from GMP may need to be considered in a patient's diet prescription
  - Factors to consider include:
    - Age
    - Degree of metabolic control
    - Severity of PKU
    - Sapropterin responsiveness
- Beneficial effects on amino acid/protein metabolism have been noted in controlled studies, but less so in an outpatient setting (i.e. real life)

Take-Aways

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- Positive effects of GMP on hunger/satiety have been noted in some studies, but individual response can vary
  - Influenced by other factors, such as energy provided by the medical food, willingness to consume MF more frequently throughout the day, etc.
- Additional research is needed before conclusions can be made of the benefit of GMP for bone, kidney and other aspects of health in the clinical setting.

Take-Aways

- Majority of studies conclude that patients find GMP products more “acceptable” than AA-based products
  - GMP-based products may help patients find an acceptable medical food and sustain their diet regimen.

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