Phenylketonuria

Introductory information
Dietary management of the condition should only be done under medical supervision.
Phenylketonuria

Phenylketones in urine

PKU
Hyperphenylalaninemia

Too much Phenylalanine in blood

HPA
Food – Components of a normal diet

Protein consists of chains of amino acids

**Natural Food**

- **Protein**
  - *Phenylalanine*
  - *Tyrosine*
  - *Valine*
  - *Leucine*
  - *Threonine*

- **Fat**

- **Carbohydrates**

- **Protein**
  - *milk, yogurt, nuts*

- **Protein**
  - *meat, poultry, fish, cheese, egg*

- **Protein**
  - *fruit, vegetables, potatoes, cereals, rice, pasta*

- **Protein**
  - *sugar, lemonade*

- **Protein**
  - *oil, margarine*

Dietary management of the condition should only be done under medical supervision.

Supported by Nutricia as a service to metabolic medicine

Written by P. Burgard & U. Wendel
Reviewed & revised for North America by S. van Calcar
Enzymes

Enzymes are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all the substances in the body. This is called metabolism.

Phenylalanine Hydroxylase (PAH) is the enzyme that converts the amino acid phenylalanine to the amino acid tyrosine.

In HPA/PKU, the activity of the PAH enzyme is deficient.
Enzymes

In order to function correctly, some enzymes need the help of cofactors (= coenzymes).

PAH is such an enzyme and BH₄ is the cofactor.

PAH requires BH₄ to become an active enzyme and function properly.

\[ \text{PAH inactive} + \text{BH}_4\text{-Cofactor} = \text{PAH active} \]
In a person without PKU – PAH works

\[ \text{Phenylalanine} \rightarrow \text{PAH} \rightarrow \text{Tyrosine} \]

**PAH is functional**

**BH\textsubscript{4} supply is sufficient**
In a person with PKU or HPA – PAH is deficient

PAH is not functional

 BH₄ supply is sufficient

Dietary management of the condition should only be done under medical supervision.
Hyperphenylalaninemias due to BH₄-deficiency

PAH is functional

BH₄ supply is insufficient
Diagnosis of PKU

At confirmation of hyperphenylalaninaemia: plasma phenylalanine concentrations range from 2.0 mg/dl to > 20 mg/dl (120 µmol/L to > 1200 µmol/L)

Conversion of phenylalanine: 1 mg/dl ≈ 60 µmol/L
Diagnosis of PKU

Disorders of phenylalanine metabolism

- Mild Hyperphenylalaninaemia
- Phenylketonuria
- BH₄-Cofactor deficiency (very rare)

Dietary management is necessary

Phenylalanine concentration in blood (mg/dl)

Normal range in plasma:
Phenylalanine: ca. 60-120 µmol/L (1.0 - 2.0 mg/dl)
Pathogenesis

High concentrations of phenylalanine damage the brain

- Impairment of brain development and function
- Behavioral and intellectual disabilities
- Information processing impairment
Food – Components of a normal diet

Protein consists of chains of amino acids

Phenylalanine → Tyrosine → Valine → Leucine → Threonine

Protein consists of chains of amino acids

Natural Food

- **Protein**: milk, yogurt, nuts
- **Fat**: eg. meat, poultry, fish, cheese, egg
- **Carbohydrates**: eg. fruit, vegetables, potatoes, cereal, rice, pasta
- **Protein**: sugar, lemonade
- **Fat**: oil, margarine

Dietary management of the condition should only be done under medical supervision.
Principles of management

Diet is very low in natural protein + metabolic formula that does not contain phenylalanine

Natural Protein

- Phenylalanine
- Tyrosine
- Valine
- Leucine
- Threonine

+ a PKU formula that contains all amino acids except phenylalanine

Natural Food

- **Protein**
  - Fat
  - Carbohydrates
- **Protein**
  - Fat
  - Carbohydrates
- **Protein**
  - Carbohydrates
- **Fat**
  - Carbohydrates
  - Carbohydrates

**eg.** milk, yogurt, nuts

**eg.** meat, poultry, fish, cheese, egg

**eg.** fruit, vegetables, potatoes, cereal, pasta, rice

**eg.** sugar, lemonade

**eg.** oil, margarine

Dietary management of the condition should only be done under medical supervision.
Dietary management during the first 4 to 6 months of life

Natural Protein

Breast milk or infant formula

Natural protein = all amino acids with phenylalanine included

Fat
Carbohydrates

PKU formula = all amino acids except phenylalanine

Fat
Carbohydrates

Phe-free infant formula

Phenylalanine
Tyrosine
Valine
Leucine
Threonine

Supported by NUTRICIA as a service to metabolic medicine
Dietary management of the condition should only be done under medical supervision.

Written by P. Burgard & U. Wendel
Reviewed & revised for North America by S. van Calcar
Foods + special low-protein products + PKU formula

Nutritional components of the PKU diet once the baby is weaned and solids are introduced

↓↓ Natural Protein

Phenylalanine  Tyrosine  Valine  Leucine  Threonine

+ a PKU formula containing all amino acids except phenylalanine

Natural low-protein food

eg. vegetables, fruits, potatoes, some cereals

Special low protein products

eg. special breads, pasta and ready-made meals

PKU formula

eg. sugar, lemonade

Fat

eg. oil, margarine

Dietary management of the condition should only be done under medical supervision.
Goals for management of PKU

**PKU-diet**
Very low-protein natural foods
+ special low-protein products
+ PKU formula

**Management Goals for all ages**
Long-term phenylalanine concentrations in blood should be:
2 to 6 mg/dl (120 to 360 µmol/L)

**Blood phenylalanine levels need to be measured frequently!**

Conversion of phenylalanine: 1 mg/dl ≈ 60 µmol/L
Monitoring the diet

Remember!

• Your child’s blood phenylalanine (phe) level needs to be checked frequently to prevent blood levels that are too high or too low.
• The metabolic team will check your child‘s clinical status and growth regularly.
• The metabolic dietitian will regularly assess the diet to assure that all nutrients (protein, fat, carbohydrates, vitamins and minerals) meet the recommendations for your child‘s age.
Treatment with BH₄

Pharmacological doses of BH₄ can reduce the blood phenylalanine levels in some individuals with PKU. This is called BH₄-responsive PKU. This may mean that the amount of phenylalanine in the diet can be increased, or for some, the PKU diet may not be needed at all.

With BH₄ treatment, the goals for blood phenylalanine levels remain the same as for those managed with diet only.

BH₄ is approved for infants, children and adults.
Chromosomes, Genes, Mutations

A **chromosome** is like a cookbook.

A **gene** is like a recipe in the cookbook.

A **mutation** is like an error in the recipe or even a complete lack of a recipe.

The **enzyme** PAH is produced constantly in the body following a specific recipe (**gene**). If the gene contains abnormal **mutations**, the **enzyme** cannot function correctly or be properly produced.
Inheritance of HPA/PKU

Both parents are carriers in autosomal-recessive inheritance

Mother is a carrier of HPA/PKU

Father is a carrier of HPA/PKU
Inheritance of HPA/PKU
There are 4 possible combinations for any child born to parents who are carriers

Mother is a carrier of HPA/PKU

Father is a carrier of HPA/PKU

Child will not be a carrier of HPA/PKU
Child will be a carrier of HPA/PKU
Child will have HPA/PKU

Dietary management of the condition should only be done under medical supervision.
Inheritance of HPA/PKU

How HPA/PKU is inherited in families

Mother is a carrier of HPA/PKU

Father is a carrier of HPA/PKU

Dietary management of the condition should only be done under medical supervision.
## Summary

### What is PKU?

<table>
<thead>
<tr>
<th>What is PKU?</th>
<th>An enzyme defect causing high phenylalanine levels in the blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑ Phenylalanine</td>
</tr>
</tbody>
</table>

### Monitoring

<table>
<thead>
<tr>
<th>Lab</th>
<th>Frequent phenylalanine and other amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Other routine lab tests</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical development</th>
<th>Height, weight, head circumference</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Nutrition</th>
<th>Frequent adjustment of the diet</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Development</th>
<th>Neuropsychology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intelligence (IQ)</td>
</tr>
</tbody>
</table>

### Optimal Management

Dietary management reduces blood phe levels to the goal range

**Result**

Normal neurological and cognitive development

### Insufficient Management

Poor dietary management increases blood phenylalanine concentrations above the goal range

**Result**

Impairment of neurological and intellectual development

---

Supported by NUTRICIA as a service to metabolic medicine

Dietary management of the condition should only be done under medical supervision.

Written by P. Burgard & U. Wendel

Reviewed & revised for North America by S. van Calcar

25