TmP/GFR is a useful marker in making a clinical diagnosis of X-linked hypophosphatemic rickets caused by the PHEX gene mutation

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Introduction

- X-linked hypophosphatemic rickets (XLH) is characterized by defects in tubular phosphate reabsorption and vitamin D synthesis. Inactivating mutations of the phosphate-regulating gene with homologies to endopeptidase on the X chromosome (PHEX) gene cause XLH.
- The clinical diagnosis of XLH is based on laboratory findings that include low serum phosphate concentration, reduced percentage of tubular reabsorption of phosphate (TmP/GFR), and a decreased ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR).
- Maintaining sufficient renal blood flow in order to calculate accurately TmPp and TmP/GFR is important.

Objectives

The aims of this study were to investigate the following points:

1. To compare between the TmPp and TmP/GFR values of XLH patients without water loading and the respective reference values.
2. To investigate the alterations in TmPp and TmP/GFR values in XLH patients during water loading.
3. To compare between the TmPp and TmP/GFR values of the XLH patients with water loading and the respective reference values.

Participants and Methods

The participants were XLH patients with proven mutations of the PHEX gene.

1. TmPp and TmP/GFR values of the XLH patients without water loading and reference values.
   - Twenty-six patients aged 0 to 50 years who had XLH.
   - Two hundred eighty-six urine and blood samples.
2. Time-dependent alterations in the TmPp and TmP/GFR values of the XLH patients with water loading.
   - Two male and two female XLH patients aged 6 months to 7 years.
   - The patients were divided into groups A and B. In group A, water loading was performed from the day before testing, whereas water loading was performed from the beginning of the test in group B. The water loading dose was equal to thrice the maintenance dose for 3 or 10 mL/kg (dose) for orally.
3. TmPp and TmP/GFR values of the XLH patients with water loading and normal values.
   - Twenty-two patients aged 0 to 40 years.
   - Forty-eight samples were obtained from the patients.
   - Twenty-seven samples were obtained from 10 male patients whose bone deformities appeared before the age of 3 years and were also evaluated as representative samples of severe cases.

Calculating formula:

- TmPp (%) = [1 - ([Urinary phosphate/Plasma phosphate]/[Urinary creatinine/Plasma creatinine])] × 100
- TmP/GFR (mg/dL) = TmP (TmP/GFR 100) + Plasma phosphate
- The reference range of the TmP/GFR values were derived from data compiled by previous reports.

Results

1. TmPp and TmP/GFR values of the XLH patients without water loading and normal values.

- Sixty-four of 286 samples for TmPp (22.3%) and four of 286 samples for TmP/GFR (1.3%) showed values within the reference range (Figs. 1 and 2).

2. Time-dependent alterations in TmPp and TmP/GFR values of the XLH patients with water loading.

<table>
<thead>
<tr>
<th>Group A</th>
<th>Patient 1 (male)</th>
<th>Patient 2 (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TmPp (%)</td>
<td>2.0</td>
<td>1.6</td>
</tr>
<tr>
<td>[Urinary phosphate/Plasma phosphate]/[Urinary creatinine/Plasma creatinine]</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>TmP/GFR (mg/dL)</td>
<td>2.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Start time (hours after test)</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

3. Time-dependent alterations in TmPp and TmP/GFR were not observed in group A.

<table>
<thead>
<tr>
<th>Group B</th>
<th>Patient 1 (male)</th>
<th>Patient 2 (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TmPp (%)</td>
<td>3.6</td>
<td>1.2</td>
</tr>
<tr>
<td>[Urinary phosphate/Plasma phosphate]/[Urinary creatinine/Plasma creatinine]</td>
<td>2.7</td>
<td>1.0</td>
</tr>
<tr>
<td>TmP/GFR (mg/dL)</td>
<td>3.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Start time (hours after test)</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

4. Time-dependent decreases in TmPp and TmP/GFR were observed in group B.

Discussion

- TmPp and TmP/GFR values depend on plasma phosphate concentration and renal function, whereas the TmP/GFR value is independent of GFR. Therefore, TmPp/GFR is generally believed to be more useful in the diagnosis of XLH.
- However, the TmP/GFR value is increased in the condition that GFR falls to lower than 40 mL/min/1.73 m².
- TmP/GFR values calculated using insulin clearance (C_i) represent the true TmP/GFR values. However, TmP/GFR values calculated with GFR derived from creatinine clearance (C_c) deviate from the true TmP/GFR value.
- In adult patients with impaired renal function, the TmP/GFR obtained using C_c was higher than that calculated using C_i.
- The reference values of TmP/GFR quoted from previous reports could possibly decrease if water loading is performed simultaneously.
- When we set the values subtracted with 0.72 mg/dL from the TmP/GFR reference values as a provisional reference value, we could compare the provisional reference values of TmP/GFR with the values from group B XLH patients (Figs. 7 and 8) and XLH patients with water loading (Fig. 8).

Conclusion

- TmP/GFR is a useful marker in the clinical diagnosis of XLH caused by the PHEX gene mutation.
- Maintaining sufficient renal blood flow is important in order to accurately calculate the TmP/GFR value.

Reference