

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

Ryojun Takeda¹, Kentaro Miyai¹, Masaki Takagi¹, Yoshie Nakamura², Eri Suzuki³, Daisuke Ariyasu⁴, Masako Izawa⁵, Junko Igaki⁶, Yukihiko Hasegawa^{1,2}

¹Division of Endocrinology and Metabolism, ²Division of Genetic Research, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan; ³Department of Pediatrics, National Hospital Organization Tokyo Medical Center, Tokyo, Japan; ⁴Division of Developmental Genetics, Institute of Resource Development and Analysis, Kumamoto University, Kumamoto, Japan; ⁵Department of Pediatric Endocrinology and Metabolism, Aichi Children's Health and Medical Center, Aichi, Japan; ⁶Division of Endocrinology and Metabolism, Gunma Children's Medical Center, Gunma, Japan

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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 (%TRP), 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 %TRP and TmP/GFR is important.

Objectives

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

- To compare between the %TRP and TmP/GFR values of XLH patients without water loading and the respective reference values.
- To investigate the alterations in %TRP and TmP/GFR values in XLH patients during water loading.
- To compare between the %TRP 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.

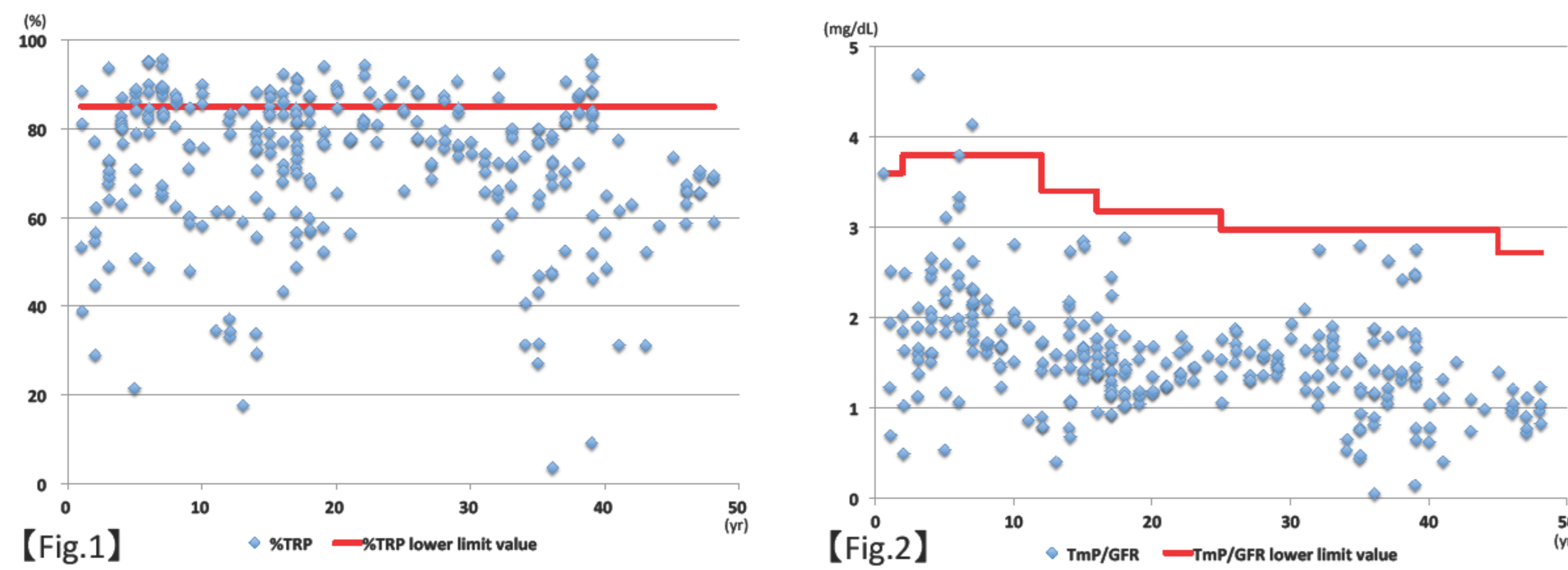
- %TRP and TmP/GFR values of the XLH patients without water loading and reference values.**
 - Twenty-six patients aged 0 to 50 years who had XLH.
 - Two hundred eighty-six urine and blood samples.
- Time-dependent alterations in the %TRP and TmP/GFR values of the XLH patients with water loading.**
 - 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 IV or 10 mL/(kg-dose) for orally.
- %TRP 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

- %TRP (%) = $[1 - \{(\text{Urine phosphate}/\text{Plasma phosphate})/(\text{Urine creatinine}/\text{Plasma creatinine})\}] \times 100$
- TmP/GFR (mg/dL) = TRP (%TRP/100) × Plasma phosphate
- The reference range of the TmP/GFR values were derived from data compiled by previous reports¹⁻³.

Results

- %TRP and TmP/GFR values of the XLH patients without water loading and normal values.**



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

- Time-dependent alterations in %TRP and TmP/GFR values of the XLH patients with water loading.**

Patient1 0y6m male						
	0min	60min	120min	lower limit value	fluid volume	start time
%TRP (%)	93.3	95.6	92.7	85	maintenance	12 hours prior to test
TmP/GFR (mg/dL)	2.8	2.9	2.8	3.6	× 1.7 (IV)	

Patient2 7y6m female						
	0min	60min	120min	lower limit value	fluid volume	start time
%TRP (%)	-	98	98.9	85	maintenance	6 hours prior to test
TmP/GFR (mg/dL)	-	2.1	2.1	3.8	× 1.0 (IV)	

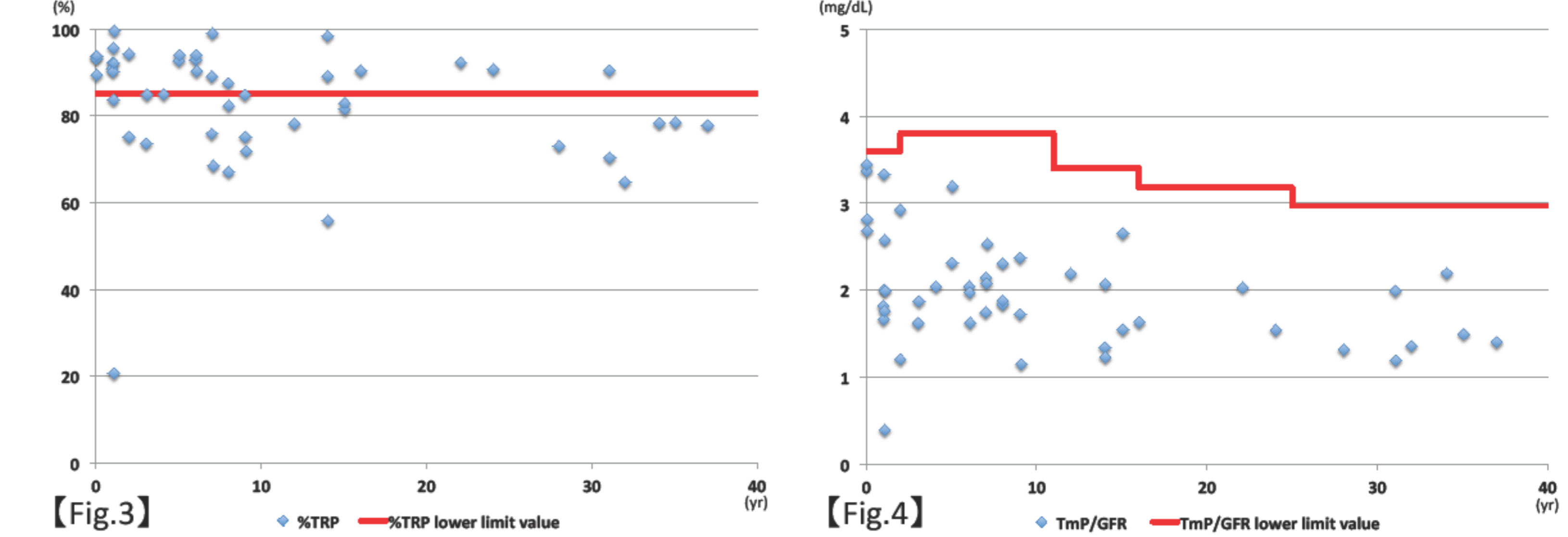
- Time-dependent alterations in %TRP and TmP/GFR were not observed in group A.

Patient3 0y6m female						
	0min	60min	120min	lower limit value	fluid volume	start time
%TRP (%)	94.9	92.7	89.3	85	maintenance	from the start testing
TmP/GFR (mg/dL)	3.6	2.9	2.7	3.6	× 3.0 (IV)	

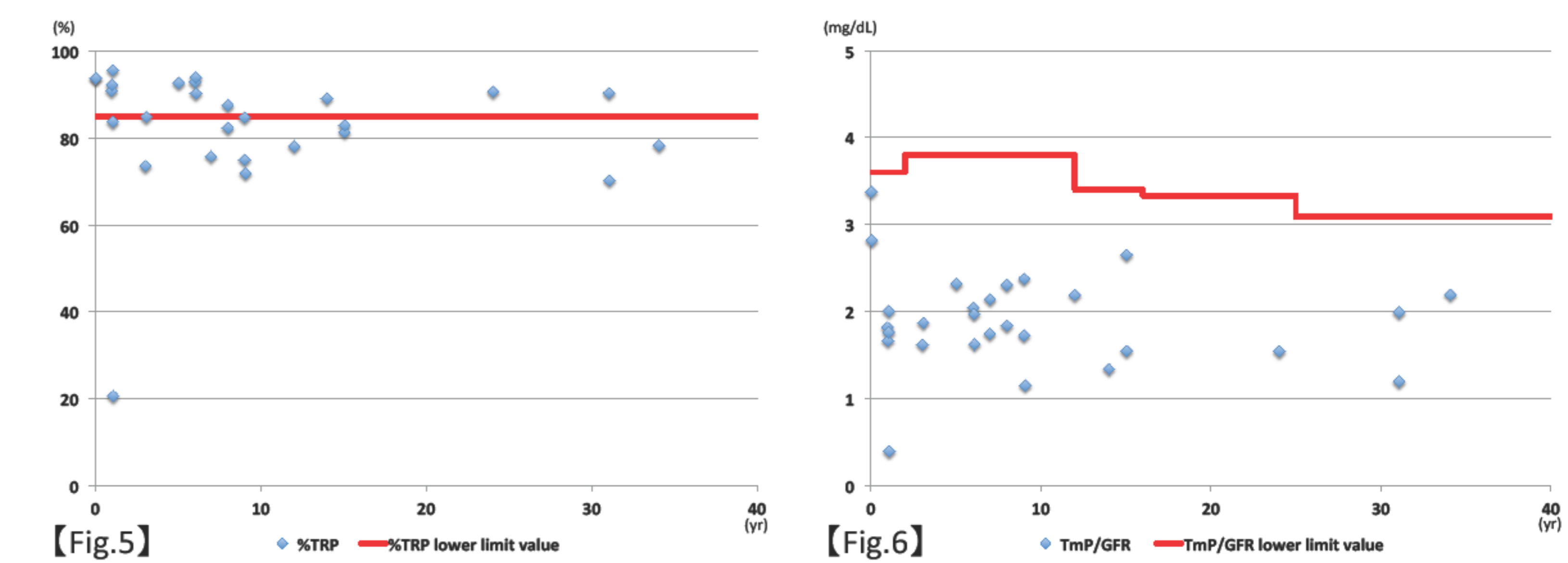
Patient4 7y2m male						
	0min	60min	120min	lower limit value	fluid volume	start time
%TRP (%)	-	94.2	89.1	85	10 mL/kg	from the start testing
TmP/GFR (mg/dL)	-	4.1	2.1	3.8	(Oral)	

- Time-dependent decreases in %TRP and TmP/GFR were observed in group B.

- %TRP and TmP/GFR values of the XLH patients with water loading.**



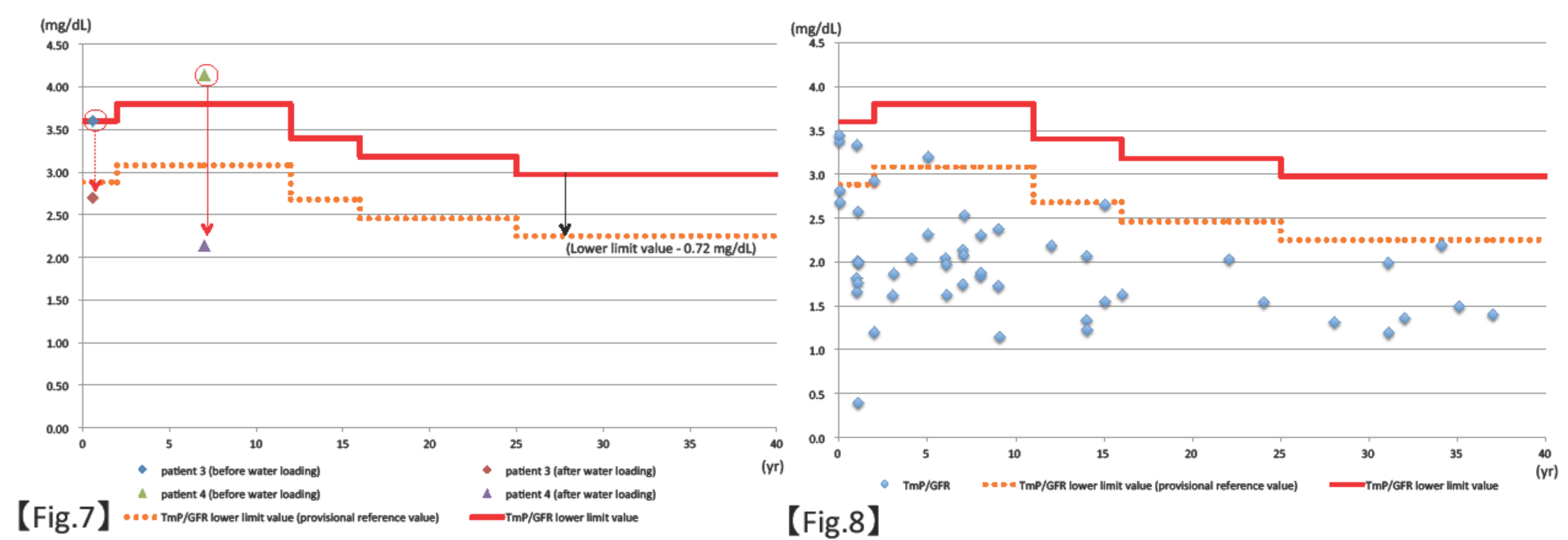
- Twenty-five of 48 samples for %TRP (52%) showed values within the reference range, and all of the samples for TmP/GFR showed values lower than the reference value (Figs. 3 and 4).



- Ten of 27 male patient samples for %TRP (37%) showed values within the reference range, and all samples for TmP/GFR showed values lower than the reference range (Figs. 5 and 6).

Discussion

- %TRP depends on plasma phosphate concentration and renal function, whereas the TmP/GFR value is independent of GFR. Therefore, TmP/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/min⁴.
- TmP/GFR values calculated using inulin clearance (C_{in}) represent the true TmP/GFR values. However, TmP/GFR values calculated with GFR derived from creatinine clearance (C_{cr}) may deviate from the true TmP/GFR value⁵. In adult patients with impaired renal function, the TmP/GFR obtained using C_{cr} was 0.72 mg/dL higher than that calculated using C_{in} ⁶.
- 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 (Fig. 7) and XLH patients with water loading (Fig. 8).



- After the water loading, the TmP/GFR values of the group B patients fell below the lower limit of the provisional reference range.
- ⇒ TmP/GFR values can be accurately calculated by performing preexamination water loading.
- Comparison between the TmP/GFR values of the XLH patients who underwent water loading and the provisional reference values. Of 48 samples, 4 remained within the reference range. These 4 samples were from patients under 7 years of age.
- ⇒ When diagnosing XLH in patients younger than 7 years, comprehensive evaluation of clinical, radiographic, and laboratory findings is important.

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

- Stark H et al. Nephron 1986. 2) Payne RB et al. Ann Clin Biochem 1998. 3) Chong WH et al. Endocr Relat Cancer 2011. 4) Bindels RJ et al. The Kidney ninth edition 2012. 5) Alon U et al. Pediatr Nephrol 1994. 6) Sutton JV et al. Nephron 1986.