A decreased soluble Klotho level with normal eGFR, FGF23, serum phosphate, and FEP in an ADPKD patient with enlarged kidneys due to multiple cysts

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disorder. ADPKD is characterized clinically by the presence of multiple bilateral renal cysts that lead to chronic renal failure. The cysts evolve from renal tubular epithelial cells that express the *Klotho* gene. Notably, Klotho acts as a co-receptor for fibroblast growth factor 23 (FGF23); in this context, it induces phosphaturia and maintains serum phosphate at a normal level. Many reports have shown that decreases in the soluble Klotho level and increases in the FGF23 level are associated with glomerular filtration rate (GFR) decline, but a recent study observed these changes in patient with normal eGFR. It remains unclear whether the decrease in the Klotho level precedes the increase in FGF23. Here, we present an ADPKD patient with enlarged kidneys due to multiple cysts who had a decreased soluble Klotho level but a normal eGFR and a normal FGF23 level. The patient's serum phosphate level was normal, as was the fractional excretion of phosphate (FEP). This appears to be the first reported case to show a decreased soluble Klotho level plus normal eGFR, FGF23, and FEP. These results suggest that Klotho decreases before FGF23 increases and further suggest that Klotho is not required to maintain normal serum phosphate levels in ADPKD if the FEP and serum phosphate levels are normal.

Keywords ADPKD · FGF23 · Klotho · Children

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disorder and the fourth leading cause of chronic kidney disease worldwide [1]. ADPKD is characterized clinically by the presence of multiple bilateral renal cysts that evolve from tubular epithelial cells in the thick ascending loop of Henle, distal tubules, and collecting ducts [2]. *Klotho* is expressed in tubular epithelial cells, especially in the distal tubules [3].

Klotho acts as a co-receptor for fibroblast growth factor 23 (FGF23) and can induce phosphaturia, especially in the proximal tubules of kidneys [4, 5]. It also helps maintain

serum phosphate at a normal level, thereby preventing phosphate toxicity [4]. It has been thought that a decrease in the Klotho level leads to hyperphosphatemia. Many studies have noted that a decrease in the soluble Klotho level and an increase in the FGF23 level are associated with glomerular filtration rate (GFR) decline [6, 7], but recently these changes were also observed with normal eGFR [2]. It remains unclear which occurs first, the decrease in the Klotho level or the increase in the FGF23 level.

Here, we present a case in which an ADPKD patient had enlarged kidneys due to multiple cysts growth and showed a decreased soluble Klotho level with a normal eGFR and a normal FGF23 level. The patient also had a normal serum phosphate level with a normal fractional excretion of phosphate (FEP). To the best of our knowledge, this is the first case to present with a decreased soluble Klotho level and normal eGFR, FGF23, and FEP.

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Case report

A 4 years old boy was diagnosed with ADPKD when he was 2 years old based on his family history and the presence of bilateral enlarged kidneys due to multiple renal cysts (Fig. 1a, b). His family history showed that his great-grandmother had chronic renal failure due to ADPKD and had been on hemodialysis since she was 72 years old; his grandfather had bilateral enlarged kidneys due to multiple renal cysts from ADPKD and had hypertension that required medication. His mother had small bilateral renal cysts without enlarged kidneys (right major axis 11.6 cm, left major axis 10.3 cm). His eldest brother, who was 10 years old, also had small bilateral renal cysts without enlarged kidneys (right major axis 7.8 cm, left major axis 8.7 cm). However, his second eldest brother, who was 9 years old, did not have any renal cysts. His mother and his two brothers had normal blood pressure and eGFR as well as normal soluble Klotho, FGF23, FEP, and intact-parathyroid hormone (intact-PTH) levels (Table 1).

Physical examination of him showed abdominal distension and the following measurements: height of 79.1 cm (+0.1 SD), body weight of 10.4 kg (+0.3 SD), hypertension of 147/96 mmHg, and enlarged kidneys due to multiple bilateral renal cysts due to ADPKD. Candesartan cilexetil (0.8 mg/day) and cilnidipine (6 mg/day) were prescribed, and he maintained normal blood pressure at 110–120/60–70 mmHg for 3 years. His laboratory data showed normal eGFR and normal FGF23, serum phosphate, FEP, and intact-PTH levels, but a decreased soluble Klotho level (Table 1). Moreover, from 2 to 5 years old the patient maintained normal levels of serum calcium (9.2–10.3 mg/dL), phosphate (4.2–5.2 mg/dL; reference

level of 2–5 years old, 3.8–6.0 mg/dL) and intact-PTH (28–42 pg/mL).

The magnetic resonance imaging showed that his kidneys had enlarged further bilaterally due to the growth of multiple cysts due to ADPKD (Fig. 1c). His mother and the three siblings all had normal levels of intact-PTH. They showed slightly decreased levels of 25(OH) vitamin D, but maintained normal levels of 1,25(OH)₂ vitamin D. No family members had polydipsia or polyuria, and the three boys had normal vasopressin levels (Table 1).

Discussion

This case report describes an ADPKD patient who had bilateral enlarged kidneys due to the growth of multiple cysts, a decreased soluble Klotho level, normal eGFR and normal FGF23, serum phosphate, and FEP levels. This suggests that in ADPKD, the soluble Klotho level decreases before the FGF23 level increases, even with normal eGFR, and further suggests that decreased soluble Klotho level does not affect phosphaturia in the initial stages of ADPKD.

The mechanisms by which kidney disease leads to decreased Klotho levels remain unknown [2]. Many reports show that a decrease in soluble Klotho levels is associated with a decrease in GFR and with increased FGF23 levels [6, 7]. In contrast, some reports show that soluble Klotho levels are decreased even in the presence of normal eGFR in patients with ADPKD. Pavik et al. reported that ADPKD patients with normal eGFR and normal serum phosphate levels show decreased soluble Klotho levels and increased FGF23 levels [2, 10]. Akiyama et al. also reported that soluble Klotho levels were significantly decreased and serum FGF23 levels significantly increased

Fig. 1 **a** The family tree, which shows that this is an inherited autosomal dominant disease. **b** MRI findings when the patient was 2 years old showed multiple bilateral cysts and enlarged kidneys. **c** MRI find-

ings when the patient was 4 years old showed multiple bilateral cysts and kidneys that were even more enlarged

Table 1 The characteristics of the family members

Family member	Age	Sex	ADPKD	Height (cm)	BW (kg)	BP (mmHg)	BUN (md/dL)	Cr (mg/dL)	Ca (mg/dL)	P (mg/dL)	eGFR (mL/min/1.73 m ²)	FEP (%)
Mother	30	F	ADPKD	171	52	124/79	13	0.60	9.2	3.3	94.5	8.59
Brother 1	10	M	ADPKD	148	35	109/69	12	0.45	9.6	4.5	126.6	4.15
Brother 2	9	M	Intact	129	27	102/64	15	0.48	9.8	4.8	94.3	3.09
Patient	4	M	ADPKD	104	16	119/79	14	0.29	9.1	4.3	120.7	7.25
	Soluble Klotho (pg/mL)	FGF23 (pg/mL)	Intact-PTH (pg/mL)	25(OH) vitamin D (ng/mL)	1,25(OH) ₂ vitamin D (pg/mL)	Vasopressin (pg/mL)						
Mother	580	21.0	29	14	47.8	NA						
Brother 1	2522	16.2	21	24	51.1	1.7						
Brother 2	1492	28.0	43	23	76.8	1.4						
Patient	242	27.6	39	22	51.2	1.6						

Reference ranges: Cr range in adult female 0.6–0.9 mg/dL, range in 9–10 years old 0.30–0.57 mg/dL, and range in 4 years old 0.20–0.40 mg/dL [8]; FEP, < 10%; FGF23, 12.9–51.2 pg/mL; soluble Klotho, range in children 952 ± 282 pg/mL, and range in adults 562 ± 146 pg/mL [9]; intact-PTH 10–65 pg/mL; 25(OH) vitamin D > 15 ng/mL; 1,25(OH)₂ vitamin D range in adult 20.0–60.0 pg/mL, range in children 20.0–70.0 pg/mL; vasopressin 0.5–2.0 pg/mL.

ADPKD autosomal dominant polycystic kidney, BW body weight, BP blood pressure, Cr creatinine, Ca calcium, P phosphate, eGFR estimated glomerular filtration rate, FEP fractional excretion of phosphate, FGF23 fibroblast growth factor 23, intact-PTH intact-parathyroid hormone

in ADPKD compared to patients in a non-diabetic CKD group who were matched for eGFR [11]. Moreover, our patient presented with a decreased soluble Klotho level but normal eGFR and serum FGF23 level. Although previous reports could not demonstrate whether soluble Klotho decreased before or after the increase in FGF23 in ADPKD, our case suggests that enlarged kidneys due to the growth of multiple cysts in ADPKD might cause the soluble Klotho level to decrease first in normal eGFR. The increase in FGF23 would be secondary to the decrease in soluble Klotho to compensate for the resulting phosphaturic effects. There have been no reports that *Klotho* knock-out causes renal cysts [5]. Therefore, our case suggests that enlarged kidneys due to the growth of multiple cysts would lead to a decreased soluble Klotho level but normal eGFR and FGF23 in ADPKD.

It is not clear how enlarged kidneys due to the growth of multiple cysts cause a decrease in soluble Klotho. In ADPKD, the cysts evolve from tubular epithelial cells [2] that express *Klotho* [3]. There are no reports that *Klotho* knock-out causes renal cysts [5]. His mother and eldest brother, who had renal cysts due to ADPKD but who had normal sized kidneys, did not show decreases in their soluble Klotho levels. Therefore, it is possible that enlarged kidneys due to the growth of cysts due to ADPKD might decrease the soluble Klotho levels but decreases in Klotho do not cause renal cysts in ADPKD. Thus, the growth of cysts in urinal tubules might lead to the downregulation of *Klotho* expression. This might explain why the decrease in soluble Klotho levels proceeds the eGFR decline in ADPKD patients.

There are several mechanisms that affect the growth of cysts in ADPKD. For example, it has been reported that vasopressin enlarges renal cysts in ADPKD [12]. However, we observed that even a patient with enlarged kidneys can have a normal vasopressin level, indicating that vasopressin by itself does not lead to a decrease in the soluble Klotho level. Further studies how the growth of multiple cysts could cause a decrease in soluble Klotho is required.

Our case also suggests that a decrease in the soluble Klotho level does not affect phosphaturia or cause vitamin D activation in the initial stages of ADPKD. The Klotho protein is predominantly expressed in kidneys, especially in distal tubes [3], and has two domains, an extracellular domain and a membrane domain. The extracellular domain of Klotho is cleaved and secreted into the blood as soluble Klotho. Thus, the soluble Klotho levels reflect the membrane Klotho levels [13]. In cooperation with FGF23, membrane-bound Klotho controls the serum phosphate level by inducing phosphaturia and thereby preventing phosphate toxicity [4, 5]. The present patient showed not only normal FEP but also a normal serum phosphate level, just like his mother and brothers. This suggests that Klotho is not required to maintain normal serum phosphate levels and that a decrease

in the soluble Klotho level does not cause vitamin D activation as long as FEP is normal.

It is also possible that soluble Klotho level does not always reflect membrane Klotho level although membrane Klotho in the kidney is the main producing site of soluble Klotho. To confirm this possibility, validation of membrane Klotho level in renal specimens is required.

Notably, Sari et al. reported that even in late stage chronic kidney disease, both soluble Klotho and the FGF23 levels in patients with ADPKD were higher than levels in a healthy control group [14]. The ADPKD patients they studied showed almost normal serum phosphate levels even in late stage renal disease. Thus, other factors might affect serum phosphate levels, which could affect Klotho expression.

Conclusion

To the best of our knowledge, this is the first case in which a patient with ADPKD presented with enlarged kidneys due to cysts and also showed decreased Klotho expression, but normal eGFR and normal FGF23, serum phosphate, and FEP levels. The mechanism by which cysts develop on the urinal tubules and lead to decreased Klotho expression awaits further elucidation.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interests exists.

Consent for publication All authors read this manuscript and approved it for publication.

Ethical standards This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Jichi Medical University (A17-0088).

Study involving human and/or animal participants All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional research committee where the studies were conducted and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study and from their parents.

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