Uremic Cardiomyopathy- A Killer for Chronic Kidney Disease Patients

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Research interests: Ion channelopathies; WNK kinases; Klotho; HTN; Mineral metabolic disorders of CKD.

Special clinical interests: acid-base and fluid-electrolyte disorders;
genetic diseases of acid-base and fluid-electrolyte disorders.

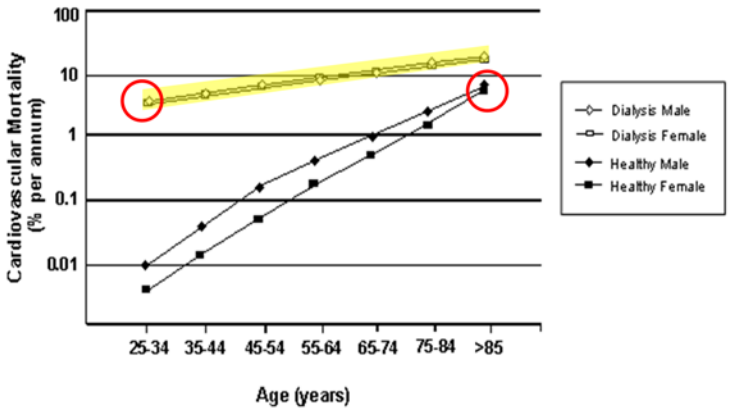
Purpose and Overview

The purpose of this presentation is to educate audience that cardiac hypertrophy is very prevalent in patients with chronic kidney disease and the main cause of death in this population. The presentation will discuss known mechanisms of uremic cardiomyopathy and that klotho deficiency may be a remaining missing link that may provide additional insight and effective treatment for the disease.

Learning Objectives:

1. Learn about multifactorial causes for uremic cardiomyopathy
2. Learn about currently available management for uremic cardiomyopathy
3. Learn about the limitations of current treatment and future development on the horizon

Chronic kidney disease (CKD) affects approximately 10% of the general population (1, 2). CKD patients are more likely to die from cardiovascular disease (CVD) than to reach end-stage kidney disease and receive dialysis. The prevalence of cardiac hypertrophy is markedly increased in patients with CKD (i.e., uremic cardiomyopathy), reaching as high as 95% in patients of advanced stages of CKD. CVD is a main cause of death for CKD patients, and among which cardiac hypertrophy plays a major role (2-5). Figure 1 shows that in normal individuals the frequency of cardiovascular mortality is predominantly a function of age. In contrast, young adults with advanced CKD patients on dialysis have ~300 fold higher rate of CVD, and age-associated increases in CV mortality in dialysis patient population are relatively less pronounced.



National Kidney Foundation Task force CV Disease, *Am J Kidney Dis 1998*

Figure 1

Conventional risk factors, such as hypertension, volume overload and anemia, are important in the pathogenesis of cardiac hypertrophy in CKD (4, 5). Yet, many CKD patients even without underlying diabetes and ischemic heart disease develop cardiac hypertrophy despite intensive control of blood pressure and fluid retention. Thus, risk factors specific to CKD also play important roles. Several CKD-specific risk factors have been proposed (4, 5). Among these include secondary hyperparathyroidism, vitamin D deficiency, retention of protein-bound uremic toxins (indoxyl sulfate, etc), phosphate retention, increases in circulating FGF23 levels, and decreases in circulating soluble klotho (Figure 2).

Mechanisms of Cardiac Hypertrophy in CKD

Cardiac hypertrophy (uremic cardiomyopathy) is as high as 90% in CKD.

Conventional: Hypertension
Volume overload
Anemia

CKD-Specific: Hyperparathyrodism
Vitamin-D deficiency
Indoxyl sulfate
Phosphate retention
Elevated FGF23
Klotho deficiency

Figure 2

Secondary hyperparathyroidism and uremic cardiomyopathy

The implication that elevated PTH levels may be causative for cardiac hypertrophy in CKD was first proposed in early 80's by Massry and colleagues (6). They showed that PTH increases Ca2+ entry in rat ventricular myocytes, involving L-type Ca2+ channels. Additionally, receptors for PTH and PTHrP are present in cardiomyocytes. Parathyroidectomy alleviates uremic cardiomyopathy in animal model of CKD and infusion of PTH aggravates the disease (7). Interestingly, patients with primary hyperparathyroidism also have increased cardiovascular

disease and mortality (8). Whether this is related to hypercalcemia-induced hypertension, cardiac, vascular and/or valvular calcification, etc, has never been clearly settled. In general, PTH is not considered a major pro-hypertrophic hormone for cardiomyocytes.

In the largest clinical trial involving HD patients ever, the EVOLVE study examined the effect of suppression of PTH on CVD (9). 3883 patients with moderate-to-severe secondary hyperparathyroidism (median level of intact PTH, 693 pg/ml [10th to 90th percentile, 363 to 1694]) undergoing hemodialysis were randomly assigned to receive either cinacalcet or placebo. All patients were eligible to receive conventional therapy, including phosphate binders, vitamin D sterols, or both. The patients were followed for up to 64 months. The primary composite end point was the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. The primary analysis was performed on the basis of the intention-to-treat principle. The median duration of study-drug exposure was 21.2 months in the cinacalcet group, versus 17.5 months in the placebo group. The primary composite end point was reached in 938 of 1948 patients (48.2%) in the cinacalcet group and 952 of 1935 patients (49.2%) in the placebo group (relative hazard in the cinacalcet group vs. the placebo group, 0.93; 95% confidence interval, 0.85 to 1.02; P=0.11). Hypocalcemia and gastrointestinal adverse events were significantly more frequent in patients receiving cinacalcet. In an unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis. After adjustment for baseline characteristics, there was a nominally significant 12% reduction in risk. The conclusion of the trial is considered as non-definitive.

Vitamin D deficiency and uremic cardiomyopathy

Vitamin D deficiency is known to be associated with decreased cardiovascular-related morbidity and mortality, possibly by modifying cardiac structure and function, yet firm evidence for either remains lacking. A double-blind, randomized placebo-controlled (PRIMO) trial among 227 patients with stage 3 and 4 chronic kidney disease, mild to moderate left ventricular hypertrophy, and preserved left ventricular ejection fraction, was conducted to determine the effects of an active vitamin D compound, paricalcitol, on left ventricular mass over 48 weeks (10). The eGFR of study patients ranged between 15 and 60 mL/min/1.73 m^2. Change in left ventricular mass index over 48 weeks was assessed by cardiovascular magnetic resonance imaging. Secondary end points included echocardiographic changes in left ventricular diastolic function. It was found that 48 week therapy with paricalcitol did not alter left ventricular mass index or improve certain measures of diastolic dysfunction in patients with chronic kidney disease.

Indoxyl sulfate/p-Cresyl sulfate and uremic cardiomyopathy

Indoxyl sulfate (IS) and p-cresyl sulfate (p-CS) both originate from bacterial protein fermentation in the large intestine. Colonic microbiota degrade tryptophan to indole (Figure 3). Further hydroxylation results in 3-hydroxy-indole, the majority of which is sulfonated to indoxyl sulfate. In parallel, fermentation of tyrosine results in p-cresol and ultimately p-cresyl sulfate (11). Most p-cresyl sulfate and indoxyl sulfate circulates noncovalently bound to albumin and

competes for the same albumin-binding sites. Being bound to albumin, IS and p-CS are not easily cleared by glomerular filtration. Normally, they are cleared from the systemic circulation predominantly by tubular secretion via organic anion transporters, OAT's. In individuals with normal GFR, the circulating levels of free IS are below detection and of total (free and bound) are ~0.5 mg/L. The level of the total may be up to ~20 mg/L in uremia. IS/p-CS have been implicated in causing many uremia-associated complications including oxidative stress, inflammation, fibrosis, endothelial dysfunction, cardiac dysfunction, etc (12). AST-120 is a carbonaceous oral adsorbent first approved for use in Japan in 1991 and later on in other Asian and European countries. It decrease serum IS/PS levels by binding and excretion through GI tract. It has been used in several regions including Japan as an agent to retard the progression of CKD.

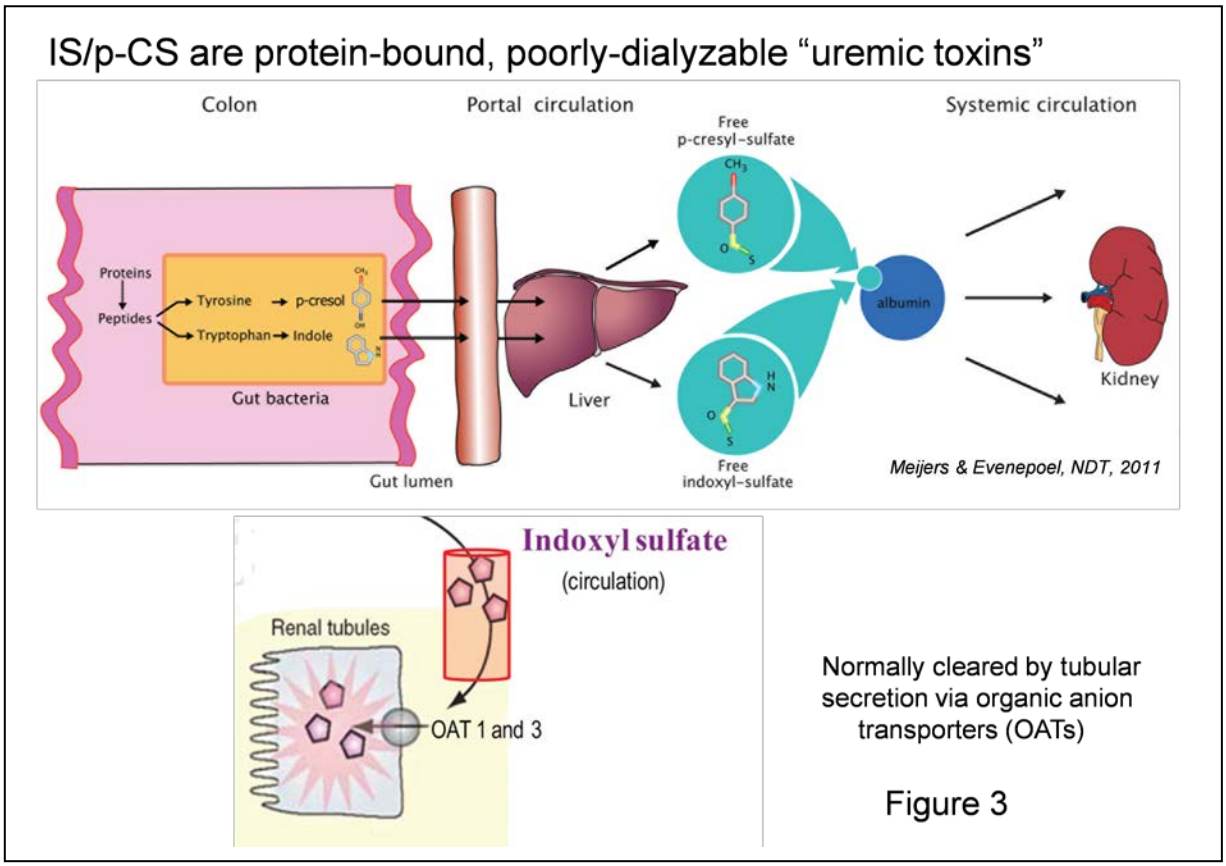


Figure 3

CAP-KD study is a RCT study of 460 CKD patients examining the effect of AST-120 on progression of CKD (13). Composite primary end point includes doubling of sCr level, increase in sCr level to 6.0 mg/dL or more, need for dialysis or transplantation, or death. During 56 weeks, numbers of primary end-point events (43 for control versus 42 for AST-120) and event-free survival (P = 0.9) did not differ between groups. Gastrointestinal adverse events were less common in the control group than the AST-120 group (2 versus 32 events). Estimated CCr decreased more in the control group than in the AST-120 group (-15% per year versus -12% per year, relative to the baseline value; [corrected] P = 0.001). However, the difference was not

significant. Thus, AST-120 did not substantially slow the progression of kidney disease in patients with moderate to severe CKD during 1 year.

This study was recently followed by a larger (EPPIC Trial) multi-center (North/Central America & Europe) RCT study of >2,000 CKD patients to examine the effect of AST-120 on progression of CKD and all-cause mortality. Again, the preliminary report of the study communicated in 2012 annual American Society of Nephrology meeting revealed no difference between placebo and AST-120.

Phosphate retention and uremic cardiomyopathy

Studies in model organism and small animals have provided evidence that dietary phosphate intake inversely correlates with lifespan independently of caloric intake. Direct examination of phosphate intake on human life span is impossible. However, several observational studies have examined relationship between hyperphosphatemia and CVD and cardiovascular mortality in populations that have shortened lifespan, for example individuals with prior events of acute coronary syndrome or with CKD. A post hoc analysis of data from the Cholesterol And Recurrent Events (CARE) study, baseline serum phosphate levels from 4127 fasting participants who were categorized into four groups: <2.5, 2.5 to 3.4, 3.5 to 3.9, and > or =4 mg/dL (14). Patients were followed up for a median of 59.7 months. Cox proportional-hazards models were used to examine the association between serum phosphate and adverse clinical outcomes after adjustment for potential confounders. During nearly 60 months of follow-up, 375 participants died. The analysis revealed a significant association between baseline serum phosphate level and the age-, race-, and sex-adjusted risk of all-cause death.

Block et al examined the relationship between mineral metabolism and mortality in dialysis patients (15). Multivariable-adjusted relative risks of death were calculated for categories of serum phosphorus, calcium, calcium x phosphorus product, and intact parathyroid hormone (PTH) using proportional hazards regression. They found that hyperphosphatemia and hyperparathyroidism were significantly associated with all-cause, cardiovascular, and fracture-related hospitalization. Hyperphosphatemia is an important risk factor for vascular calcification, which may contribute to cardiac hypertrophy, by causing vascular calcification, decreasing vascular compliance, and thus systolic hypertension (4,5). Whether phosphate is a direct toxin for the heart and causes cardiac hypertrophy independently of vascular and hemodynamic factors are not known.

Mineral metabolism disorder of CKD: role of FGF23 and Klotho

FGF23 is a bone-derived endocrine hormone that potently lowers serum phosphate levels by suppressing 1,25-$(OH)_2$-vitamin D synthesis (thus decreasing gut absorption of phosphate) and inhibiting renal phosphate reabsorption mediated by Na-phosphate cotransporter (16). Serum FGF23 levels rise in early stages of CKD and increase progressively in advanced stages to the levels 100's and 1000's fold of normal serum levels (17, 18). The mechanism for the increase in FGF23 levels in CKD remains incompletely understood, but phosphate retention plays an important role. In early stages of CKD, renal resistance to FGF23 due to decreases in the abundance of membranous klotho in the diseased kidney (thus with

impairment of its FGF23 co-receptor function and elevation of 1,25-dihydroyvitamin D levels) may play a key role. As CKD progresses, phosphate retention as the result of decreased renal excretion further stimulates FGF23 production from the bone (19, 20). Increases in circulating FGF23 levels suppress 1,25-$(OH)_2$-vitamin D, which causes an increase in PTH levels by releasing inhibition by 1,25-(OH)2-vitamin D in the parathyroid glands. In the early stages of CKD, rises in FGF23 and PTH levels coupled with the decreases in 1,25-$(OH)_2$-vitamin D keep serum phosphate levels from rising beyond the normal range (Figure 4).

Thus, rise of FGF23 in CKD is considered an adaptive mechanism to combat phosphate retention (17, 19, 20). Consistent with this notion, many studies have found that circulating FGF23 levels strongly correlate with the stages of CKD and its cardiovascular complications (19-22). Recently, a study reported that rise in FGF23 levels in CKD may be mal-adaptive; that is, it stimulates cardiac myocyte growth to induce cardiac hypertrophy (22). However, other studies have not found evidence supporting the notion that FGF23 directly induces cardiac hypertrophy (23).

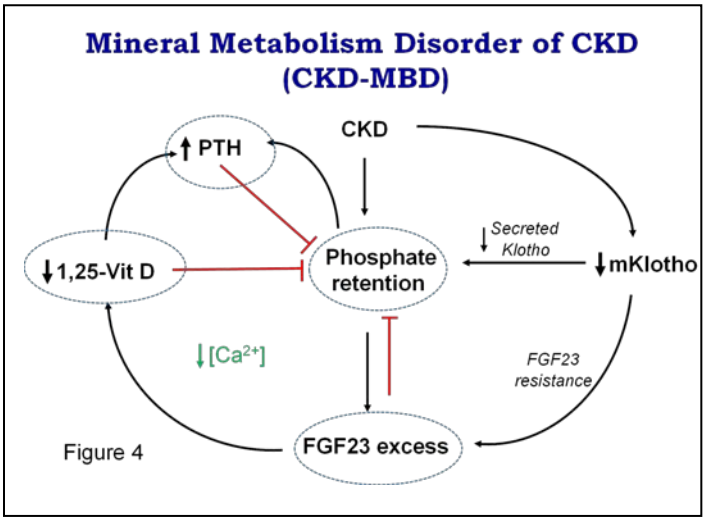


Figure 4

Klotho and its role in phosphate metabolism

Klotho is a type-1 membrane protein predominantly produced in the kidney that exerts some anti-aging function (24). Mice homozygous for hypomorphic klotho (kl) allele, due to disruption of the promoter region by a randomly inserted transgene, show multiple phenotypes resembling premature human aging, including shortened lifespan, growth retardation, skin atrophy, hypogonadism, hyperphosphatemia, and tissue calcification (24).

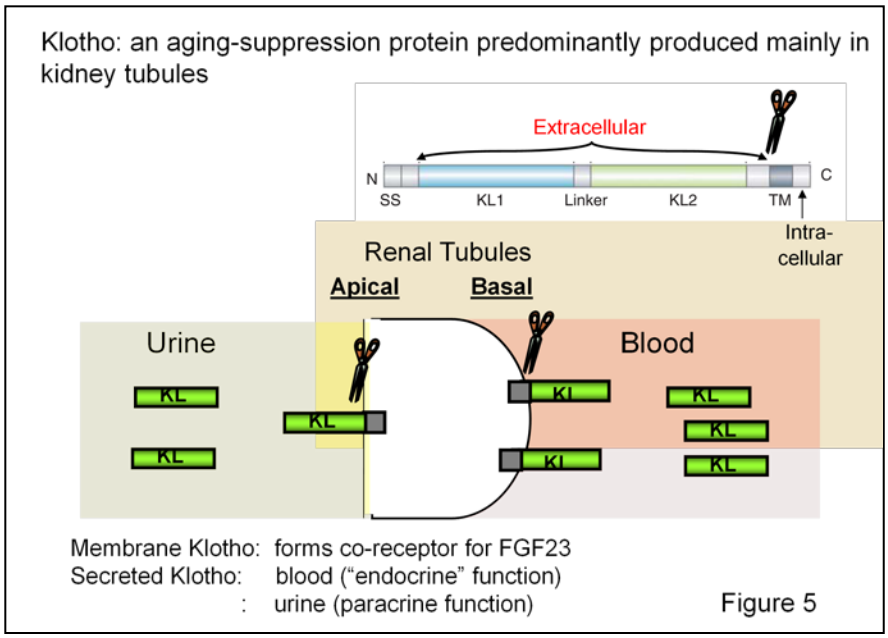


Figure 5

Conversely, overexpression of klotho transgene results in extended lifespan and increased resistance to

oxidative stress (25). The extracellular domain of klotho consisting of the homologous KL1 and KL2 repeats can be cleaved and released into the extracellular fluid such as blood, urine and cerebrospinal fluid (24-26). Thus, klotho exists in two different forms in vivo: a full-length membranous klotho and a shed soluble klotho ectodomain, each with own separate function (24-26).

Soluble klotho has been shown to regulate ion transport and growth factor signaling acting as a paracrine or endocrine factor (25, 27). Membranous klotho interacts with fibroblast growth factor receptor (FGFR) and functions as co-receptor for the ligand FGF23 (28, 29). Activation of membranous klotho-FGFR co-receptor complex by FGF23 suppresses renal synthesis of 1,25-$(OH)_2$-vitamin D (therefore decreasing gastrointestinal phosphate absorption) and inhibits renal phosphate reabsorption by sodium-phosphate cotransporter (16, 17, 28, 29). Recent studies have indicated that regulation of phosphate metabolism by FGF23 via klotho and FGFR co-receptor complex plays a critical role in the aging suppression by klotho. Mice homozygous for fgf23 deletion have profound hyperphosphatemia and the same premature aging phenotypes as in homozygous klotho-hypomorphic mice (17). Dietary phosphate restriction rescues premature aging and death in both fgf23 knockout and homozygous klotho-hypomorphic mice (17, 30, 31).

Decrease in circulating soluble klotho contribute to uremic cardiomyopathy

The kidney being the major organ for production of klotho, CKD is known to be a klotho-deficient state (32). It is recently reported that soluble klotho protects the heart against stress-induced cardiac hypertrophy by downregulation of calcium-permeable TRPC6 channels in the heart (33). Ca^{2+} entry through TRPC6 channels activates calcineurin and nuclear factor of activated T cells (NFAT) signaling cascade which plays a pivotal role in the pathogenesis of pathological cardiac hypertrophy (34, 35). Further studies show that indeed decreases in circulating soluble klotho levels contribute to uremic cardiomyopathy in mice (induced by 5/6th nephrectomy) independently of FGF23 and phosphate.

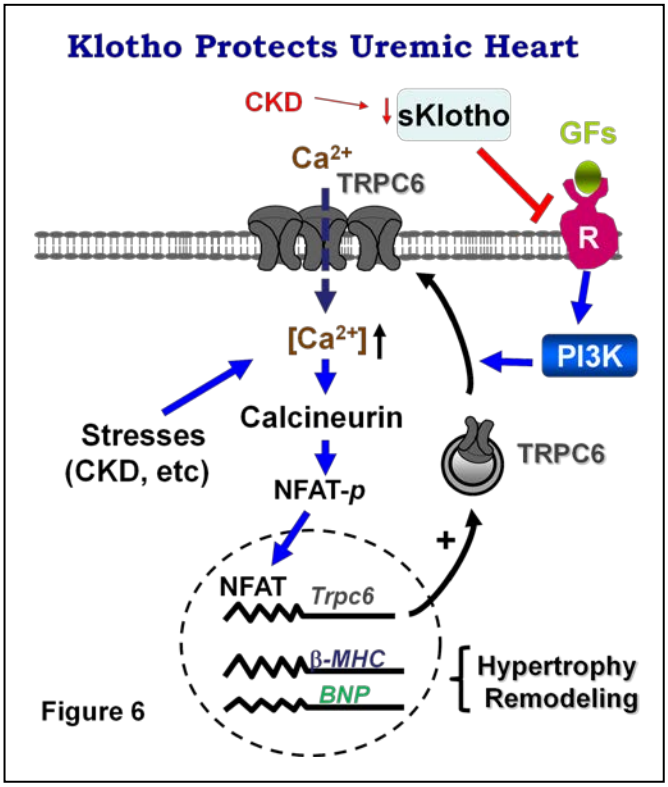


Figure 6

Summary and Conclusion

A large number of CKD patients die from cardiovascular disease before reaching dialysis. Uremic cardiomyopathy characterized by left ventricular hypertrophy is a major cause

of CV death in CKD, by causing arrhythmia, sudden, CHF, etc. Multiple causes for uremic cardiomyopathy exist. Despite intense management of currently known causes, uremic cardiomyopathy remains a significant problem in CKD. Other causes exist and remain to be identified. Exciting recent results in animal models suggest that deficiency of circulating klotho may be an important missing cause for uremic cardiomyopathy. Its role in human CKD patients and as a potential therapeutic will be important focus of future studies. Finally, klotho replacement will not be a magic bullet and, if anything, will likely be a part of comprehensive management of cardiomyopathy in CKD patients typically plagued with multisystem disorders.

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