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Total Kidney Volume as a Biomarker of Disease Progression in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Purpose of review: Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder characterized by the formation of kidney cysts and kidney enlargement, which progresses to kidney failure by the fifth to seventh decade of life in a majority of patients. Disease progression is evaluated primarily through serum creatinine and estimated glomerular filtration rate (eGFR) measurements; however, it is known that serum creatinine and eGFR values typically do not change until the fourth or fifth decade of life. Until recently, therapy only existed to target complications of ADPKD. As therapeutic agents continue to be investigated for use in ADPKD, a suitable biomarker of disease progression in place of serum creatinine is needed.

Sources of information: This review summarizes recent research regarding the use of total kidney volume as a biomarker in ADPKD, as presented at the Canadian Society of Nephrology symposium held in April 2015.

Findings: Measurement of patients' total kidney volume made using ultrasound (US) or magnetic resonance imaging (MRI) has been shown by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study to be directly correlated with both increases in cyst volume and change in glomerular filtration rate (GFR). Additional studies have shown total kidney volume to have an association with complications of ADPKD as well.

Limitations: Areas for further study continue to exist in comparison of methods of measuring total kidney volume.

Implications: We believe that the evidence suggests that total kidney volume may be an appropriate surrogate marker for ADPKD disease progression.

Abrégé

Mise en contexte et objectif de la revue: La polykystose rénale autosomique dominante (PKD) est une maladie héréditaire caractérisée par la formation de kystes aux reins et par l'hypertrophie des reins. Chez la majorité des patients atteints, la PKD évolue vers l'insuffisance rénale entre l'âge de 50 et de 70 ans. La progression de la maladie est essentiellement évaluée par la mesure de la créatinine sérique et du débit de filtration glomérulaire estimé (DFGe). Toutefois, règle générale, ce n'est que vers l'âge de 40 à 50 ans que l'on observe des changements dans ces paramètres. Jusqu'à tout récemment, les traitements ne ciblaient que les complications de la PKD. Bien que des médicaments fassent l'objet d'études en vue de leur utilisation pour traiter la PKD, on constate l'importance d'identifier un biomarqueur qui remplacerait le dosage de la créatinine sérique et qui faciliterait le suivi de la progression de la maladie.

Sources: La revue fait la synthèse des recherches menées récemment au sujet de l'utilisation de la mesure du volume total des reins comme biomarqueur de la PKD, comme présenté lors du symposium de la Société canadienne de néphrologie qui s'est tenu en avril 2015.

Constatations: L'étude CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) a démontré que les mesures du volume rénal total des patients, effectuées par ultrasons (US) ou par imagerie par résonance magnétique (MRI), sont directement corrélées à une augmentation du volume des kystes de même qu'à des variations du débit de filtration glomérulaire (DFG).

Limites de l'étude: Plusieurs domaines de comparaison entre les différentes méthodes de mesure du volume total des reins sont encore à explorer.

Conclusion: Nous sommes d'avis que les données probantes suggèrent que la mesure du volume total des reins pourrait s'avérer un marqueur substitut adéquat pour suivre la progression de la PKD.

Keywords
total kidney volume (TKV), autosomal dominant polycystic kidney disease (ADPKD), biomarker, disease progression

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What was known before

The use of total kidney volume (TKV) as a biomarker of disease progression in autosomal dominant polycystic kidney disease is an area of active, ongoing research. Recent studies have looked at the suitability of TKV as a biomarker, the settings in which TKV is appropriate for use, and comparisons of various methods for measuring TKV.

What this adds

This article provides an overview and summary of recent findings.

Background

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder characterized by progressive kidney cyst formation and kidney enlargement.[1] Over time, this leads to disruption of kidney function and ultimately kidney failure between the fifth and seventh decades of life in a majority of patients.[2] ADPKD is the most common of the group of inherited kidney cystic diseases, shown to affect between 1/400 and 1/1000 of the population.[3] In addition, ADPKD is the most common inherited kidney disorder and the fourth leading cause of kidney failure.[1]

Mutations of 2 different genes in ADPKD cause the majority of cases as ascertained from chronic kidney disease (CKD) clinics or dialysis units: *PKD1* (85% of cases) and *PKD2* (15% of cases).[3]. However, a more recent population-based study suggests that *PKD2* may be as common as 25%.[4] *PKD1* and *PKD2* encode membrane proteins, polycystin-1 and -2, which are located in the primary cilium of tubular epithelial cells of the kidney. Results of the mutations are disruptions to intracellular calcium signaling, cell proliferation and the development of fluid-filled cysts, distortion of normal parenchyma tissue, and loss of kidney function.[5] Both mutation types are inherited in an autosomal dominant manner, and display a wide range of disease severity clinically, likely attributed in part to the specific mutation type[6] and genetic modifiers.[7] Generally, patients with truncating *PKD1* mutations have more severe kidney disease than patients with *PKD2* mutations with a mean age of onset of end-stage renal disease (ESRD) at 55 and 75 years, respectively.[2,6] As an inherited disorder, family history often plays a role in detection of the disease. The diagnosis is typically made based on imaging, with ultrasonography being used most frequently for its high diagnostic accuracy, safety, accessibility, and cost-effectiveness.[8,9] The specific diagnostic criteria for at-risk individuals with a positive family history differ depending on their age.[8] Molecular-based diagnostic tests are also available for use when imaging is inconclusive.[8,10]

At this time, management of ADPKD is limited to reducing morbidity and mortality due to disease complications.[3] Several medications have completed or are undergoing clinical trials for ADPKD, including tolvaptan (a vasopressin V2 receptor antagonist), mammalian target of rapamycin (mTOR) inhibitors, somatostatin analogues, and estimated glomerular filtration rate (eGFR) pathway inhibitors.[11] Due to the nature of ADPKD's slow lifetime progression from diagnosis to kidney failure, clinical trials face a challenge in this population when looking at rates of progression to kidney failure as the outcome of interest, as this would require an unfeasibly long follow-up period for the trial.[3] Thus, it is becoming increasingly necessary to determine an alternative practical and valid method of evaluating individual patients' risk of progression of CKD and downstream progression to kidney failure. One such method that has been evaluated and shown to have merit is the use of total kidney volume (TKV) measurements as a biomarker of disease severity and progression.[1,12,13]

The Canadian Society of Nephrology held a symposium on the topic of TKV as a biomarker for disease severity and progression in ADPKD in April 2015. This review is intended to summarize the discussion and findings presented at that symposium.

Discussion Questions

Why Should We Measure TKV?

ADPKD is a disease that progresses over decades, until kidney failure is finally reached by the fifth to seventh decade of life in a majority of patients. Typically, the disease is

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monitored through changes in serum creatinine levels and eGFR; however, this provides limited information especially early in disease progression, as serum creatinine levels do not typically rise (eGFR does not decrease) until the fourth or fifth decade of life.[1] Thus the use of a surrogate marker for disease progression is needed.

Measurement of TKV is one method that can be used to help determine a patient's risk of eventually progressing to kidney failure, at an earlier point in his or her disease course. This is especially of value in the setting of clinical trials, as this would aid in selection of participants who would be most likely to benefit from the trial.[12] In addition, there may be a role for the change in TKV as a biomarker of treatment effect in drug trials, as a more sensitive measure of disease progression than glomerular filtration rate (GFR) or serum creatinine. TKV has already been used as the primary efficacy end point in several trials, including phase 3 studies evaluating tolvaptan,[14] mTOR inhibitors everolimus[15] and sirolimus,[16,17] octreotide,[18] pravastatin,[19] and antihypertensives targeting the renin-angiotensin-aldosterone system.[20] Despite this, some controversy still exists as to whether TKV is universally suitable as a therapeutic effect biomarker.[12,21] It is thought that in more advanced stages of ADPKD, GFR may be the more appropriate primary end point, whereas TKV is more suitable for studies in early to moderate stages of the disease.[22] TKV is an appropriate measure as it correlates with increased cyst volume. One of the largest studies that has shown this to be the case was done by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). CRISP was a prospective longitudinal observational cohort study of ADPKD patients that used magnetic resonance imaging (MRI) to determine whether change in TKV can be detected over a short time period and whether it is correlated with decline in kidney function.[23] Results of the study show that although kidney growth curves are highly variable from one individual to another, in the majority of patients, kidney volume does increase over time and this is attributed to increase in cyst volume. At baseline, mean TKV for 241 patients was 1076 mL, and total cyst volume was 534 mL, as compared with the mean volume of normal kidneys: 196 mL. Over a 3-year period, TKV increased by 204 mL ($P < .001$ vs. baseline) and total cyst volume increased by 218 mL ($P < .001$) in 210 patients. The correlation between change in TKV and cyst volume was $r = 0.95$ ($P < .001$). In addition, the study showed that cyst and kidney growth occur as a continuous, steady rate in most patients.[1]

What Are the Data That Support the Association of TKV With Kidney Function?

The CRISP study showed that increase in TKV is not only correlated to increased kidney cyst volume but also related to change in GFR. A slope of change in GFR from baseline to 3 years in 234 patients was compared with the slope of change in TKV in 232 patients and found to have significant correlation (−0.186, $P < .005$).[1] This supports the view that enlarging cyst volume plays an important role in the decline in kidney function,[1] or at the very least through its correlation to decline in GFR, TKV is a suitable marker of disease progression.

An extended follow-up of CRISP looked at height-adjusted TKV (htTKV) as a predictor of onset of renal insufficiency and found that the correlations between htTKV and GFR increased from −0.22 at baseline to −0.65 at year 8, indicating that at the eighth year, htTKV explains approximately 42% of the variance for GFR—a feature of a modestly good predictor. Multivariable analysis showed that a baseline htTKV increase of 100 cc/m significantly predicted stage 3 CKD development within 8 years with a 1.48 odds ratio (95% confidence interval, 1.29-1.70). Baseline htTKV of 600 cc/m best predicted the risk of developing stage 3 CKD within 8 years with an area under the curve of 0.84 (95% confidence interval, 0.79-0.90).[13] It was found to be a better predictor than baseline age, serum creatinine, blood urea nitrogen (BUN), urinary albumin, or monocyte chemotactic protein-1 excretion ($P < .05$), and was independent of age, sex, and race. It appears to also be independent of ADPKD genotype, although the analysis performed did not separate the truncating (severe) and nontruncating (milder) *PKD1* mutations when compared with the milder *PKD2* mutations, which may have affected this finding.[13]

Irazabal et al[24] also looked at the use of htTKV combined with patient age to classify patients into categories that may help predict disease severity and likelihood of progression. Patients were classified as class 1 based on typical ADPKD findings on baseline imaging, or class 2 with imaging findings of atypical ADPKD such as unilateral or segmental kidney involvement. Class 1 was further subclassified into 1A to 1E. Subclasses were defined based on estimated kidney growth rates from a theoretical starting htTKV of 150 mL/m and yearly increases of less than 1.5% (subclass 1A), 1.5% to 3% (1B), 3% to 4.5% (1C), 4.5% to 6% (1D), or greater than 6% (1E). Individual patients fit into given subclasses according to their baseline htTKV and htTKV limits for their age. The investigators found that the estimated frequency of kidney failure (ESRD) in the study population increased from subclass A to E (2.4%, 11.0%, 37.8%, 47.1%, 66.9%, respectively) and increased from subclass C to E in the 12-year younger CRISP cohort (2.2%, 14.6%, 22.3%, respectively). Median age at ESRD decreased as well from subclass B to E in the Mayo cohort and from C to E in the CRISP cohort. Risk for ESRD was increased at each progressive subclass in a multivariable Cox model controlling for eGFR at the time of TKV0 (hazard ratio, 1.84; 95% confidence interval, 1.49-2.26; $P < .001$). Despite the requirement of an MRI-based TKV for use of these models, we believe that this study demonstrates a clear potential application of TKV to clinical settings and in identification of clinical trial candidates, with subclasses 1C to 1E being ideal trial or treatment candidates as they are most likely to benefit from therapy.

Table 1. Relationship Between Kidney Volume and ADPKD Complications.[a]

Variable	Number studied	Mean kidney volume (mL) ± SD		*P* value
		With variable	Without variable	
Proteinuria	270	1190 ± 93	578 ± 32	<.0001
Microalbuminuria	49	853 ± 87	535 ± 52	<.01
Hypertension	241	628 ± 48	352 ± 33	<.0001
Gross hematuria	191	820 ± 87	588 ± 52	<.03
Progressive loss of kidney function	220	598 ± 368	366 ± 168	<.0001

[a]Table adapted from Grantham et al.[25]

What About the Association of TKV With Other Complications?

While the predominant characteristic of ADPKD is the development of kidney cysts and subsequent kidney dysfunction, numerous other complications may occur as well.[3] Grantham et al[25] looked at the association between large kidney volume and kidney complications using data from the CRISP study and found that higher TKV is associated with several ADPKD complications, including proteinuria, microalbuminuria, hypertension, gross hematuria, and progressive loss of kidney function, as shown in Table 1. Mean kidney volume in patients with each of these variables was approximately 1.5 to 2 times greater than in similar patients without the complication, indicating TKV may be useful as a measure of disease severity and morbidity in addition to its role as a surrogate of serum creatinine for kidney function. Hemorrhage, for instance, is estimated to occur in approximately 60% of ADPKD patients, due to the increased susceptibility of kidneys to injury, which can lead to gross hematuria or subcutaneous ecchymosis. This not only affects the quality of life but also is associated with accelerated loss of kidney function.[25] Therefore, the association of TKV with complications such as hemorrhage may increase the utility of TKV as a tool for prediction of increased morbidity and more severe disease course.

How Should We Measure TKV?

TKV can be measured in several ways, with techniques utilizing MRI, computed tomography (CT), or ultrasound. Although ADPKD is typically diagnosed using ultrasound,[3,10] ultrasound should not be used for measuring TKV as it does not have sufficient precision to provide accurate measurements, in part due to high intraobsever and interobserver variability and because large kidneys exceed the sweep of the ultrasound probe.[26] Ultrasound kidney length (>16.5 cm) may have a role as opposed to TKV as an alternative predictor for the development of stage 3 CKD, as shown in a recent study.[27] CT and MRI with their greater precision are both options for measuring TKV. CT may be more readily accessible in some centers, but the radiation exposure and use of iodinated contrast in CT favors usage of MRI.[26,28] Most large trials looking at TKV have used MRI as the imaging modality.[1,13,28]

To actually measure TKV, the gold standard method is direct measurement using boundary tracing or stereology—techniques in which area measurements and slice thickness of a series of contiguous images are used to determine the volume of individual kidneys.[12,28] These methods are time-consuming, taking approximately 45 to 55 min to complete.[12,29] Other techniques using magnetic resonance images to estimate TKV have been developed which are meant to be more efficient and practical. The ellipsoid formula [kidney volume = length × width × thickness × (π/6)] is a method to calculate TKV, and requires only 5 to 7 minutes to complete.[12,29] A study comparing ellipsoid formula measurements with stereology measurements in 590 patients with ADPKD found that ellipsoid measurements correlated well with CT/MRI stereology measurements (R^2 = 0.98) without systematic overestimation or underestimation.[8] However, the percentage difference between TKV by stereology versus ellipsoid within the same patient can vary by 20% to 30% in less than 10% of patients. A simple calculator tool has been developed and made available on the Mayo website[30] in which dimensions are entered and the ellipsoid formula calculates TKV. The tool can adjust for height and age as well, and classifies patients into categories that can be used to assess risk of progression to kidney failure.

An additional method is the midslice method, which was developed by the CRISP investigators and involves first determining the midslice magnetic resonance image of each kidney, followed by summing the kidney volume calculated for the left and right kidney halves using a specific formula. This method requires special software and takes 15 minutes to complete.[29] A recent study compared the gold standard manual tracing method to the ellipsoid and midslice methods, and found that both estimation methods (ellipsoid and midslice) performed reasonably well compared to manual tracing in terms of bias, accuracy, precision, and ability to detect changes in estimated TKV.[29] The investigators concluded that the ellipsoid method, with the shortest completion time of the 3 methods, and greater accessibility of use due to the lack of special equipment

required, was the preferred method for calculating TKV in a clinical setting.

Another recently published article describes yet another method developed for measurements of TKV, this time utilizing an automated image processing technique. This study was able to show TKV measurements with comparable accuracy to manual methods of TKV measurement in a study of 20 patients. This method shows promise as an additional measurement tool that is faster and more cost-effective than manual measurements.[31]

Are There Any Patients Who Should Not Have Their TKV Measured?

TKV has been shown to be an appropriate biomarker only in patients with typical presentations of ADPKD, that is, bilateral diffuse distribution of kidney cysts. Patients with atypical presentation such as unilateral, segmental, asymmetric, lopsided, bilateral with unilateral atrophy and bilateral with bilateral atrophy would not be suitable for TKV measurements for risk stratification, as kidney volume has not been shown to predict change in kidney function in these presentations.[24] It has been shown that atypical cyst burden occurs in about 10% of patients, which unfortunately limits the use of TKV for individual patients.[12,24]

How Often Do We Need to Measure TKV?

The appropriate frequency of TKV measurements would depend on the intended use of the information. In everyday clinical practice, the purpose of measurement would likely be to define a patient's risk of progression to kidney failure, with the intention of using this information to determine the patient's suitability for treatment with tolvaptan, for instance, or enrollment in a clinical trial. In this scenario, a 1-time measurement may suffice, with perhaps a repeat measurement every 1 to 2 years if the first is inconclusive. If the purpose is to assess response to a drug treatment, serial measurements will be required and more accurate measurement by stereology or boundary tracing should be used. It has been reported that intervals of 6 months between TKV measurements may be sufficient to determine a more than 50% reduction in volume progression following drug treatment, in patients classified as having rapidly progressive disease (defined as >5% increase TKV per year).[25,32] In terms of practicality, availability of equipment and trained personnel to perform the analytic measurements to accurately assess TKV may be a limiting factor for frequency of TKV measurements in clinical practice. As such, we believe that the current evidence and resource availability do not support frequent measurements of TKV in clinical practice.

Conclusion

ADPKD is a common disease for which a suitable biomarker of progression is necessary due to the nature of the disease course. We believe that the evidence suggests that TKV may be an appropriate surrogate marker for ADPKD disease progression. Future studies comparing different methods of measuring TKV (ie, 3-dimensional ultrasound vs. CT vs. MRI) and the prognostic accuracy of these measures in predicting a meaningful decline in kidney function are needed.

List of Abbreviations

ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; CRISP = Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; CT = computed tomography; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; htTKV = height-adjusted total kidney volume; MRI = magnetic resonance imaging; mTOR = mammalian target of rapamycin; TKV = total kidney volume.

Author Contributions

NT, AA, RP, PM, and YP developed the content of, and presented at the seminar at the annual meeting of the Canadian Society of Nephrology. IH drafted the manuscript. All authors read, edited, and approved the final manuscript.

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