European Journal of Radiology 95 (2017) 56–65

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Systematic Review

Correlations between renal function and the total kidney volume measured on imaging for autosomal dominant polycystic kidney disease: A systematic review and meta-analysis

Woo Ri Jo[a,1], Seong Hee Kim[b,1], Kyung Won Kim[a,*], Chong Hyun Suh[a], Jeong Kon Kim[a], Hyosang Kim[c], Jong Gu Lee[b], Woo Yong Oh[b], Seong Eun Choi[b], Junhee Pyo[d]

[a] Department of Radiology, Asan Image Metrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Clinical Research Division, National Institute of Food and Drug Safety Evaluation, MFDS, Cheong Ju, Republic of Korea
[c] Department of Nephrology, Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[d] WHO Collaborating Center for Pharmaceutical Policy and Regulation, Department of Pharmaceutical Science, Utrecht University, Netherlands

ARTICLE INFO

Keywords:
Total kidney volume
Review
Autosomal dominant polycystic kidney disease
Meta-analysis
Biomarker

ABSTRACT

Purpose: To provide a systematic summary of total kidney volume (TKV) as an imaging biomarker in clinical trials for autosomal dominant polycystic kidney disease (ADPKD), focusing on the correlation between TKV and renal function.

Methods: A computerized literature search was performed using MEDLINE and EMBASE databases for studies that evaluated the correlation between TKV and the glomerular filtration rate (GFR) and between the TKV growth rate and GFR decline rate. A meta-analysis was performed to generate the summary correlation coefficient (r). A qualitative review was performed to evaluate the characteristics of TKV as an imaging biomarker.

Results: Eighteen articles including a total sample size of 2835 patients were retrieved. Meta-analysis revealed substantial correlations between TKV and GFR [r, −0.520; 95% confidence interval (CI), −0.60 to −0.43] and between the TKV growth rate and GFR decline rate [r, −0.320; 95% CI, −0.54 to −0.10]. The quantitative review revealed that baseline TKV can affect the TKV growth rate and GFR decline rate, such that patients with a higher baseline TKV showed faster TKV growth and GFR decline. There was significant variability in image acquisition and analysis methods.

Conclusion: There were significant negative correlations between TKV and GFR as well as between TKV growth and GFR decline rates, suggesting that TKV imaging is a useful biomarker in clinical trials. However, standardization—or at least trial-specific standardization—of image acquisition and analysis techniques is required to use TKV as a reliable biomarker.

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by non-malignant cystic tissue in the kidney and is caused by a hereditary or acquired mutation. ADPKD occurs worldwide and in all ethnicities with a prevalence estimated to be between 1/400 (including observed and estimated autopsy cases) and 1/1000 (clinically diagnosed cases) [1]. Proper diagnosis and management of ADPKD is critical because ADPKD causes structural abnormalities, impairs renal function, and eventually leads to end-stage renal disease (ESRD) in approximately half of the patients [2]. The primary mechanism of renal function impairment is excessive cyst growth, which compresses and replaces the renal parenchyma and ultimately results in renal parenchyma loss within the interstitial fibrosis.

In the last decade, glomerular filtration rate (GFR) and serum creatinine have been the only available biomarkers for treatment response assessment in clinical trials in patients with ADPKD. These serum- or urine-based biomarkers are excellent for evaluating renal function but they cannot detect structural abnormalities. Most of the new therapeutics target the inhibition of cyst growth, which can in turn preserve renal function [3]. Thus, there remains a need to find effective biomarkers that can directly evaluate cyst growth.

Total kidney volume (TKV) measurement has gained popularity as a good mechanism-driven biomarker that can objectively evaluate the

* Corresponding author at: Kyung Won Kim, MD, Department of Radiology, Asan Image, Metrics, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic−ro 43-gil, Songpa−gu, Seoul 138−736, Republic of Korea.
E-mail addresses: kyungwon.kim@amc.seoul.kr, medimash@gmail.com (K.W. Kim).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ejrad.2017.07.023
Received 4 April 2017; Received in revised form 7 July 2017; Accepted 26 July 2017

pathogenic processes or the pharmacologic responses to a therapeutic agent [4]. TKV can be accurately measured using imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography (US). These imaging modalities are readily available in most clinics. An increasing number of clinical trials have adopted imaging studies to measure TKV. Furthermore, TKV was recently approved as a qualified imaging biomarker by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for clinical trials of new drugs for ADPKD [5,6]. Therefore, the use of TKV will be rapidly increasing in both routine practice and clinical trials.

Recently, multiple studies have reported on TKV as a pharmacodynamics biomarker and on the relationship between TKV and renal function in patients with ADPKD [7–24]. However, the results have varied and no systematic review and meta-analysis have been conducted to explore the correlations between TKV and renal function. Hence, we believe that it is timely and critical to establish a systematic summary on the relationship between TKV and renal function in patients with ADPKD. Accordingly, we performed this meta-analysis to provide data on the evidenced-based of TKV in clinical trials and clinical practice.

2. Methods

2.1. Literature search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for accomplishing and reporting this study [25]. A comprehensive search of the PubMed-MEDLINE and EMBASE databases was conducted to identify relevant, original publications concerning the correlation between TKV and estimated renal function in patients with ADPKD.

The following search terms were used: (“autosomal dominant polycystic kidney disease” OR ADPKD OR PKD) AND (“total kidney volume” OR “TKV” OR “kidney volume” OR “renal volume”) AND (“GFR” OR “glomerular filtration rate” OR “clearance”). The use of the terms “autosomal dominant polycystic kidney disease” OR ADPKD OR PKD was intended to specify the patient group. The use of “total kidney volume” OR “TKV” OR “kidney volume” OR “renal volume” was intended to find literature on various imaging modalities for TKV measurement. The use of “GFR” OR “glomerular filtration rate” OR “clearance” was intended to identify works on various types of renal function estimation. No limitations on study dates were used. We searched the literature published prior to February 28th 2017. Our search was restricted to human patients and English-language studies. For the management of literature searches, Endnote version X7 (Thomson Reuters, New York, NY) was used.

2.2. Terminology

TKV is defined as the sum of the volume of the left and right kidneys [5] and is measured by MRI, CT, or US imaging. TKV can be measured by a volume estimation formula based upon an ellipsoid volume equation using three semi-axes on three planes. Alternatively, it can be measured by quantitative volumetry through boundary tracing or by summing the regions of interest on multiple 2D images (i.e., 2D volumetry) or 3D volume measurements (i.e., 3D volumetry). In some studies, an adjusted TKV by body surface area or height was used. In our systematic review, TKV included all types of TKV values, which included those using a volume estimation formula or direct volumetry with/without adjustment.

Renal function is evaluated by the GFR, which is the volume of fluid filtered from the renal glomerular capillaries into the Bowman’s capsule per unit time. Several different techniques are used to measure or estimate GFR. The measured GFR (mGFR) can be calculated by quantifying the clearance of inulin, creatinine, or ^{125}I-iothalamate [7,8,11,12,20]. The estimated GFR can be calculated by the Cockcroft–Gault equation, the Modification of Diet in Renal Disease equation, or the CKD–EPI equation.

In ADPKD patients, GFR usually declines over time, while TKV increases. In our systematic review, the term “GFR decline rate” refers to the speed of the decline in GFR, which was expressed in a slightly different manner in the literature, for example, yearly GFR decline, rate of GFR decline, GFR slope, or GFR change rate. Likewise, the term “TKV growth rate” refers to the rate of increase in TKV over time.

2.3. Inclusion criteria

Studies (or subsets of studies) that investigated the correlation between TKV or the total cyst volume and renal function were eligible for inclusion in the analysis. Studies (or subsets of studies) that satisfied all of the following criteria were included:

(a) Population: studies that included nine or more patients with adult ADPKD who underwent imaging to measure TKV or the total cyst volume;
(b) Reference standard: studies in which the renal function was measured based on GFR or creatinine clearance (CrCl);
(c) Study design: clinical trials and observational studies (i.e., retrospective or prospective);
(d) Outcomes: results were reported in sufficient detail to evaluate the correlation coefficients between TKV and renal function and that between TKV growth rate and GFR decline rate.

2.4. Exclusion criteria

The exclusion criteria included the following:

(a) Case reports and series with sample sizes of less than nine patients and studies with potential selection biases, e.g. non-consecutive series;
(b) Review articles, editorials, letters, comments, and conference proceedings;
(c) Studies on topics other than the correlation between TKV or the total cyst volume and renal function in patients with ADPKD;
(d) Studies with insufficient data for evaluating the correlation coefficient between TKV or total cyst volume and renal function.

2.5. Data extraction

From the selected studies, we extracted the following data into standardized data forms: (a) study characteristics such as authors, year of publication, hospital or medical school, and study design; (b) demographic and clinical characteristics of the patients, namely, age, sex, state of ADPKD, and population size; (c) image acquisition methods of MRI, CT, and ultrasonography and imaging analysis methods to measure TKV; (d) methods to estimate renal function, including indirect GFR estimation and direct GFR measurement using clearance methods; (e) outcomes of the studies, that is, the statistical method and results for investigating the correlation between TKV and renal function at one time point or during the follow-up period. Two reviewers (W.R.J. and S.H.K.) independently extracted the data from the studies and all discrepancies were resolved by consensus with a third reviewer (K.W.K.).

2.6. Quality assessment

The Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were used to estimate the methodological quality of the evaluated studies. The STROBE recommendations include a checklist of 22 items designed to evaluate literature quality. The 22-criteria checklist evaluates three main clinical study designs: cohort, case-control, and cross-sectional. Two reviewers