Published in final edited form as:

Am J Kidney Dis. 2015 January ; 65(1): 41–48. doi:10.1053/j.ajkd.2014.05.017.

Segmental Kidney Volumes Measured by Dynamic Contrast-Enhanced Magnetic Resonance Imaging and Their Association With CKD in Older People

Todd Woodard, PhD¹, Sigurdur Sigurdsson, MS², John D. Gotal, MSEE¹, Alyssa A. Torjesen, BS¹, Lesley A. Inker, MD³, Thor Aspelund, PhD^{2,4}, Gudny Eiriksdottir, PhD², Vilmundur Gudnason, MD^{2,4}, Tamara Harris, MD, MS⁵, Lenore J. Launer, MS, PhD⁵, Andrew S. Levey, MD³, and Gary F. Mitchell, MD¹

¹Cardiovascular Engineering Inc, Norwood, MA ²Icelandic Heart Association, Kopavogur, Iceland ³Tufts Medical Center, Boston, MA ⁴University of Iceland, Reykjavik, Iceland ⁵National Institute on Aging, National Institutes of Health, Bethesda, MD

Abstract

Background—Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a potentially powerful tool for analysis of kidney structure and function. The ability to measure functional and hypofunctional tissues could provide important information in groups at risk for chronic kidney disease (CKD) like the elderly.

Study Design—Observational study with a cross-sectional design.

Setting & Participants—493 volunteers (72–94 years old; 278 women; mean estimated glomerular filtration rate [eGFR], 67±15 ml/min/1.73 m²; 40% with CKD) in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik study.

© 2014 The National Kidney Foundation, Inc. Published by Elsevier Inc. All rights reserved.

Address correspondence to: Gary F. Mitchell, MD, Cardiovascular Engineering, Inc., 1 Edgewater Drive, Suite 201A, Norwood, MA 02062, Phone: 781-788-4900, Fax: 781-788-4901, GaryFMitchell@mindspring.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure:

The other authors declare that they have no other relevant financial interests.

Contributions: Research area and study design: GFM, SS, LJJ, TH, LAI, ASL; data acquisition: GFM, SS, GE, VG; data analysis/interpretation: GFM, TW, SS, JDG, AAT, LAI, ASL, LJJ, TH; statistical analysis: GFM, TW, TA, AAT; supervision or mentorship: GFM, VG, ASL, TH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. GFM takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Supplementary Material

Table S1: Reproducibility of total and segmental volumes.

Figure S1: AGES-Reykjavik MRI study participant recruitment.

Figure S2: Typical signal-time curves for automatically segmented kidney compartments.

Item S1: Methods supplement.

Note: The supplementary material accompanying this article (doi: _____) is available at www.ajkd.org

Predictor—DCE-MRI kidney segmentation data.

Outcomes & Measurements—eGFR, urine albumin-creatinine ratio (ACR), and risk factors for and complications of CKD.

Results—After adjustment for age, sex and height, eGFR was related to kidney volume ($R^2=0.19$; $P<0.001$), cortex volume ($R^2=0.14$; $P<0.001$), medulla volume ($R^2=0.18$; $P<0.001$) and volume percentages of fibrosis ($R^2=0.03$; $P<0.001$) and fat ($R^2=0.01$; $P=0.03$). In similarly adjusted models, log(ACR) was related to kidney volume ($R^2=0.02$; $P<0.001$) and fibrosis volume percentage ($R^2=0.03$; $P<0.001$). Using multivariable regression models adjusted for eGFR, ACR, age, sex, and height, kidney volume was related positively to body mass index ($\beta=29.9\pm 2.1$ ml [SE]; $P<0.001$), smoking ($\beta=19.7\pm 7.7$ ml; $P=0.01$) and diabetes mellitus ($\beta=14.8\pm 7.1$ ml; $P=0.04$) and negatively to hematocrit ($\beta=-4.4\pm 2.1$ ml; $P=0.04$ [model $R^2=0.72$; $P<0.001$]); relations were per 1-SD greater value of the variable. Fibrosis volume percentage was associated positively with body mass index ($\beta=0.28\pm 0.03$; $P<0.001$), cardiac output ($\beta=0.15\pm 0.03$; $P<0.001$), and heart rate ($\beta=0.08\pm 0.03$; $P=0.01$) and negatively with hematocrit ($\beta=-0.07\pm 0.3$; $P=0.02$) and augmentation index ($\beta=-0.06\pm 0.03$; $P=0.04$ [model $R^2=0.49$; $p<0.001$]); again, relations are per 1-SD greater value of the variable.

Limitations—Automatic segmentations were not validated by histology. The limited age range prevented meaningful interpretation of age effects on measured data or the automatic segmentation procedure.

Conclusions—Kidney volume, cortex volume, and hypofunctional volume fraction assessed by DCE-MRI may provide information about CKD risk and prognosis beyond that provided by eGFR and urine ACR.

Keywords

Automatic segmentation; magnetic resonance imaging (MRI); chronic kidney disease (CKD); fibrosis; dynamic contrast enhancement (DCE); kidney imaging; segmental kidney volume; hypofunctional tissue

Kidney function is ascertained using glomerular filtration rate (GFR), while the primary marker for damage is albuminuria. However, GFR is regulated in response to various insults and disease states, and albuminuria is only one of several markers of kidney damage. Pathological abnormalities can provide additional information about the extent of kidney damage but kidney biopsy is invasive and restricted to only a small portion of patients with kidney disease. The detailed structural information about the kidneys provided by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can potentially contribute useful data about both the structure and function of the kidney that is supplementary to GFR and albuminuria.

Kidney imaging has been used for years to diagnose and investigate renal lesions as well as ureteral and vascular abnormalities in the kidneys. Several small studies have also recently examined the possibility of using automated or semi-automated computer analysis to estimate the volumes of the individual kidney compartments.^{1,2,3,4} We developed a method for automatically estimating the volume of cortex, medulla, collecting system, fat, and fibrosis based on the patterns of tissue enhancement caused by the appearance of contrast

following injection of the paramagnetic contrast agent gadopentetate dimeglumine diethylenetriaminepentaacetic acid (Gd-DTPA). This procedure was performed on 3-dimensional (3D) DCE-MRI series acquired in 493 elderly participants in the Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) Study. We then examined relations of the automatic segmentations to risk factors for and consequences of CKD in order to test the hypotheses that 1) kidney structure assessed by DCE-MRI is related to kidney disease as assessed by estimated GFR (eGFR) and urine albumin-creatinine ratio (ACR), and 2) that structural data provided by DCE-MRI, including total and segmental kidney volumes and volume fractions, can provide additional information about risk and complications in CKD beyond eGFR and albuminuria.

Methods

Participants

The rationale and design of the AGES-Reykjavik Study have been presented in detail.⁵ From 2008 through 2011 we conducted a second AGES-Reykjavik examination (AGES-II) in which 3,411 men and women participated in detailed evaluations of cardiovascular, neurocognitive, musculoskeletal and metabolic phenotypes. AGES-II was approved by the National Bioethics Committee in Iceland, which acts as the institutional review board for the Icelandic Heart Association, and by the National Institute on Aging Intramural Institutional Review Board. All participants gave written informed consent.

A random subset of the AGES-II cohort with eGFR >30 ml/min/1.73 m² was recruited to participate in a comprehensive MRI evaluation of aortic and cardiac structure and function. Images were acquired in 602 of the 633 participants initially recruited into the MRI study; these 602 participants represent the base sample for this analysis.⁵ As outlined in Figure S1 (provided as online supplementary material), 493 of the participants had complete, usable data. The final sample consisted of 278 women and 215 men with an age range of 72–94 years.

Laboratory Variables

Tonometry data were acquired with participants supine following 10 minutes of rest. Auscultatory blood pressure was obtained with a semi-automated computer-controlled device. Arterial tonometry and simultaneous electrocardiography were obtained from the brachial, radial, femoral, and carotid arteries with a custom transducer. Augmentation index was computed using the inflection point of the carotid pressure wave-form.⁶ Cardiac output was computed using phase contrast MRI.^{7,8} Glomerular filtration rate was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine–cystatin C equation.⁹

Serum creatinine was measured at the Icelandic Heart Association using the Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay (Roche Diagnostics Corporation, Indianapolis, IN, 46250; CV = 2.5%). Cystatin C was measured at the University of Minnesota using the Dade Behring BN100 nephelometer (Dade Behring Inc, Deerfield, IL 60060, CV = 4.7%). Urine albumin was measured on the ProSpec nephelometric analyzer

(Dade Behring GMBH, Marburg, Germany D-35041; CV = 3.2%). Urine creatinine was measured on the Roche Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN 46250; CV = 4.3% at a concentration of 18.39 mg/dL and 1.5% at a concentration of 96.57 mg/dL). All other laboratory tests were performed at the Icelandic Heart Association laboratory.

Automatic Segmentation

Images were acquired using a 1.5T scanner (Signa Excite, General Electric Medical Systems, Waukesha, WI) and an 8-channel torso phased array coil. The imaging sequence was modeled after Lee, et al.¹⁰ Item S1 provides complete details of the imaging protocol. Raw images were pre-processed in order to reduce the signal nonuniformities caused by radiofrequency inhomogeneity.¹¹ Each 3D image was then automatically registered to a pre-contrast reference image to compensate for breathing and patient movement during the acquisition. Registration was performed on each kidney individually using a rigid voxel-based method utilizing the correlation ratio as a measure of similarity.¹² Finally, a region of interest defined by a single contour surrounding the kidney and immediate hilum was specified by intensity thresholding of the unenhanced kidney images with manual editing of ambiguous regions as needed. Major cysts (diameter >1 cm) were detected as nonenhancing regions and were outlined manually by thresholding during enhancement. This initial image preparation by a trained analyst required approximately 15 minutes per case (2 kidneys).

Templates for tissue-specific signal intensity-time curves were developed iteratively based on manual segmentations of 29 kidneys selected on the basis of image quality and lack of evident pathology from among 40 randomly selected kidneys. For the initial hand segmentations used in template creation, cortex, medulla, and collecting system were identified by thresholding according to timing of contrast enhancement. Fat and fibrosis were defined empirically as tissue with low contrast uptake and persistently high or low signal intensity, respectively.

During automatic segmentation analysis, kidney intensity-time series were temporally aligned with the templates based on the time of arrival of contrast in the abdominal aorta. Signal intensity was normalized by linearly rescaling the 5th and 95th intensity percentiles of the midplane region of the kidney images to the mean of the same percentiles taken over the same region of the template images. Each voxel in the kidney region of interest was classified by comparison with the templates using a combination of mean squared deviation minimization and correlation maximization. A detailed description of the image processing and analysis procedure is available in Item S1.

Statistical Methods

Sample characteristics, hemodynamic and imaging measures were tabulated by sex. Normality of data was assessed by quantile-quantile plots. Non-normal distributions were appropriately transformed as necessary by standard techniques (power and log transformations). Augmentation index was left untransformed because it could not be normalized but had a quantile-quantile R^2 of 0.95 and yielded normal residuals in the multivariable models.

Relations between segmentation results and eGFR and ACR were assessed using linear regression analysis adjusted for age, sex, and height. Further multivariable analyses were performed in order to evaluate the relevance of the segmentations in the context of current understanding of CKD. These consisted of several stepwise multiple regressions with both the current standard tests (eGFR and ACR) and segmentation results considered as dependent variables. All stepwise models were adjusted for age, sex, and height, and were offered the following supplementary explanatory variables: BMI, heart rate, total cholesterol, high-density lipoprotein cholesterol, serum triglycerides, fasting blood glucose, hematocrit, systolic and diastolic blood pressure, cardiac output, and augmentation index. Diabetes mellitus status, treatment for hypertension, treatment for hyperlipidemia, current smoking, and history of cardiovascular disease were offered as categorical explanatory variables. The linear models relating segmentation results to risk factors and complications of CKD were additionally adjusted for eGFR and ACR in order to assess the clinical relevance of the image analysis after accounting for results of typical laboratory tests for kidney function and damage. All multivariable regressions were computed using sex-specific standardized residuals as the independent variables. A two-way ANOVA was used to analyze differences in kidney volume and cortex and medulla volume percentages among groups defined by gender and quartiles of fibrosis volume percentage. A $p < 0.05$ was considered significant for all analyses.

Results

Characteristics of the sample are presented in Table 1. Participants were aged 72–94 (median, 79) years and 56% were women. Mean eGFR was 67 ± 15 ml/min/1.73 m² (34% with eGFR < 60 ml/min/1.73 m²) and median urine ACR was 7.4 (interquartile range, 4.8–13.6) mg/g (10% with ACR > 30 mg/g). A total of 40% of participants had CKD. Consistent with the advanced age of the participants, average systolic blood pressure was in the hypertensive range and more than two thirds of the participants were taking antihypertensive medications.

A typical example of automatic segmentation results is presented in Figure 1, and the segmental signal-time curves for this case are shown in Figure S2. The kidneys were composed predominantly of cortex (light blue) and medulla (dark blue). Fibrosis (green) can be seen along the interface of the cortex and medulla in both kidneys and in the hilum of the left kidney. Collecting system (yellow) and fat (pink) are evident in the hilum, particularly in the left kidney where the imaging plane passes directly through the renal pelvis.

A summary of total and segmental kidney volumes is presented in Table 2. Cortex and medulla accounted for an average of nearly four fifths of the total kidney volume. Men had larger kidneys than women even after indexing to body surface area ($p < 0.001$; Table 2). Men also had a larger fibrosis volume and volume percentage than women ($p < 0.001$ for both; Table 2). The amount of fat within the kidney contour was modest and occupied a similar fraction of the kidney volume in men and women. Fibrosis and fat volume percentages were assessed as a volume fraction of summed kidney volume minus cyst volume. Cysts were detected in 145 participants (29%), and the median cyst volume in these

cases was 21 (interquartile range, 5–66) ml. Reproducibility of the segmental measurements was generally good; details are provided in Item S1 and Table S1.

Figure 2 presents an overview of structural differences in kidneys relative to the amount of fibrosis. Participants were grouped according to sex-specific quartiles of fibrosis volume percentage. A larger fibrosis volume percentage was related to larger total kidney volume ($P<0.001$) and smaller cortical ($P<0.001$) and medullary ($P=0.01$) fractions.

Age-, sex-, and height-adjusted relations of total and segmental volumes with eGFR and ACR are presented in Table 3. Higher total, cortex and medulla volumes were related to greater eGFR, while both of the hypofunctional volume percentages (fibrosis and fat) were associated with lower eGFR. Only total kidney volume and fibrosis volume percentage were (positively) associated with ACR (Table 3). In a multivariable model for eGFR that included total kidney volume and cortex and fibrosis volume percentage, and adjusted for demographics, risk factors, and complications of CKD, both kidney volume and fibrosis volume percentage were simultaneously related to eGFR ($\beta=9.8\pm0.6$ ml/min/ 1.73 m^2 per 1-SD greater kidney volume and $\beta=-3.4\pm0.7$ ml/min/ 1.73 m^2 per 1-SD greater fibrosis volume percentage; $p<0.001$ for both), whereas no association between cortex volume percentage and eGFR was found ($p=0.8$). In an identical adjusted model for ACR, each 1-SD greater kidney volume was associated with a $13\pm5\%$ greater ACR ($p=0.004$) and each 1-SD greater fibrosis volume percentage was associated with a $12\pm5\%$ greater ACR ($p=0.02$) while cortex volume percentage was not significantly associated with ACR ($p=0.3$) when all three were included.

Table 4 further examines the associations of total kidney volume and fibrosis volume percentage with risk factors for and complications of kidney disease. The base models adjust for eGFR and ACR in addition to age, sex and height. Higher BMI was related to larger kidneys and a higher fibrosis volume percentage. Diabetes and current smoking were associated with larger total kidney volume. A moderate negative association was found between hematocrit and both kidney size and fibrosis volume percentage. In addition, greater fibrosis volume percentage was related to higher heart rate and cardiac output and lower wave reflection as assessed by augmentation index.

Discussion

We evaluated an automated method for functional segmentation of the kidney using DCE-MRI in a large, community-based sample of older people. In addition to delineating cortex and medulla, we identified two types of hypofunctional tissue with limited contrast enhancement and either persistently high or low signal intensity, which we identified as fat and fibrosis, respectively. We found strong relations between total and segmental volumes determined by DCE-MRI and measures of kidney function (eGFR) and damage (urine ACR). After adjustment for eGFR and ACR, DCE-MRI measures were persistently related to a number of important risk factors for kidney disease, such as obesity, diabetes, smoking and augmentation index. The DCE-MRI measures were also related to various complications of CKD, such as lower hematocrit, as well as markers of sympathetic excess such as higher resting heart rate and cardiac output. Our findings are supportive of the

hypothesis that structural data provided by DCE-MRI can provide useful information about risk and complications in CKD beyond that provided by eGFR and albuminuria.

While a few studies have examined and attempted to validate the ability of MRI to measure total kidney volume,^{13,14} very little has been done to assess the potential of DCE-MRI to estimate the volume of segmental tissues or their level of functionality. Studies that have used varying degrees of automation have been proposed to segment the kidney into cortex, medulla, and collecting system.^{1,2,3,4} However, none of these studies distinguished between functional and hypofunctional tissues. Importantly, the clinical relevance of computerized segmental measurements was previously unexplored, due largely to the small size of the samples examined in prior studies. Our study is an advance over prior studies in several ways. First, we developed an objective system that automatically segments the kidney tissues. Second, we distinguished normal and hypofunctional tissue, which allowed us to examine associations of hypofunctional tissue with various risk factors for and complications of kidney disease; the resulting associations raise the possibility that the distinction between normal and hypofunctional tissue may be clinically important. Third, by performing the measurements in a large, well-characterized, community-based cohort of older people, we were able to examine the association of key clinical characteristics, including eGFR and ACR, with various segmental kidney volumes. Our findings provide support for the hypothesis that the DCE-MRI approach to automatic analysis of kidney images provides novel and unique information regarding kidney structure and function.

MRI is known to provide an accurate basis for measuring kidney volume by voxel counting, and our results are consistent with previously reported values.¹⁴ We were able to find only one prior study that examined segmental volumes in post-mortem kidneys against which to compare the results of our segmentations.¹⁵ Among the cases presented in that work, only nine were in the same age range as our participants. The mean cortical fractions in our study and in the prior pathology study were comparable (approximately 60%). Our automatic segmentations, however, produced smaller estimates for medulla fraction than the post-mortem analyses (20% vs 27%).

The multivariable models presented in this study help to put the structural and anatomical information provided by the segmentations into context with the current clinical understanding of kidney disease. Persistent association of fibrosis volume percentage with eGFR and ACR after adjustment for body size, risk factors, kidney size and cortical fraction suggests that the relative amount of hypofunctional tissue that we have identified in the kidneys provides novel, potentially clinically relevant information regarding kidney health. The alternative models presented in Table 4 further underscore the potential relevance of structural information provided by kidney size and fibrosis volume percentage within the kidney. The observation that each of these DCE-MRI-derived measures was associated with important correlates of kidney disease, such as BMI, hematocrit and diabetes, separately from relations with eGFR and ACR suggests that DCE-MRI imaging variables provide novel information regarding kidney disease beyond that ascertained by widely used laboratory tests for CKD.

Our analyses indicate that while a larger kidney volume is predictably related to a higher eGFR, it may also be a sign of damage; this possibility is indicated by a positive association of kidney volume with ACR, even after adjustment for sex, BMI and cortical fraction. Furthermore, in the alternative eGFR- and ACR-adjusted model presented in Table 4 (with kidney size taken as the dependent variable), larger kidney volume was associated with a higher BMI, prevalence of current smoking and diabetes, and a lower hematocrit, reinforcing the concept that kidney damage may be associated with enlargement rather than reduction in total kidney volume. These findings agree with the results of a similar study which recently found a positive correlation between both kidney and cortex volume and urine ACR.¹⁶

Along the same lines, we found that a greater volume percentage of fibrosis in the kidney was associated with larger total kidney size and a substantial reduction in cortex volume percentage as well as a modest reduction in medulla volume percentage (Figure 2). This pattern of associations suggests that fibrosis accumulation occurs preferentially within the cortex. In addition, these observations suggest that the process measured by the fibrosis signal in our studies is expansive in nature or that processes that initially expand kidney size, such as obesity, are subsequently associated with replacement of cortex with hypofunctional tissue.

The empirically defined fibrosis signal measured in this study was related to several correlates of kidney disease. The relation of fibrosis volume percentage to higher resting heart rate and cardiac output in a model that includes age, sex, height, BMI, and eGFR may reflect the connection between kidney disease and sympathetic excess.¹⁷ The negative relation between augmentation index and fibrosis volume percentage may seem counterintuitive in light of prior studies showing relations between higher augmentation index and adverse outcomes in patients with advanced kidney disease.¹⁸ However, in contrast to findings in a dialysis cohort, lower augmentation index in our relatively healthy, community-based sample may be a sign of reduced impedance mismatch associated with stiffening of the aorta out of proportion to the muscular arteries.^{19,20,21} Finally, fibrosis was associated with adiposity, suggesting that excess weight is associated with higher levels of both functional and hypofunctional kidney volume.

There are several limitations to our study that should be considered. While the sample is relatively large, it consists entirely of older people. In addition to potential survivor bias, the narrow age range prevents meaningful interpretation of the effects of age on the templates (which are based on sample data), segmentation method, and models presented. Additional studies in a sample with a broad age range will be required in order to address these concerns. Another important limitation of this and other studies of noninvasive *in vivo* segmentation using DCE-MRI is the lack of histological validation of the segmentation results. The cross-sectional analyses presented in this work provide important clinical validation of the template-based segmentation process, but their interpretation assumes that the segmentations are correct. While the clinical correlates of fibrosis volume percentage that we identified are plausible, without histological evidence we cannot be sure whether we are measuring fibrosis or perhaps some surrogate for fibrosis, such as local hypoperfusion or ischemia. Finally, gadolinium-based contrast agents like the one used in this study have been

associated with nephrogenic systemic fibrosis in individuals with low eGFR. As a result, our study was restricted to individuals with eGFR > 30 ml/min/1.73 m² as per guidelines established by the US Food and Drug Administration; no negative side effects related to the contrast media were reported. However, due to the eGFR restriction, it is possible that both CKD and diabetes were slightly underrepresented in our study sample relative to the full AGES-Reykjavik sample.

In addition to the study limitations, there were also several limitations specific to the imaging. Inconsistent signal attenuation due to body size and radiofrequency inhomogeneity caused by the use of multiple phased receiver coils are common issues with MRI imaging. We attempted to account for these concerns by using an established image correction pre-processing strategy,¹¹ rescaling image signal intensities to a common range prior to analysis, and adjusting models for BMI. However, it is still possible that some of the association between fibrosis and BMI is attributable to these effects. Our images were also susceptible to chemical shift artifacts at fat-kidney interfaces.²² These artifacts can sometimes present problems for the segmentation algorithm, as can be seen along the bottom edge of both kidneys in Figure 1, and cause small amounts of contamination of the fibrosis and cortex signals. Finally, the duration of the imaging protocol (5 minutes) was too short to visualize maximal enhancement in the collecting system in some kidneys with reduced function. Since the template matching for collecting system was done with correlation, minor early enhancement was adequate for accurate segmentation in most cases. However, in some cases unenhanced collecting system may have been misclassified as hypofunctional tissue; while this issue was not prevalent, it may contribute to the negative association between fibrosis and eGFR. It is also possible that in some cases small, undetected cysts may have been misclassified as fibrosis.

Nevertheless, our study provides evidence that DCE-MRI may represent a new tool to quantify kidney structure, including fibrosis, in a clinically meaningful way. Fibrosis is an endpoint of virtually all types of kidney disease, and yet there remains no proven non-invasive method for measuring fibrosis and monitoring progression. The clinical correlates of empirically defined fibrosis underscore the potential of this technology to fulfill an important void in the diagnosis and monitoring of kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Support: This work was supported by the National Institutes of Health (NIH; contract N01-AG-12100), the National Institute on Aging Intramural Research Program, Hjartavernd (the Icelandic Heart Association), the Althingi (the Icelandic Parliament), and a grant from the National Heart, Lung and Blood Institute (HL094898). The funders of this study had no role in study design; collection, analysis, or interpretation of data; writing the report; or the decision to submit the report for publication.

Dr Mitchell is owner of Cardiovascular Engineering Inc, a company that develops and manufactures devices to measure vascular stiffness, serves as a consultant to and receives honoraria from Novartis and Merck, and is funded by research grants HL094898, DK082447, HL107385 and HL104184 from the NIH. Dr Woodard, Mr Gotal and Ms Torjesen are employees of Cardiovascular Engineering Inc.

References

1. Chevaillier, B.; Collette, J.; Mandry, D.; Claudon, M.; Pietquin, O. Functional Semi-Automated Segmentation of Renal DCE-MRI Sequences Using a Growing Neural Gas algorithm. In: Zaher, A., editor. Recent Advances in Signal Processing. Rijeka, Croatia: InTech; 2009. p. 69-80.
2. Li S, Zollner F, Merrem A, Peng Y, Roervik J, Lundervold A, et al. Wavelet-based segmentation of renal compartments in DCE-MRI of human kidney: initial results in patients and healthy volunteers. *Comput Med Imaging Graph.* 2012; 36(2):108–118. [PubMed: 21704499]
3. Rusinek H, Boykov Y, Kaur M, Wong S, Bokacheva L, Sajous J, et al. Performance of an automated segmentation algorithm for 3D MR renography. *Magn Reson Med.* 2007; 57(6):1159–1167. [PubMed: 17534915]
4. Zollner F, Sance R, Rogelj P, Ledesma-Carbayo M, Rorvik J, Santos A, et al. Assessment of 3D DCE-MRI of the kidneys using non-rigid image registration and segmentation of voxel time courses. *Comput Med Imaging Graph.* 2009; 33(3):171–181. [PubMed: 19135861]
5. Harris T, Launer L, Eiriksdottir G, Kjartansson O, Jonsson P, Sigurdsson G, et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol.* 2007; 165(9):1076–1087. [PubMed: 17351290]
6. Nichols, W.; O'Rourke, M. McDonald's Blood Flow in Arteries: Theoretical, experimental and clinical principles. 4th ed.. London, UK: Arnold; 1998.
7. Lotz J. Flow measurements in cardiac MRI. *Radiologe.* 2007; 47(4):333–341. [PubMed: 17318470]
8. Srichai M, Lim R, Wong S, Lee V. Cardiovascular applications of phase-contrast MRI. *AJR Am J Roentgenol.* 2009; 192(3):662–675. [PubMed: 19234262]
9. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012; 367(1):20–29. [PubMed: 22762315]
10. Lee V, Rusinek H, Bokacheva L, Huang A, Oesingmann N, Chen Q, et al. Renal function measurements from MR renography and a simplified multicompartmental model. *Am J Physiol Renal Physiol.* 2007; 292(5):F1548–F1559. [PubMed: 17213464]
11. Sled J, Zijdenbos A, Evans A. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging.* 1998; 17(1):87–97. [PubMed: 9617910]
12. Roche A, Pennec X, Malandain G, Ayache N. The Correlation Ratio as a New Similarity Measure for Multimodal Image Registration. *Proceedings MICCAI'98.* 1998; 1496:1115–1124.
13. Bakker J, Olree M, Kaatee R, de Lange E, Beek F. In vitro measurement of kidney size: comparison of ultrasonography and MRI. *Ultrasound Med Biol.* 1998; 24(5):683–688. [PubMed: 9695271]
14. Cheong B, Muthupillai R, Rubin M, Flamm S. Normal values for renal length and volume as measured by magnetic resonance imaging. *Clin J Am Soc Nephrol.* 2007; 2(1):38–45. [PubMed: 17699385]
15. Dunnill M, Halley W. Some Observations on the Quantitative Anatomy of the Kidney. *Journal of Pathology.* 1972; 110(2):113–121. [PubMed: 4125872]
16. Wang D, Liu M, Hao Z, Tao W. Association between reduced kidney function and clinical outcomes after ischaemic stroke with atrial fibrillation. *Eur J Neurol.* 2014; 21(1):160–166. [PubMed: 24237478]
17. Grassi G, Quarti-Trevano F, Seravalle G, Arenare F, Volpe M, Furiani S, et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension.* 2011; 57(4):846–851. [PubMed: 21300663]
18. London G, Blacher J, Pannier B, Guerin A, Marchais S, Safar M. Arterial wave reflections and survival in end-stage renal failure. *Hypertension.* 2001; 38(3):434–438. [PubMed: 11566918]
19. Mitchell G, Parise H, Benjamin E, Larson MG, Keyes M, Vita J, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension.* 2004; 43(6):1239–1245. [PubMed: 15123572]
20. Mitchell G. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol.* 2008; 105(5):1652–1660. [PubMed: 18772322]

21. Vyas M, Izzo J Jr, Lacourciere Y, Arnold J, Dunlap M, Amato J, et al. Augmentation index and central aortic stiffness in middle-aged to elderly individuals. *Am J Hypertens*. 2007; 20(6):642–647. [PubMed: 17531921]
22. Lee, V. Cardiovascular MRI: Physical Principles to Practical Protocols. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

Figure 1. Typical segmented kidneys

(a) One 6 mm slice of a pre-contrast MRI image of the kidneys. **(b)** Results of automatic segmentation of the same slice. Segmented tissues are colored as follows: cortex, light blue; medulla, dark blue; collecting system, yellow; fat, pink; fibrosis, green; none of the above, black.

Figure 2. Kidney remodeling and fibrosis

Total kidney volume and cortex and medulla as a percentage of total kidney volume were evaluated in groups defined according to sex-specific quartiles of fibrosis volume percentage. Refer to Table 3 for the cutoffs used to define fibrosis groups. P-values were computed based on a two-way ANOVA. Error bars represent 95% confidence intervals. Relations between fibrosis group, sex and the interaction were as follows: Total kidney volume: fibrosis group, $P < 0.001$; sex, $P < 0.001$; P for interaction = 0.02. Cortex volume

percentage: fibrosis group, $P<0.001$; sex, $P=0.03$; P for interaction=0.2. Medulla percentage: fibrosis group, $P=0.01$; sex $P<0.001$, P for interaction=0.2.

Table 1

Characteristics of the Sample

Variable	Total (N=493)	Women (n=278)	Men (n=215)
Age (y)	79 ± 4	79 ± 4	79 ± 3
Height (cm)	168 ± 9	162 ± 5	177 ± 6
Weight (kg)	77 ± 14	71 ± 12	84 ± 13
Heart rate (beats per min)	64 ± 10	65 ± 10	62 ± 10
Cardiac output (ml/s)	65 ± 15	60 ± 14	71 ± 14
Augmentation index (%)	9 ± 14	10.8 ± 15.1	6.7 ± 11.9
Blood pressure (mm Hg)			
Systolic	142 ± 20	143 ± 18	141 ± 22
Diastolic	64 ± 10	64 ± 10	65 ± 9
Fasting blood glucose (mg/dL)	99 (92, 104)	97 (92, 104)	101 (94, 106)
Diabetes	44 (9)	22 (8)	22 (10)
Triglycerides (mg/dL)	93 (73, 122)	98 (77, 125)	89 (67, 112)
Cholesterol (mg/dL)			
Total	203 (173, 237)	218 (188, 251)	182 (158, 212)
HDL	60 (49, 72)	67 (55, 76)	52 (45, 64)
Cardiovascular disease	124 (25)	41 (15)	83 (39)
Treated hypertension	356 (72)	210 (76)	146 (68)
Body mass index (kg/m ²)	27.0±4.1	27.3±4.3	26.7±3.9
Obese	105 (21)	67 (24)	38 (18)
Current tobacco use	36 (7)	20 (7)	16 (7)
Hematocrit (%)	41±4	40±3	42±4
eGFR (ml/min/1.73 m ²)	67±15	66±16	68±15
eGFR < 60 ml/min/1.73 m ²	167 (34)	101 (36)	66 (31)
Urine ACR (mg/g)	7.4 (4.8, 13.6)	7.1 (5.0, 10.5)	9.1 (4.8, 18.2)
Urine ACR >30 mg/g	49 (10)	18 (7)	31 (14)
Chronic kidney disease	196 (40)	110 (40)	86 (40)

Note: Values for categorical variables are given as number (percentage); values for normal continuous variables are given as mean ± standard deviation and for non-normal continuous variables as median [interquartile range]. Conversion factors for units: blood glucose in mg/dL to mmol/L, ×0.05551; triglycerides in mg/dL to mmol/L, ×0.01129; cholesterol in mg/dL to mmol/L, ×0.02586.

eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio. HDL, high-density lipoprotein

Table 2

Results of Automatic Segmentation

Variable	Women (n = 278)	Men (n = 215)
Total kidney volume		
Raw (ml)	291 ± 53	394 ± 76
BSA-normalized (ml/1.73 m ²)	287 ± 47	338 ± 56
Segmental volume (ml)		
Cortex	174 (146, 202)	228 (194, 260)
Medulla	59 (49, 70)	67 (56, 85)
Collecting system	23 (17, 28)	27 (20, 35)
Fat	13 (9, 17)	19 (14, 27)
Fibrosis	12 (8, 21)	37 (23, 54)
Cyst	0 (0, 0)	0 (0, 12)
None of the above	0.5 (0.2, 1.4)	0.4 (0.1, 1.1)
Segmental volume percentage (%)		
Cortex	61 (56, 66)	59 (54, 64)
Medulla	20 (17, 23)	17 (15, 22)
Fat	4.4 (3.2, 5.8)	4.8 (3.7, 6.6)
Fibrosis	4.4 (2.9, 7.4)	9.5 (6.5, 12.8)

Note: values for normal continuous variables are given as mean ± standard deviation and for non-normal continuous variables as median [interquartile range]. Volume percentages are expressed relative to non-cyst kidney volume.

Table 3

Associations of total and segmental kidney volume with eGFR and Urine ACR.

Variable	eGFR			Urine ACR		
	$\beta \pm SE$	R ²	p	$\beta \pm SE$	R ²	p
Total kidney volume	7.2 $\pm$ 0.6	0.189	< 0.001	0.158 $\pm$ 0.043	0.024	< 0.001
Cortex volume	5.9 $\pm$ 0.6	0.135	< 0.001	-	-	0.9
Medulla volume	6.6 $\pm$ 0.6	0.177	< 0.001	-	-	0.3
Fibrosis volume percentage	-2.8 $\pm$ 0.7	0.031	< 0.001	0.171 $\pm$ 0.041	0.032	< 0.001
Fat volume percentage	-1.5 $\pm$ 0.7	0.007	0.03	-	-	0.9

Note: Coefficients are presented as the difference in eGFR or ACR (dependent variable) for a 1-standard deviation higher value of the independent variable. Since ACR is log transformed, the coefficients should be interpreted as a percentage difference per 1-standard deviation higher value of the independent variable. All models adjusted for age, sex, and height; R² represents the change in adjusted R² when the variable is added to the multivariable model. Fibrosis and fat volume percentages are based on non-cyst kidney volumes.

eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio (log transformed). SE, standard error

Table 4

Association of risk factors and complications of kidney disease with total kidney volume and fibrosis volume percentage

Variable	Total kidney volume		(Fibrosis volume percentage)	
	$\beta \pm \text{SE}$	p	$\beta \pm \text{SE}$	p
BMI	29.9 ± 2.1	< 0.001	0.28 ± 0.03	< 0.001
Cardiac output	-	-	0.15 ± 0.03	< 0.001
Current smoking	19.7 ± 7.7	0.01	-	-
Heart rate	-	-	0.08 ± 0.03	0.01
Hematocrit	-4.4 ± 2.1	0.03	-0.07 ± 0.03	0.02
Diabetes mellitus	14.8 ± 7.1	0.04	-	-
Augmentation index	-	-	-0.06 ± 0.03	0.04
Model R²	0.72	< 0.001	0.49	< 0.001

Note: Base models adjusted for age, sex, height, estimated glomerular filtration rate, and urine albumin-creatinine ratio. Potential explanatory variables offered stepwise are presented in the Methods. Coefficients are expressed as units of the dependent variable per 1-SD difference of the independent variable. Since fibrosis volume percentage is square root transformed, the effect in actual percentage points $\hat{\beta}$ of changing a single variable by n SDs can be computed from the presented coefficient β using the reverse square-root transformation $\hat{\beta} = (2.22 + \beta n)^2 - 4.93$, where the constants 2.22 and 4.94 (which is 2.22^2) represent the contribution of the constant term in the transformed regression model. For example, the β for BMI is 0.28; thus a 1-SD higher BMI would be associated with $(2.22 + 0.28*1)^2 - 4.94 = 1.3\%$ more of the kidney being occupied by fibrosis.

BMI, body mass index; SD, standard deviation; SE, standard error.