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Renal Adiposity Confounds Quantitative Assessment of Markers of Renal Diffusion with MRI: A Proposed Correction Method

Behzad Ebrahimi, Ph.D.¹, Ahmed Saad, M.B., B.Ch.¹, Kai Jiang, Ph.D.¹, Christopher M. Ferguson, M.S.¹, Hui Tang, M.D.¹, John R. Woollard, M.S.¹, James F. Glockner, M.D., Ph.D.², Stephen C. Textor, M.D.¹, and Lilach O. Lerman, M.D., Ph.D.¹

¹Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

²The Department of Radiology, Mayo Clinic, Rochester, Minnesota

Abstract

Objectives—Recent studies have indicated that excessive fat may confound assessment of diffusion in organs with high fat content, such as the liver and breast. However, the extent of this effect in the kidney, which is not considered a major fat deposition site, remains unclear. This study tested the hypothesis that renal fat may impact DWI parameters, and proposes a three-compartment model (TCM) to circumvent this effect.

Methods—Using computer simulations, we investigated the effect of fat on assessment of apparent diffusion coefficient (ADC), intravoxel incoherent-motion (IVIM) and TCM-derived pure-diffusivity. We also investigated the influence of MR repetition (TR) and echo time (TE) on DWI parameters as a result of variation in the relative contribution of the fat signal. ADC, IVIM and TCM DWI parameters were calculated in domestic pigs fed a high-cholesterol (Obese) or normal diet (Lean), and correlated to renal histology. IVIM-derived pure diffusivity was also compared among fifteen essential hypertension (EH) patients classified by BMI (high vs. normal). Finally, pure diffusivity was calculated and compared in eight patients with atherosclerotic renal artery stenosis (ARAS) and five healthy subjects using IVIM and TCM.

Results—Simulations showed that unaccounted fat results in the underestimation of IVIM-derived pure-diffusivity. The underestimation increases as the fat fraction increases, with higher pace at lower fat contents. The underestimation was larger for shorter TR and longer TE values due to the enhancement of the relative contribution of the fat signal. Moreover, TCM, which incorporates highly diffusion-weighted images ($b > 2500 \text{ s/mm}^2$), could correct for fat-dependent underestimation. Animal studies in Lean and Obese confirmed lower ADC and IVIM pure-diffusivity in Obese vs. Lean pigs with otherwise healthy kidneys, while pure-diffusivity calculated using TCM were not different between the two groups. Similarly, EH patients with high BMI had lower ADC (1.9 vs. $2.1 \times 10^{-3} \text{ mm}^2/\text{s}$) and pure-diffusivity (1.7 vs. $1.9 \times 10^{-3} \text{ mm}^2/\text{s}$) than those with normal BMI. Pure-diffusivity calculated using IVIM was not different between the ARAS and healthy subjects, but TCM revealed significantly lower diffusivity in ARAS.

Conclusions—Excessive renal fat may cause underestimation of renal ADC and IVIM-derived pure-diffusivity, which may hinder detection of renal pathology. Models accounting for fat contribution may help reduce the variability of diffusivity calculated using DWI.

Keywords

Renal adiposity; Diffusion-weighted imaging; intravoxel incoherent motion; obesity

Introduction

Over the past two decades, diffusion-weighted imaging (DWI) has evolved to an important tool for studying neurological disorders (1–3), while application of this method for characterization of abdominal pathological conditions awaited improved hardware and robust pulse sequences over nearly a decade (4). In the kidney, DWI has been used to investigate chronic kidney disease (CKD) (5), renal lesions (6), and deteriorating allografts (7). Nevertheless, the contribution of tubular flow and hemodynamics to the apparent diffusion constant (ADC), the diffusion quantitative index of the single compartment mono-exponential model, complicates tissue characterization and renal DWI analysis (8). This encouraged implementation of models incorporating a larger number of compartments to differentiate pure diffusion from pseudo-diffusive components. Indeed, in the kidney the intra-voxel incoherent motion (IVIM) analytical method, which utilizes a two-compartment model associated with pure diffusion and flow, showed superiority over the mono-exponential decay model (9–11).

However, recent studies on hepatic DWI identified fat as a potential third compartment with a significant confounding effect (12, 13), even in non-steatotic livers (14, 15). Similar outcomes were also observed in other organs (16, 17). Abdominal DWI is typically performed using an echo-planar imaging (EPI) readout, which uses a water-only excitation. Selected excitation or fat suppression methods prevent contribution of the fat signal associated with peaks spectrally distant from water, but cannot effectively eliminate the signal from fat components with resonance frequencies close to water proton frequency. For instance, peaks between 4.2–5.3 ppm associated with triglycerides, which account for nearly 8.7% of the total in vivo fat content, remain unsuppressed (12). Moreover, in the kidney, which is located in the vicinity of bowel, susceptibility artifacts may significantly reduce the efficacy of spectral fat suppression. Because the diffusion constant of lipid molecules is orders of magnitude smaller than that in water and remains nearly unattenuated over the conventional range of b-values, the amplitude of the fat signal, especially at high b-values, can be prominent compared to the attenuated water signal (18), and therefore has a considerable impact on DWI parameters assessment (19).

The epidemic of obesity stresses the importance of characterization of the effect of ectopic fat on DWI parameters, particularly in subjects with high body mass index (BMI). Increased renal adiposity (20, 21) may potentially interfere with interpretation of DWI in the kidney in obese subjects, but to date this effect has not been evaluated. The aim of this study was to explore the effect of renal fat accumulation and suboptimal suppression on DWI parameters. We investigated this effect using computer simulations and verified the error in a large

animal model of obesity, in healthy human subjects, and in the presence of renal pathological conditions in humans. We hypothesized that residual MR signal from fat causes underestimation of renal ADC and IVIM pure-diffusivity, the magnitude of which may approximate a reduction in these parameters elicited by renal pathology. Moreover, we suggest that the fat-dependency of DWI parameters may be corrected by estimating the MR signal of excessive fat using heavily diffusion-weighted images.

Materials and Methods

Assuming that an unattenuated fat signal acts as an independent compartment, we formulated our model by adding a third exponential decay term to the bi-exponential IVIM model to account for the contribution of fat:

$$y = (1 - (C + f))e^{-(D_{fast} b)} + C e^{-(D_{slow} b)} + f e^{-(D_{fat} b)} \quad (1)$$

In our notation, C and f are the tissue (extravascular/extra-tubular) and fat-driven signal fraction in the DWI signal. D_{fast} , D_{slow} , and D_{fat} are diffusion coefficients for the flow-dependent component (pseudo-diffusion), tissue diffusion (pure-diffusivity), and fat, respectively. The product of the fat diffusion coefficient and the b-values over the conventional range of b-values is small, such that the exponential part of the third term can be approximated by one. This simplifies the last term in Equation (1) to a constant signal offset as follows:

$$y = (1 - (C + f))e^{-(D_{fast} b)} + C e^{-(D_{slow} b)} + f \quad (2)$$

Considering that at higher b-values ($> 500 \text{ s/mm}^2$), conventionally used in DWI, the water-component of the signal intensity decays to nearly a small fraction of its value at b_0 ($b=0 \text{ s/mm}^2$), while the fat-related fraction (FRF), f , remains nearly unattenuated over the imaging b-value spectrum, the magnitude of FRF and its impact on calculated DWI parameters becomes significant.

I. Simulations

Simulations in this study pursued two aims. First, to investigate if the calculated ADC and particularly IVIM pure-diffusivity would be influenced by presence of an unaccented fat compartment, as illustrated in equation (1). Second, to examine the effect of MR TR and TE parameters on pure-diffusivity. Generally, the TR and TE-dependency are removed when the MR signal is normalized to the corresponding value in b_0 image, assuming that the T1 and T2 of the first two compartments are close. In the presence of unattenuated fat, with significantly different T1 and T2 values this assumption would not be valid and the choice of TR and TE would influence the FRF.

We simulated the total MR signal using the TCM, including fast and slow decays associated with intra- and extravascular fluid, as well as the FRF signal as a third compartment. Simulations were performed for diffusion parameters similar to DWI values reported for the

kidney (10), over a range of FRFs (0–10%), and TR values (1250, 2500 and 5000ms) (Table 1). Moreover, we simulated DWI signal with long TR (TR=5000ms) to verify the effect of TE (60, 80 and 100ms). Min allowed TE increases as higher b-values are employed, which affects the FRF, based on T2 difference of the fat and water (22). IVIM and TCM were used to extract DWI parameters. In TCM, the total MR signal intensity for all b-values was subtracted by the signal intensity from the corresponding voxel of the high b-value ($>2500 \text{ s/mm}^2$) image, and the data were then fitted to a bi-exponential model. Table 1 shows the values used in the simulations.

II. Animal study

All animal procedures in this study pursued the Care and Use of Laboratory Animals Guideline (National Research Council, National Academy Press, Washington, DC, 1996) and were authorized by the IACUC at Mayo Clinic.

Twenty-two domestic swine in this study were fed ad lib for 16 weeks. Eleven animals consumed a normal diet (Controls), and the other half (Obese) a high fat/carbohydrate diet (5B4L; Purina Test Diet, Richmond, IN) containing (in % kcal) 17% protein, 20% complex carbohydrates, 20% fructose, and 43% fat and supplemented with 2% cholesterol and 0.7% sodium cholate, which induces obesity and adiposity (23).

Diffusion-weighted MRI scans were performed at the completion of diet. Renal volume and hemodynamics were assessed 2–3 days apart from MR scans, using multi-detector computed tomography (MDCT). Anesthesia was induced with the injection of (Telazol 5mg/kg and xylazine 2mg/kg in saline), and then retained with intravenous injection of ketamine (0.2 mg/kg/min) and xylazine (0.03 mg/kg/min) cocktail (during the CT scans), or inhaled 1–2% isoflurane (during the MRI scans) throughout the course of imaging.

Animals were euthanized 2–3 days after the in vivo studies by injecting 10cc of heparin and a lethal intravenous dose of sodium pentobarbital (100 mg/kg). Then the kidneys were removed and immersed in saline containing heparin. The tissue was stored at -80°C or preserved in formalin for histology.

a. Diffusion-weighted Imaging (DWI)—MRI scans were performed on a 3T scanner (GE Medical Systems, Milwaukee, Wisconsin) equipped with a torso array coil. In all animals, 4–6 coronal slices in oblique planes were acquired using a single-shot echo-planar sequence with bipolar gradient. All animals were scanned for b-values 50, 100, 200, 300, 600, 800 and 1000 s/mm^2 . Additionally, a subset of animals (4 Obese and 4 Controls) was scanned for b-values 2000 and 3000 s/mm^2 . MR parameters were as follows: TR/TE 1800/79ms, bandwidth 648Hz/pixel, slice thickness 2.5mm, and matrix size 128×128 . The field of view was 35cm and number of averages was set to 3. All acquisitions were performed during suspended respiration.

b. MDCT imaging—To ensure adequate renal function, renal hemodynamics were assessed from contrast-enhanced MDCT (Somatom Sensation 64; Siemens Medical Solutions, Forchheim, Germany) images, according to the method mentioned in reference (24). A bolus of iopamidol (0.5 ml/kg over 2s) was injected, and 140 consecutive images

were acquired over approximately 3 minutes, followed by an additional contrast injection for the volume assessment. Axial images were acquired at helical acquisition with thickness of 0.6mm and resolution of 512×512, which were reconstructed at 5mm thickness.

c. Lipid Panel—Lipid (total cholesterol, triglyceride, high density lipid (HDL)) was measured (Roche) at the Immunochemical Core Laboratory from blood samples, and low-density lipid (LDL) was calculated.

d. Morphological Studies—Images were acquired using an ApoTome microscope (Carl ZEISS SMT, Oberkochen, Germany). Tubular dilation was measured in Periodic acid-Schiff (PAS)-stained slides counterstained with Hematoxylin. Renal fibrosis was quantified by colorimetric measurements in 5µm slides stained for trichrome (blue), as the % stained surface area. Intracellular lipid accumulation was similarly assessed in colorimetric Oil-Red-O (red) stained slides from frozen tissue counterstained with Hematoxylin.

III. Human study

The study was approved by the Institutional Review Board of the Mayo Clinic, in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA) guidelines. All patients provided written informed consent before enrollment.

Patients were recruited from another on-going study (25). Fifteen patients with essential hypertension (EH) were recruited to investigate the effect of renal fat on DWI parameters. Patients were divided in two groups based on their BMI: an obese group (n=10, BMI 30kg/m²) and a lean group (n=5, BMI 20–25kg/m²). Additionally, diffusion parameters assessments in healthy vs. impaired (post-stenotic) kidneys, with and without fat correction, were compared in eight patients with atherosclerotic renal artery stenosis (ARAS) (25) and five healthy controls.

a. DWI—In patients 3–8 axial images were acquired on 3T scanner (GE Medical Systems, Milwaukee, WI and Siemens Medical Systems, Erlangen, Germany). In EH patients the MR parameters TR/TE, Bandwidth, Slice thickness, and matrix size were set to 2000–2400/60–94ms, 1953 Hz/pixel, 7mm, 128×128 or 160×160, with b-values 100, 300, 600, 900 (s/mm²). In ARAS and Control subjects the TR/TE were 2600–4286/59–112ms. Pure-diffusivity was calculated from b-values about the threshold (300 s/mm²) and fat-related fraction was assessed from images with b-values of either 2000 or 2500 s/mm².

b. Clinical parameters and Lipid Panel—Clinical and laboratory parameters including age, sex, weight, BMI, blood pressure, serum creatinine, estimated glomerular filtration rate (eGFR), and lipid panel levels were evaluated at study entry by standard procedures.

IV. Data analysis

a. DWI—ADC, and IVIM analysis were performed on the EH, ARAS and the corresponding control group, as well as all Obese and Control swine. Additionally, TCM analysis was conducted on the ARAS and the Control as well as the Obese and the Control

swine with high b-values, but not the EH. Pixel-by-pixel maps of quantitative indices of mono-exponential model, ADC, and bi- and tri-exponential models, IVIM and TCM parameters, respectively, were generated, as shown previously (26). The threshold for fast vs. slow components was set to 300s/mm² in both animal and patient studies (27).

Large cortical regions of interest (ROIs) were drawn on b₀ DWI images and transferred to the maps as detailed before (26). Mean values of ADC, IVIM, and TCM DWI parameters were calculated by averaging values in all corresponding ROIs for all slices in the subject.

b. MDCT—Using contrast-enhanced MDCT in animals, single-kidney volume, GFR, perfusion, and renal blood flow (RBF) were calculated. To calculate renal function and hemodynamics, the cortical signal attenuation vs. time curves were fitted to an extended Γ -variate model. Regional blood volume was calculated to estimate cortical perfusion and blood flows (products of perfusion and the corresponding volumes). Finally, GFR was evaluated using the slope of the cortical proximal tubular curve, as previously shown (24), and used as a measure of renal function.

Data Analysis software: All analyses were performed in MATLAB® (MathWork, Natick, MA, USA) and Analyze™ (Biomedical Imaging Resource, Mayo Clinic, MN, USA).

V. Statistical Analysis

Simulation results are shown as mean $\pm$ STD, and in vivo results as Median [First Quartile - Third Quartile]. Minimum sample size was calculated using power analysis for minimum power value of 0.8. Non-parametric Mann-Whitney was used for comparison among groups. For p values <0.05, differences were considered significant.

Results

I. Simulations

In the presence of fat, TCM continued to yield the simulated (true) values, while ADC and IVIM underestimated the diffusion parameters. Figure 1.A shows the ADC, IVIM and TCM-estimated diffusion parameters vs. FRF. Systems with larger pure-diffusivity are prone to greater relative underestimations, and the greatest underestimation rate occurred at low FRFs (Figure 1.B). While in the absence of fat IVIM and TCM yield similar values for pure-diffusivity, independent of TR, in the presence of fat, underestimation in pure-diffusivity and TR related inversely (Figure 1.C). Similarly, when no fat was present, TCM and IVIM calculated pure-diffusivity were independent of TE and close to the true value, however, in the presence of fat with longer T2 than water, underestimation of the pure-diffusivity grow along the TE value (Figure 1.D).

Similar pattern of underestimation was observed in pseudo-diffusion. While the TCM pseudo-diffusion values, regardless of the FRF and TR values, remained within 4% of the true values, the underestimation in IVIM pseudo-diffusion was 11–15% at FRF=5% and 21–30% at FRF=10% with higher underestimations belonging to the shorter TR values. Concordantly, for FRF 5% the TCM pseudo-diffusion values were within 2% of the true value for all TEs, but for FRF=10% and TE=100ms, this parameter showed a significant

deviation (~9%) from the true values. The ration of IVIM pseudo-diffusion to the true value for FRF=10% and TE=60, 80, 100ms were 0.61, 0.57, 0.44, respectively. Variation in tissue and fluid fractions were insignificant.

II. Animal study

At 16 weeks, the Obese swine weighed significantly more than the Controls, and their lipid levels were elevated. The blood volume fraction was higher in the obese (Table 2), but tubular injury scores and trichrome staining, indices of pathological conditions that might change tissue diffusion characteristics, showed no difference in the level of tubular injury, interstitial fibrosis, or glomerulosclerosis. In contrast, Oil-Red-O staining revealed macrovesicular steatosis and significantly greater intracellular lipid content in obese animals (Figure 2). ADC ($p=0.02$) and IVIM pure-diffusivity ($p=0.03$) were lower in the cortex of obese compared to control animals. Pure-diffusivity did not correlate with interstitial fibrosis or tubular injury score, while regression analysis showed a moderate but significant inverse linear and logarithmic correlations between the pure-diffusivity and the intracellular lipid content ($R^2=0.32$, $p=0.013$ and $R^2=0.34$, $p=0.014$, respectively). In contrast to IVIM, TCM analysis showed no difference in pure-diffusivity between the two groups. However, it revealed significantly higher FRF and fluid fraction in Obese pigs, yet the latter did not correlate with the blood volume. Similar to pure-diffusivity, TCM calculated pseudo-diffusion significantly increased over those calculated using IVIM, and was similar between the two groups.

I. Human study

In EH patients, blood pressure, hemodynamic parameters, and GFR were not different between the obese and lean groups (Table 3), but total cholesterol and triglycerides tended to be, and LDL was, significantly higher in Obese compared to control subjects ($p=0.07$, $p=0.07$, and $p=0.03$, respectively). Renal ADC and pure diffusivity were reduced in the Obese compared to the control group ($p=0.001$), whereas other IVIM parameters were statistically not different between them.

Finally, in ARAS patients compared to Normal controls, serum creatinine was significantly higher and GFR lower (Table 4). Despite a similar BMI, FRF was higher in controls compared to ARAS. DWI parameters were calculated from the maps (Figure 3). In IVIM analysis, pure-diffusivity was similar between the two groups. When fat-corrected TCM analysis was performed, pure-diffusivity significantly rose in both groups, yet was lower in ARAS vs. Control (Figure 4).

Discussion

This study shows that renal adiposity confounds calculation of DWI parameters using conventional models, and may lead to underestimation of renal diffusion and pseudo-diffusion, even at low fractions of the fat signal. We introduced a three-compartment model (TCM) that accounts for the fat contribution, and using simulations, a pig model, and in human subjects, showed that this model improves estimation of tissue integrity in obese subjects.

In the kidney, a change in tissue pure-diffusivity has been usually attributed to morphological alterations, particularly interstitial fibrosis and tubular injury (22). However, in this study, the preserved function and absence of signs of tubular injury or interstitial fibrosis in obese pig kidneys, argues against their primary role in the decline in DWI parameters compared to control animals. Taken together with our simulation studies and the correlation between IVIM and renal lipid accumulation, these observations support our hypothesis that DWI parameters in the kidney are sensitive to unsuppressed fat, and that conventional models, which fail to account for fat, may underestimate diffusion markers.

The confounding effect of fat on hepatic DWI parameters has been suggested by several recent studies, demonstrating an inverse correlation of ADC and pure-diffusivity with fat content (13, 15), and its significance emphasized even in non-steatotic livers (14). In contrast to a previously reported study in a fat-water mixed phantom (12), our simulations and in vivo observations suggested that underestimation of renal diffusion coefficients may be significant even at low fractions of the fat signal, and the rate of underestimation decreases until the curve nearly plateaus. Dijkstra et al showed that the correlation of pure-diffusivity and FRF is stronger using a log-linear compared to linear correlation (14), concordant with our observed correlation of this marker and Oil-Red-O. Taken together, these findings support a non-linear relationship between the FRF and pure-diffusivity (28). The importance of this observation stems from the implication that due to the non-linear behavior of pure-diffusivity, notable particularly at low FRF, the confounding effect of fat on underestimation of DWI parameters extends to early stages and to organs with traditionally limited fat deposition, like the kidney. While a reduction in pure-diffusivity has been attributed mainly to interference of free water diffusion in the presence of fat and/or enlarged hepatic cells, our simulations indicated that the inadequacy of the IVIM model alone might cause underestimations in the scale observed in vivo.

The modest correlation of pure-diffusivity with Oil-Red-O implicates sources other than triglycerides alone in this offset signal. Large susceptibility difference in the adjacent tissues and field inhomogeneity in the abdomen are important causes of suboptimal fat suppression. Additionally, the MR signal at the boundaries of the kidneys, surrounded with perirenal fat, is prone to contamination by chemical shift-misregistered fat signal (29). Approaches developed for suppressing the fat signal in DWI included spectral fat suppression methods, which use the chemical shift difference between fat and water to selectively suppress fat, and inversion recovery-based techniques that rely on the difference in T1 relaxation times of fat and water (30, 31). However, it is important to differentiate between fat suppression for qualitative (visual) vs. quantitative purposes. Most of these methods, including hybrid methods, have remarkable performance and significantly reduce the visible fat residual signal (32). However, as we showed with simulations and in vivo, even minor residual fat signal may introduce a meaningful error to quantitative assessments of diffusion parameters. Indeed, regardless of the source of the MR fat-related component, TCM may circumvent the confounding effect.

Moreover, similar to pure-diffusivity, IVIM pseudo-diffusion showed a FRF-dependency. The FRF dependency manifested as lower values compared to TCM-driven values. In animal study, this parameter was similar among Lean and Obese when either IVIM or TCM used.

However, fluid fraction, which was identical among the groups when IVIM model was used, demonstrated significantly higher value in Obese when TCM model was used. Significantly higher blood volume in Obese might have contributed to the difference of the fluid content in the kidneys of the two group, yet lack of correlation with the blood volume suggests that higher pseudo-diffusion in Obese is likely influenced by the volume of tubular fluid as well.

Finally, our simulations suggested that MR TR and TE parameters may affect the DWI assessment (33). In the presence of unsuppressed fat with significantly shorter T1 compared to that of water, longer TR would reduce the FRF signal, which would result in smaller underestimation in IVIM. Moreover, optimal TE selection based on the T2 of the water and fat may reduce the FRF component of DWI signal.

Limitations

Due to intrinsic distortions in EPI images, which in the kidney could be enhanced by the susceptibility issues caused by bowel, co-registration with MR images with enhanced cortico-medullary differentiation is challenging. Therefore, b_0 DWI images were used for cortical ROI selection, which might have introduced a selection error. Yet, this error should be small, as special care was taken to avoid the medulla by confining ROIs to the outer cortex. Moreover, FRF reduction reduces the SNR. Algorithms have been suggested for optimal b-value sampling to enhance the precision in IVIM DWI parameters assessment [25]. Similar approaches may be implemented to minimize the effect of noise in the TCM. Additionally, pseudo-diffusion estimations using Least-squares fitting are not very robust even in IVIM, and lower SNR in TCM further destabilizes estimation of this parameter. Clearly, models such as TCM with higher degrees of freedom can benefit from more powerful regression methods.

As mentioned earlier, the data in human studies were collected from ongoing trials. Since DWI was not the focus of those studies, the full range of b-values was not available in some patients (i.e. EH patients) which prevented us from assessing some of the parameters or performing TCM in those patients. Instead, we have tried to include a comprehensive study in similar pathological model in swine to cover the areas which we could not thoroughly investigate in the human study due to the limitation on the available data.

As simulations demonstrated, the higher the pure-diffusivity, the greater was its underestimation. Although our in vivo results supported this finding, we cannot exclude a possible influence of different b-values used in human and swine studies. The lack of high b-values data in EH patients prevented application of TCM, whereas in ARAS patients we were short on sufficiently low b-values. We also did not have biopsy samples to verify renal adiposity in patients. Alternatively, data from water-fat signal separation methods (e.g. Dixon) could potentially help to further verify sources contributing to fat-related fraction and its correlation with renal fat. Future studies with larger sample sizes and different pathological conditions are needed to validate the TCM.

In conclusion, the fat-related component of MR signal intensity remains unattenuated over a large range of b-values, and can be modeled by adding a constant coefficient to the IVIM model. Signal from components with resonance frequency close to water, imperfect fat

suppression due to field inhomogeneity, and other fat-related sources, may all contribute to offset MR signal. This study further introduces a novel TCM model, which may partly account for the contribution of this excessive fat signal. The error introduced by fat may be comparable to the change in the diffusion marker imposed by pathological conditions. Hence, unless more comprehensive models such as TCM are used, the reliability of DWI might be reduced and the distinction between healthy and diseased kidneys hampered. Considering the epidemic of obesity, this error may be increasingly encountered, and warrants implementation of appropriate correction techniques. Additional studies are needed to confirm these findings and validate the TCM approach in other renal disease models and pathological conditions.

References

1. Rovaris M, Gass A, Bammer R, et al. Diffusion MRI in multiple sclerosis. *Neurology*. 2005; 65(10): 1526–32. [PubMed: 16301477]
2. Zhang Y, Schuff N, Du AT, et al. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain*. 2009; 132(Pt 9):2579–92. [PubMed: 19439421]
3. Ciccarelli O, Catani M, Johansen-Berg H, et al. Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. *Lancet Neurol*. 2008; 7(8):715–27. [PubMed: 18635020]
4. Koh DM, Collins DJ, Orton MR. Intravoxel incoherent motion in body diffusion-weighted MRI: reality and challenges. *AJR Am J Roentgenol*. 2011; 196(6):1351–61. [PubMed: 21606299]
5. Carbone SF, Gaggioli E, Ricci V, et al. Diffusion-weighted magnetic resonance imaging in the evaluation of renal function: a preliminary study. *Radiol Med*. 2007; 112(8):1201–10. [PubMed: 18074195]
6. Goyal A, Sharma R, Bhalla AS, et al. Diffusion-weighted MRI in inflammatory renal lesions: all that glitters is not RCC! *Eur Radiol*. 2013; 23(1):272–9. [PubMed: 22797980]
7. Thoeny HC, De Keyzer F. Diffusion-weighted MR imaging of native and transplanted kidneys. *Radiology*. 2011; 259(1):25–38. [PubMed: 21436095]
8. Zhang JL, Sigmund EE, Chandarana H, et al. Variability of renal apparent diffusion coefficients: limitations of the monoexponential model for diffusion quantification. *Radiology*. 2010; 254(3): 783–92. [PubMed: 20089719]
9. Wittsack HJ, Lanzman RS, Mathys C, et al. Statistical evaluation of diffusion-weighted imaging of the human kidney. *Magn Reson Med*. 2010; 64(2):616–22. [PubMed: 20665805]
10. Chandarana H, Lee VS, Hecht E, et al. Comparison of biexponential and monoexponential model of diffusion weighted imaging in evaluation of renal lesions: preliminary experience. *Invest Radiol*. 2011; 46(5):285–91. [PubMed: 21102345]
11. Schneider MJ, Dietrich O, Ingris M, et al. Intravoxel Incoherent Motion Magnetic Resonance Imaging in Partially Nephrectomized Kidneys. *Invest Radiol*. 2016; 51(5):323–30. [PubMed: 26713966]
12. Hansmann J, Hernando D, Reeder SB. Fat confounds the observed apparent diffusion coefficient in patients with hepatic steatosis. *Magn Reson Med*. 2013; 69(2):545–52. [PubMed: 23161434]
13. Leita HS, Doblas S, d'Assignies G, et al. Fat deposition decreases diffusion parameters at MRI: a study in phantoms and patients with liver steatosis. *Eur Radiol*. 2013; 23(2):461–7. [PubMed: 22935901]
14. Dijkstra H, Handayani A, Kappert P, et al. Clinical implications of non-steatotic hepatic fat fractions on quantitative diffusion-weighted imaging of the liver. *PLoS One*. 2014; 9(2):e87926. [PubMed: 24505333]
15. Bulow R, Mensel B, Meffert P, et al. Diffusion-weighted magnetic resonance imaging for staging liver fibrosis is less reliable in the presence of fat and iron. *Eur Radiol*. 2013; 23(5):1281–7. [PubMed: 23138385]

16. Partridge SC, Singer L, Sun R, et al. Diffusion-weighted MRI: influence of intravoxel fat signal and breast density on breast tumor conspicuity and apparent diffusion coefficient measurements. *Magn Reson Imaging*. 2011; 29(9):1215–21. [PubMed: 21920686]
17. Dieckmeyer M, Ruschke S, Eggers H, et al. ADC Quantification of the Vertebral Bone Marrow Water Component: Removing the Confounding Effect of Residual Fat. *Magn Reson Med*. 2016
18. Luna, A., Ribes, R., Soto, JA. Diffusion MRI outside the brain: a case-based review and clinical applications. Springer Science & Business Media; 2011.
19. Ababneh ZQ, Beloeil H, Berde CB, et al. In vivo lipid diffusion coefficient measurements in rat bone marrow. *Magn Reson Imaging*. 2009; 27(6):859–64. [PubMed: 19167181]
20. Li Z, Woollard JR, Wang S, et al. Increased glomerular filtration rate in early metabolic syndrome is associated with renal adiposity and microvascular proliferation. *Am J Physiol Renal Physiol*. 2011; 301(5):F1078–87. [PubMed: 21775485]
21. Zhang X, Li ZL, Woollard JR, et al. Obesity-metabolic derangement preserves hemodynamics but promotes intrarenal adiposity and macrophage infiltration in swine renovascular disease. *Am J Physiol Renal Physiol*. 2013; 305(3):F265–76. [PubMed: 23657852]
22. Ozhinsky E, Kohi MP, Ghanouni P, Rieke V. T2-based temperature monitoring in abdominal fat during MR-guided focused ultrasound treatment of patients with uterine fibroids. *J Ther Ultrasound*. 2015; 3:15. [PubMed: 26366288]
23. Pawar AS, Zhu XY, Eirin A, et al. Adipose tissue remodeling in a novel domestic porcine model of diet-induced obesity. *Obesity (Silver Spring)*. 2015; 23(2):399–407. [PubMed: 25627626]
24. Daghini E, Primak AN, Chade AR, et al. Assessment of renal hemodynamics and function in pigs with 64-section multidetector CT: comparison with electron-beam CT. *Radiology*. 2007; 243(2):405–12. [PubMed: 17456868]
25. Saad A, Wang W, Herrmann SM, et al. Atherosclerotic renal artery stenosis is associated with elevated cell cycle arrest markers related to reduced renal blood flow and postcontrast hypoxia. *Nephrol Dial Transplant*. 2016; 31(11):1855–63. [PubMed: 27474749]
26. Ebrahimi B, Rihal N, Woollard JR, et al. Assessment of renal artery stenosis using intravoxel incoherent motion diffusion-weighted magnetic resonance imaging analysis. *Invest Radiol*. 2014; 49(10):640–6. [PubMed: 24743589]
27. Ebrahimi B, Textor SC, Lerman LO. Renal relevant radiology: renal functional magnetic resonance imaging. *Clin J Am Soc Nephrol*. 2014; 9(2):395–405. [PubMed: 24370767]
28. Guiu B, Petit JM, Capitan V, et al. Intravoxel incoherent motion diffusion-weighted imaging in nonalcoholic fatty liver disease: a 3.0-T MR study. *Radiology*. 2012; 265(1):96–103. [PubMed: 22843768]
29. Hernando D, Karampinos DC, King KF, et al. Removal of olefinic fat chemical shift artifact in diffusion MRI. *Magn Reson Med*. 2011; 65(3):692–701. [PubMed: 21337402]
30. Bydder G, Steiner R, Blumgart L, et al. MR imaging of the liver using short TI inversion recovery sequences. *Journal of computer assisted tomography*. 1985; 9(6):1084–9. [PubMed: 4056142]
31. Delfaut EM, Beltran J, Johnson G, et al. Fat suppression in MR imaging: techniques and pitfalls. *Radiographics*. 1999; 19(2):373–82. [PubMed: 10194785]
32. Kaldoudi E, Williams SC, Barker GJ, Tofts PS. A chemical shift selective inversion recovery sequence for fat-suppressed MRI: theory and experimental validation. *Magn Reson Imaging*. 1993; 11(3):341–55. [PubMed: 8505868]
33. Schmidt H, Gatidis S, Schwenzer NF, Martirosian P. Impact of measurement parameters on apparent diffusion coefficient quantification in diffusion-weighted-magnetic resonance imaging. *Invest Radiol*. 2015; 50(1):46–56. [PubMed: 25247326]
34. de Bazelaire CM, Duhamel GD, Rofsky NM, Alsop DC. MR imaging relaxation times of abdominal and pelvic tissues measured in vivo at 3.0 T: preliminary results. *Radiology*. 2004; 230(3):652–9. [PubMed: 14990831]

Figure 1.

(A). Simulations showed progressively larger underestimations in ADC and IVIM pure-diffusivity as FRF increased. (B). The rate of underestimation decreased as FRF increased. (C). Pure-diffusivity calculated using IVIM was TR-dependent, since unaccounted fat has a significantly shorter T1 compared to the two other compartments. The bar graph shows normalized pure-diffusivity calculated using IVIM for TR=1250, 2500, and 5000ms (corresponding to I, II, and III, respectively). (D). Similarly, simulations showed IVIM was dependent on the TE as a consequence of longer T2 of fat compared to the tissue. The bar graph depicts normalized pure-diffusivity calculated using IVIM for TE=60, 80, and 100ms (corresponding to I, II, and III, respectively).

Figure 2.

In swine, PAS staining (×40) showed some glomerular hypertrophy and Bowman capsule expansion, but no major tubular injury or dilation (A). Interstitial fibrosis was similar among the groups (B and D) and Oil-Red-O staining revealed lipid vesicles and excessive lipid accumulation (C), which was significantly higher in obese compared to control pig kidneys. Pure-diffusivity moderately but significantly correlated with Oil-Red-O (E).

Figure 3.

Anatomic (A) and normalized DWI maps including pure-diffusivity, pseudo-perfusion, FRF, diffusion and perfusion fractions (B–F), respectively. The fractional volumes have been normalized to the MR intensity at B_0 . Schematic graph showing the major deviation between the TCM and IVIM occurs at high b-values, where FRF is dominant (G).

Figure 4.

Comparison of the pure-diffusivity parameter calculated in ARAS and Control kidneys using IVIM and TCM (A). Diffusivity in healthy and ARAS show no difference when calculated using IVIM. Eliminating the confounding effect of FRF using TCM, renal diffusivity was significantly smaller in ARAS compared to healthy subjects. FRF was significantly higher in the Control compared to ARAS (b).

Table 1

Values used to simulate MR signal in swine and human renal cortex (10, 22, 34).

Diffusion parameters		MR parameters	
$D_{\text{slow}} (\times 10^{-3} \text{ mm}^2/\text{s})$	1.7, 2.5	TR	1250, 2500, 5000 ms
$D_{\text{fast}} (\times 10^{-3} \text{ mm}^2/\text{s})$	17.0	TE	60, 80, 100 ms
$D_{\text{fat}} (\times 10^{-3} \text{ mm}^2/\text{s})$	1.0×10^{-2}	T_1 (water)	1194 ms
Fat Fraction	0–10%	T_2 (water)	56 ms
Fluid Fraction (%)	30%	T_1 (fat)	240 ms
Diffusion Fraction (%)	70% – FRF	T_2 (fat)	150 ms

Table 2

Systemic and diffusion parameters in obese and control pigs after 16 weeks of diet.

	Control	Obese
Body Weight (kg)	66 [64–78]	93 [91–94] *
MAP (mmHg)	104 [93–106]	117 [107–129] *
Lipid Panel		
Cholesterol (mg/dL)	78 [73–84]	466 [411–509] *
LDL (mg/dL)	24 [24–33]	343 [266–433] *
HDL (mg/dL)	43 [39–47]	143 [117–174] *
Triglyceride (mg/dL)	8 [7–10]	10 [8–12]
Hemodynamic Parameters		
Perfusion (mL/gr/min)	4.2 [3.7–5.0]	4.1 [3.7–4.5]
Blood Volume Fraction (%)	36.0 [35.2–37.3]	39.0 [37.1–41.4] *
Normalized GFR (mL/gr/min)	0.69 [0.65–0.73]	0.69 [0.63–0.84]
Mono-exp Model Parameter		
ADC (mm ² /s)	1.45 [1.32–1.51]	1.10 [0.93–1.30] *
IVIM Diffusion Parameters		
D _{slow} (×10 ⁻³ mm ² /s)	1.24 [1.15–1.28]	1.03 [0.80–1.16] *
D _{fast} (×10 ⁻³ mm ² /s)	12.0 [11.5–12.3]	12.0 [11.8–12.2]
Fluid Fraction (%)	35.4 [33.8–38.0]	35.5 [32.1–38.5]
TCM Diffusion Parameters		
D _{slow} (×10 ⁻³ mm ² /s)	2.69 [2.57–2.70]	2.50 [2.45–2.63]
D _{fast} (×10 ⁻³ mm ² /s)	17.9 [17.5–18.7]	17.5 [17.2–17.9]
Fluid Fraction (%)	22.0 [20.2–24.0]	34.2 [22.2–40.1] *
Fat-related fraction (%)	5.7 [5.4–6.1]	7.3 [6.2–8.2] *

Mean arterial pressure (MAP), low density lipid (LDL), high density lipid (HDL), glomerular filtration rate (GFR), Apparent diffusion coefficient (ADC)

*
p<0.05 vs. Control

Table 3

Demographics and DWI parameters in lean and obese hypertensive patients.

	Lean	Obese
Age (years)	63 [39–76]	61 [43–73]
Statin-treated	40%	50%
Number of AHT Medications	2 [2–4]	3 [2–3]
Years since Diagnosis	12 [7–14]	14 [10–35]
BMI (kg/m ²)	23 [23–25]	34 [32–41] *
MAP (mmHg)	119 [109–123]	111 [105–122]
Lipid Panel		
Cholesterol (mg/dL)	180 [164–182]	196 [181–213]
LDL (mg/dL)	81 [80–106]	110 [107–123] *
HDL (mg/dL)	53 [42–61]	45 [41–49]
Triglycerides (mg/dL)	93 [87–143]	144 [97–192]
Hemodynamics		
RBF (mL/min)	297 [285–439]	446 [251–646]
GFR (mL/min)	83 [71–97]	97 [91–122]
Diffusion Parameters		
ADC ($\times 10^{-3}$ mm ² /s)	2.1 [2.1–2.2]	1.9 [1.8–2.0] *
D _{slow} ($\times 10^{-3}$ mm ² /s)	1.9 [1.8–2.0]	1.7 [1.6–1.8] *
D _{fast} ($\times 10^{-3}$ mm ² /s)	8.4 [5.5–9.6]	8.8 [6.3–10.0]
Fluid fraction (%)	0.30 [0.24–0.42]	0.29 [0.23–0.36]

Mean arterial pressure (MAP), low density lipid (LDL), high density lipid (HDL), estimated glomerular filtration rate (GFR), Renal Blood Flow (RBF), Anti-hypertensive (AHT)

*
p<0.05 vs. Control.

Table 4

Clinical and DWI parameters in ARAS and the Control patients.

	ARAS	Control
Age (years)	68 [61–72]	44 [33–68]
Serum Creatinine (mg/dL)	1.6 [1.2–1.7]	0.90 [0.9–0.9] *
eGFR	45 [42–58]	98 [86–100] *
BMI (kg/m ²)	28 [26–31]	25 [23–26]
Diffusion Parameters		
D _{slow} (×10 ⁻³ mm ² /s) (IVIM)	1.5 [1.5–1.6]	1.7 [1.3–1.7]
D _{slow} (×10 ⁻³ mm ² /s) (TCM)	2.1 [2.0–2.3]	2.5 [2.4–2.6] *
Fat-related fraction (%)	4.5 [3.8–5.4]	5.6 [4.6–9.1] *

*
p<0.05 vs. Control