

# Influence of Type 2 Diabetes on Intramyocellular Lipids among Patients with Chronic Kidney Disease

J. Ren<sup>1</sup>, M. Shah<sup>2</sup>, M. Museitiff<sup>2</sup>, L. Roetzer<sup>2</sup>, A. D. Sherry<sup>1,3</sup>, C. R. Malloy<sup>1,2</sup>, and D. Choudhury<sup>2</sup>

<sup>1</sup>Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States, <sup>2</sup>VA North Texas Health Care System,

<sup>3</sup>Department of Chemistry, University of Texas at Dallas, Richardson, Texas

## Introduction

Chronic kidney disease (CKD) and type 2 diabetes are both highly prevalent and complex disorders. Because type 2 diabetes may cause CKD, it is not surprising to find a large number of patients with both type 2 diabetes and CKD. However, CKD also independently causes insulin resistance. Increased intramyocellular lipids (IMCL) have been associated with insulin resistance and diabetes but the role of the compartmental distribution of lipids in normal physiology and disease is still debated (1-5). This study was designed to test the hypothesis that patients with type 2 diabetes and CKD have higher levels of IMCL compared to patients with CKD but without overt type 2 diabetes.

## Methods

CKD patients, all male, with or without T2DM, were recruited from local clinics. Patients who were unable to tolerate 7 T imaging because of an implanted metallic device, claustrophobia, inability to recline, or abdominal girth greater than 50 inches were excluded from study participation. The protocol was approved by the Institutional Review Board. Informed consent was obtained from all participants (n = 20, mean age = 61.1 ± 12.1 yr, BMI 31.2 ± 5.4). Of the CKD patients, 18 had CKD stages 3, 4 or 5. The left calf of each subject was placed on a customized 2-channel T/R partial volume coil with the leg parallel to B<sub>0</sub>. Anatomical T2w images were acquired for voxel placement in the muscle. Localized single voxel <sup>1</sup>H MR spectra were obtained from the soleus muscle using a 7 Tesla Achieva scanner (Philips Medical Systems, Best, The Netherlands) and a STEAM sequence (TR = 2000 ms and TE = 140, NSA = 192) without water-suppression. The voxel (typical size: ~2-5 mL) was chosen at the leanest site to avoid obvious fat tissues, muscle boundary and blood vessels. Spectra were fit with a Voigt lineshape using ACD software. A subset of patient (n = 9) was also scanned with longer TE of 280 ms to further increase IMCL resolution and quantify its content (in mmol/kg wet weight) relative to total creatine, using a previously reported method (6).

## Results and Discussion

Typical images are shown in Figure 1. Shimming was feasible in all patients and was adequate as indicated by the excellent resolution between creatine methyl group (3.02 ppm) and carnitine TMA signal (3.20 ppm) (Fig. 2). Nevertheless IMCL was resolved in only 12/20 patients and IMCL/EMCL could not be adequately resolved in 8/20 cases (Fig. 2a and b). Of these 12 CKD patient with IMCL resolved, 5 were diabetic and 7 non-diabetic; surprisingly, the IMCL level, as measured by intensity of IMCL-CH<sub>2</sub> resonance at 1.5 ppm relative to creatine methyl group (TE = 140 ms), were about the same between the diabetic and non-diabetic subgroups (4.0 ± 0.9 vs 3.4 ± 1.9), and was comparable to the average of healthy subjects scanned in our lab (3.5 ± 1.3, n = 80, BMI = 25.2 ± 5.1). This was supported by the higher resolution data at TE = 280, which showed nearly equal IMCL concentration between the diabetic and non-diabetic subgroups (7.0 ± 4.7 vs 6.8 ± 1.1 mmol/kg ww), and comparable to that of the healthy subjects previously reported (7.7 ± 2.4 mmol/kg ww, n = 25) (6).

The concentration of carnitine, which is responsible for carrying long chain fatty acids into mitochondria for beta-oxidation, was also about the same between diabetic (n = 9) and nondiabetic (n = 8) subgroups (15.4 ± 6.0 vs 13.7 ± 4.0 mmol/kg ww), but they are higher than in a healthy control population (10.0 ± 2.4, n = 80 and age 30.3 ± 9.0 yr).

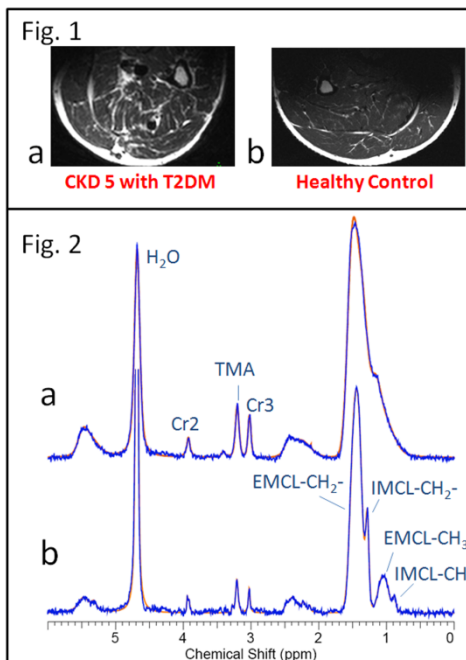
Interestingly, of those 8 CKD patients with unresolved IMCL due to overwhelming EMCL, 7 were diabetic and 1 nondiabetic. This is in parallel to the observation that, of the 12 CKD patients with resolved IMCL, the ratio of EMCL-to-IMCL was found to be significantly higher in diabetic than in non-diabetic subgroup (23.9 ± 6.3 vs 9.9 ± 8.9).

Furthermore, a most typical observation in CKD patients is the striking marbling patterns on the T2w MRI images (Fig. 1), suggesting loss of muscle mass in those CKD and that the possible muscle tissue atrophy was accompanied by EMCL expansion. It appears more severe in diabetic CKD patients, suggesting presence of more disoriented/dispersed fibers. These observations were in line with other research finding that fatty infiltration is commonly seen around or in disused or atrophic organs such as liver and kidney.

## Conclusion

The chemical shift resolution of IMCL vs. EMCL was poor in patients with CKD compared to normal controls. Among patients with adequate chemical shift resolution, IMCL was not significantly different in diabetic vs. nondiabetic CKD patients. However, the chemical shift resolution between IMCL and EMCL was often poor in patients with both CKD and type 2 diabetes.

**References** 1. Machann J et al Diabetes Obes Metab 2004 6:239; 2. Muoio DM, Biochim biophys Acta 2010 180:281; 3. Goodpaster BH et al J Clin Endocrinol Metab 2001 86:5755; 4. Kemalramani G et al Curr Opin Clin Nutr Metab Care 2010 13:382; 5. Krssak M et al Diabetologia 1999 42:113; 6. Ren J et al, MRM 2010 64:662.



**Figure 1.** Calf muscle T2w MRI images showing severe fat infiltration in CKD stage 5 patient (a) as compared to an age-matched healthy control.

**Figure 2.** Typical soleus 7T <sup>1</sup>H MR spectra of CKD patients, showing two different patterns with (b) or without (a) resolved IMCL.