

Diabetic Complications Consortium

Application Title: MR Elastography for Noninvasive Assessment of Fibrosis in Diabetic Kidney Disease

Principal Investigator: Robert S. Brown, MD

1. Project Accomplishments:

As of Sep 15, 2015, we have studied, using an updated protocol of 3 dimensional MR elastography (MRE), 9 healthy volunteers and 21 subjects with diabetes mellitus who had varying degrees of diabetic kidney disease. We had hoped that the imaging would have detected a clear separation of those with diabetic nephropathy from the normal subjects (as an initial pilot study of 5 patients with non-diabetic chronic kidney disease had done). However, there appears to be an association of MRE kidney shear “stiffness” results related to the subjects’ ages, a factor that has been reported for sonoelastography of the kidneys (*Goya et al AJR 2015; 204: 324-329*). This finding will necessitate additional studies in healthy volunteers and diabetic subjects of varying ages to assess and compare. We are also reviewing our results of renal blood flow as determined by MR arterial spin technique to assess how renal perfusion may affect MRE measurements of kidney shear stiffness in normal and diabetic subjects.

2. Specific Aims:

Specific Aim 1 – To determine that kidney shear stiffness as measured noninvasively by MRE correlates with fibrosis graded by kidney biopsy (the gold standard) in patients with diabetic nephropathy:

a. Who have undergone clinically indicated kidney biopsies graded for degree of fibrosis by blinded histopathology. MRE results in subjects with diabetes will be compared with non-diabetic subjects with normal estimated glomerular filtration rate (eGFR) of similar age, gender, and race

Results: Our goal was to study 10 subjects with kidney biopsies having diabetic nephropathy, but since so few patients with diabetes undergo kidney biopsies, we have only studied 2 thus far. No results are yet available for this aim.

b. Results will be correlated with simultaneous measurements of renal blood flow by MR techniques (including arterial spin labeling (ASL) and phase contrast imaging) and with creatinine and/or cystatin C based eGFR to assess hemodynamic and functional variables

Results: Same as above.

Specific Aim 2 – To determine whether MRE measured shear stiffness is associated with eGFR in patients with diabetic kidney disease with reduced eGFR who have not undergone kidney biopsies:

a. Who have CKD Stages 2, 3, 4, and 5 as determined by creatinine-based eGFR levels to correlate whether MRE shear stiffness can serve as a noninvasive surrogate marker for kidney fibrosis

Results: First, to validate the updated 3D MRE protocol for the kidney in normal subjects, our goal was to study 10 healthy volunteers. To date, we have completed 9 subjects. Our findings have become complicated by the following unexpected results: (1) several healthy volunteers have surprisingly low eGFRs despite no indication of prior kidney disease, and (2), there appears to be a significant correlation of MRE shear stiffness with age. This will require additional healthy volunteer subjects of various ages to resolve this matter and we plan to do that after submitting an amendment to the IRB.

In patients with diabetic nephropathy, we have studied the following:

- a. CKD stage II (Kidney damage with mild decrease in eGFR 60-89 ml/min/1.73 m²) - We have completed 3 subjects in this category.
- b. CKD stage III (Moderate decrease in eGFR 30-59 ml/min/1.73 m²) - We have completed 8 subjects in this category.
- c. CKD stage IV (Severe decrease in eGFR 15-29 ml/min/1.73 m²) - We have completed 5 subjects in this category (though one with incomplete data).
- d. CKD stage V (ESRD with eGFR < 14 ml/min/1.73 m²) - We have completed 0 subjects in this category.

Comparing these 16 patients with diabetic nephropathy with the 9 healthy volunteers has not shown significant results differentiating them to date. This may be due to the variation that we have found to be associated with the subject's age and/or the unexpectedly low eGFR in some of our healthy volunteers. We are now also analyzing renal blood flow measured by MR to see if kidney "stiffness" may be affected or correlate with renal blood flow rates. In addition, we plan to adjust our analysis for BMI and kidney depth in the future as these factors have been found to be predictors of stiffness using ultrasound elastography recently (*Samir et al. BMC Nephrology (2015) 16:119 DOI 10.1186/s12882-015-0120-7*).

Specific Aim 3 – To determine whether MRE measured shear stiffness is abnormal and can detect early diabetic kidney fibrosis in diabetic patients with hyperfiltration and/or microalbuminuria prior to reductions in eGFR:

- a. Who have microalbuminuria and normal eGFR to assess whether differences in MRE shear stiffness may detect preclinical diabetic nephropathy
- b. Who have glomerular hyperfiltration as determined by increased creatinine and cystatin C based eGFR to assess whether differences in MRE shear stiffness may detect preclinical kidney fibrosis since increased glomerular filtration may be a forerunner of diabetic nephropathy

Results: So far, we have studied one diabetic subject with microalbuminuria and a normal eGFR and two diabetic subjects with eGFRs greater than 90 ml/min/1.73 m² (with another scheduled). We will need additional subjects in these categories to analyze our findings.

2. Publications:

None.