NON-INVASIVE IDENTIFICATION OF BIOMARKERS FOR CHRONIC LIVER COMPLICATIONS OF DIABETES MELLITUS USING CHEMICAL SHIFT AND IVIM-DWI IMAGING

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Purpose

Diabetes Mellitus has a high prevalence which, according to the World Health Organization, affects more than 300 million people worldwide and appears as an important cause of morbidity and death in many countries of the western world. It has a multi-systemic scope and its chronic complications include retinopathy, neuropathy, cardiovascular disease and non-alcoholic fatty liver disease (NAFLD) [1]. NAFLD comprises a wide range of pathologies of increasing severity which can go from simple liver fat accumulation (steatosis) to non-alcoholic steato-hepatitis (NASH), fibrosis and cirrhosis. The identification and staging of these different phases, which is important to evaluate the risk of hepatocellular carcinoma development, is often made with biopsy. However, the latter procedure is prone to the development of complications and it is inherently associated with a sampling error. Recently, several studies using either multi-echo gradient-echo (ME-GRE) [2] or intra-voxel incoherent-motion (IVIM) imaging [3] have been respectively used to non-invasively probe the liver for fat content or to calculate diffusion parameters sensitive to the degree of tissue change. In this work, ME-GRE and IVIM imaging are applied to non-invasively identify biomarkers of NAFLD in the context of liver complications associated with Type II Diabetes Mellitus.

Methods

In this study, 32 patients (20 females, mean age 60±8) and 37 controls (23 females, mean age 49±7) were enrolled and gave written informed consent. The patient group consisted of men and women with type II diabetes, diagnosed at least 1 year prior, age 40-74 years. The control group was age matched and without history of neuropsychiatric, renal, liver, heart, ocular or any other severe non-age disease, not related to diabetes.

Magnetic resonance liver imaging was performed on a whole body 3T imaging system (Magnetom Trio Tim, Siemens Medical Solutions, Erlangen, Germany) using a 4-channel or a 16-channel body coil. Respiratory triggered IVIM imaging was acquired using conventional SE-EPI with acquisition parameters: FOV=400×400 mm, 3.12×3.12 mm in-plane resolution, 1 slice 10 mm thick, TR/TE=3800/67 ms, parallel imaging factor 2, 5 or 3 averages using the 4- or 16-channel coil respectively, 16 b-values (0, 5, 10, 15, 20, 25, 30, 35, 40, 50, 70, 90, 100, 200, 400, 800). ME-GRE imaging was acquired in breath-hold on the same slice with TR/TE=30/2.46, 3.69, 4.92, 6.15, 7.38, 8.61, 9.84, 11.07, 12.3, 13.53, 14.76, 15.99 ms, 2.08×2.08 mm in-plane resolution, parallel imaging factor 2, 5 averages. Liver fat fraction (*FF*) and *T2** relaxation values, assuming that $T2^*_{water} = T2^*_{water}$, were computed according to [2] and the true diffusion coefficient (*D*), diffusion due to perfusion (*D**), and fraction of perfusion (*fp*) were computed according to [3]. The calculations were obtained from regions-of-interest (ROIs), which in the case of the IVIM data, were positioned on the inferior right lobe of the liver avoiding blood vessels and contained on average approximately 10 voxels. In the case of the ME-GRE data, the ROI was defined in approximately the same position, but it contained a larger area of liver parenchyma. Eight controls and 5 patients were excluded from IVIM parameter analysis due to image artifacts or poor image SNR. Data was analyzed using software developed in-house and implemented in Matlab (Mathworks, Natick, Mass).

Results

Figure 1 shows a scatterplot of the estimations of *FF* for patients and controls. It shows that patients consistently have a local liver fat content which is higher than that of controls. In the course of the analysis, 2 controls were found to have a *FF* value larger than 10% and were therefore excluded from further analysis.

Figure 2 shows a typical fit of IVIM data in order to estimate *D*, *D** and *fp*, for one of the controls. Table 1 contains an overview of the results regarding IVIM parameter estimation that were obtained for both patients and controls. When comparing patients and controls, it can be seen that the difference in *D*, *D** and *fp* are only very small, with the parameters of the patients being slightly inferior to those of the controls. However, the *D* and *D** parameters of the (10) steatotic patients were significantly smaller than those of controls (p=0.05), while *fp* was slightly higher but without statistical significance.

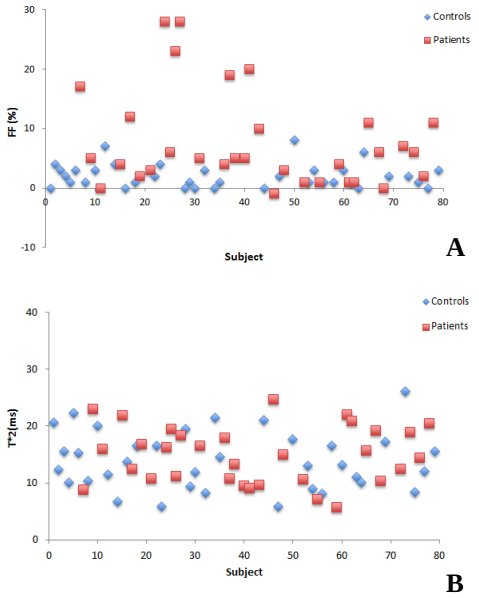

Figure 1. A) Fat fraction estimations b) T2* estimations

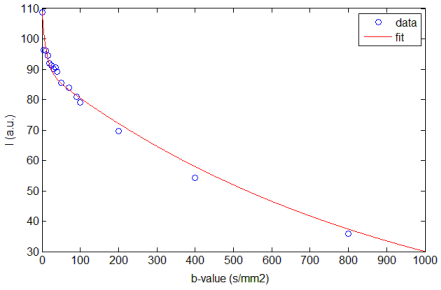

Figure 2. A) Typical example of IVIM data fit. D=1.15 and D*=79 ($\times 10^{-3}$ mm^2/s), fp=0.21

Discussion

The use of ME-GRE imaging quantified, in a non-invasive way, the local liver *FF* and allowed a clear differentiation of patients and controls, as 10 out of 32 patients had more than 10% local *FF*. As for the *T2** relaxation time, no difference was found between patients and controls, which is in agreement with the fact that these patients are not yet expected to have disturbances in iron kinetics.

The use of IVIM imaging with calculation of parameters *D*, *D** and *fp* also revealed to be sensitive to the presence/absence of pathology. Here, although there was no appreciable difference between controls and patients, the distinction became clear when comparing controls and steatotic patients. The *D* and *D** values of the latter were significantly lower than those of controls, thus in agreement with the recent findings of the study in [4].

Conclusions

The combined use of ME-GRE and IVIM imaging are sensitive to the hepatic complications of type II Diabetes Mellitus. They have thus the potential to provide biomarkers susceptible to non-invasively stage the complications associated with disease progression. This will ultimately improve both prognosis and therapeutics.

References

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	D($\times 10^{-3}$ mm^2/s)	D*($\times 10^{-3}$ mm^2/s)	fp
Controls	1.22±0.27	66±28	0.27±0.08
Patients	1.17±0.27	65±24	0.26±0.09
Patients with steatosis (N=10)	1.04±0.13	54±10	0.29±0.10

Table 1. IVIM parameter estimation