The role of IVIM and Chemical Shift imaging in detecting early hepatic complications of Diabetes Mellitus Type 2

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Target audience: Clinicians, Basic scientists

Purpose

Diabetes Mellitus Type 2 (DM 2) has a high prevalence 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 progressive forms of the disease such as non-alcoholic steato-hepatitis (NASH), fibrosis and cirrhosis. If the link between vision, neurological, cardiac complications and DM 2 has been clearly established, the association between DM 2 and NAFLD has been more recently recognized. There is however evidence that patients with NAFLD who have DM 2 are at a higher risk of developing the progressive forms of NAFLD. For that reason, identification and staging of these different phases in the context of DM 2 is important to evaluate the risk of hepatocellular carcinoma development in this group of patients. In this work, ME-GRE (multi-echo gradient-echo) [2] and IVIM (intra-voxel incoherent-motion) [3] imaging are applied to non-invasively identify staging biomarkers of NAFLD associated with Type II Diabetes Mellitus.

Methods

In this study, 57 patients (28 females, mean age 60±8) and 69 controls (37 females, mean age 50±8) 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.

Magnetic resonance liver imaging was performed on a whole body 3T imaging system (Magnetom Trio Tim, Siemens Medical Solutions, Erlangen, Germany) using a 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, 3 averages, 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] (fig. 1), the true diffusion coefficient (*D*), diffusion due to perfusion (*D**), and fraction of perfusion (*fp*) were computed according to [3] (fig. 2) and the perfusion rate was calculated as $pr = D^* \times fp$. Parameter values were obtained on a voxel-by-voxel basis and average values for the whole liver were calculated and compared between groups of subjects. Data was analyzed using software developed in-house and implemented in Matlab (Mathworks, Natick, Mass).

Results

Table 1. shows how liver *FF* (averaged over the whole liver) varies in the population. It shows that most of controls have a value for *FF* below 10% and are furthermore dominant in the 0-10% FF range. In the patient group, although most subjects belong to the 0-10% *FF* range, they are dominant in the 10-20% and 20-40% ranges. Results show that the mean *FF* in patients (9%) is significantly smaller than the mean *FF* in controls (5.75%), p=0.05. No significant differences were found between the mean T2* values of patients (18 ms) and controls (20 ms). The comparison between IVIM parameters for controls and patients show that only the values of *D* and *fp* are significantly different, D=1.27(1.09)×10^{-3} mm^2/s, *fp*=0.34(0.30) for controls(patients), p=0.05. Diffusion parameters depend on the nature of the extra-cellular environment and for that reason, the presence of large fat molecules in the liver should influence these [4]. For that reason, a more detailed analysis of IVIM parameters was carried-out to take into consideration the FF range and the subject category (Table 2) for those subjects where both IVIM and ME-GRE was available. For patients with FF<10%, the values of *D* and *fp* are significantly lower than those of controls with FF<10% whereas for patients with FF≥10%, all parameters are significantly lower than those of controls, p= 0.05 (Table 2). Within each subject category, only D appears to be significantly lower for subjects where FF≥10%, when compared to those where FF<10%. Nevertheless, all parameters show a tendency to decrease with increasing FF. Furthermore, IVIM parameters tend to be lower in patients, when compared to controls.

Discussion

The use of ME-GRE imaging quantified, in a non-invasive way, the *FF* distribution in the liver and allowed a clear differentiation of patients and controls, based on the population distribution of the average liver FF amongst different ranges, furthermore compared by the significant difference between the average FF values of both populations. 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. IVIM imaging parameters (*D*, *D**, *fp and pr)* also revealed to be sensitive to early pathology (progression). Here, although there was no appreciable difference between controls and patients, the distinction became clear when comparing controls without steatosis and patients with steatosis. *D* and *D** values of the latter were significantly lower than those of controls [4], but so were the values of *fp* and *pr*. Even within each subject group, these parameters showed a variation tendency: all parameters, including *fp* and *pr*, tend to decrease with increasing FF and tend to be lower in patients than in controls.

Conclusions

The combined use of ME-GRE and IVIM imaging is sensitive to the (early) hepatic complications of DM 2. It has the potential to provide biomarkers to non-invasively stage (the progression of) NAFLD in the context of DM 2.

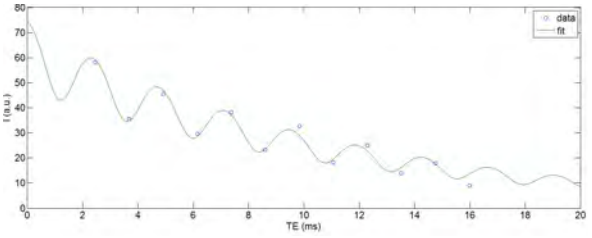

Figure 1. Example of FF quantification data fit. FF=18%, T2*=11 ms

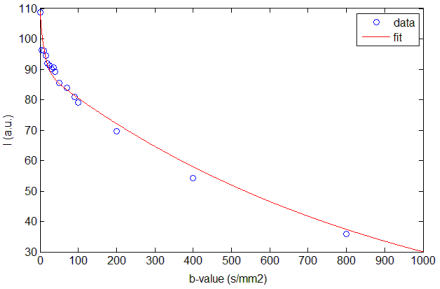

Figure 2. Typical example of IVIM data fit. D=1.15 and D*=79 (×10^{-3} mm^2/s), fp=0.21

			Subject classification		
			Control	Patient	Total
Fat fraction range	0-10 %	Count	59	40	99
		% within Fat fraction range	59.6%	40.4%	100.0%
	10-20%	Count	7	10	17
		% within Fat fraction range	41.2%	58.8%	100.0%
	20-40%	Count	3	7	10
		% within Fat fraction range	30.0%	70.0%	100.0%
Total		Count	69	57	126
		% within Fat fraction range	54.8%	45.2%	100.0%

Table 1. FF population distribution

	N	D (×$10^{-3}$$mm^2/s$)	D* (×10^{-3} mm^2/s)	Fp	pr (×10^{-3} mm^2/s)
Controls (FF<10%)	49	1.31*	111*	0.35*	0.045*
Controls (FF≥10%)	8	1.02*	102	0.32	0.042
Patients (FF<10%)	36	1.16*	105	0.29*	0.040
Patients (FF≥10%)	18	0.97*	95*	0.29*	0.037*

Table 2. In each column the symbol * indicates values that are significantly different from at least one other value in the column, for p=0.05. See text for further details

References

[1] Neuschwander-Tetri et al., Hepatology, 37(5), 1202-1219, 2003;[2] O'Reegan et al., Radiology, 247(2), 550-557, 2008; [3] Luciani et al., Radiology, 249 (3), 891-899, 2008; [4] Guiu et al., Radiology, 265, 96-103, 2012

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