The effect of intravenous gadoxetic acid disodium (Gd-EOB-DTPA) on diffusion-weighted imaging (DWI) of normal upper abdominal tissues at 1.5 Tesla.

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**Aims and objectives**

Quantitative Gd-EOB-DTPA uptake and apparent diffusion coefficient (ADC) measurements are both used for the functional assessment of diffuse liver disease. Studies show that decreases in ADC values in diffuse liver disease correlate with the grade of liver fibrosis (Taouli et al. (2009)). Similarly lower enhancement after Gd-EOB-DTPA occurs with diffuse liver disease (Kyung et al. (2012)).

Previous studies have demonstrated that Gd-EOB-DTPA had no significant effect on the calculated ADC values for focal liver lesions (Muhi et al (2012), Choi et al. (2010) and Kim et al. (2009)). However no studies have systematically analyzed the effects of Gd-EOB-DTPA on liver parenchymal water diffusivity. Thus the purpose of this study was to evaluate the effects of Gd-EOB-DTPA on ADC values in normal liver parenchyma and other normal upper abdominal tissues.
Methods and materials

Data acquisition:

65 patients underwent abdominal MRI at 1.5T before after intravenous Gd-EOB-DTPA. Patients were identified via a prospectively maintained database. All examinations were undertaken for the detection and characterization of focal liver lesions observed on other imaging modalities.

All patients were examined with a 1.5 T MRI (Avanto, Siemens Healthcare, Erlangen, Germany). Non breath-hold routine liver MRI sequences (T1W (ip/op), T2W (moderate and heavy T2-weighting) with and without FS) were acquired with body matrix and spine coils.

EPI diffusion sequences using 3 scan trace technique, b-values of 0, 100, 250, 500 & 750 s/mm$^2$ were used (spectral fat suppression; 5 mm slices; matrix 128 x 128; FOV = 35 cm; TR 5800; TE 74; FA 90°) were performed before and 12 minutes after Gd-EOB-DTPA.

Gd-EOB-DTPA was injected as an IV bolus according to manufacturer recommendations at a dose of 0.1 mol/kg bw.

Data analysis:

All ADC maps were calculated by MRI vendor software with mono-exponential fitting. $\text{ADC}_{\text{total}}$ (using all b-values (b0-b750)) and $\text{ADC}_{\text{high}}$ (b-values>100 s/mm$^2$) were generated. Unenhanced and enhanced b500 images from both datasets were selected and linked with respective ADC maps.

Regions of interest (ROIs) were drawn synchronously allowing the ROIs to be comparable between the unenhanced and enhanced images. ROIs were measured from 2 segments of normal liver parenchyma preferably in the right lobe (2 ROIs; segments 6 & 7).

Normality of liver signal was assessed by an oncologically trained radiologist of >15 years experience (hyperintense T1-weighted liver parenchyma compared to spleen and
Further ROIs were placed in the posterior renal cortices bilaterally (2 ROIs), spleen, L4 vertebral body bone marrow.

As large as possible ROIs were drawn allowing for artefacts in each organ. For each ROIs the area (cm$^2$), mean SI (arbitrary units; AU), standard deviation SI (AU), mean and standard deviation of ADC$_{total}$ and ADC$_{high}$ ($\mu m^2/s$) values were recorded.

For the normalising tissue signal ROIs were placed on the psoas muscle adjacent to the L4/L5 vertebral body. Noise levels were also assessed by placing the ROIs on the background signal within air, adjacent to the body in the lateral aspect away from phase encoding artefacts.

Muscle normalized b500 signal intensity (nSI) values and signal to noise ratios (SNR) were calculated.

Statistical analysis:

Descriptive statistics, box-whisker and spread plots were used to evaluate the data. Non-parametric Wilcoxon-Signed Ranks test was used to assess the statistical significance of changes in ADC (total and high), SNR and nSI values between the unenhanced and enhanced images. A p<0.05 was considered statistically significant. StatsDirect and Medcalc software were used.
Results

$\text{ADC}_{\text{total}}$ & $\text{ADC}_{\text{high}}$ for normal liver on enhanced images were significantly lower after Gd-EOB-DTPA (mean difference: -20 & -43 $\mu$m$^2$/s respectively; $p<0.007$ & $p<0.0001$). There were no ADC differences for the remaining organs (Tables 1 and 2; Figure 1).

Enhanced normalized b500 SI values of liver were significantly lower (-0.23 AU; $p<0.001$) after Gd-EOB-DTPA. However, the nSI of the spleen and kidneys, were significantly higher (+0.28 & +0.13 AU respectively; $p<0.0006$ & $p<0.0001$). However for the bone marrow, the b500 nSI difference was insignificant (Table 3; Figure 2).

Enhanced SNR of the liver was also significantly lower (-10; $p<0.0001$) but not significantly different in the remaining organs (Table 4; Figure 3).
Table 1: ADCtotal mean values pre vs. post Gd-EOB-DTPA

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<table>
<thead>
<tr>
<th>ADCtotal (µm²/s)</th>
<th>Unenhanced</th>
<th>Enhanced</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1324 ± 135</td>
<td>1344 ± 135</td>
<td>0.0070</td>
</tr>
<tr>
<td>Kidneys</td>
<td>2031 ± 111</td>
<td>2034 ± 95</td>
<td>0.82</td>
</tr>
<tr>
<td>Spleen</td>
<td>975 ± 226</td>
<td>961 ± 225</td>
<td>0.09</td>
</tr>
<tr>
<td>Muscle</td>
<td>1277 ± 138</td>
<td>1277 ± 145</td>
<td>0.71</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>559 ± 133</td>
<td>579 ± 169</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Table 2: ADChigh mean values pre vs. post Gd-EOB-DTPA

<table>
<thead>
<tr>
<th>ADChigh (µm²/s)</th>
<th>Unenhanced</th>
<th>Enhanced</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1075 ± 137</td>
<td>1032 ± 137</td>
<td>0.0001</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1890 ± 111</td>
<td>1891 ± 106</td>
<td>0.87</td>
</tr>
<tr>
<td>Spleen</td>
<td>885 ± 191</td>
<td>883 ± 188</td>
<td>0.79</td>
</tr>
<tr>
<td>Muscle</td>
<td>1151 ± 173</td>
<td>1146 ± 186</td>
<td>0.49</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>509 ± 126</td>
<td>519 ± 159</td>
<td>0.81</td>
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</tbody>
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**Fig. 1:** Box-whisker and spread plots of ADChigh pre and post Gd-EOB-DTPA in various tissue types

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Table 3: nSI mean values pre vs. post Gd-EOB-DTPA

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Fig. 2: Box-whisker and spread plots of nSI pre and post Gd-EOB-DTPA in various tissue types

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Table 4: SNR mean values pre vs. post Gd-EOB-DTPA

<table>
<thead>
<tr>
<th></th>
<th>Unenhanced</th>
<th>Enhanced</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>57 ± 25</td>
<td>47 ± 20</td>
<td>0.0001</td>
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<tr>
<td>Kidneys</td>
<td>114 ± 49</td>
<td>114 ± 49</td>
<td>0.86</td>
</tr>
<tr>
<td>Spleen</td>
<td>161 ± 91</td>
<td>163 ± 95</td>
<td>0.90</td>
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<tr>
<td>Muscle</td>
<td>36 ± 16</td>
<td>35 ± 15</td>
<td>0.22</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>68 ± 36</td>
<td>65 ± 36</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Fig. 3: Box-whisker and spread plots of SNR pre and post Gd-EOB-DTPA in various tissue types
Conclusion

Discussion:

In order to optimise imaging workflow of liver MRI scans with Gd-EOB-DTPA, many groups recommend that DWI and T2-weighted sequences are done after the administration of IV contrast (Motosugi et al. (2009)). The justification for this comes from reports of several investigators that Gd-EOB-DTPA has no significant effect on the calculated ADC values for focal liver lesions and therefore does not impair lesion characterization (Muhi et al. (2012), Choi et al. (2010) and Kim et al. (2009)). However, to our knowledge no studies have systematically analyzed the effects of Gd-EOB-DTPA on liver parenchymal water diffusivity. This is important to determine because both DWI as well as Gd-EOB-DTPA are being suggested as methods for the assessment of diffuse liver disease (Taouli et al. (2009)).

Studies have shown that ADC values are lower in fibrotic livers, with a negative correlation with more severe grades of fibrosis (Taouli et al. (2009)). In addition, Lewin et al. (2007) showed the ADC value to be a good predictor of moderate and severe fibrosis, inflammation scores and possibly even steatosis. Hepatic function can be inferred through liver MRI with Gd-EOB-DTPA, by assessing the degree and timing of enhancement, with cirrhotic disease showing delayed and less intense enhancement (Kyung et al. (2012)). Thus, any external factor which potentially influences ADC measurements may affect the ability of DWI to reliably assess liver parenchyma.

Approximately 50% of Gd-EOB-DTPA is taken up by hepatocytes and furthermore Gd-EOB-DTPA demonstrates almost two times an increase in the T1 and T2 relaxation times (Choi et al. (2010)). Retained Gd-EOB-DTPA within hepatocytes will result in increased susceptibility which will affect both the DW signal intensity and ADC values in the liver, as demonstrated in this study. These susceptibility related effects could be counteracted by increased ADC values from enhancement of the perfusion component on the ADC<sub>total</sub> maps. The ADC lowering effect of Gd-EOB-DTPA was also seen when the perfusion component of ADC was minimized using ADC<sub>high</sub> values. Interestingly the change on ADC ADC<sub>high</sub> was greater than on ADC<sub>total</sub> (-34 vs. -22 µm<sup>2</sup>/s; p<0.0001 mw U-test).

Limitations:
This study was performed on patients with apparently normal liver parenchyma, but the effects of Gd-EOB-DTPA on ADC measurements in the setting of diffuse liver disease needs to be undertaken to see what the magnitude of the effect would be.

However, we note that the differences in ADC values after Gd-EOB-DTPA are of small magnitude ($\text{ADC}_{\text{total}} -22$ & $\text{ADC}_{\text{high}} -43 \, \mu m^2/s$) although highly statistically significant. This difference needs to be compared with expected difference in liver parenchymal ADC values for different grades of liver cirrhosis. Do et al. (2010) reports approximately a -160 $\mu m^2/s$ difference between different cirrhotic groups. Similarity Lewin et al. (2007) reported approximately a -170 $\mu m^2/s$ difference in cirrhosis scores. These comparisons suggest that ADC measurements after Gd-EOB-DTPA may not have a significant effect on the characterization of fibrosis grades but this requires confirmation in the setting of diffuse liver disease.

Conclusions:

We have demonstrated that Gd-EOB-DTPA significantly lowers normal liver parenchymal $b500$ nSI, SNR & ADC values. This may have implications for scanning protocols for diffuse liver disease but it is unclear whether Gd-EOB-DTPA would significantly impair diffuse liver disease characterization. Thus to maximize the potential of liver MRI with DWI and Gd-EOB-DTPA in the assessment of diffuse liver disease, DWI sequences should ideally be performed before Gd-EOB-DTPA administration, unlike the current recommendations for focal hepatic lesions where DWI is acquired after Gd-EOB-DTPA.


