Applications of magnetic resonance spectroscopy for noninvasive assessment of hepatic steatosis
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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

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Hepatic steatosis

Hepatic steatosis is characterized by increased lipid accumulation in the liver. The prevalence of hepatic steatosis is increasing rapidly throughout the world. This is largely attributed to the association with obesity and insulin resistance in nonalcoholic fatty liver disease (NAFLD) [1,2]. It is estimated that one-third of the current Western adult population is affected by liver steatosis [3,4]. Detection and quantification of hepatic steatosis is clinically important in several situations. In NAFLD, steatosis is the hepatic manifestation of the metabolic syndrome and the earliest biomarker for the development of liver fibrosis in the more severe condition of nonalcoholic steatohepatitis (NASH). The prevalence of NASH is estimated to be approximately 20% among the obese and 3% of the lean population [5-7]. Furthermore, it is estimated that 20-30% of patients with NASH will develop cirrhosis [8-11]. Early diagnosis and treatment of NASH can prevent the potential development of fibrosis, cirrhosis and ultimately end-stage liver disease and hepatocellular carcinoma (HCC), posing a significant burden on liver transplantation waiting lists [12,13]. Moreover, recent reports suggest that the majority of cryptogenic hepatocellular carcinoma is caused by NAFLD [14]. It is predicted that the rise in NAFLD prevalence could lead to an increased incidence of hepatocellular carcinoma in the next decades [15]. Together with increased cardiovascular morbidity and mortality [16], NAFLD is becoming a large burden on health care systems and the economy in general.

In liver transplantation surgery, the presence of steatosis impairs the regenerative capacity of the liver in both donor and recipient [17,18]. Moreover, clinical studies identified severe hepatic steatosis (>66%) as an exclusion criterion for patients requiring major liver resection because of the concomitant high risk of postoperative complications [12,19]. In morbidly obese patients hepatic steatosis is present in approximately 85% to 95% [20,21]. These patients have an increased risk to develop NASH, fibrosis and liver failure. Bariatric surgery is increasingly performed to treat morbid obesity and the majority of patients with NAFLD show significant improvement after bariatric surgery [22-24].

Reference standard for hepatic steatosis

Percutaneous liver biopsy remains the reference test for the histopathological evaluation of hepatic steatosis, inflammation (NASH) and fibrosis in NAFLD. Unfortunately, due to the risk of complications, interobserver variability, sampling error and patient’s
discomfort, this procedure is not applicable for population screening [25-27]. Furthermore, histopathological assessment of a needle biopsy specimen is potentially inaccurate since heterogenic manifestation of hepatic steatosis can lead to underscoring of the degree of steatosis or to false-positive results [28]. Moreover, the determination of hepatic steatosis is semiquantitative. Also, in the (morbidly) obese population the risk of complications is increased and conventional liver biopsy is technically more difficult in (morbidly) obese patients. Consequently there is a need for a noninvasive diagnostic tool for the detection and quantification of hepatic steatosis and monitoring.

**Imaging of hepatic steatosis**

Since the early 1980s, many studies focused on the role of imaging modalities as a noninvasive alternative to liver biopsy for detecting and quantifying hepatic steatosis [29-31]. Several imaging techniques are used to detect hepatic steatosis: Ultrasonography (US), Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and $^1$H-Magnetic Resonance Spectroscopy ($^1$H-MRS). Initially, most studies evaluated the accuracy of US and CT. US is a widely available and low cost technique. However, ultrasonography is not quantitative, is inaccurate in obese patients [32] and is not useful for the detection of low levels of steatosis [33,34]. CT is accurate in semiquantitative diagnosis of macrovesicular steatosis of 30% or greater [35], but its use for monitoring treatment response is somewhat limited due to exposure to ionizing radiation.

Currently, magnetic resonance imaging (MRI) and proton magnetic resonance proton spectroscopy ($^1$H-MRS) are the primary focus of research [36]. MRI is performed by gradient-echo chemical shift imaging (Dixon method), either as a readily available T1-weighted dual echo, or triple, multi echo sequence and multi-interference methods [37,38]. $^1$H-MRS is considered as the most sensitive noninvasive modality for the detection of hepatic fat [39]. However, in most centers $^1$H-MRS largely remains a research tool. Some studies have compared imaging modalities to assess steatosis and showed strong significant correlation between MRI and $^1$H-MRS ($r= 0.96-0.99$) and between $^1$H-MRS and CT ($r= 0.83$). These results were not compared to liver biopsy results [40-43]. Other studies did however compare imaging modalities with histopathology and showed substantial variation in correlations [13,44-48]. Furthermore, the reported sensitivities and specificities between different imaging modalities and between different studies investigating the same modality vary substantially. Although $^1$H-MRS is generally considered the best modality and is increasingly used as reference standard instead of liver biopsy, no evidence-based consensus currently exists as to which modality is best.
MRI and $^1$H-MRS permit the breakdown of the MR signal into water and fat signal components and allow quantification of hepatic fat. To date there are three clinically used MR imaging techniques for the detection and quantification of hepatic fat including chemical shift imaging, frequency-selective imaging and $^1$H-MRS. Each technique has advantages and disadvantages and is increasingly used in diagnosis, treatment and follow-up of NAFLD [49-51].

A clinical important advantage of $^1$H-MRS over the other techniques is the capability to quantify hepatic triglyceride content (HTGC) in situ [52]. It enables the quantitative evaluation of hepatic lipid content by measuring the MR signal generated by hydrogen atoms of fatty acid chains in a magnetic field. The various fatty acids can be differentiated from the water signal by the small shifts in nuclear resonance of the hydrogen atoms bound to different structured carbon chains. This technique has shown to correlate well with histological data from liver biopsies in healthy individuals and patients with hepatic steatosis ($r=0.9$, $p<0.001$) [48,52]. $^1$H-MRS is also suitable for grading and following up patients with NAFLD who participate in clinical trials [53]. Clinical experience with this technique is limited to 1.5 Tesla magnets [12,48,54]. There is sparse literature on addressing hepatic steatosis in humans at higher magnetic field strengths (3.0 Tesla or higher) [55,56]. Due to the higher spectral resolution, the use of increased magnetic fields may allow quantification of various fatty acid components in more detail, e.g. differentiation of resonances from unsaturated fatty acid chains (UFA) and polyunsaturated fatty acids (PUFA) in steatotic liver triglycerides [57-60]. There is increasing evidence that hepatic UFA play an important role in the development of NAFLD [61,62].

Previous studies using cylindrical MR scanners for $^1$H-MRS showed the beneficial effect of bariatric surgery on hepatic steatosis [63-66]. Unfortunately, the bore of clinical cylindrical MR scanners prevents imaging of morbidly obese patients. Given the present obesity epidemic, increasing number of patients will not fit in the bore of a standard cylindrical MR scanner. Therefore, $^1$H-MRS measurements of hepatic fat content in these patients are practically impossible despite the fact that these patients are at high risk for NAFLD. For the obese population $^1$H-MRS in an open MR scanner could be the alternative to cylindrical MR scanners. More recently high field open 1.0T MR scanners became available for clinical use and make good quality $^1$H-MRS possible.
OUTLINE OF THIS THESIS

This thesis focuses on the applications of $^1$H-MRS (primarily on 3T) for noninvasive assessment of hepatic steatosis. Several aspects were studied such as accuracy, reproducibility, comparison of available imaging modalities for hepatic steatosis assessment, evaluation of hepatic steatosis in an experimental rat model, feasibility of $^1$H-MRS for hepatic lipid composition analysis and hepatic steatosis assessment in a cohort of morbidly obese patients.

To determine the best available imaging technique for the detection of hepatic steatosis as reported in the literature, a meta-analysis of literature was performed in chapter 2. This meta-analysis investigated the diagnostic accuracy of US, CT, MRI and $^1$H-MRS for the evaluation of hepatic steatosis compared to liver biopsy.

Recently $^1$H-MRS became the focus of many papers as the imaging technique of choice for noninvasive hepatic steatosis assessment. Despite the increasing use of $^1$H-MRS in determining hepatic steatosis, there is sparse literature addressing the reproducibility of this technique. Therefore a reproducibility study of $^1$H-MRS at 3T was performed in chapter 3.

In chapters 4 and 5 clinical studies were performed. In chapter 4 we provide a clinical study to compare the accuracy of ultrasonography, computed tomography, T1-weighted dual echo MRI and $^1$H-MRS at 3T for the assessment of hepatic steatosis in patients undergoing liver resection. In chapter 5 we investigated the assessment of hepatic steatosis in morbidly obese patients before and after Roux-en-Y gastric bypass surgery using $^1$H-MRS in an open 1.0T MR scanner.

In chapters 6 and 7 more experimental research was performed in a steatotic rat model at 3T. In chapter 6 we investigated noninvasive quantification of hepatic steatosis using $^1$H-MRS with histopathological and biochemical confirmation. In chapter 7 we studied hepatic lipid composition using $^1$H-MRS with histopathological and biochemical confirmation.

Finally, in chapter 8 we investigated the capability of $^1$H-MRS to assess unsaturated fatty acids in the liver in patients with nonalcoholic fatty liver disease at 3T.

In chapter 9 we provide a summary, general discussion and implications. In chapter 10 this summary is provided in Dutch.
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Chapter 1: Introduction

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