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● *Original Contribution*

QUANTITATIVE ULTRASOUND FOR STAGING OF HEPATIC STEATOSIS IN PATIENTS ON HOME PARENTERAL NUTRITION VALIDATED WITH MAGNETIC RESONANCE SPECTROSCOPY: A FEASIBILITY STUDY

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Abstract—Patients on home parenteral nutrition are at risk for developing liver dysfunction, which is due partly to the accumulation of lipids in the liver (steatosis) and may progress to end-stage liver disease with overt liver failure. Therefore, a timely diagnosis with easy access to repeated assessment of the degree of liver steatosis is of great importance. A pilot study was performed in 14 patients on long-term home parenteral nutrition using the computer-aided ultrasound method. Ultrasound radio frequency data were acquired using a phased array transducer and were converted into conventional B-mode images. All patients were subjected to proton magnetic resonance spectroscopy measurement of liver fat content for reference. Computer-aided ultrasound parameters similar to those in a previous validation study in cows revealed significant correlations with fat content measured by magnetic resonance spectroscopy. The most significant parameters were the residual attenuation coefficient ($R = 0.95, p < 0.001$) and the lateral speckle size ($R = 0.77, p = 0.021$). These findings indicate the potential usefulness of computer-aided ultrasound for staging of hepatic steatosis. (E-mail: gert.weijers@radboudumc.nl)

Key Words: **Home parenteral nutrition, Ultrasound, Magnetic resonance spectroscopy, steatosis, Liver, Computer-aided ultrasound, Radiofrequency, 2-D ultrasound, B-Mode, Residual attenuation coefficient, Quantitative, Transcutaneous.**

INTRODUCTION

Intestinal failure implies that patients cannot maintain their nutritional status and health by means of a normal diet, mostly because of surgical resection, disease-related loss of absorption or severe gastrointestinal motility disorders (Wanten et al. 2011). Patients with severe long-term intestinal failure eventually have to be treated with parenteral (intravenous) nutrition, which is administered in the home setting (called home parenteral nutrition [HPN]). Patients on HPN frequently develop liver dysfunction, mostly as a result of fat accumulation (steatosis) and eventually fibrosis, which may progress to overt end-stage liver failure. Patients on HPN receive all their nutrition through cycled infusion of a sterile aqueous admixture that comprises all macronutrients (lipids, carbohydrates, amino acids) and micronutrients (vitamins, trace elements) during the night. The composition of the nutritional formulation mostly remains constant over time unless metabolic complications develop, such as when disturbed liver function is detected through tests. If the nutrition energy intake is not balanced with the consumed energy, the liver may accumulate the fatty components, which may cause serious liver dysfunction over time (Amusquivar et al. 2008; Peyret et al. 2011).

Accumulation of fat in the liver is also a risk factor for the development of insulin resistance and, thus, for the development of type 2 diabetes (Muurling et al. 2004). This pilot study was undertaken to investigate whether the computer-aided ultrasound (CAUS) method, which was developed and tested for staging the hepatic fat content in cows, can be used to quantify liver fat content in patients on HPN (Starke et al. 2010; Thijssen et al. 2008; Weijers et al. 2010; 2012).

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The liver parenchyma consists mainly of liver lobules organized in a honey comb-like manner. The six edges are formed by portal triads that contain a vein, an artery and a bile duct. A central artery runs through the center of the lobule. When intracellular fat droplets are present, liver scattering and attenuation become increasingly dominated by the droplets (Joseph et al. 1979). The B-mode gray level has been reported to increase diffusively in US fatty liver images, generally called “bright liver” (Joseph et al. 1979), together with posterior beam attenuation (Oosterveld et al. 1991; 1993; Saverymuttu et al. 1986; Taylor et al. 1981), tightly packed echo pattern (Joseph et al. 1991) and loss of anatomic details (*i.e.*, featureless appearance) (Saverymuttu et al. 1986). Qualitatively performed B-mode studies (Joseph et al. 1979; Saverymuttu et al. 1986) have obtained good results for classification of steatosis into several risk groups. However, B-mode gray levels are dependent not only on histologic structure, but also on equipment and depth. Therefore, the equipment settings that are used need to be carefully calibrated, and depth-dependent corrections are required to perform quantitative analysis.

Qualitative echography (Dasarathy et al. 2009; Joseph and Saverymuttu 1991; Saverymuttu et al. 1986) and quantitative echography have been investigated for many years. The latter can be divided into two different methods: spectral analysis of radiofrequency (RF) echograms (Cloostermans and Thijssen 1983; Garra et al. 1987; Lizzi et al. 2006; Sasso et al. 2010; Thijssen 2000) and analysis of B-mode image gray level statistics and textures (Edens et al. 2009; Gaitini et al. 2004; 2005; Knipp et al. 1997; Szebeni et al. 2006; Thijssen et al. 2008; Valckx et al. 2000). The main advantage of the B-mode technique is its applicability to all standard US modalities. Therefore, the authors chose the latter technique for further exploration and comparison with the gold standard of magnetic resonance spectroscopy (MRS)-based estimation of liver fat content. Because data were initially acquired in RF mode, they were converted to conventional B-mode images.

In most of the published B-mode studies, no correction for the ultrasound beam inhomogeneity due to focusing and diffraction was performed. This results in an analysis range limitation of the attenuation estimation to the far field, because only there is linear decay of the logarithmic echo level present.

In other studies, thickness-dependent attenuation correction for the abdominal wall (skin, muscle and subcutaneous fat layers) was not performed. A thicker fat layer absorbs more of the energy of the ultrasound signal before it reaches the liver and affects the mean echo level backscattered from the liver, so correction for the fat layer thickness is required. We assumed an overall attenuation by skin and subcutaneous layers of 1 dB/cm/MHz (Weijers et al. 2012).

When only a single A-line (Gaitini et al. 2004; Sasso et al. 2010) is acquired and analyzed, the precision of the results is limited and, moreover, vulnerable to artifacts caused by anatomic structures (such as large hepatic vessels). The authors therefore developed and tested a quantitative US B-mode method (Thijssen et al. 2008) for diagnosing and staging hepatic steatosis using calibrated US equipment (Thijssen et al. 2007). Calibration was performed using a tissue-mimicking phantom (TMP) containing objects with known nominal contrast. This procedure enabled expression of the relative echo level in decibels relative to the background level of the phantom used, as well as estimation of the dynamic range chosen in the pre-processing settings of the equipment. The mean echo level in decibels versus depth, called the “depth profile” of the phantom, is used to estimate and compensate for the “normal” depth dependence of liver images. The latter procedure yields the residual attenuation coefficient (RAC) and is expressed in decibels per centimeter (dB/cm). The depth dependence of the echo levels due to the RAC is compensated for. The authors also developed an adaptive segmentation method for the automated exclusion of hepatic blood vessels and bile ducts. After segmentation, the RAC was estimated again and corrected for (Weijers et al. 2010).

The hypothesis of the CAUS method is that with increasing liver fat content, increasing RAC values will be obtained because of increased backscattering and attenuation by the fat. To be able to detect and distinguish subtle attenuation differences, a transducer with a central frequency of approximately 5 MHz is needed (Saverymuttu et al. 1986). The attenuation will also be reflected in the lateral speckle size (LAT), because it is dependent on the central frequency (Thijssen 2003; Wagner et al. 1983), which will shift downward as a result of the attenuation. In RF data, this technique is called the spectral center downshift (CDS) method (Fink et al. 1983; Kuc and Schwartz 1979). In B-mode imaging, this phenomenon is reflected by an increase in LAT with depth (Oosterveld et al. 1985).

The CAUS protocol was extensively validated using US acquisitions in 151 dairy cows, with subsequent histologic analysis of liver biopsies (Starke et al. 2010; Thijssen et al. 2008). The authors found that liver fat content can be classified into different risk groups with high reliability, as indicated by the linear regression value, R^2, of 0.62, and area under the receiver operating characteristic (ROC) curve (AUC) value of 0.93 using the RAC parameter only (Starke et al. 2010; Weijers et al. 2010). In several other studies, attenuation parameters were found to be useful for staging liver fat content (Edens et al. 2009; Gaitini et al. 2004; Garra