1H MRS DETERMINATION OF INTRAHEPATIC TRIGLYCERIDE CONTENT IN HIV PATIENTS UNDER HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) AND ITS RELATIONSHIP WITH THE METABOLIC SYNDROME

A. Moreno-Torres[1], J. Pujol[1], J. Arroyo[2], P. Domingo[2]

[1]Department of Research, Centre Diagnostic Pedralbes (Cetir Grup Medic), Esplugues de Llobregat, Spain, [2]Department of Internal Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Introduction

Morbidity and mortality due to HIV infection have been considerably reduced since the introduction of highly active antiretroviral therapy (HAART). However, antiretroviral drugs used in HAART have a wide range of adverse effects such as dyslipemia, insulin resistance and abdominal obesity, which have been proposed as part of an underlying metabolic syndrome. Hepatic steatosis is also frequently found [1,2] and liver fat content has been correlated with insulin resistance features in HIV+ patients with lipodystrophy and controls [3]. The aim of the present study was to use localized proton magnetic resonance spectroscopy (1H-MRS) to evaluate the deposit of hepatic fat in HIV-infected patients under HAART and further correlate such a deposit with biochemical and other variables related to the metabolic syndrome. Our method included patients breathing normally and a post-processing correction of phase and frequency on a frame-to-frame basis. 1H-MRS has proved to be a specific and sensitive method to determine intracellular hepatic triglyceride content [4-7] and the post-processing schema used was seen to produce similar signal intensities compared to the breath-hold approach in MRS of the kidney [8], an organ with MR challenges similar to those of the liver.

Methods

The study population consisted of 29 non-obese HIV-infected patients who had been receiving HAART for at least the previous 6 months. The MR examinations were performed using a 1.5 T whole body system and the imaging body coil (General Electric Medical Systems, Milwaukee, WI, USA). Localized water-unsuppressed single voxel proton spectra of the liver were recorded by using the stimulated-echo acquisition mode sequence. A voxel (approx. 2x2x2 cm) was selected within the right lobe of the liver avoiding vascular structures and at a sufficient distance so as to reach the abdominal subcutaneous fat (figure 1). Quantitative assessment of triglycerides was performed from the extrapolated MRS signals of hepatic water and methylene protons of triglyceride fatty acids to zero echo time [4-5]. T2 calculations were performed on spectra at seven different TE (20, 30, 45, 70, 100, 200, and 400 ms), with TR of 5000 ms. Three consecutive spectra were acquired at TE = 20 ms in the same session to evaluate the short term reproducibility. Spectra were acquired as 16 individual FIDs. Other acquisition parameters were: Mixing time, TM=13.7 ms; 4 dummy scans; 2048 data points; 2500-Hz spectral width. Spectra processing was performed on the individually acquired FIDs and post-processed by using a frame-to-frame phase correction and frequency registration method slighty modified from the one previously demonstrated in the kidney [8]. This method included zero-filling to 4096 points prior to Fourier transform, zero-order phase correction, alignment of the spectra by using the water signal as reference (4.70 ppm), spectra averaging and inverse Fourier transform. The resulting averaged FIDs were quantified in the time domain with a non-linear least square fitting algorithm using the variable projection method and prior knowledge [9]. Anthropometric and standard serum biochemical measurements were also performed. Pearson's correlation coefficient was used to detect correlations of hepatic triglycerides with such measurements.

Results

Correction of the individual spectral frames by phase and frequency prior to averaging resulted in a significant improvement in spectral quality (figure 2). The resulting spectra showed, in addition to the intense water resonance, a single resonance of the methylene protons at a variable degree in the liver of 17 patients (figure 1). The chemical shift of this resonance was 1.31 ± 0.02 ppm and allowed its assignation to intracellular methylene protons of triglyceride hepatic fatty acids [6]. Repeated measurements at TE=20 ms showed an excellent reproducibility: When absent, no methylene fatty acids resonance was present in any of the 3 repeated spectra,and, when present, the coefficient of variation of the water and methylene resonances was 0.60 ± 0.38 % and 2.64 ± 1.76 %, respectively. The calculated hepatic triglycerides content [4,7] ranged from 0.91 to 10.05 g/100 g of liver wet weight with 5 patients showing values higher than 5%. Blood biochemical analysis results showed dyslipidemia to be the most common finding with 86.2 % of cases (25 patients). Other relevant plasmatic alterations were: hyperlactatemia (3 patients), mild acidosis (16 patients), hyperglucemia (3 patients), hyperinsulinemia, (3 patients) and hepatic transaminases high in 13 patients. The following strong correlations were found: Body mass index, waist to hip ratio, variables related with metabolism of glucose (lactate, insulin, HOMA-R index and pH) and lipids (Triglycerides, HDL- and VLDL-cholesterol and beta-globulin). All correlations were positive with the exception of pH and HDL. No correlation was found with the presence of lipodystrophy, hepatic transaminases, drug type or treatment time.

Conclusion

Our results showed excellent reproducibility and no extra-hepatic lipid contamination which suggests that 1H-MRS acquired under patients free quiet breathing and post-processing with frame-to-frame phase correction and frequency registration is a suitable technique for evaluating the deposit of hepatic triglycerides in HIV-infected HAART patients and probably in the general population. In our patient group, 58.6% showed hepatic triglyceride presence and only 17.2% a content higher than 5%, which would agree with a clinical diagnosis of hepatic steatosis [10]. Strong correlations with hepatic triglycerides were found for variables related to insulin resistance, dyslipemia and central obesity. Such results suggest that the accumulation of triglycerides within the liver is also a part of the metabolic syndrome in HAART patients. Nonetheless, it remains to be determined to what extent it is a cause rather than an effect in such patients.

References

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Figure 1. Voxel selection and typical spectra (TE =20 ms)

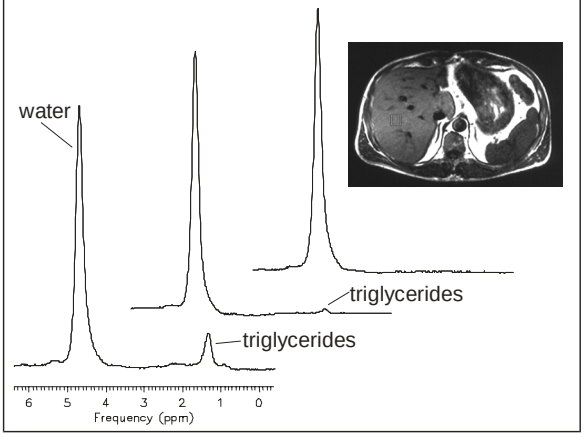

Figure 2. Effect of the applied post-processing correction