Title

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Journal

Clinical Gastroenterology and Hepatology, 19(11)

ISSN

1542-3565

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Publication Date

2021-11-01

DOI

10.1016/j.cgh.2020.10.029

Peer reviewed

HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2023 April 12.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2021 November ; 19(11): 2441–2443. doi:10.1016/j.cgh.2020.10.029.

Dynamic PET/CT Imaging correlate of non-alcoholic steatohepatitis

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Introduction:

Non-alcoholic steatohepatitis (NASH) is a severe form of non-alcoholic fatty liver disease (NAFLD) characterized by lobular inflammation and hepatocyte injury and is a key determinant of clinical outcome[1]. Liver biopsy remains the 'gold standard' for diagnosis but is limited by risks of the procedure and inter-observer variability. Although magnetic resonance imaging (MRI)-based technology may provide novel means to identify NASH[2], there remains a significant need for other modalities to diagnose NASH non-invasively. Glucose transport, an integral tissue process altered in NASH,[3] is measurable with ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG PET). As unenhanced computed tomography (CT) scan can detect hepatic steatosis quite reliably[4], and PET combines unenhanced CT for attenuation correction, we hypothesized that measurement of the combination of glucose transport by PET and steatosis by CT could yield a reliable radiologic correlate of NASH.

Methods:

The study was approved by the institutional review board. Patients with NAFLD, age ≥18 years, without risk factors of concomitant liver disease and who had undergone liver biopsy, were enrolled. The biopsy was scored according to established NASH-CRN (Clinical Research Network) criteria[5] by expert pathologists. Liver biopsies were assessed according to NAFLD activity score (NAS), the sum of steatosis (0–3), lobular inflammation (0–3) and ballooning degeneration (0–2). 'Clinical NASH' was defined as NAS ≥4, with a score of at

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least 1 in each of the NAS categories. 'Fibrotic NASH' was defined as those with clinical NASH plus fibrosis stage ≥2 by NASH-CRN criteria. All patients underwent dynamic PET scan on a GE Discovery 690 PET/CT scanner within 6 months of liver biopsy (mean 2±1.3 months). Diabetic patients were instructed to hold their short- and/or long-acting insulin after midnight and fasting pre-PET blood glucose was measured with goal ≤200mg/dL (mean 114±25mg/dL). Each patient received a bolus injection of 10 mCi ^{18}F-FDG, and dynamic images were acquired for 60-minutes. Regions-of-interest (ROI) were placed in the liver to extract a time activity curve of the liver from the dynamic sequence[6]. Utilizing an optimization-derived kinetic modeling that accounts for liver dual blood supply[6, 7], the liver FDG blood-to-tissue transport rate (K_1) was determined. At the end of PET scan, low dose CT scan was performed for attenuation correction with tube voltage 140 kVp and current 100 mAs. Liver CT Hounsfield units (CTHU) were measured from the ROIs. Patients also underwent MRI-proton density fat fraction (MRI-PDFF). Correlations were calculated using the Spearman correlation. The PET-derived liver K_1 value was linearly combined with CTHU to form a multivariate logistic regression for receiver operating characteristics (ROC) analysis.

Results:

Of 44 enrolled patients, 31 were female, age 55±13 years, BMI 34.1±5.8 kg/m^2, 68% Whites, 23% Hispanics and 14 with known diabetes. On liver biopsy, 82% of patients had clinical NASH with mean NAS score of 5±2 with 59% having NAS ≥5 and 52% with fibrotic NASH. As we showed previously, PET scan measurement of liver glucose (FDG) transport rate K_1 correlated with the sum of lobular inflammation and ballooning degeneration[6]. Steatosis scored on biopsy or by MRI-PDFF correlated significantly with CTHU ($r=-0.805$ and -0.8789, respectively; $p<0.0001$). The dual-variate model combining K_1 with CTHU (K_1+CTHU or 'PET-NAS': $8.7732*K_1 + 0.1759*CTHU$) <18.72475 was able to detect clinical NASH with sensitivity=0.92, specificity=1 and fibrotic NASH with sensitivity=0.96, specificity=0.48 (Figure 1). PET-NAS correlated with total NAS score ($r=-0.78$, $p<0.001$), while PET-NAS <17.389 predicted NAS ≥5 with sensitivity=80.8% and specificity=83.3%.

Discussion:

Utilizing dynamic FDG-PET, we have derived a novel radiologic tool that demonstrates high sensitivity and specificity for identification of NASH. While our previous study focused on understanding the linkage between FDG K_1 kinetics and distribution in the context of liver inflammation, the current study brings forth novel PET/CT correlate of histologic NASH. The negative correlation of K_1 with NASH may reflect decreased glucose transport with increased liver inflammation and injury in NASH (secondary to inherent apoptotic processes)[3]. While this is a small, single center study with a predominance of patients with advanced NASH, it provides essential preliminary data for a larger study that includes a more diverse cohort of patients. Although radiation exposure is a research risk, effective dose remains low and comparable to abdominal CT[8]. Our FDG PET/CT imaging cannot detect fibrotic NASH reliably due to lack of marker for fibrosis but remains of future interest.

To summarize, in this proof-of-concept study, we demonstrate that dynamic FDG-PET/CT scan is a potential tool for detection of NASH, a rising epidemic with few non-invasive tools for assessment.

Disclosures:

SS: Advisory board for Genfit, Eisai; Grant (to UC Davis) from Gilead Sciences; None of the other authors has relevant conflicts of interest (financial or personal)

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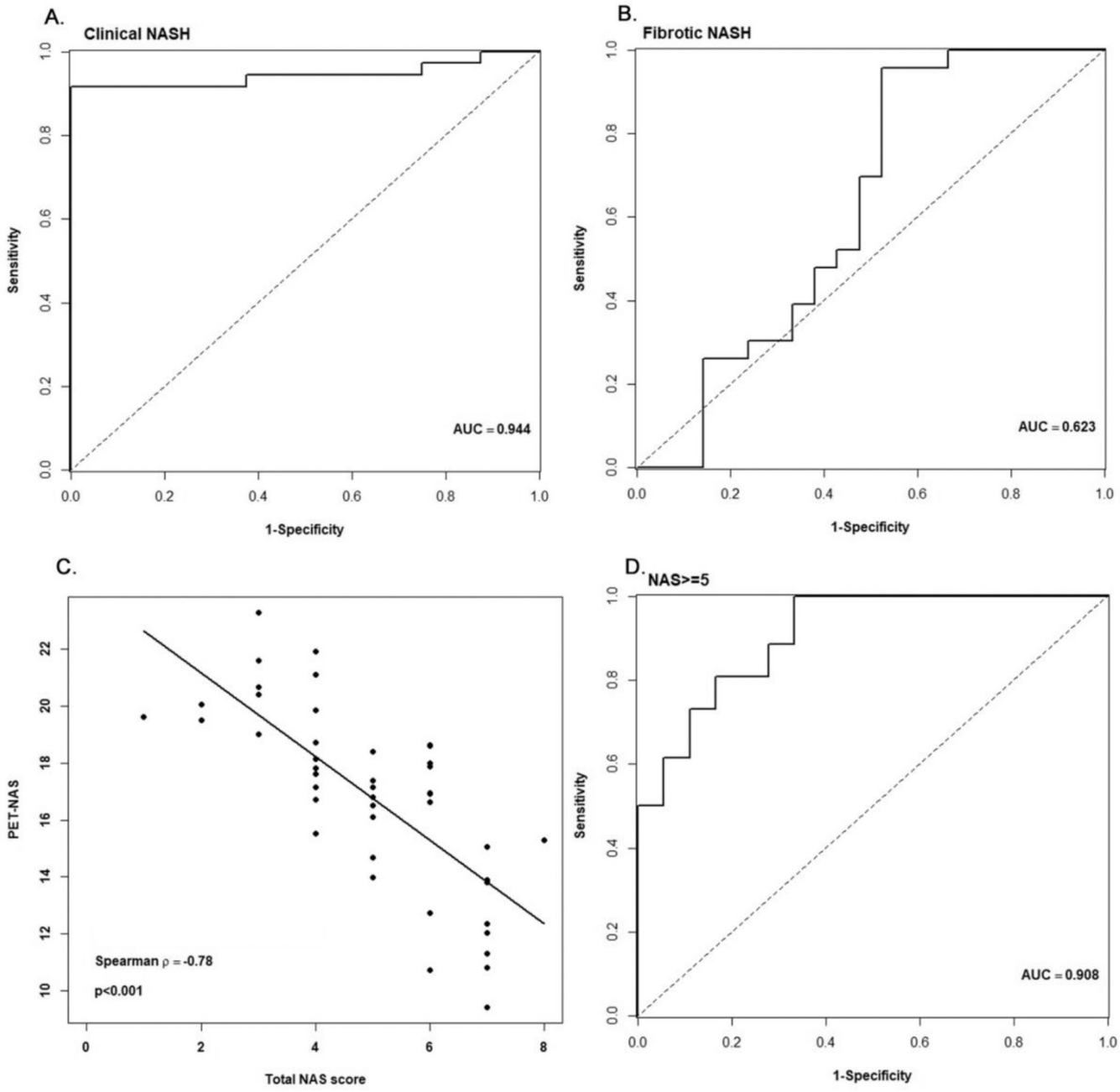

Figure 1:

A. Area under the Receiver operating characteristics (AUROC) curve of K_1 and combined K_1+CTHU ('PET-NAS) to detect Clinical NASH, **B.** Fibrotic NASH, **C.** correlation of PET-NAS with NAS or NASH severity and **D.** for NAS≥5