ORIGINAL ARTICLE

Quantitative assessment of global hepatic glycolysis in patients with cirrhosis and normal controls using ^{18}F-FDG-PET/CT: a pilot study

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Abstract

Objective To compare differences in global measures of hepatic metabolism between control subjects and subjects with cirrhosis.

Materials and methods FDG-PET/CT scans of 33 subjects either without or with cirrhosis were analyzed retrospectively and classified as follows: group 1 includes subjects without cirrhosis or extrahepatic malignancy (1a) ($n = 11$) and subjects without cirrhosis but with history of extrahepatic malignancy (1b) ($n = 10$); group 2 includes subjects with cirrhosis and history of extrahepatic malignancy ($n = 12$). Subjects with focal hepatic lesions, prior hepatic surgery, co-existing liver pathology, or who received chemotherapy or radiation therapy within the last 6 months were excluded. The hepatic volumes, hepatic mean standardized uptake value (SUVmean), and global hepatic glycolysis (GHG) were compared between groups.

Results Subjects with cirrhosis showed a lower average hepatic SUVmean as compared to non-cirrhotic patients (1.55 ± 0.29 for group 2 versus 1.81 ± 0.23 for group 1; *p* value = 0.009) and lower average values for GHG (2238.29 ± 903.60 for group 2 versus 2974.67 ± 829.16 for group 1; *p* value = 0.024). No differences were noted between the non-cirrhotic subgroups (i.e., between the groups 1a and 1b) without and with associated extrahepatic malignancy, respectively.

Conclusions We hypothesize that presence of fibrosis, reduction of active inflammation, and decreased hepatic metabolism and function are potential causes of the lower FDG uptake in cirrhotic livers. Our results also indicate that extrahepatic cancer status does not influence FDG uptake in the non-cirrhotic liver in subjects without hepatic metastases.

Keywords FDG-PET/CT · Cirrhosis · Liver metabolism · Hepatic SUVmean · Global hepatic glycolysis (GHG)

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Introduction

Chronic liver disease and cirrhosis engender major health costs, accounting for more than 29,000 deaths annually and comprise the seventh leading cause of death among people aged 25–64 years in the United States [1]. Cirrhosis is the final stage of a complex pathophysiological process in response to chronic liver injury that is characterized by histological development of regenerative nodules surrounded by fibrous bands [2, 3]. Chronic hepatocyte injury is most commonly caused by such factors as alcohol use, hepatitis B and C infection, or fatty liver disease [4]. Recent data suggest that cirrhosis is a dynamic process and that cirrhosis regression or even reversal has been documented in several forms of liver disease following

treatment of the underlying cause [2, 5, 6]. In addition, emerging treatment modalities and clinical interest in predicting or evaluating remnant liver function following therapy led to an increased clinical demand for noninvasive methods that can evaluate global and regional metabolic function and heterogeneity of liver in a single investigation [7].

Various imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance elastography (MRE) and ultrasonography (US) have commonly been used to evaluate morphological changes in the liver associated with cirrhosis [2, 8–12]. Nuclear medicine techniques such as technetium-(99m) galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography (SPECT)/computed tomography (CT) and (99m)Tc-DTPA-galactosyl serum albumin (where DTPA is diethylene triamine pentaacetic acid) SPECT, have also been used to quantify liver fibrosis and hepatic functional reserve in patients with cirrhosis [7, 13–17]. Positron emission tomography (PET) has been widely shown to be a useful tool in cancer diagnosis, staging, and management, and is now increasingly being utilized to assess infectious, inflammatory and degenerative diseases [18, 19]. [^{18}F]-2-deoxy-D-glucose (FDG) is the most commonly used radiotracer for PET studies and allows one to explore differences in the glycolytic rate between normal and diseased tissues [18, 20]. The normal pattern of uptake of FDG in the liver is generally at a low level and diffuses. However, heterogeneity of FDG uptake with regions of higher background activity can also be seen in the liver, related to higher glucose metabolism of the liver parenchyma, abundant expression of Glut-1 and hexokinase II, as well as to a variety of pathophysiological conditions [21, 22]. As such, evaluation of global hepatic metabolic activity can help to minimize sampling errors related to local radiotracer heterogeneity and potentially provide more accurate information about global liver function.

The concept of global metabolic activity was first introduced by Alavi and coworkers [23], in assessment of the brain in patients with Alzheimer disease and then has been investigated in a variety of disorders for the past two decades [24–31]. This group suggested adopting a similar quantitative approach to assess global normal organ function and overall disease activity, emphasized the importance of tissue segmentation of various components of organs, and described the potential applications of such quantitative techniques [32]. Subsequently, the methodology was employed to compare hepatic standardized uptake values (SUVs) and hepatic metabolic volumetric products (HMVPs) in patients with diffuse hepatic steatosis and healthy controls [33]. They found that HMVPs mean hepatic SUVs, and maximum hepatic SUVs were significantly greater in subjects with diffuse hepatic steatosis compared to those in the control group.

In the current study, we aimed to extend this approach using FDG-PET/CT for the quantitative assessment of global hepatic function to gain insight into the effects of cirrhosis upon hepatic metabolism.

Materials and methods

Study population

This retrospective study was performed at the Hospital of the University of Pennsylvania following Institutional Review Board approval and Health insurance portability and accountability act (HIPAA) waiver. It included subjects with and without cirrhosis who underwent an FDG-PET/CT scan between July 2006 and November 2010. The medical records of all subjects were reviewed to evaluate for any history of malignancy, hepatic surgery, focal hepatic lesions or associated liver pathology, as well as for history of prior chemotherapy or radiation therapy. All prior medical imaging was also reviewed. Subjects with focal hepatic lesions, prior hepatic surgery, or co-existing liver pathology as well as subjects treated with chemotherapy or radiation therapy within the last 6 months prior to FDG-PET/CT imaging were excluded. To evaluate whether presence of extrahepatic malignancies influences hepatic FDG uptake, the non-cirrhotic subjects were further divided into two subgroups based on the absence or presence of extrahepatic tumors. A total of 33 subjects met the inclusion criteria and were divided into the following groups (Table 1).

Group 1: subjects without cirrhosis including 11 healthy controls (1a) with no history of cancer, prior hepatic surgery, or focal hepatic lesions and 10 subjects (1b) with various types of extrahepatic malignancy (lung, $n = 4$; head and neck, $n = 2$; uterine, $n = 1$; anal, $n = 1$; gastric, $n = 1$; thyroid, $n = 1$), but without cirrhosis, focal hepatic

Table 1 Subject distribution and characteristics

Group	Number of subjects	Gender (male/female)	Age in years (mean ± SD)
1a	11/33	9/2	48.0 ± 5.5*
1b	10/33	5/5	59.4 ± 13.7*
2	12/33	8/4	65.4 ± 9.0

1a subjects without cirrhosis and without extrahepatic malignancy, *1b* subjects without cirrhosis but with history of extrahepatic malignancy, *2* subjects with cirrhosis and with history of extrahepatic malignancy

* The mean ± SD age of all subjects in group 1(1a + 1b) was 57.1 ± 11.58

lesions, or prior hepatic surgery. Group 2: 12 subjects with cirrhosis due to various underlying causes (autoimmune, $n = 1$; hepatitis B virus, $n = 1$; hepatitis C virus, $n = 1$; alcohol related, $n = 1$; alcohol and hepatitis C virus, $n = 1$; cryptogenic, $n = 7$). All subjects with cirrhosis also had extrahepatic malignancy without liver involvement (head and neck, $n = 6$; lymphoma, $n = 3$; colon, $n = 1$; esophagus, $n = 1$; breast, $n = 1$). None of the subjects in groups 1 or 2 received chemotherapy or radiation therapy within the last 6 months prior to FDG-PET/CT imaging. Apart from documentation of cirrhosis in the medical records based on available histopathological and clinical assessments, the diagnosis of cirrhosis was alternatively confirmed by the presence of morphological imaging findings characteristic of cirrhosis, such as presence of a nodular hepatic contour, hypertrophy of the left hepatic lobe or caudate lobe, presence of a posterior right hepatic notch sign, and/or a decrease in hepatic size.

PET/CT image acquisition and analysis

All FDG-PET/CT scans were acquired using a LYSO whole-body PET/CT scanner with time-of-flight capabilities (Gemini TF, Philips Healthcare, Bothell, WA, USA). All patients fasted for at least 6 h before being injected intravenously with 444–555 MBq (11–15 mCi) of FDG, and had fingerstick blood glucose levels of <200 mg/dL just prior to FDG administration. PET images were acquired from the base of the skull to the mid thighs approximately 60 min following FDG injection for 3 min per bed position. Image reconstruction was performed using LOR-TF-RAMLA ("BLOB-OS-TF") with 33 ordered subsets and 3 iterations. The manufacturer's software included time-of-flight, normalization, attenuation, randoms, and scatter corrections. Energy rescaled low-dose CT images were used for attenuation correction of PET images. PET and CT images were reconstructed at 4 mm slice thickness.

PET/CT images were analyzed using dedicated image visualization and analysis software (Extended Brilliance Workstation, Philips Healthcare, Bothell, WA, USA). Regions of interest (ROI) were drawn manually around the anatomical boundaries of the liver on every axial slice of fused PET/CT images. The hepatic hilum, inferior vena cava, and gallbladder were excluded. Sectional hepatic mean standardized uptake value (sSUVmean) and ROI area (cm^2) were measured for all individual slices (Fig. 1). The sectional hepatic volume (sHV) of a slice was obtained by multiplying the area of ROI (cm^2) by the slice thickness (4 mm). The slice sectional hepatic glycolysis (sHG) was calculated by multiplying the slice sHV by sSUVmean. The hepatic volume (HV) was obtained by summing the sHVs of all slices, while the global hepatic glycolysis (GHG) was obtained by summing the sHG of all slices. Lastly, the hepatic SUVmean was calculated by dividing the GHG by the HV.

Statistical analysis

Statistical analysis was performed using Stata 11 software (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). Continuous variables for HV, GHG, and hepatic SUVmean were expressed as mean ± standard deviation and tested for distribution normality. Student's t test was used to compare the values between groups 1 and 2, as well as between subgroups 1a and 1b when they followed a normal distribution; otherwise a non-parametric (Mann–Whitney) test was used. A p value of less than 0.05 was considered to be statistically significant.

Results

Hepatic SUVmean

The subjects with cirrhosis showed a statistically significant lower hepatic SUVmean compared to non-cirrhotic subjects (1.55 ± 0.29 for group 2 versus 1.81 ± 0.23 for group 1, p value = 0.009). No statistically significant difference in hepatic SUVmean was noted between the non-cirrhotic subgroups without and with associated extrahepatic malignancy (1.85 ± 0.19 for subgroup 1a versus 1.77 ± 0.27 for subgroup 1b, p value = 0.43) (Tables 2, 3).

Hepatic volume

The HV was slightly lower in subjects with cirrhosis compared to non-cirrhotic patients (1,485.55 ± 628.72 cm^3 for group 2 versus 1,641.16 ± 397.69 cm^3 for group 1), although the difference did not reach statistical significance in our cohort (p value = 0.39). No difference in the average HV was noted between the non-cirrhotic subgroups without and with associated extrahepatic malignancy (1,586.28 ± 340.13 cm^3 for subgroup 1a versus 1,701.53 ± 463.89 cm^3 for subgroup 1b, p value = 0.52) (Tables 2, 3).

Global hepatic glycolysis (GHG)

The subjects with cirrhosis showed a statistically significant lower average GHG compared to non-cirrhotic subjects (2238.29 ± 903.60 cm^3 for group 2 versus 2974.67 ± 829.16 cm^3 for group 1, p value = 0.024). No statistically significant difference in GHG was noted

Fig. 1 Axial FDG-PET (**a**), low-dose CT (**b**) and fused FDG-PET/CT (**c**) images. Regions of interest (ROIs) delineating liver boundaries were drawn manually on every axial slice to calculate sectional hepatic volume (sHV) and sectional mean standardized uptake value (sSUVmean)

Table 2 Hepatic SUVmean, hepatic volume, and global hepatic glycolysis in subjects without and with cirrhosis

	Group 1 (1a + 1b)		Group 2		p value
	Mean ± SD	95 % CI	Mean ± SD	95 % CI	
Liver SUVmean	1.81 ± 0.23	1.71–1.92	1.55 ± 0.29	1.61–1.82	0.009
HV (cm^3)	1641.16 ± 397.69	1460.14–1822.19	1485.55 ± 628.72	1086.08–1885.03	0.39
GHG (cm^3)	2974.67 ± 829.16	2597.24–3352.10	2238.29 ± 903.60	1667.27–2812.51	0.024

1a subjects without cirrhosis and without extrahepatic malignancy, *1b* subjects without cirrhosis but with history of extrahepatic malignancy, *2* subjects with cirrhosis and with history of extrahepatic malignancy, *SUVmean* mean standardized uptake value, *HV* hepatic volume, *GHG* global hepatic glycolysis, *SD* standard deviation, *CI* confidence interval

Table 3 Hepatic SUVmean, hepatic volume, and global hepatic glycolysis in the two subgroups of subjects without cirrhosis

	Group 1a		Group 1b		p value
	Mean ± SD	95 % CI	Mean ± SD	95 % CI	
Liver SUVmean	1.85 ± 0.19	1.73–1.98	1.77 ± 0.27	1.58–1.96	0.43
HV (cm^3)	1586.28 ± 340.13	1357.78–1814.78	1701.53 ± 463.89	1369.69–2033.38	0.52
GHG (cm^3)	2928.87 ± 654.31	2489.30–3368.44	3025.04 ± 1023.09	2293.17–3756.91	0.80

1a subjects without cirrhosis and without extrahepatic malignancy, *1b* subjects without cirrhosis but with history of extrahepatic malignancy, *2* subjects with cirrhosis and with history of extrahepatic malignancy, *SUVmean* mean standardized uptake value, *HV* hepatic volume, *GHG* global hepatic glycolysis, *SD* standard deviation, *CI* confidence interval

between the non-cirrhotic subgroups without and with associated extrahepatic malignancy (2928.87 ± 654.31 cm^3 for subgroup 1a versus 3025.04 ± 1023.09 cm^3 for subgroup 1b, *p* value = 0.80) (Tables 2, 3).

Discussion

Cirrhosis is often preceded by the presence of hepatitis and hepatic steatosis. Few studies have evaluated the effect of liver steatosis upon hepatic FDG uptake, reporting either no significant difference or greater hepatic SUVs and GHG in affected patients [33–35]. To the best of our knowledge,

this is the first study to investigate the effects of cirrhosis upon hepatic SUVmean and GHG.

The lower hepatic SUVmean and GHG noted in our group of subjects with cirrhosis are in contrast to the findings that we have previously observed in subjects with hepatic steatosis. In a study evaluating the effect of liver steatosis on hepatic metabolic activity, Bural et al. [33] report a greater mean and maximum hepatic SUV as well as greater hepatic metabolic volumetric product (the equivalent of GHG) in subjects with diffuse hepatic steatosis. The authors suggest the active inflammation associated with diffuse hepatic steatosis as a probable cause for the mild increase in hepatic metabolic activity seen in these patients.

Recent studies suggest that cirrhosis is a dynamic process, where fibrogenesis is initially counterbalanced by removal of excess extracellular matrix molecules by proteolytic enzymes such as certain matrix metalloproteinases [2]. However, chronic damage usually favors fibrogenesis over fibrolysis [2]. The mechanisms are in concordance with our findings, and provide a plausible explanation for previously described higher or unchanged hepatic metabolic activity in the presence of hepatic steatosis [33–35], and a lower hepatic metabolic activity in subjects in the presence of cirrhosis. The lower hepatic SUVmean and GHG obtained in our group of subjects with cirrhosis are compatible with the decreased metabolic activity of fibrotic tissue. This observation may also have clinical implications, as hepatic SUVmean is commonly used as a reference background measure to evaluate the metabolic activity of other structures as well as for comparing the SUVs between different scans.

In cirrhosis evolution, the liver is often initially enlarged; however, with disease progression, it typically becomes smaller and its surface, irregular. In our study, the average hepatic volume in subjects without cirrhosis (1641.16 ± 397.69 cm^3; 95 % CI 1460.14–1822.19 cm^3) was within the range of normal limits as described by Geraghty et al. [36]. In their measurements based on 149 adult abdominal CT studies, the investigators obtained a median volume of a healthy adult liver = 1710.2 cm^3 [36]. The slightly lower average HV in our group of subjects with cirrhosis (1485.55 ± 628.72 cm^3) is compatible with the often smaller size of cirrhotic livers. However, in our study, this difference did not reach statistical significance, which may be related to a small sample size and relative heterogeneity regarding disease staging, the only inclusion criteria being the presence of cirrhosis.

Previous studies have shown that age and body mass index (BMI) may influence hepatic FDG uptake [37], and have reported a positive association between hepatic metabolic activity and increasing age and BMI [22, 38]. In the current study, there was an age difference between subjects without cirrhosis and those with cirrhosis (57.1 ± 11.58 years old for subjects without cirrhosis versus 65.4 ± 9.0 years old for subjects with cirrhosis; p value = 0.004). However, this slight age difference would not account for the lower hepatic FDG uptake or lower GHG observed in subjects with cirrhosis, but instead may have diminished the actual magnitude of difference in average hepatic metabolism between the two subjects groups. On the other hand, however, the BMI of subjects without cirrhosis was slightly higher (0.7 kg/m^2) than subjects with cirrhosis, the difference was not statistically significant (p value = 0.63).

We also speculated that cancer status may be another confounding variable affecting hepatic metabolism and liver FDG uptake due to systemic tumor effects. For this reason, two subgroups of non-cirrhotic subjects without and with associated extrahepatic malignancy have been included in the study. However, no statistically significant difference in average hepatic SUVmean or average GHG was observed between the two subgroups. These results suggest that extrahepatic cancer status does not influence FDG uptake by the liver. This is in contradistinction to the results of a study by Bural et al. [39], where hepatic SUVmean was observed to be significantly greater in subjects with evidence of active primary or metastatic lung cancer compared with subjects who had benign lung nodules and no evidence of active malignant disease.

In the majority of clinical settings, the Child-Turcott-Pugh (CTP) or the Model for End-Stage Liver Disease (MELD) scoring systems are often used to assess the severity of end-stage liver disease. These systems are mostly based on the results of laboratory testing, and have been tested in several studies. Yet, both have some limitations in the prediction of overall outcomes of patients with cirrhosis, and several studies [40–42] have suggested that the addition of other laboratory indices or simultaneous application of these scoring systems could potentially improve their predictive value. Liver biopsy is another method to assess cirrhosis. However, it is an invasive method that may lead to complications, and may be associated with diagnostic sampling errors. As demonstrated in the current study, global FDG-PET/CT based parameters may be useful to serve as imaging biomarkers of global liver metabolic activity in patients with cirrhosis.

This approach of noninvasive global hepatic assessment can also be applied to quantify the uptake of other PET radiotracers in the liver to evaluate global hepatic function. Some studies have suggested the application of novel radiotracers such as [^{18}F]-fluoro-2-deoxy-D-galactose (FDGal), [^{18}F]-neoglycoalbumin ([^{18}F]-FNGA), 8-cyclopentyl-3-(3-[^{18}F]-fluoropropyl)-1-propylxanthine ([^{18}F]-CPFPX), [^{15}O]-water, and [^{13}N]-ammonia to enhance the diagnostic capability of PET/CT in cirrhotic patients [43–48]. For example, Sorensen et al. [43, 49] demonstrated that short (20 min) dynamic FDGal-PET/CT can provide an accurate in vivo measurement of human galactose metabolism and can be useful for quantification of regional hepatic metabolic function in patients with cirrhosis. Through measurement of the hepatic systemic clearance of FDGal in the liver parenchyma via PET/CT, the authors demonstrated a decrease in hepatic metabolic function in cirrhotic livers (0.157 ml blood/ml liver tissue/min) compared to normal control livers (0.274 ml blood/ml liver tissue/min). These results are in agreement with our findings, and may account for the lower hepatic SUVmean and lower GHG seen in subjects with cirrhosis relative to non-cirrhotic subjects. In their study, Sorensen et al. [43] also

reported that patients with cirrhosis demonstrated a higher degree of intrahepatic metabolic heterogeneity compared to healthy subjects. As such, to minimize sampling errors, we utilized global PET/CT based parameters to evaluate global hepatic metabolism.

Our study has some limitations. First, because of the retrospective nature of this study and the relatively small number of subjects, we did not stratify subjects based on CTP or MELD scoring systems. As such, we may have included a heterogeneous group of cirrhotic subjects. Such heterogeneity usually decreases the statistical power of a study. Despite this, we still observed statistically significant differences in liver metabolism between cirrhotic and non-cirrhotic subjects. Second, we did not correlate PET/CT imaging measurements with laboratory based or histopathological measurements of liver pathophysiology. This may be useful to assess in larger scale prospective studies. Third, the method of liver segmentation and measurement on a slice by slice basis was very time consuming and may be impractical to utilize in routine practice. However, automated computer-assisted techniques will likely become available for this purpose, which can make this global assessment approach practical in the clinical setting.

Conclusions

Subjects with cirrhosis had lower average hepatic SUV-mean and GHG compared to non-cirrhotic subjects. We hypothesize that presence of fibrosis, reduction of active inflammation, and decreased hepatic metabolism and function are potential causes of the lower FDG uptake in cirrhotic livers. Our results also indicate that extrahepatic cancer status does not influence FDG uptake in the non-cirrhotic liver in subjects without hepatic metastases. The study also showed that volume-based FDG-PET/CT parameters may be useful to evaluate the global metabolic activity of the liver in non-cirrhotic and cirrhotic subjects. In particular, GHG based on FDG-PET/CT may be useful to serve as a biomarker of the severity of end-stage liver disease. Further prospective large scale studies will be required for validation and determination of diagnostic performance of this approach.

Conflict of interest The authors declare no conflict of interest.

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