RESEARCH ARTICLE

Mean standardized uptake value (SUVmean) and global hepatic glycolysis as potential imaging markers reflecting hepatic functional capacity: evidence from 18F-FDG PET/CT

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Abstract

Background: Hepatic cirrhosis caused by hepatic steatosis and hepatitis is irreversible. Early and non-invasive diagnosis of these diffuse hepatopathies calls for possible imaging markers. The purpose of this study was to explore the changes in global hepatic glucose metabolism following hepatic steatosis, hepatitis, or cirrhosis on ^{18}F-2-fluoro-2-D-deoxyglucose-positron emission tomography (^{18}F-FDG PET)/computed tomography (CT).

Methods: A total of 178 subjects (51 healthy controls, 41 patients with hepatic steatosis, 50 patients with chronic hepatitis, and 36 patients with hepatic cirrhosis) were recruited, and their hepatic ^{18}F-FDG PET/CT images were reviewed retrospectively. The hepatic volume (HV; cm^3), mean standardized uptake value (SUV_{mean}) in the global liver, and accordingly, global hepatic glycolysis (GHG; cm^3) were measured. SPSS 19.0 was used for statistical analysis with ANOVA and LSD t-tests, and $p < 0.05$ was considered statistically significant.

Results: Statistical differences were observed in SUV_{mean} among the hepatic steatosis group (2.44 ± 0.40), hepatitis group (2.47 ±0 .37), control group (2.23 ± 0.42), and hepatic cirrhosis group (2.01 ± 0.36) except between the steatosis group and hepatitis group. Statistical differences were observed in GHG among the hepatic steatosis group (2,918.44 ± 962.67), hepatitis group (2,466.66 ± 668.33), control group (2,230.46 ± 549.47), and hepatic cirrhosis group (1,693.81 ± 666.21) except between the hepatitis group and control group.

Conclusions: SUV_{mean}, together with GHG, can reflect hepatic functional capacity, which can be regarded as potential imaging markers in assessing diffuse hepatopathies. HIPPOKRATIA 2018, 22(4): 162-166.

Keywords: ^{18}F-FDG PET/CT, positron emission tomography, computed tomography, hepatic functional capacity, standardized uptake value, global hepatic glycolysis

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Introduction

Hepatic cirrhosis refers to the end stage of chronic liver injury with a complex pathophysiological process. The causes of hepatic cirrhosis include alcoholic or non-alcoholic hepatic steatosis and hepatitis[1]. In Western countries, hepatic steatosis is the primary cause of hepatic cirrhosis, characterized by hepatocyte inflammation due to accumulation of triglycerides in the cytoplasm of hepatocytes. In Asian countries, chronic hepatitis, especially hepatitis B, is a common cause of hepatic cirrhosis. More and more studies revealed that hepatic steatosis or hepatitis, hepatic fibrosis, and hepatic cirrhosis are dynamic processes and that these pathological conditions may be reversible before cirrhosis occurs[2,3]. It is thus essential to determine the cause and stage of hepatic cirrhosis and monitor liver function during treatment. Beyond laboratory blood tests for liver function and invasive liver biopsy for pathology, it is also important to find some accurate and non-invasive imaging markers which could reflect liver function as well as pathological features in the different diffuse hepatopathies.

Imaging examinations such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and single-photon emission CT (SPECT) have been widely applied in clinical studies and animal experiments evaluating the liver morphology and quantifying the liver functional capacity after the development of hepatic cirrhosis[4-7]. Positron emission tomography/CT (PET/CT) is a practical tool in clinical practice that has been used for the diagnosis, staging, and prognostic evaluation of malignancies, and increasing attention has been paid to its application in infectious and inflammatory diseases[8]. ^{18}F-2-fluoro-2-D-deoxyglucose (^{18}F-FDG) is a common radiotracer used in PET that can provide quantified information on the glycolytic rate of organs or lesions in vivo[8,9]. Under normal condition, the uptake of FDG is diffuse and high in the liver. However, this diffuse FDG uptake may vary under different pathophysiological conditions[10,11]. Previous related studies have even shown controversial results in diffuse hepatopathies. Bural et

al have found that the liver has a higher FDG uptake in patients with diffuse hepatic steatosis as compared with healthy controls[12]. Keramida et al held similar conclusions, although they found it was maximum standardized uptake value, not mean standardized uptake value (SUV_{mean}) that showed this difference more obviously[13-15]. However, other investigators have shown that the occurrence and progression of hepatic steatosis have no significant influence on glucose metabolism by the liver[16-18].

In consideration of this, we measured the overall glucose metabolism of liver on ^{18}F-FDG PET/CT in patients with hepatic steatosis, chronic hepatitis B, and hepatic cirrhosis, and made a comparison with healthy controls. We aimed to evaluate global hepatic glucose metabolism quantitatively and found some possible imaging markers to diagnose and monitor these diffuse hepatopathies in clinics non-invasively.

Materials and Methods

Clinical information

We enrolled consecutive patients who underwent ^{18}F-FDG-PET/CT for physical examination, tumor staging or further evaluation of liver diseases in our hospital from March 2016 to December 2016 and their ^{18}F-FDG-PET/CT findings and clinical information were retrospectively reviewed. The study was approved by the Medical Ethics Committee of Zhongshan Hospital Xiamen University (decision No: 2016017, date: 04/03/2016). The exclusion criteria were i) intrahepatic space-occupying lesions, ii) concomitant liver diseases, iii) any history of liver surgery, iv) radiotherapy and/or chemotherapy within previous six months, and v) subjects with bad co-registration of PET and CT images in diaphragm due to motion artifacts. Among evaluated subjects, 45 subjects were excluded, and we finally enrolled into the study a total of 178 subjects, including 41 subjects with diffuse hepatic steatosis [the mean liver CT attenuation value was lower than the mean spleen attenuation value, negative blood test for hepatitis B surface antigen (HBsAg)], 50 subjects with chronic hepatitis [confirmed by histopathological results and positive blood tests for HBsAg, hepatitis B viral protein (HBeAg), and hepatitis B virus antigen (anti-HBC) with a history more than six-month], 36 subjects with hepatic cirrhosis (confirmed by histopathological results), and 51 healthy controls with normal liver function, negative HBsAg and no history of liver disease (the mean liver attenuation value was not lower than the mean spleen attenuation value). There is evidence that malignancy may not influence FDG uptake in the liver[12], and thus extrahepatic malignancy was not excluded. The demographics of participants in each group are shown in Table 1.

Table 1: Demographics of the 178 participants recruited in the study.

Group	n	Gender (M/F)	Age (years)
Hepatic steatosis	41	22/19	52.0 ± 12.4
Chronic hepatitis	50	21/29	55.6 ± 11.5
Hepatic cirrhosis	36	23/13	57.3 ± 11.2
Control	51	25/26	53.4 ± 12.5
Total	178	91/87	54.5 ± 12.0

Values for age are mean ± standard deviation, n =number, M =male, F =female.

Image acquisition and analysis after PET/CT

All examinations were performed on Discovery Elite PET/CT (GE Discovery PET/CT 690; GE Healthcare, Waukesha, Wisconsin, USA). Patients fasted for over six hours before the intravenous injection of FDG at about 6 MBq/kg. Before FDG injection, blood glucose was controlled at less than 150 mg/dl. PET/CT was performed from the top of the head to the mid-thigh with three-dimensional PET data collection and an axial CT slice thickness of 3.8 mm. The region of interest (ROI) was selected along the borderline of the liver in each axial CT image after exclusion of the liver hilum, inferior vena cava, and gallbladder on the accompanied workstation. After delineating all ROIs axially, one three-dimensional ROI was generated and further adjusted from the coronal and sagittal views accordingly. Thus, the hepatic volume (HV) and SUV_{mean} were auto-generated based on this three-dimension ROI. The product of HV and SUV_{mean} was global hepatic glycolysis (GHG =HV x SUV_{mean}; cm^3). ROI illustrations are shown in Figure 1. Each axial ROI for the same subject was delineated twice by one experienced radiologist with board certifications in both

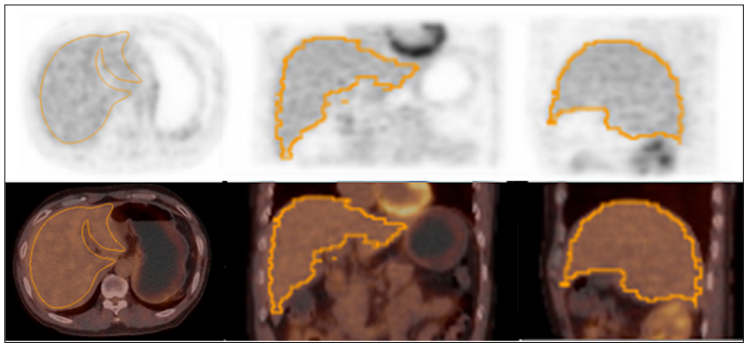

Figure 1: Axial, coronal, and sagittal views of regions of interest (ROIs) delineating liver boundaries are drawn manually on every axial slice to calculate hepatic volume (HV) and mean standardized uptake value (SUV_{mean}) in a whole liver. The first row are ^{18}F-2-fluoro-2-D-deoxyglucose-positron emission tomography (^{18}F-FDG PET) of liver and the second row are fused images of PET and computed tomography (CT).

Nuclear Medicine and Radiology, and the average value for this two-time results was finally adopted.

Statistical Analysis

Statistical analysis was performed with the IBM SPSS Statistics for Windows, Version 19.0, (IBM SPSS, IBM Corp., Armonk, NY, USA). The mean and standard deviation of each parameter were calculated in each group. One-way analysis of variance was employed for comparisons of SUV_{mean}, HV, and GHG among groups, followed by the Fischer's least significant difference (LSD) test when a significant difference was preset. A value of $p < 0.05$ was considered statistically different. A value of $p < 0.01$ was considered significantly different.

Results

The results from the ANOVA are shown in Table 2. As shown in Figure 2, the HV was 1,188.81 ± 292.67 cm^3, 1,011.54 ± 283.22 cm^3, 1,018.70 ± 272.95 cm^3, and 861.48 ± 273.41 cm^3, in the hepatic steatosis group, hepatitis group, control group, and cirrhosis group, respectively, and statistical differences were observed between the groups except for hepatitis and control groups. The SUV_{mean} values were 2.44 ± 0.40, 2.47 ± 0.37, 2.23 ± 0.42, and 2.01 ± 0.36, in the hepatic steatosis group, chronic hepatitis group, control group, and cirrhosis group, respectively, and statistical differences were observed between any two groups except for steatosis and hepatitis groups. The GHG was 2,918.44 ± 962.67 cm^3, 2,466.66 ± 668.33 cm^3, 2,230.46 ± 549.47 cm^3, and 1,693.81 ± 666.21 cm^3 in the hepatic steatosis group, chronic hepatitis group, control group, and cirrhosis group, respectively, and significant differences were observed between the groups except for hepatitis and control groups.

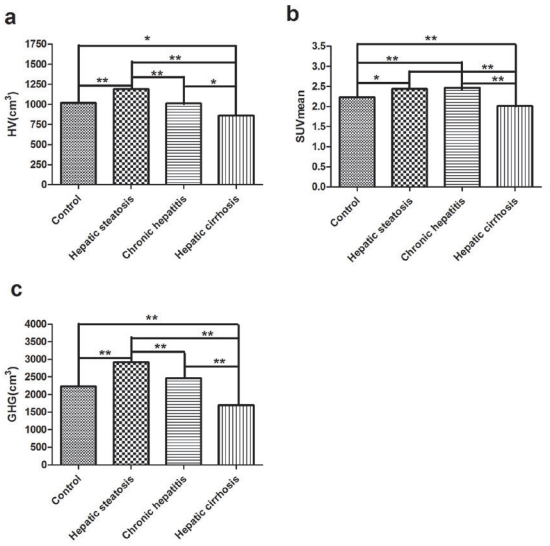

Figure 2: The results of Fischer's least significant difference (LSD) test when a significant difference was observed in ANOVA.
*: statistical difference; **: significant statistical difference.

Discussion

As known, there is dynamic progress from diffuse hepatic steatosis and hepatitis to hepatic fibrosis and eventually to hepatic cirrhosis. Histologically, hepatocytes may become swollen, and some matrix metalloproteinases may degrade the extracellular matrix to remove the fibrous tissues at early stages of diffuse hepatopathies, which is a compensatory process in the presence of hepatic steatosis or chronic hepatitis[1]. Anatomically, compensatory enlargement of the liver is present in the early stages and shrinkage in the liver volume may occur after cirrhosis, which is consistent with our findings for HV. However, our HV results showed that this enlargement was more apparent and possibly more compensatory for hepatic steatosis than for hepatitis. It was also expected that hepatitis and control groups showed no difference in HV, as morphology imaging markers can hardly differentiate hepatitis which may reflect more robust changes in liver function than in structure.

Currently, evaluation of liver function in patients with liver diseases is mainly dependent on blood test results. For hepatic cirrhosis, the Child-Pugh grading system and Model for End-Stage Liver Disease system, which both employ laboratory findings, are widely applied in the clinical practice. Increasingly, investigators proposed that both systems had limitations in the evaluation of the prognosis of patients with hepatic cirrhosis and needed to be improved[19]. Liver biopsy has been the gold standard in the diagnosis of diffuse hepatopathies; however, it is invasive and prone to sampling error, which significantly limits its wide application in clinical practice. Our study

Table 2: One-way analysis of variance between the hepatic steatosis group, chronic hepatitis group, control group, and hepatic cirrhosis group.

Group	HV (cm^3)	SUV_{mean}	GHG (cm^3)
Hepatic steatosis	1,188.81 ± 292.67	2.44 ± 0.40	2,918.44 ± 962.67
Chronic hepatitis	1,011.54 ± 283.22	2.47 ± 0.37	2466.66 ± 668.33
Control	1,018.70 ± 272.95	2.23 ± 0.42	2230.46 ± 549.47
Hepatic cirrhosis	861.48 ± 273.41	2.01 ± 0.36	1693.81 ± 666.21
F value	8.824	12.302	18.573
p value	0.003	0.005	<0.001

HV =hepatic volume, SUV_{mean} =mean standardized uptake value, GHG =global hepatic glycolysis.

showed that use of SUV_{mean} and GHG as imaging markers could reflect the liver glucose metabolism in patients with diffuse hepatopathies. We speculated that the development of a standard reference range for SUV_{mean} and GHG would be helpful in the evaluation of liver function, on the basis of liver metabolism, which would allow accurate diagnosis and thorough assessment of diffuse hepatopathies, and possibly facilitate the clinical follow-up and prognosis estimation of patients with hepatic cirrhosis.

Hepatic steatosis and chronic hepatitis are common causes and reversible stages of hepatic cirrhosis. Our results accord with previous evidence which showed that the SUV_{mean} and hepatic metabolism value products (similar to GHG in our study) in patients with diffuse hepatic steatosis increased as compared with those in healthy controls[12-15]. According to Bural et al, this increase of liver FDG uptake was ascribed to diffuse inflammation in the liver when hepatic steatosis occurred[12]. We herein doubt this explanation and suggest that compensatory liver function should meantime be highlighted based on the results in hepatic steatosis and hepatitis as highlighted in our study. Admittedly, the consistent increase in SUV_{mean} for hepatic steatosis and hepatitis (compared to controls) is mainly ascribed to active inflammation in the liver[12,15]. However, increased GHG for hepatic steatosis without a difference in GHG for hepatitis (compared to controls) may reflect their different pathophysiological functional conditions with higher (for hepatic steatosis) and normal (for hepatitis) global liver metabolic functions. SUV_{mean}, together with GHG, may indicate and differentiate hepatic steatosis, hepatitis, and healthy controls. Moreover, the obviously decreased SUV_{mean} and GHG in patients with hepatic cirrhosis indicate their potential roles as imaging markers in evaluating hepatic cirrhosis, which is pathologically related with decreased hepatocyte metabolic function and relieving inflammation after the formation of pseudolobules and hepatic fibrosis. We speculate that the reduction of SUV_{mean} is more ascribed to the fibrous tissue deposition with low metabolism in the liver, and that decreased GHG is more correlated to low glucose metabolism function of hepatocytes after cirrhosis[20].

Previous studies have shown that radiotracers, such as 2-[^{18}F]-fluoro-2-deoxy-D-galactose (^{18}F-FDGal) and 8-cyclopentyl-3-(3-fluoropropyl)-1-propylxanthine ([^{18}F]-CPFPX), can be used for the quantitative evaluation of the liver metabolism[21-23]. Currently, ^{18}F-FDG is the most widely used radiotracer in clinical practice. Findings from studies on different tracers are consistent with ours, suggesting that it is feasible and scientifically valid to use measurements related to the liver metabolism to reflect liver pathology, and has potentially broad clinical applications[21,22]. In addition, hepatocytes are cells with an active metabolism, and there is focal heterogeneity in FDG uptake by the liver tissue[10,11]. Sorensen et al also found that, when compared with controls, the focal heterogeneity in liver FDG uptake increased in patients with hepatic cirrhosis[21]. Thus, SUV_{mean}, together with GHG, was employed in the present study to evaluate the global liver metabolism functions under different pathological conditions. This is helpful in order to reduce sampling error and provide more accurate information than the evaluation of focal radioactive aggregation. GHG based on global liver metabolism is thus preferable to SUV_{mean}, to reflect actual metabolic function by taking into consideration liver volume.

Our study had some limitations. First, the sample size was small, especially for hepatic cirrhosis. Group subdivisions should be made according to the course or the severity of different diffuse hepatopathies in a future study[24]. Also, hepatic fibrosis was not discussed in our study, which is a complicated and transitional process from hepatitis to hepatic cirrhosis. The criterion for staging hepatic fibrosis in pathology is wide and complicated. We speculate that imaging results of fibrosis in the early stage should be similar to those of hepatitis and that cut-off values for late-stage fibrosis should be merged into those of hepatic cirrhosis[25]. Our future dedicated analysis will focus on this field. Finally, this was a retrospective study, and information regarding changes in liver function was not available in these patients. That is, we failed to investigate dynamic changes in liver function in these patients. This will also be the focus of a future study.

In conclusion, increased SUV_{mean} indicates increased FDG uptake in the liver during hepatic steatosis and chronic active hepatitis, which may be explained by hepatocyte inflammation. However, the difference between GHG in hepatic steatosis and chronic active hepatitis might indicate different liver metabolic functions. SUV_{mean} and GHG are reduced in patients with liver cirrhosis, suggesting reduced FDG uptake and further global liver metabolic functions. This may be ascribed to the formation of pseudolobules and deterioration of hepatic fibrosis. Our study finally suggests that SUV_{mean} and GHG can be taken as useful imaging markers to evaluate hepatic functional capacity in the diffuse hepatopathies.

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