Clinical Usefulness of ^{18}F-FDG PET/CT for the Screening of Metabolic Liver Disorders

Sumiko Irie[1], Naomi Hayashida[1], Tetsuko Shinkawa[1,3], Toshihiko Kamasaki[1], Akihide Matsunaga[4], Izumi Miyamoto[5], Toshiya Usui[5], Kenya Chiba[5], Takashi Kudo[2] and Noboru Takamura[1]

[1]Department of Global Health, Medicine and Welfare and [2]Department of Radioisotope Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[3]Department of Nursing, Nagasaki University School of Health Sciences, Nagasaki, Japan
[4]Nagasaki University School of Medicine, Nagasaki, Japan
[5]Nishi-Isahaya Hospital PET/CT Diagnostic Imaging Center, Isahaya, Nagasaki, Japan
takamura@nagasaki-u.ac.jp

Objective: Non-alcoholic fatty liver disease (NAFLD) comprises a wide spectrum of liver injuries, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). In clinical practice, there is so far no method of differentiating reliably between simple steatosis and steatohepatitis solely on the basis of non-invasive diagnostic tests. Thus, the development of a conventional screening method for NAFLD is definitely needed for its effective and early diagnosis. The aim of this study is to clarify the capability of 18F-FDG PET/CT for the screening of NAFLD. **Methods:** We explored the relationship among liver images on FDG-PET/CT screening, individual information, and laboratory findings from 123 Japanese male. Images of FDG-PET/CT were assigned according to the pattern of FDG uptake, i.e., "homogenous pattern" and "heterogenous pattern". Differences in hematological and laboratory values between the homogenous pattern group and the heterogenous pattern group were statistically evaluated. **Results:** Body mass index, diastolic blood pressure, and mean blood pressure were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group. Also, log aspartate aminotransferase, log alanine aminotransferase, and log gamma-glutamyltranspeptidase values were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group. Furthermore, hemoglobin, log triglyceride, uric acid, and blood glucose were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group. High-density-lipoprotein cholesterol was significantly higher in the homogeneous pattern group than in the heterogeneous pattern group. **Discussion:** Heterogeneous 18F-FDG uptake on PET/CT images of the liver may represent the findings of NAFLD.
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1. Introduction

Metabolic liver disorder (MLD) such as non-alcoholic fatty liver disease (NAFLD) comprises a wide spectrum of liver injuries, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) (Yilmaz et al. 2012). Clinically, most patients with MLD exhibit no liver symptoms. The disease is typically suspected in patients with metabolic syndrome (MS) on the grounds of mildly raised transaminase and/or gamma-glutamyltranspeptidase (γ-GTP) levels (Adams, 2007; Perlemuter, 2007). Liver ultrasonography results correlate well with the histological finding of fatty infiltration, but they are not sufficiently sensitive to detect inflammation and fibrosis (Kim, 2009). However, in clinical practice, there is so far no method of differentiating reliably between simple steatosis and steatohepatitis solely on the basis of non-invasive (e.g., laboratory chemical) diagnostic tests, only by a liver biopsy (Tannapfel, 2011). Thus, the development of a conventional screening method for MLD such as NAFLD is definitely needed for its effective and early diagnosis.

It has been reported that PET with ^{18}F fluorodeoxy glucose (18F-FDG) shows accumulation of the tracer not only in malignant tumors but also in inflammatory lesions (Cook, 2007; Ichiya, 1996), because ^{18}F-FDG displays glucose uptake by cells and therefore local metabolic activity (Som et al. 1980). Several studies have been performed to evaluate the association between diffuse fatty infiltration of the liver and ^{18}F-FDG uptake in the liver, through the evaluation of standardized uptake value (SUV) (Abele, 2010; Abikhzer, 2011; Kamimura,. 2010). Kamimura et al. found that ^{18}F-FDG uptake of subjects with MS was significantly higher than that of subjects without MS and concluded that a subject with a high liver ^{18}F-FDG uptake should be screened for MS (Kamimura, 2010). On the other hand, Abele et al. reported that no

association between liver attenuation and ^{18}F-FDG uptake measured in terms of SUV was observed (Abele, 2010). The discrepancy of these results is probably caused by the inconsistent evaluation of SUV, because SUV may vary by the method of region of interest (ROI) placement, protocol for analyzing SUV values, and types of PET/CT scanner.

Through the PET/CT screening among the general population, we noticed that a considerable portion of the healthy population shows heterogeneous ^{18}F-FDG uptake, as well as homogeneous uptake in the liver and assumed that the ^{18}F-FDG uptake pattern may be a hint for the development of the conventional screening for MLD. However, there has been no previous evaluation of the usefulness of visual FDG uptake pattern as a screening of MLD.

In this study, we evaluated a general population who visited hospital for cancer screening, to clarify the availability of ^{18}F-FDG PET/CT for the screening of MLD.

2. Material and Methods

Study population

Prior to the study, ethical approval was obtained from the ethics committee of Nagasaki University (project registration number: 08102891). The study was conducted during the cancer screening program for individuals by PET/CT at the Nishi-Isahaya Hospital PET/CT diagnostic imaging center in Nagasaki Prefecture, Japan.

We performed a retrospective case-control study to compare hepatic FDG uptake patterns in subjects. We evaluated 298 healthy male subjects who underwent PET/CT screening between 2005 and 2010 at Nishi-Isahaya Hospital PET/CT Diagnostic Imaging Center, Nagasaki, Japan. Participants who were shown to be seropositive with hepatitis B virus and/or hepatitis C virus antibodies were excluded from the study, Participants who were pointed out malignancies were also excluded.

FDG PET/CT

The PET/CT imaging study was performed on a PET/CT scanner (Discovery ST; GE Healthcare [WI. USA]). The PET/CT imaging was started 50 min after intravenous injection of ^{18}F-FDG through an anterior cubital vein. The FDG doses were calculated by each subject's weight (4 MBq/kg), with individual doses ranging from 182.1 to 400 MBq. The subjects fasted for 6 hours before FDG injection and the glucose level of each subject was measured before FDG injection. The acquisition time was 2.5 min per bed position, with 7-8 bed positions, covering the whole body in a three-dimension (3D) mode. The acquisition parameters for dual-detector helical CT were 140 kV, 30 mA, 3.75-mm slice thickness, and a pitch of 1.5. The PET/CT images were evaluated on a Xeleris workstation (GE Healthcare). Details of this procedure are described elsewhere (Chiba, 2010; Minami, 2007).

The PET/CT images of each study participant were independently assigned according to the pattern of FDG uptake, i.e., "homogeneous pattern" and "heterogeneous pattern", by three researchers (N.H., A.M., and S.I.), who were masked from the past history and laboratory data of each study participant. The definition of the homogeneous pattern was "FDG uptake diffusely accumulated with pale monotony in the liver" and that of the heterogenous pattern was "FDG uptake with irregular and nodular accumulation in the liver". In cases with a heterogeneous pattern, the size of each nodule was less than 1.5 cm and no obvious additional uptake was identified. The typical case of "homogeneous pattern" and "heterogeneous pattern" were represented on the Figures 1 and 2 respectively. All those PET images, fusion PET/CT images and CT images are presented with same window level/width.

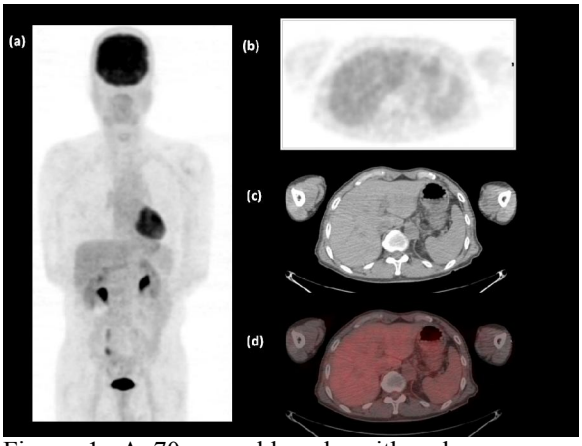

Figure 1. A 70-year-old male with a homogenous pattern on the 18F-FDG–PET/CT image of the liver. (a) PET volume image, (b) PET cross-section image, (c) CT images, and (d) fusion PET/CT image.

Image with consistent interpretation among two or three of the three observers (N.H., A.M., and S.I.) were finally assigned as either having the homogeneous pattern or heterogeneous pattern for further evaluation. Finally, we included 53 cases with a homogeneous pattern and 70 cases with a heterogeneous pattern. For the remaining 175 cases, the three observers could not reach agreement of the diagnosis, thus not included in the further evaluation.

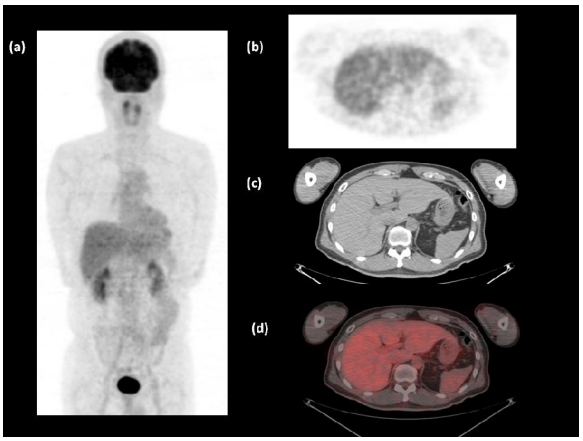

Figure 2. A 55-year-old male with a heterogenous pattern on the 18F-FDG–PET/CT image of the liver. (a) PET volume image, (b) PET cross-section image, (c) CT images, and (d) fusion PET/CT image. Window level and width are same as Figure 1.

Data collection and laboratory measurement

At each examination, a trained nurse collected individual information including smoking status and current treatment for hypertension, dyslipidemia, and diabetes mellitus.

Body weight and height were measured and body mass index (BMI; kg/m2) was calculated as an index of obesity. Systolic blood pressures (SBP) and diastolic blood pressures (DBP) were recorded at rest. Mean blood pressures (MBP) was calculated as DBP + (SBP-DBP) / 3. Blood samples were collected from the subjects after fasting overnight. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), γ-GTP, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), white blood cells (WBC), hemoglobin (Hb), platelets (PLT), blood urea nitrogen (BUN), uric acid (UA), creatinine (Cr), blood glucose (Glu), C-reactive protein (CRP), L triglyceride (TG), high-density-lipoprotein cholesterol (HDL-C), and low-density-lipoprotein cholesterol (LDL-C) were measured using standard laboratory procedures. In addition, tumor markers such as carcinoembryonic antigen (CEA), α-fetoprotein (AFP), and carbohydrate antigen 19-9 (CA19-9) were measured by standard laboratory procedures.

Statistical analysis

Results are expressed as mean ± standard deviation or median (25th to 75th quartiles) and differences in laboratory values between the homogeneous pattern and heterogeneous pattern were evaluated using the t-test or Mann-Whitney U test. Differences in the smoking status, alcohol intake, and the ratio of current treatment for hypertension (HT), diabetes mellitus (DM), and dyslipidemia (DL) in the homogeneous pattern and heterogeneous pattern were evaluated using the $\chi 2$ test. Analysis of covariance (ANCOVA) was adjusted for age and HT to evaluate the FDG pattern and other parameters. Because AST, ALT, TB, γ-GTP, TG, and CRP levels were distributed in a skewed manner, logarithmic transformation was performed for ANCOVA. A probability value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS software, v. 18.0 for Windows (SPSS Japan, Tokyo, Japan).

3. Results

Characteristics of the study participants are shown in Table 1. Age was not significantly different between the groups (57.6 ± 11.1 years vs. 56.3 ± 9.0 years, P= 0.49). Body mass index, DBP, and MBP were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group. There was no difference in alcohol intake between the groups.

Table 1. Characteristics of the study participants.

Variables	Homogenous (n=53)	Heterogenous (n=70)	*P* Value
Age (y)	57.6±11.1	56.3±9.0	0.49
BMI (kg/m^2)	20.9±2.0	27.3±2.5	<0.001
SBP (mmHg)	124.7±14.2	128.9±14.9	0.12
DBP (mmHg)	77.5±10.1	82.9±12.3	0.009
MBP (mmHg)	91.4±16.4	98.2±11.3	0.011
Smoker†, n (%)	42 (80.8)	49 (70.0)	0.18
Alcohol intake‡, n (%)	39 (76.5)	54 (77.1)	1.0
HT, n (%)	9 (18.0)	24 (34.3)	0.049
DL, n (%)	4 (8.0)	7 (10.4)	0.67
DM, n (%)	1(1.9)	4 (5.7)	0.29

BMI, body mass index; SBP, systolic blood pressure; DBP diastolic blood pressure; MBP, mean blood pressure; HT, current treatment for hypertension; DL, current treatment for dyslipidemia; DM, current treatment for diabetes mellitus.
Smoker: past and current
Alcohol intake: 1 day or more/ week
Values are means ±standard deviation or number (percentage

As shown in Table 2, AST, ALT, and γ-GTP levels were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group. Hemoglobin, TG, UA, Glu, and CRP levels were also significantly higher in the heterogeneous pattern group than in the homogeneous pattern group. On the other hand, HDL-C was significantly higher in the homogeneous pattern group than in the heterogeneous pattern group.

Table 2. FDG uptake pattern and laboratory finding.

Variables	Homogenous (n=53)	Heterogenous (n=70)	*P* Value
AST (U/L)	20.0 (17.5-23.0)	25.5 (21.0-36.3)	<0.001
ALT (U/L)	16.0 (13.0-21.0)	31.0 (22.8-46.0)	<0.001
TB (mg/ L)	8.00 (6.00-10.00)	7.00 (6.00-9.00)	0.18
γ-GTP (U/L)	26.0 (21.5-39.0)	57.5 (36.0-87.3)	<0.001
ALP (U/l)	219.9±67.6	214.1±52.4	0.61
LDH (U/L)	177.1±27.7	186.7±33.8	0.084
Hb (g/ L)	148±14	155±10	0.002
TG (g/L)	0.87 (0.65-1.11)	1.26 (0.94-2.06)	<0.001
HDL-C (g/L)	0.60±0.12	0.50±0.11	<0.001
LDL-C (g/L)	1.23±0.34	1.24±0.36	0.82
BUN (g/dL)	1.48±0.41	1.49±0.37	0.89
UA (mg/L)	55.2±9.3	66.4±14.7	<0.001
Cr (mg/L)	7.78 ±1.16	8.23±1.47	0.062
Glu (g/L)	0.92±0.11	1.04±0.25	0.001
CRP (mg/L)	0.50 (0.50-1.38)	1.00 (0.50-1.75)	0.033
CEA (μg/L)	1.80 (0.95-2.80)	1.50 (0.90-2.30)	0.033
AFP (μg/L)	4.30 (2.85-6.35)	4.15 (3.28-5.40)	0.75
CA 19-9 (U/L)	53 .0 (26.5-100.0)	76.0 (38.8-121.3)	0.27

AST, aspartate aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin; γ-GTP, γ-glutamyltranspeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; WBC, white blood cells; Hb, hemoglobin; Plt, platelets; TG, triglyceride; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; BUN, blood urea nitrogen; UA, uric acid; Cr, creatinine; Glu, blood glucose; CRP, C-reactive protein; CEA, carcinoembryonic antigen; AFP, α-fetoprotein; CA19-9, carbohydrate antigen 19-9.
Values are means ±standard deviation or median (25th-75th percentile).

There were no significant differences in TB, ALP, LDH, TC, LDL-C, BUN, and Cr between the groups. Also, there were no significant differences of tumor markers, such as CEA, AFP, and CA 19-9, between the groups. The frequency of hypertension was marginally higher in the heterogeneous pattern group than in the homogeneous pattern group (34.3% vs. 18.0%, P=0.049). On the other hand, there were no significant differences between the groups in the ratio of smoking, alcohol intake, DL, and DM.

When adjusted by HT and age, BMI, DBP, and MBP were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group (BMI: 27.1±0.3 k/m2 vs. 21.1±0.3 k/m2, P<0.001; 82.4±1.3 mmHg vs. 77.6 ±1.6 mmHg, P=0.024; 97.6±1.6 mmHg vs. 91.8±1.9 mmHg, P=0.021). Also, log AST, log ALT, and log γ-GTP were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group (log AST: 1.45 ±0.02 vs. 1.34 ±0.03, P=0.001; log ALT: 1.51±0.03 vs. 1.27±0.03, P<0.001; log γ-GTP: 1.77±0.04 vs. 1.52±0.04, P<0.001). Furthermore, Hb, log TG, UA, and Glu were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group (Hb: 155±10 g/L vs. 147±20 g/L, P=0.001; log TG: 2.14±0.03 vs. 1.93±0.03, P<0.001; UA: 66.2±1.7 mg/L vs. 55.7±1.9 mg/L, P=0.001; Glu: 1.04±0.25 g/L vs.0.93±0.29 g/L, P=0.004). The HDL-C level was significantly higher in the homogeneous pattern group than in the heterogeneous pattern group (0.60±0.17 g/L vs. 0.50±0.14 g/L, P<0.001). On the other hand, log CRP was no longer significantly different between the homogeneous pattern group and the heterogeneous pattern group (-1.08±0.05 vs. -0.95±0.04, P=0.11) (Table 3).

4. Discussions

We evaluated the hepatic ^{18}F-FDG uptake pattern on PET/CT and found that heterogeneous FDG uptake in the liver showed higher BMI, DBP, MBP, TG, UA, and Glu and lower HDL-C, as well as higher AST, ALT, and γ-GTP. Because there is no difference of alcohol intake frequency between the groups, our current results suggest that heterogeneous ^{18}F-FDG uptake on PET/CT in the liver may represent the findings of MLD.

Table 3. FDG uptake pattern adjusted for HT and age. Values are means ±standard error.

Variables	Homogenous	Heterogeneous	*P* Value
BMI	21.1±0.3	27.1±0.3	<0.001
SBP	125.3±1.9	128.3±1.5	0.21
DBP	77.6±1.6	82.4±1.3	0.024
MBP	91.8±1.9	97.6±1.6	0.021
log AST	1.34 ±0.03	1.45±0.02	0.001
log ALT	1.27±0.03	1.51±0.03	<0.001
log T-Bil	-0.11±0.02	-0.14±0.02	0.21
log γ-GTP	1.52±0.04	1.77±0.04	<0.001
ALP	220.4±8.6	213.0±7.2	0.51
LDH	177.8±4.5	186.5±3.8	0.15
Hb	147±20	155±10	155±10
log TG	1.93±0.03	2.14±0.03	<0.001
HDL-C	0.60±0.17	0.50±0.14	<0.001
LDL-C	1.21±0.55	1.21±0.55	0.60
BUN	1.47±0.54	1.51±0.45	0.56
UA	55.7±1.9	66.2±1.7	<0.001
Cr	7.78 ±0.19	8.21±0.16	0.091
Glu	0.93±0.29	1.04±0.25	0.004
log CRP	-1.08±0.05	-0.95±0.04	0.006

We showed that BMI, DBP, MBP, and UA were significantly higher in the heterogeneous pattern group than in the homogeneous pattern group, whereas HDL-C was significantly higher in the homogeneous pattern group than in the heterogeneous pattern group. These results strongly suggest that findings of heterogeneous ^{18}F-FDG uptake in the liver by PET/CT are related with components of MS. It is well known that fatty liver is closely related with the risk factors of MS, such as obesity, hypertension, dyslipidemia, and glucose intolerance (Baba, 2007; Kamimura, 2010; Kim et al. 2009; Marchesini, 2001; Radu, 2008; Tsuneto, 2010). Furthermore, Angelico et al. evaluated clinical features in subjects with different severities of steatosis diagnosed by ultrasonography and showed a progressive increase in the prevalence of obesity, type 2 diabetes, ALT elevation, and hypertriglyceridemia from the control group to the groups with mild, moderate, and severe steatosis (Angelico, 2003). Further studies are needed to clarify the possible role of ^{18}F-FDG PET/CT. Our results showed that ^{18}F-FDG PET/CT may be useful to be a screening tool of metabolic disorders.

Interestingly, we showed that Hb was significantly higher in the heterogeneous pattern group than in the homogeneous pattern group. Recently, Yilmaz et al. investigated the differences between patients with biopsy-proven NAFLD with and without MS and found that hemoglobin is the main independent predictor of the severity of the liver lesions in patients with biopsy-proven NAFLD without MS (Yilmaz, 2012). Previous studies have shown that hemoglobin may serve as a marker for disease associated with glycemia, oxidative stress, hypertension, insulin resistance, obesity, and diabetes (Alayash, 2001; Watanabe, 2007; Zhang, 2004). The possible mechanism leading to increased hemoglobin levels in NAFLD needs further investigations, but it might be a consequence of hepatic hypoxia resulting in a stimulation of erythropoietin production.

Radiological evaluation of NAFLD is widely used. However, because its accuracy in establishing a diagnosis and its utility in the management of NAFLD has not been well established (Saadeh, 2002), pathological evaluation through liver biopsy is necessary for the accurate diagnosis of NAFLD (Angulo, 2007; Pilleul, 2005). Our current results showed that ^{18}F-FDG-PET/CT may be helpful for the diagnosis of MLD. Further studies, including a comparison of ^{18}F-FDG-PET/CT images and histological findings, will be needed to evaluate the capability of ^{18}F-FDG-PET/CT for the diagnosis of MLD such as NAFLD.

There are several limitations of our study. In this study, we investigated only healthy men, since the metabolic disorder more frequently has observed the men than women. Since distribution of laboratory and biological data including liver functions is different between men and women, further studies expanding to female subjects were definitely needed. Also, we studied only cases which represent typical homogenous and heterogenous FDG uptake findings, and excluded 175 cases which every observer could not reach agreement. Furthermore, since the purpose of current study was to evaluate clinical usefulness of the visual evaluation of the heterogenous FDG uptake, we did not measure SUV values. Further studies such as evaluation of their SUV values and of "borderline" cases are needed.

Because it was a retrospective study, complete data on all variables were not obtained. We could not perform the pathological and cytological evaluations through liver biopsy. Also, we could not rule out the possibility of autoimmune hepatitis, drug-induced hepatitis, and hemochromatosis. These additional information will be available to confirm the availability of ^{18}F-FDG PET/CT for the screening of MLD.

In conclusion, we found that heterogeneous ^{18}F-FDG uptake on PET/CT in liver were related with laboratory values of MLD such as higher TG, UA, and Glu and lower HDL-C, as well as higher AST, ALT, and γ-GTP.

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Corresponding Author:
Professor Noboru Takamura
Professor and Chairman, Department of Global Health, Medicine and Welfare
Atomic Bomb Disease Institute, Nagasaki University
1-12-4 Sakamoto, Nagasaki 852-8523, Japan
E-mail: takamura@nagasaki-u.ac.jp

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