Impacts of biological and procedural factors on semiquantification uptake value of liver in fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging

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Background: Increased metabolic activity of fluorodeoxyglucose (FDG) in tissue is not only resulting of pathological uptake, but due to physiological uptake as well. This study aimed to determine the impacts of biological and procedural factors on FDG uptake of liver in whole body positron emission tomography/computed tomography (PET/CT) imaging.

Methods: Whole body fluorine-18 (^{18}F) FDG PET/CT scans of 51 oncology patients have been reviewed. Maximum standardized uptake value (SUV_{max}) of lesion-free liver was quantified in each patient. Pearson correlation was performed to determine the association between the factors of age, body mass index (BMI), blood glucose level, FDG dose and incubation period and liver SUV_{max}. Multivariate regression analysis was established to determine the significant factors that best predicted the liver SUV_{max}. Then the subjects were dichotomised into four BMI groups. Analysis of variance (ANOVA) was established for mean difference of SUV_{max} of liver between those BMI groups.

Results: BMI and incubation period were significantly associated with liver SUV_{max}. These factors were accounted for 29.6% of the liver SUVmax variance. Statistically significant differences were observed in the mean SUV_{max} of liver among those BMI groups (P<0.05).

Conclusions: BMI and incubation period are significant factors affecting physiological FDG uptake of liver. It would be recommended to employ different cut-off value for physiological liver SUV_{max} as a reference standard for different BMI of patients in PET/CT interpretation and use a standard protocol for incubation period of patient to reduce variation in physiological FDG uptake of liver in PET/CT study.

Keywords: Fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT); body mass index (BMI); incubation period; liver; maximum standardized uptake value (SUV_{max})

Introduction

Integrated positron emission tomography/computed tomography (PET/CT) is becoming an important tool for clinical investigation with increase clinical utilization. The utilisation of this integrated imaging modality in cancer diagnosis has been well documented (1) as it offers several advantages over conventional scintigraphic techniques in terms of functional and morphological interpretation in a single imaging session, faster examination, greater topographic resolution and more accurate lesion localization (2-5). Both systems complement each other in improving diagnostic capabilities by enabling accurate lesion localization

unlike standing alone for PET or CT system.

The radiotracer most frequently used in PET for oncology application is fluorine-18 fluoro-2-deoxy-D-glucose (^{18}F-FDG). ^{18}F-FDG PET is a functional imaging modality which reflects cellular glucose metabolism (6,7). In clinical practice, ^{18}F-FDG PET images are analysed either qualitatively using visual comparison of the glucose metabolism in lesions in relative to normal tissues, or semiquantitatively using standardized uptake values (SUV) (8). Accumulation and trapping of fluorodeoxyglucose (FDG) allow the visualization of increased uptake in most malignant cells compared to normal cells. However, increased FDG uptake is not limited to malignant tissue alone (9-13) but in inflammatory lesions as well (14,15).

The FDG uptake as manifested by SUV could be affected by multiple factors such as weight, plasma glucose level, length of uptake period, partial volume effects and recovery coefficient (16,17). In PET/CT imaging, liver FDG uptake is commonly used as the reference standard for diagnosis (18,19), therapy assessment (20), prognosis (21) and quality control (22). It has been reported that age (23), blood glucose level (24), body mass index (BMI) (25), incubation time (26) and hepatic steatosis (27) influence the liver FDG uptake. The association between states of overweight and obesity with non-alcoholic fatty liver has been reported (28-30) in which alteration in normal glucose metabolism was found in metabolic syndrome. The intensity of physiological FDG uptake in the liver varies. It is important to be familiar with the varying degree of FDG accumulation that represents normal distribution and physiological changes, before attempting to interpret whole-body PET imaging for abnormality detection.

The aim of this study was to evaluate the impacts of biological and procedural-related factors that influence the semiquantification value of liver involving patients undergoing whole body ^{18}F-FDG PET/CT for oncological disease using maximum SUV (SUV_{max}). Then the study was extended to determine the difference of liver SUV_{max} among four BMI groups of patients.

Materials and methods

Patients

This study includes the analysis of ^{18}F-FDG PET/CT images from 51 patients who referred for ^{18}F-FDG PET/CT whole body imaging in our centre from January 2012 to September 2013. Patients presenting metabolically FDG-avid in the liver in the context of primary or metastatic involvement were excluded from the study. Demographic data and biological parameters including age (years), weight (kg), height (cm), fasting blood glucose (mmol/L) and injected dose of FDG (millicurie), were collected from patient records. Patient consents were acquired as they were undergoing the PET/CT scan. Ethics approval was obtained from our local Medical Research Ethics Committee.

The BMI was calculated according to the formula: weight/height squared, and the nutritional status of the patients was classified according to the classification of World Health Organization (31). According to the value of BMI obtained, the patients were grouped into four categories of nutritional status; patients were considered to have underweight with a BMI less than 18.5, normal or adequate weight was considered in patients with BMI values between 18.5 to 25, overweight was considered with BMI values between 25 to 30, and patients with BMI more than 30 was considered as obese.

Patient preparation

All patients were instructed to fast for at least 6 hours prior to scanning session and only oral hydration with glucose-free water was allowed. Fasting blood glucose was checked in all patients. Dilute gastrografin solution (sodium meglumine diatrizoate; BerliMed S.A., Madrid, Spain) was given orally to the patients in three divided doses before administration of the radiopharmaceutical agent. Mean of 327.69±35.63 megabecquerel (MBq) of FDG was injected intravenously. All patients were put to rest in a special uptake room for an average of 84.05±59.57 (ranging from 30-282) minutes and empty the bladder before underwent the PET/CT imaging session.

PET/CT imaging protocol

Image acquisition was performed using an integrated Siemens Biograph 64 TruePoint PET/CT system (Siemens Medical Solutions USA Inc.) consisting of a PET scanner with lutetium oxyorthosilicate (LSO) crystals detector and a 64-multi detector CT scanner (MDCT). A scout view was performed in cranio-caudal direction to plan the study and then followed by non-contrast enhanced CT (NECT) protocol in caudo-cranial direction for the purpose of anatomical localisation and attenuation correction. Diagnostic protocol was then carried out with intravenous (IV) injection of non-ionic contrast, iohexol (omnipaque 350 mg/mL, GE Healthcare, Shanghai,
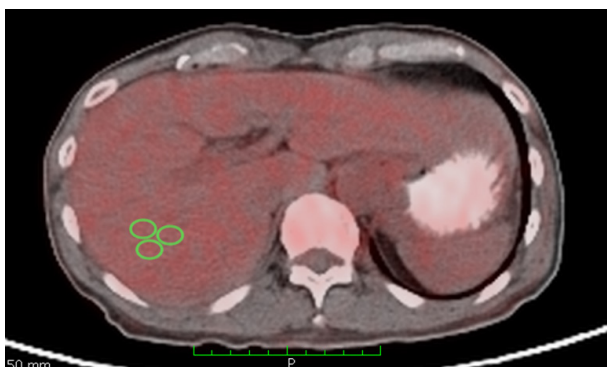
Figure 1 Three oval regions of interests were drawn over the right lobe of the liver at the segment VII to quantify the maximum standardized uptake value of the liver normalised to body weight.

China) [84.07 (mean; ranging from 50-110) mL] using dual head automatic pressure injector (Mallinckrodt, MO, USA) with flow rate at 2.5 mL per second and followed by 20 mL saline flush. Subsequently the contrast-enhanced CT scan (CECT) acquisition started in caudo-cranial direction with 80 seconds delay, ensuring optimal IV contrast in the circulation and tissue enhancement. Afterwards, a PET scan was acquired contemporaneously at 2 minutes per bed position using a three-dimensional acquisition mode. The total duration of PET/CT examination was about 23 minutes, with approximately 8 minutes to complete two CT scans and about 15 minutes to acquire PET emission data.

Image reconstruction

NECT and CECT data were reconstructed with 5 mm slice thickness in the axial plane and increment of 3 mm. PET images were reconstructed by using TrueX reconstruction algorithm with three iterations and 21 subsets using Gaussian filter with full width at half maximum (FWHM) of 4 mm. The CECT datasets were employed for attenuation correction with the same set of PET images. The NECT, CECT and attenuation corrected PET images dataset were copied into Apple Macbook Pro laptop (Apple Inc, California, USA) and displayed in transaxial, coronal and sagittal planes using OsiriX imaging software DICOM viewer 32-bit version (Pixmeo, Geneva, Switzerland) along with maximum intensity projection (MIP) images.

Image analysis

Three oval regions of interests (ROIs) with diameter of

1.00 ± 0.010 cm^2 were drawn over the right lobe of the liver at the segment VII to quantify the liver SUV$_{max}$ (*Figure 1*). The intensity of FDG uptake in the tissues can be assessed visually using four points scale of intensity with reference to the liver uptake. This scale included grade 0= no uptake; grade 1= slight uptake (tissue uptake lower than liver uptake); grade 2= moderate uptake (tissue uptake similar to liver uptake); and grade 3= intense uptake (tissue uptake higher than liver uptake) (32). We have utilised the SUV$_{max}$ values for quantification of FDG uptake because maximum pixel value is the most preference in PET/CT study (15). The average values from those three ROIs from each tissue were calculated.

Statistical analysis

The descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables including age, BMI, blood glucose level, incubation period and FDG dose. The differences between mean of FDG uptake among the BMI groups were evaluated using analysis of variance (ANOVA). The association between the SUV$_{max}$ of liver and those factors were analysed by Pearson coefficients of correlation. Multivariate regression models were established to determine the best predictors of liver SUV$_{max}$ among those factors. Multicollinearity between covariates was tested and none was identified. Then ANOVA was performed to determine the significance difference of the mean SUV$_{max}$ of liver among the four categories of BMI. All hypothesis tests were two sided with a significant level of 0.05. The Statistical Package for Social Sciences program for Windows 21.0 (SPSS 21) (IBM Corp, Somers, New York, USA) was used for the statistical analysis.

Results

The analysis included 51 patients with 28 males and 23 females. The demographic data of patients are shown in *Table 1*. A statistically significant positive association was found with the SUV$_{max}$ of liver and BMI, however, statistically significant negative association was observed between the semiquantification value and incubation period (*Table 2*). After adjusting for all other covariates in the final model of multivariate regression analysis, it was demonstrated that BMI and incubation period were significantly associated with SUV$_{max}$ of liver (*Table 3*). These covariates were accounted for 29.6% of the liver SUV$_{max}$ variance. BMI had the strongest association as marked by

Table 1 Demographic data of subjects

Variable	Mean ± SD	95% CI
Age	54.04±13.16	50.34-57.74
Body mass index	24.53±5.49	22.99-26.07
Blood glucose level (mmol/L)	5.26±1.68	4.74-5.65
FDG dose (MBq)	327.69±35.63	318.88-339.67
Incubation period (minutes)	80.05±55.57	64.94-96.20
SUV$_{max}$ of liver	2.72±0.62	2.57-2.81

SD, standard deviation; CI, confidence interval; FDG, fluorodeoxyglucose; MBq, megabecquerel; SUV$_{max}$, maximum standardized uptake value.

Table 2 Association between SUV$_{max}$ of liver and biological and procedural related factors

Factor	Pearson correlation	P value
Age	0.162	0.255
Body mass index	0.460	0.001
Blood glucose level (mmol/L)	−0.163	0.253
FDG dose (MBq)	0.174	0.221
Incubation period (minutes)	−0.371	0.007

SUV$_{max}$, maximum standardized uptake value; FDG, fluorodeoxyglucose; MBq, megabecquerel.

Table 3 Impact of biological and procedural related factors on SUV$_{max}$ of liver in multivariate regression analysis

Variable	Adjusted unstandardized beta coefficient	Adjusted standardised beta coefficient	P value
Age	0.008	0.248	0.039
Body mass index	0.033	0.421	0.001
Fasting blood glucose level	−0.066	−0.252	0.035
FDG dose	0.002	0.164	0.168
Incubation period	−0.002	−0.304	0.013

The final model demonstrates body mass index and incubation period are statistically significant (P<0.05). SUV$_{max}$, maximum standardized uptake value; FDG, fluorodeoxyglucose.

Table 4 Mean SUV$_{max}$ of liver according to the different BMI groups of the patients

BMI	Liver SUV$_{max}$	
	Mean ± SD	95% CI
Underweight	2.38±0.39	1.98-2.79
Normal weight	2.58±0.33	2.44-2.72
Overweight	2.81±0.47	2.54-3.08
Obese	3.06±0.39	2.73-3.38

SUV$_{max}$, maximum standardized uptake value; BMI, body mass index; SD, standard deviation; CI, confidence interval.

higher value of adjusted standardised beta coefficient as compared to the incubation period (*Table 3*). The mean SUV$_{max}$ of liver in four BMI groups are shown in *Table 4* and they were significantly different among those groups (P<0.05).

Discussion

Some physiological FDG uptake can cause misinterpretation of a PET scan; as a result it may lead to false-positive or false-negative interpretation, hence reducing the accuracy of the technique (33-36). Several factors contributing to physiological variation in FDG distribution have been reported (37-39). The variations in liver concentration of ^{18}F-FDG in relation to BMI (25) and age (23) have been documented previously. A correlation study between liver and different BMI groups was reported, but it was limited to fatty liver as study population and only involved three BMI groups (40).

Our investigation demonstrated that ^{18}F-FDG accumulation in liver was significantly higher in patients with increased BMI. This is likely due to very little fat accumulation in a fasting state and thus higher FDG uptake is characterized by non-fatty tissue (41). In the final model of regression analysis, BMI showed significant effect on the SUV$_{max}$ of liver when adjusted for all other covariates. Moreover, the mean SUV of liver for each BMI group of patients was lower than those obtained by Batallés and his co-workers (42). This discrepancy might be due to variations in shape and size of the patients, method of ROI measurement and different type of scanner and workstation setting used. In contrast to the prior studies, we adjusted for age, blood glucose level, FDG dose and incubation period

when we established the impact of BMI on the FDG uptake of liver. Other clinical and biological factors which were excluded from this study such as blood lipid profile (25), hepatic steatosis (43), diabetic status (44) and insulin (44) have been reported to have a significant effect on liver FDG uptake.

Obesity is associated with an increase in plasma levels of inflammatory cytokines such as tumour necrosis factor alpha (TNF-α) and interleukins-6 (IL-6) (45). Kupffer cells are residents macrophages distributed along the liver sinusoid (46). The similar cytokines including TNF-α and IL-6 are secreted by these Kupffer cells (47). Bioactive molecules generated by Kupffer cells and liver endothelial cells in response to varied stimuli have the capacity to contribute to the regulation of hepatic metabolism. Altered long-term expression of liver metabolic enzymes by TNF-α and IL-6 may be critical in the transition to the chronic inflammatory state (46). The sites of accumulation of ^{18}F-FDG in infectious lesions are considered as secretory macrophages of these proinflammatory substances (48,49). It is thought that the areas of greatest FDG-avid usually observed in obese patients are due to inflammatory response of this chronically altered parenchyma which results to increase in the hepatic SUV (43). This present findings might explain strong correlation of physiological FDG uptake of liver with BMI is likely due to inflammatory state of the liver present in obese patients.

Incubation or uptake period is another factor which significantly affects the physiological uptake of liver. Longer incubation period tends to reduce the physiological FDG uptake of liver as signified by negative correlation in the Pearson correlation analysis and negative value of standardized beta coefficient in the multilinear regression analysis. It is likely increased FDG uptake of tumour and decreased uptake of background with longer FDG uptake time in PET/CT study (41). Application of dual time point imaging has made use the benefits of comparison between two time points study for assessment of tumour uptake with relative uptake period (50,51). It has been reported by a recent study that FDG uptake period could affect the liver SUV corrected for lean body mass at dual-phase FDG PET/CT (52).

On the contrary, this study showed fasting blood glucose level had no significant impacts on the liver SUV$_{max}$ when adjusted for all other covariates. Our findings are contradicted with previous studies on the impact of blood glucose factor (24,41). Contrary to the prior studies, we adjusted for age, BMI, FDG dose and incubation period

when we established the effect of fasting blood glucose and liver FDG uptake. We noted that mean SUV normalised to lean body mass was utilized in the study by Malladi *et al.* (41), otherwise maximum SUV normalised to body weight was employed in this study. However, our findings are in accordance with a study by Büsing *et al.* (44) and Kuruva *et al.* (53). Busing and his co-workers reported a significant impact of blood glucose level on ^{18}F-FDG uptake was only observed in the organ consuming high glucose metabolism such as brain, whereas organs less consuming glucose such as liver and spleen showed insignificant effect (44).

Furthermore, this study also found the liver FDG uptake was not affected by age and FDG dose as well when adjusted for all other covariates. These findings are contradicted with the study previously which reported significant effect of age on the liver FDG uptake (23,41). FDG dose can affect the FDG uptake of liver, but it has only minimal effect compared with the other covariates, as it was applied within the range of injected doses for clinical studies (41).

This study did have some limitations. Only a small number of patients were available in the underweight and obese groups as compared to the other two BMI groups. Additionally, we did not investigate all the possible factors that could affect the liver FDG uptake such as hepatic steatosis, diabetic status, abnormal lipid profile and liver function abnormalities which some were excluded and not available in this study.

Conclusions

BMI and incubation period significantly affect the physiological FDG uptake of liver which accounted for 29.6% of the liver SUV$_{max}$ variance. These impacts demonstrated a progressive increase in the semiquantification value with increasing BMI but progressive decrease with increasing incubation period. Higher impact was observed in BMI as compared to incubation period after adjustment for all other covariates. As physiological FDG uptake of liver was significantly different among varied BMI groups, it would be recommended to use different cut-off value of liver SUV$_{max}$ as a reference standard for different BMI of patients in interpretation of whole body PET imaging.

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