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Title: Assessment of the Effect of Fat Infiltration on Hepatic FDG Uptake

Running Head: Hepatic Fat Infiltration And Suvmax Values

Turkish Title: Yağ Infiltrasyonunun Karaciğer FDG Tutulumu Üzerine Etkisinin Değerlendirilmesi

Turkish Running Head: Karaciğer Yağ Infiltrasyonu ve SUVmax Değerleri

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Öz

Giriş ve Amaç: FDG PET/BT çalışmalarında fizyolojik karaciğer FDG tutulumu, maligniteler dahi lolmak üzere patolojik süreçlerde FDG tutulumunun değerlendirilmesinde referans olarak kullanılmıştır. Karaciğer atenüasyonunun ve karaciğerdeki FDG tutulumunun etkisi konusunda devam eden bir tartışma vardır. Yağ infiltrasyonunun karaciğerdeki standart uptake değeri (SUV) üzerindeki olası etkisini değerlendirmeyi amaçladık.

Yöntem ve Gereçler: Bu çalışmaya toplam 88 hasta dahil edildi. Denekler, PET/BT çalışmasının kontrastsız BT bölümünden karaciğerin Hounsfield biriminin (HU) hesaplanması ve bunu dalağınkiyle karşılaştırılmasıyla 2 gruba ayrıldı. Yağlı karaciğer grubu, yaş ortalaması 59,6 ± 11,6 olan 42 hasta (26 kadın, 16 erkek), control grubu ise yaş ortalaması 60,2 ± 11 olan 22 hasta (22 kadın, 24 erkek) idi. Ortalama karaciğer atenüasyon değeri, HU bakımından, dalağa eşit ve büyük olan hastalar control grubuna kaydedildi, ortalama karaciğer atenüasyon değeri dalaktan düşük olan hastalar yağlı karaciğer grubuna alındı. Dalak ve Karaciğer arasındaki HU değeri 10 veya daha fazla (HUS-HUL> 10) olan yağlı karaciğer grubundaki hastaların bir alt kümesi ayrı değerlendirildi. Yaş, DM ve kemoterapi öyküsü, deneklerin ağırlığı, serum ALT ve AST seviyeleri, PET taraması sırasında eşzamanlı kan şekeri düzeyleri ve FDG enjeksiyonu ile PET taraması başlangıcı arasındaki geçen sure kaydedildi.

Bulgular: Ortalama SUVmean ve SUVmax değerleri, sırasıyla yağlı karaciğer grubunda 2,7±0,7 ve 3,6±0,9; HUS-HUL> 10 grubunda 2,8±0,7 ve 3,8±1; kontrol grubunda 3,3±0,6 ve 4,4 +/- 0,9, olarak bulundu. Yağlı karaciğer grubu ve HUS-HUL>10 grubunun ortalama SUVmean ve SUVmax değerleri control grubundaki değerlerden anlamlı olarak farklıydı ($p < 0.05$). Yağlı karaciğer grubundaki hastalar kontrol grubundaki hastalara gore daha yüksek ALT ($p = 0,025$), kilo ($p=0,001$), glukoz düzeyleri ($p=0,001$) ve DM ($p=0,002$) oranı gösterdi.

Tartışma ve Sonuç: Karaciğer steatozu Karaciğerde SUVmean ve SUVmax değerlerinde istatistiksel olarak anlamlı bir düşüşe neden olur. Bu nedenle karaciğeri bir iç referans organı olarak kullanırken dikkatli olmalıyız.

Anahtar Kelimeler: Hepatosteatoz, Standart Alım Değeri, Flor 18-Florodeoksiglukoz- Pozitron Emisyon Tomografisi

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Abstract

Introduction and Aim: Physiological liver FDG uptake in FDG PET/CT studies, has been used as a reference in the assessment of the FDG uptake in pathological processes including malignancies. There is an ongoing debate on the effect of liver attenuation and the liver's FDG uptake. We aimed to assess the any possible effect of fatty infiltration on the standardized uptake value (SUV) of the liver.

Methods: A total of 88 patients were included in this study. Subjects were divided into 2 groups by calculating the Hounsfield unit (HU) of the liver from the unenhanced CT part of the PET/CT study and comparing it with that of the spleen. The fatty liver group included 42 patients (26 female, 16 male) with a mean age of 59,6±11,6, while the control group were consisted of 46 patients (22 female, 24 male) with a mean age of 60,2±11. The patients whose mean liver attenuation value in terms of HU, equal and greater than that of spleen were enrolled in the control group, while the patients with a mean attenuation value of liver lower than spleen were assigned to fatty liver group. A subset of patients from the fatty liver group with a HU difference between liver and spleen of 10 or more (HUS-HUL >10) were evaluated separately. The age, DM and chemotherapy history, weight of the subjects, serum ALT and AST levels, simultaneous blood glucose levels during PET scan and the elapsed time between the FDG injection and beginning of PET scan were recorded.

Results: The average SUVmean and SUVmax values were calculated as 2,7+/-0,7 and 3,6+/-0,9, in the fatty liver group, 2,8±0,7 and 3,8±1 in the HUS-HUL >10 group and 3,3+/-0,6 and 4,4+/-0,9, in the control group respectively. The average SUVmean and SUVmax values in the fatty liver group and the subset of of HUS-HUL >10 group were significantly different from the values in the control group ($p< 0.05$). The patients in the fatty liver group showed higher ALT ($p=0,025$), weight ($p=0,001$), glucose levels ($p=0,001$) and ratio of DM ($p=0,002$), than the patients in the control group.

Discussion and Conclusion: Hepatic steatosis causes a statistically significant decrease in SUVmean and SUVmax values in liver. Therefore we must be cautious while using the liver as an internal reference organ.

Keywords: Hepatosteathosis, Standard Uptake Value, Flor 18-Fluorodeoxyglucose, Positron Emission Tomography

INTRODUCTION

The use of standardized uptake values (SUVs) in determining malignant nature of lesions, aggressiveness of malignancies and therapy response in clinical (Flor 18-Fluorodeoxyglucose-Positron Emission tomography/Computerized Tomography) ^{18}F-FDG-PET/CT oncology imaging is ever increasing. SUV is a semiquantitative measurement which corresponds to measured activity normalized for body weight/surface area and injected dose. The formula for calculation of SUV is region of interest (ROI) activity (mCi/mL) x body weight (g) / injected dose (mCi). Although the application of SUV obviate the uncertainity caused by the inconstancies in patient size and the amount of injected FDG to a some extent, it is still liable to many weaknesses which can cause misleading results. SUV is a proportional value without units, rather than being an absolute value in characterization of lesions, so for the quantification of tumour FDG uptake there was always a need for a site in the body which is presumed to have normal FDG uptake. Liver has long been used as a reference organ for this purpose (1-4). If the ^{18}F-FDG uptake in the target lesion is greater than in the liver in terms of SUV, the hypermetabolic focus would be considered abnormal.

Fatty liver disease reflects a wide spectrum of conditions characterized histologically by excessive accumulation of triglycerides and cholesterols within the cytoplasm of hepatocytes. Fatty infiltration of the liver is further subdivided as alcohol- related fatty liver disease or non–alcohol-related fatty liver disease (NAFLD). NAFLD is the most common chronic liver condition in the developed countries, with an estimated prevalence of 20%–30% in adult populations (5, 6).

NAFLD encompasses two pathological entities; simple steatosis and steatohepatitis (NASH) which is a more serious condition that can eventually progress to cirrhosis and promote hepatocellular carcinoma (7).

There has been several studies made for investigating the possible effect of fatty infiltration on the SUVs of the liver (8-15). Some of these studies reported no correlation between low attenuation due to high fat content of liver and ^{18}F-FDG uptake (10, 13). In one study significantly negative correlation between the severity of fatty liver and SUVmax of liver on FDG PET was found (15). Increased FDG uptake due to steatohepatitits was also reported in other studies (9, 14, 16).
These contradictory results prompted us to investigate the relation between fat infiltration of liver and FDG uptake in fatty liver in terms of SUVmax and SUVmean values.

METHODS

Patients

FDG PET/CT examinations performed at our institution from September 1, 2016, to April 1, 2017, were assessedretrospectively by investigating the patient's medical charts.
Because of its retrospective nature, study approval by the clinical research ethics committee is waived while the study was approved by the local institutional review board.Among the patients who had undergone PET/CT imaging during this period a total of 88 patients were enrolled in this

study. Patients with liver metastasis or known liver disease which can effect hepatic uptake were not included in this study. Subjects were divided into 2 groups by calculating the Hounsfield unit (HU) of the liver from the unenhanced CT part of the PET/CT study and comparing it with that of the spleen. The fatty liver group included 42 patients (26 female, 16 male) with a mean age of 59,6±11,6, while the control group were consisted of 46 patients (22 female, 24 male) with a mean age of 60,2±11. The patients whose mean liver attenuation value in terms of HU, equal and greater than that of spleen were enrolled in the control group, while the patients with a mean attenuation value of liver lower than spleen were assigned to fatty liver group. A subset of patients from the fatty liver group with a HU difference between liver and spleen of 10 or more (HUS-HUL >10) were evaluated separately. The age, DM and chemotherapy history, weight of the subjects, serum ALT and AST levels, simultaneous blood glucose levels during PET scan and the elapsed time between the FDG injection and beginning of PET scan were recorded. The primary malignancies of the patients were lung cancer in 12 patients (13.6%) colorectal cancer in 8 patients (9%), breast cancer in 24 patients (27.2%), bladder cancer in 6 patients (6.8%), head and neck cancer in 6 patients (6.8%), sarcoma in 5 patients (5.6%), gynecological malignancies in 14 patients (15.9%), skin cancer in 5 patients (5.6%), neuroendocrine tumor in 1 patient (1.1%), carcinoma of unknown primary in 4 patients (4.5%), gastrointestinal stromal tumor in 1 patient (1.1%), multiple myeloma in 1 patient (1.1%), thyroid cancer in 1 patient (1.1%).

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Imaging

PET/CT images were obtained using an integrated PET/CT scanner which consisted of a full-ring HI-REZ LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL). Patients were instructed to fast for at least 6 h before ^{18}F -FDG injection. Blood glucose levels were measured before the study and 18F-FDG was injected only when the blood glucose level was below 11.11 mmol/l. The patients were injected with 296-555 MBq^{18}F -FDG according to body weight. After 50 min of waiting relaxed in a semireclining chair, the patients were imaged using an integrated PET/CT scanner. The CT portion of the study was done without intravenous administration of contrast medium only for defining anatomical landmarks and making attenuation correction on the PET images. The CT scan was performed first with the following parameters: 50 mAs, 140 kV and 5-mm section thickness. Whole-body CT was performed in a craniocaudal direction. The images were obtained while the arms of patients were up in order to avoid spurious increase in liver FDG uptake due to beam-hardeningeffects.

Measurement of SUV and HU Values

A region of interest (ROI) of 2-cm diameter was placed over the right lobe of the liver. Same ROIs were drawn on the PET and CT scans of the liver avoiding any lesions, biliary, vascular structures and artefacts. SUVmean and SUVmax of the liver were measured for each ROI with the formula;

ROI activity (mCi/mL) x body weight/injected dose (mCi).Mean attenuation value by Hounsfield unit (HUmean) were measured also from the ROI drawn on CT portion of the study.(Figure 1)

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analyzes for the evaluation of thedata obtained in the study.The normal distribution of the parameters was evaluated by the Shapiro Wilks test. Student t test was used for comparison between two groups of normal distribution parameters, and Mann Whitney U test was used for comparison between two groups of parameters without normal distribution. Comparison of control groupwith the fattyliver disease group regarding Liver SUVmean andSUVmax values is done by using a Student t test formeans. Fisher's Exact Chi-Square test and Continuity (Yates) correction were used for the comparison of qualitative data of gender, DM and chemotherapy status, GGT, AST and ALT elevation, elapsed time and glucose levels. Significance was assessed at $p<0.05$.

RESULTS

Liver SUVmax and Liver SUVmean averages of the patients with fatty liver were statistically significantly lower than the control group ($p<0.05$). Spleen SUVmean and Spleen SUVmax averages of fatty liver patients were also statistically significantly lower than control group

($p<0.05$) (Table 1). Also the mean values of Liver SUVmaxand LiverSUVmean in patients in the subset of fatty liver group (HUS-HUL >10) were statistically significantly lower than the control group ($p<0.05$) (Table 2). Comparison data of fatty liver and control group in terms of clinical parameters are presented in Table 3. The fatty liver group showed a significantly higher mean body weight (84,95±13,76 kg) compared with the control group (74,45±14,28 kg). There were 16 patients (38,1%) with DM in the fatty liver group while there were 4 patients (8,7%) in the control group. The serum ALT values were significantly higher in the fatty liver group than the control group. Serum glucose levels were also higher in the the fatty liver group 115,74±33,11 than the control group (91,63±14,40).

DISCUSSION

There has always been a search for a non invasive method that can distinguish benign lesions from malignancies. FDG PET has been utilized for this purpose depending on the the fact that malignant lesions generally have a higher glucose consumption rate and consequently higher FDG uptake. In the beginning semiquantitative SUV measurements as an indicator of amount of FDG uptake seemed to be a robust method in the characterization of malignant lesions and regarded by some authors as “metabolic biopsy” (17, 18). But in clinical practice it turned out to have numerous limitations like partial volume and spillover effects, attenuation correction,the reconstruction method and parameters for scanner type, the count noise bias effect, elapsed time between radiotracer injection and imaging,competing transport effects, and body size (19). So to rely on a

certain static SUVmax threshold in distinguishing benign lesions from malignant ones is not realistic in this context. Qualitative visual interpretation of ^{18}F-FDG uptake by using liver as a reference standard became a common practice to overcome this shortcoming. Fatty liver disease, which means accumulation of fat in the form of triglycerides and cholesterol in the liver cells, theoretically might cause a decrease in the uptake of FDG in hepatocytes. Since this possible decrease in FDG showing itself in the form of a reduction in SUVmax compared with normal livers has important clinical implications as a consequence of misinterpretation of FDG positive lesions, we tried to assess whether liver ^{18}FDG uptake was affected by hepatosteatosis. In our study we found thatLiver SUVmax and Liver SUVmean averages of the patients with fatty liver were statistically significantly lower than the control group ($p<0.05$). Also the mean values of Liver SUVmaxand LiverSUVmean in patients in the subset of fatty liver group (HUS-HUL >10) were statistically significantly lower than the control group ($p<0.05$). In the literature conflicting results have been reported by several studies examining the relationship between hepatic steatosis and hepatic FDG uptake. One of the oldest studies made for this purpose by Qazi et al. (20) reported that liver SUVmax/spleen SUVmax ratio of the fatty livergroup was significantly lower than that of the control group (1.1 vs 1.4, $p=0.002$). There were limitations for this preliminary report such as the relatively small number of subjects enrolled in the study and measurement of SUVmax instead of SUVmean which may give rise to less reliable results in the evaluation of a large organ like liver. Abikhzer et al. (11), in their prospective case–control study, analyzed the effect of fat infiltration on hepatic metabolic activity on 37 patients. Authors found that patients with hepatic

steatosis had statistically significant low hepatic metabolic activity in terms of SUVmax measurements, compared with control subjects, when the SUV is corrected for lean body mass and not for body weight. Even though the results were statistically significant , the degree of the change in SUVmax values were not found satisfactory by authors to be accepted as clinically significant. Lin et al. (15) reported that hepatic steatosis had a significantly negative impact on hepatic metabolic activity as measured by SUVmax. They retrospectively analysed ^{18}F-FDGPET studies of 173 patients who had been investigated for nononcologic disease conditions. They divided the patients in four groups according to the findings on ultrasonography: no fatty liver,mild-degree, moderate-degree, and severe-degree fatty liver. The mean SUVmax of liver in subjects without fatty liver mild degree, moderate-degree and severe-degree fatty liver were 3.13±0.49, 3.08±0.45, 3.01±0.44, and 2.43±0.27 respectively. The differences in SUVmax of liver on FDG PET was statistically significant. They concluded that the liver cannot be used as a comparator ofincreased FDG activity in the lesions of patients with fatty liver disease.These findings are in accordance with our results which indicated that there was a negative relation between SUVmax and HU values. But there are also other reports in the literature which contradict our findings. Pak et al (21) retrospectively analyzed FDG PET/CT studies of 96 consecutive patients who were being screened for cancer and found that there has been no significant difference of liver SUVmean and liver SUVmax between controls and fatty liver groups.

Dostbil et al. (13) assessed the relation between fatty infiltration of liver and hepatic metabolic activity in 79 patients with hepatosteatosis on an ^{18}FDG PET/CT.The control group in their study

included 77 patients with a mean liver HU value greater than their mean spleen HU value and the patient group included 79 patients in whom the mean liver HUvalue was lower than or equal to the mean spleen HU value. The authors further divided the patient group into subsets according to their degree of hepatic steatosis. They did not observe any statistically significantdifference between the patients with fatty liver disease and the subjects in the control group for the mean and maximum liver SUVs. Abele et al. (10) made a study to evaluate the association between diffuse fatty infiltration and average FDG uptake in the liver with the assumption of enlargement of hepatocytes due to fat accumulation could give rise to a decrease in cellular densityand eventually a decrease in the SUV mean. The average SUVmean for the control group was 2.18±0.36 and this value was not significantly different from those for fatty liver disease (2.03±36) and more strictly defined subset of fatty liver disease (2.07±0.24) groups.

Some authors described a controversial increase in Liver SUVmean values in patients with fatty liver. Liu et al. (12) reported a positive relation between Liver SUVmean and fat infiltration when the degree of severity is mild to moderate, while there is a negative effect when it is more severe. They also noted that FDG uptake of liver gradually increase in patients as the BMI increases from underweight to overweight, but a decrease in SUVmean values occur when the patient is obese.

It has been well known that high degree of ^{18}F-FDG uptake is seen in inflammatory cells which even lead to the use of FDG PET as a potential imaging method in infectious diseases. Keramida et al. (14), reported that FDG uptake at liver is increased in NASH, due to irreversible uptake in inflammatory cells superimposed on reversible hepatocyte uptake. Bural et al (22) compared

hepatic standardized uptake values (SUVs) and hepatic metabolic volumetric products (HMVP) between patients of diffuse hepatic steatosis and control subjects with normal livers. They found an increase in HMVP as a result of increased hepatic metabolic activity likely related to the inflammatory process in diffuse hepatic steatosis. The increase of FDG uptake in liver with high fat content could be accounted for the increased activity of Kupffer cells which is a kind of macrophage that acts by engulfing FDG (23).This accumulation of FDG uptake at focal hepatic steatosis can cause a diagnostic dilemma on imaging by mimicking metastasis (24, 25). Conversely, focal fat spared area in a liver with diffuse fatty infiltration can demonstrate focal FDG uptake masquerading as liver metastases, probably when steatosis is not accompanied with inflammation (26, 27)

In our study we found statistically significant differences between the body weight ($p<0.001$), serum ALT levels (0.025), DM status (0.002), and glucose levels ($p<0.001$) of the patients with fatty livers and those from the control group. There may be a positive correlation between serum liver enzyme levels and SUVs of liver on FDG-PET which can affect diagnostic sensitivity of hepatic malignant or infectious lesions on FDG-PET (28). Patients with fatty liver disease shows higher ASTand ALT levels (21). Although the patients in fatty liver group in our study showed higher serum enzyme levels, we could not detect any positive relation between SUVs and ALT, AST levels. BMI levels of the patients with fatty livers are known to be higher than those of the normal patients (13, 21). In our study we could not calculate BMI of patients since we did not get their height values,but mean of body weights of the patients with hepatic steatosis were

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significantly higher. All of the subjects in the patient and control groups had oncological diseases and there was not any statistically significant difference among two groups regarding chemotherapy history. Lin et al. found that age had a significant and positive impact on both maximum and mean standard uptake values of the liver on FDG PET imaging. In our study mean ages of the patients was not significantly different between two groups (8).

Interestingly Spleen SUVmean and Spleen SUVmax averages of fatty liver patients were also statistically significantly lower than control group ($p<0.05$) in our study. This issue needs to be clarified by additional studies.

We preferred to rely on unenhanced CT part of the PET CT in the diagnosis of fatty liver, as assessment of liver attenuation by use of unenhanced CT represents an objective and noninvasive means for detection of asymptomatic hepatic steatosis (29, 30). The diagnosis could be done with biopsy and histopathology and this can be a limitation of our study.

CONCLUSION

Contrary to most of the studies reported in the literature hepatic steatosis causes a statistically significant decrease in SUVmean and SUVmax values in liver, unless it is associated with inflammatory conditions as NASH. Therefore, we must be cautious while using the liver as an internal reference organ.

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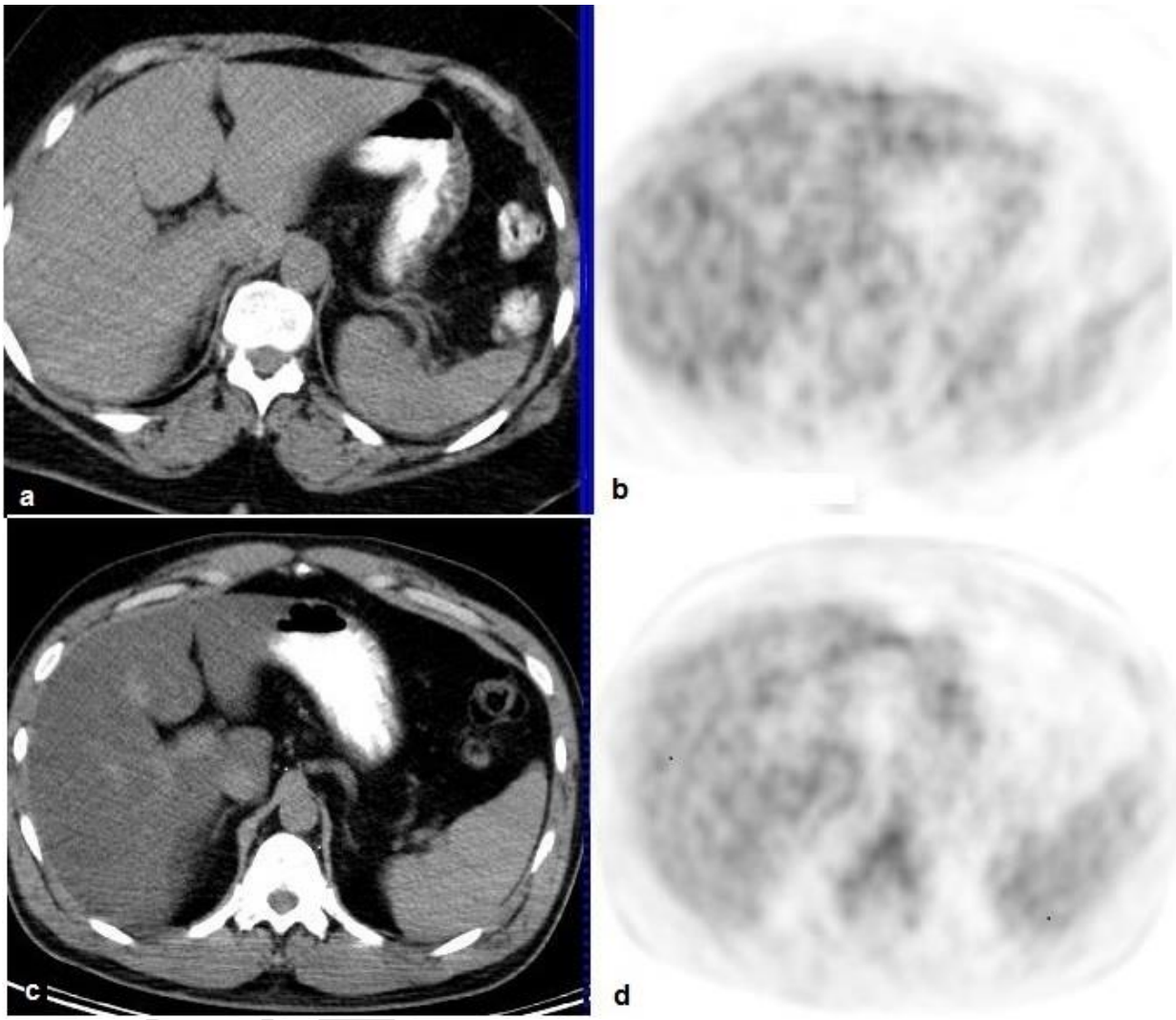

Figure 1. a-d. Axial CT and PET slices of patient from control group (a, b) and fatty liver group (c, d)

Table 1. Evaluation of Groups

	Fatty Liver Patients (n=42)	Control (n=46)	p value
	Mean±SD	Mean±SD	
Liver SUV max	3,61±0,97	4,41±0,94	0,001*
Liver SUV mean	2,70±0,70	3,34±0,66	0,001*
Liver mean HU	36,43±9,63	57,08±6,36	0,001*
Spleen SUV mean	2,29±0,63	2,62±0,48	0,008*
Spleen SUV max	2,93±0,76	3,27±0,66	0,028*
Spleen mean HU	47,29±5,59	40,46±9,16	0,001*

*p<0.05 Student t test

Table 2. Evaluation of Groups

	Patients with severe fatty liver (n=23)	Control (n=46)	p value
	Mean±SD	Mean±SD	
Liver SUV max	3,84±1,10	4,41±0,94	0,028*
Liver SUV mean	2,87±0,79	3,34±0,66	0,010*
Liver mean HU	32,08±10,39	57,08±6,36	0,001*

*p<0.05 Student t test

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Table 3. Evaluation of Clinical Parameters of Groups

	Fatty Liver Patients (n=42)	Control (n=46)	p value
Age *Meant±SD*	59,69±11,61	60,22±11,04	[1]0,828
Gender *n,%*			
Female	26 (%61,9)	22 (%47,8)	[2]0,267
Male	16 (%38,1)	24 (%52,2)	
DM *n,%*	16 (%38,1)	4 (%8,7)	[2]0,002*
ALT elevation *n,%*	7 (%16,7)	1 (%2,2)	[3]0,025*
AST elevation *n,%*	2 (%4,8)	0 (%0)	[3]0,225
GGT *n,%*	7 (%16,7)	5 (%10,9)	[2]0,631
Chemotherapy *n,%*	12 (%28,6)	13 (%28,3)	[2]1,000
Elapsed time *Meant±SD (median)*	70,48±15,94 (65)	76,72±17,35 (70)	[4]0,049*
Glucose *Meant±SD (median)*	115,74±33,11 (109)	91,63±14,40 (89,5)	[4]0,001*
Weight *Meant±SD*	84,95±13,76	74,45±14,28	[1]0,001*

* $p<0.05$

[1]Student t test; [2]Continuity (yates) correction; [3]Fisher's Exact Test; [4]Mann Whitney U Test

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