Metabolic Activity in the Visceral and Subcutaneous Adipose Tissues by FDG-PET/CT in Obese Patients

Avaliação da Atividade Metabólica do Tecido Adiposo Visceral e Subcutâneo por FDG-PET/CT em Doentes Obesos

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ABSTRACT

Introduction: The emerging role of the ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography in the study of the metabolic activity and inflammation in adipose tissue indicates that it might be a reliable tool to complement the risk stratification in obesity. The aims of this study were the evaluation of ^{18}F-fluorodeoxyglucose uptake by visceral adipose tissues and subcutaneous adipose tissues and to determine eventual differences in patients with and without obesity.

Material and Methods: Retrospective study of adult patients who underwent whole body ^{18}F-fluorodeoxyglucose-positron emission tomography/ computed tomography scanning between July and August of 2016. Statistical analysis: SPSS™ software v.20. Statistical significance: $p < 0.05$.

Results: We assessed fluorodeoxyglucose-positron emission tomography/computed tomography scans from 156 patients (58.3% of males) with a mean age of 61.0 ± 14.1 years. Half of the patients had a body mass index ≥ 25.0 kg/m^2 and 15.4% (n = 24) were obese. In both groups, the mean ^{18}F-fluorodeoxyglucose uptake was higher in visceral adipose tissues. There were no differences in ^{18}F-fluorodeoxyglucose uptake in visceral adipose tissues between the groups. Obese patients had lower density of adipose tissue, both in subcutaneous adipose tissues and in visceral adipose tissues. Abdominal circumference and density of visceral adipose tissues had a positive predictive value in the mean ^{18}F-fluorodeoxyglucose uptake in visceral adipose tissues.

Discussion: Through a non-invasive test, this study demonstrated a significant higher metabolic activity in visceral adipose tissues in both obese and non-obese patients. According to our results, abdominal circumference was an important determinant in ^{18}F-fluorodeoxyglucose uptake in visceral adipose tissues. We also demonstrated that obese patients had differences in adipose tissue quality.

Conclusion: Our findings reinforce the importance of the adipose tissue quality and distribution for metabolic risk stratification.

Keywords: Adipose Tissue/diagnostic imaging; Fluorodeoxyglucose F18; Intra-Abdominal Fat/diagnostic imaging; Obesity/diagnostic imaging; Positron-Emission Tomography; Subcutaneous Fat/diagnostic imaging

RESUMO

Introdução: O ^{18}F-fluorodesoxiglucose-tomografia por emissão de pósitrons/tomografia computorizada tem sido aplicado ao estudo da atividade metabólica e da inflamação do tecido adiposo, constituindo uma possível ferramenta para complementar a estratificação de risco na obesidade. Os objetivos deste estudo foram a avaliação da captação de ^{18}F-fluorodesoxiglucose pelo tecido adiposo visceral e pelo tecido adiposo subcutâneo e a determinação de eventuais diferenças em doentes com e sem obesidade.

Material e Métodos: Estudo retrospetivo de doentes adultos submetidos a ^{18}F-fluorodesoxiglucose-tomografia por emissão de pósitrons/tomografia computorizada entre julho e agosto de 2016. Análise estatística: *software* SPSS™ versão 20. Significância estatística: $p < 0,05$.

Resultados: Foram avaliados os exames ^{18}F-fluorodesoxiglucose-tomografia por emissão de pósitrons/tomografia computorizada de 156 doentes (58,3% eram homens) com idade média de 61,0 ± 14,1 anos. Metade dos doentes apresentava índice de massa corporal ≥ 25,0 kg/m^2 e 15,4% (n = 24) eram obesos. Em ambos os grupos, a captação média de ^{18}F-fluorodesoxiglucose foi superior no tecido adiposo visceral. Não houve diferenças na captação de ^{18}F-fluorodesoxiglucose no tecido adiposo visceral entre os grupos. Os doentes obesos apresentaram menor densidade do tecido adiposo, quer no tecido adiposo visceral como no tecido adiposo subcutâneo. A circunferência abdominal e a densidade do tecido adiposo visceral tiveram um valor preditivo positivo na captação média de ^{18}F-fluorodesoxiglucose no tecido adiposo visceral.

Discussão: Através de um exame não invasivo, demonstrou-se a existência de atividade metabólica significativamente maior no tecido adiposo visceral, comparativamente ao tecido adiposo subcutâneo, em doentes com e sem obesidade. De acordo com os nossos resultados, a circunferência abdominal foi um determinante importante na captação de ^{18}F-fluorodesoxiglucose no tecido adiposo visceral. Demonstramos ainda que os doentes obesos apresentaram diferenças na qualidade do tecido adiposo.

Conclusão: Os nossos resultados reforçam a importância da qualidade e da distribuição do tecido adiposo para a estratificação do risco metabólico.

Palavras-chave: 18F-Fluorodesoxiglucose; Gordura Intra-Abdominal/diagnóstico por imagem; Gordura Subcutânea/diagnóstico por imagem; Obesidade/diagnóstico por imagem; Tecido Adiposo/diagnóstico por imagem; Tomografia por Emissão de Pósitrons

INTRODUCTION

Adipose tissue is an active endocrine organ with a central role in lipid and glucose metabolism. It produces a large number of hormones and cytokines involved in the development of metabolic syndrome, diabetes mellitus and vascular diseases.[1] The overall adiposity excess is associated with cardiovascular morbidity and mortality but

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the different distribution of fat depots is associated with differential metabolic risk. It is well established that increased visceral adipose tissue (VAT) is strongly correlated with an adverse metabolic risk profile. By contrast, the increased subcutaneous adipose tissue (SAT) seems to have less importance on adverse risk profile.[2–4]

The differences between VAT and SAT concerning secretion of inflammatory mediators, gene expression and cell morphology have already been documented. Recently, ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) combined with computed tomography (CT) imaging has been used for the study of glucose metabolic activity and inflammation in adipose tissue. It has been demonstrated that metabolic activity in the VAT and SAT might be differentially regulated and FDG-PET/CT imaging could be a reliable tool for evaluating this parameter and to complement the cardiometabolic risk calculation.[5,6]

The aims of this study were the evaluation of the uptake of FDG by VAT and SAT and to determine differences in patients with and without obesity who underwent whole body ^{18}FDG-PET/CT scanning for clinical purposes (cancer diagnosis or staging).

MATERIALS AND METHODS

Subjects and protocol

We retrospectively analyzed 156 consecutive adult patients who underwent whole body ^{18}FDG-PET/CT scanning for clinical purposes (diagnosis or staging of cancer) between July and August of 2016.

Information regarding diabetes (medical history of diabetes and/or medication), hypertension and dyslipidemia was obtained from medical records.

Weight and height were self-reported and thereafter BMI (body mass index) was calculated. Obesity was considered in patients with a BMI greater than 30 kg/m^2. Abdominal circumference from cross-sectional CT image was measured using the software recommended by the National Institutes of Health - ImageJ.[7]

After fasting for six hours, the patients received FDG intravenously (if blood glucose was ≤ 250 mg/dL). Whole body images were acquired on a PET/CT scanner (Siemens Biograph 6) 50 to 90 minutes after tracer administration. Low-dose, non-contrast CT scan was performed for attenuation correction and anatomical localization. PET scan was acquired in 3-dimensional mode from base of skull to mid-thigh. Siemens Syngo MI Applications VA60A software was used for image analysis.

Regions of interest (ROIs) in VAT (epiploon), SAT (L3 level), liver (right hepatic lobe), psoas muscle and myocardium were drawn and the intensity of FDG uptake (maximum and mean SUV) was analyzed in these locations. Also, to determine the density of VAT and SAT, the Hounsfield units (HU) were recorded.

Statistical analysis

Normal distribution of the variables was evaluated through histogram. Continuous variables were expressed as mean and standard deviation or as median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Group comparisons were made using the t test or Mann–Whitney U test for continuous variables and the chi-square (χ^2) test for categorical variables. Linear regression analysis was performed to identify independent parameters associated with the mean FDG uptake in VAT and SAT. Statistical significance was defined at $p < 0.05$. All statistical analysis was performed using SPSS™ software version 20.

RESULTS

The mean age of the 156 patients was 61.0 ± 14.1 years and there was a predominance of males (n = 91; 58.3%). Half of the patients (n = 78; 50%) were overweight [body mass index (BMI) ≥ 25.0 kg/m^2] and 15.4% (n = 24) were considered obese (BMI ≥ 30 kg/m^2). The detailed clinical characteristics of the study population are presented in Table 1.

The study population was divided in two groups (obese and non-obese) with similar age and gender distribution. Differences in clinical characteristics and FDG uptake values between the groups are represented in Table 2.

The mean FDG uptake was higher in VAT than in SAT in both groups (0.5 *vs* 0.26; $p < 0.001$ and 0.6 *vs* 0.28; $p < 0.001$, obese and non-obese patients respectively).

Table 1 – Characteristics of the study population (n = 156)

Variables	Results
Age (years) (mean ± SD)	61.0 ± 14.1
Gender (female // male) (%)	41.7 // 58.3
Diabetes (%)	14.7
Hypertension (%)	42.3
Dyslipidemia (%)	34.0
Obesity (%) (BMI ≥ 30 kg/m^2)	15.4
Overweight (%) (25 kg/m^2 ≤ BMI < 30 kg/m^2)	34.6
BMI (kg/m^2) (mean ± SD)	25.6 ± 4.6
Abdominal circumference (cm) (mean ± SD)	97.4 ± 11.2
Fasting glucose (mg/dL) (median; IQR)	104.0; 96.0 - 116.0

SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index

Table 2 – Differences in clinical characteristics and FDG uptake values between groups

Variables	Obesity (n = 24)	Without obesity (n = 132)	Total (n = 156)	*p* value
Age (years) (mean ± SD)	65.8 ± 10.2	60.1 ± 14.6	61.0 ± 14.1	0.07°
Female gender (%)	54.2	39.4	41.7	0.2*
BMI (kg/m^2) (mean ± SD)	33.7 ± 2.7	24.1 ± 3.1	25.6 ± 4.6	< 0.001°
Diabetes mellitus (%)	16.7	13.6	15.4	0.7*
Abdominal circumference (cm) (mean ± SD)	112.6 ± 9.0	94.6 ± 9.2	97.4 ± 11.2	< 0.001°
Fasting glucose (mg/dL) (median; IQR)	102.0; 22.0	104.5; 19.0	104.0; 20.0	0.6†
VAT maximum FDG uptake (median; IQR)	1.4; 0.8	1.25; 0.6	1.28; 0.6	0.2†
VAT mean FDG uptake (median; IQR)	0.5; 0.3	0.6; 0.3	0.6; 0.3	0.4†
VAT density (HU) (median; IQR)	-101.9; 7.7	-93.4; 20.2	-96.5; 18.7	< 0.001†
SAT maximum FDG uptake (median; IQR)	0.7; 0.3	0.6; 0.3	0.6; 0.3	0.03†
SAT mean FDG uptake (median; IQR)	0.26; 0.09	0.28; 0.2	0.26; 0.2	0.008†
SAT density (HU) (median; IQR)	-111.5; 11.0	-106.5; 18.0	-107.5; 15.0	0.008†
Muscle mean FDG uptake (median; IQR)	0.9; 0.2	0.7; 0.2	0.7; 0.2	< 0.001†
Liver mean FDG uptake (median; IQR)	2.4; 0.4	2.1; 0.7	2.2; 0.6	0.001†
Myocardium maximum FDG uptake (median; IQR)	4.3; 3.2	5.1; 4.8	5.1; 4.7	0.6†

SD: Standard deviation; BMI: Body mass index; IQR: Interquartile range; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; FDG: ^{18}F-fluorodeoxyglucose; HU: Hounsfield units; ° *t*-test; † Mann-Whitney U test; * Chi-square tests

There were no differences in FDG uptake in VAT (mean and maximum SUV) between the groups.

Obese patients had higher maximum FDG uptake (0.7 *vs* 0.6; $p = 0.02$) but lower mean FDG uptake (0.26 *vs* 0.28; $p = 0.008$) in SAT. Also, this group had higher FDG uptake in liver (2.4 *vs* 2.1; $p = 0.001$) and in muscle (0.9 *vs* 0.7; $p < 0.001$).

We observed lower density, determined by HU, of VAT (-101.9 *vs* -93.4; $p < 0.001$) and SAT (-111.5 *vs* -106.5; $p = 0.008$) in obese patients.

Table 3 and 5 shows the coefficients of correlation (Spearman correlation) between the mean uptake in VAT and in SAT, respectively, and the different studied variables. Subsequently, a multiple linear regression analysis was performed to identify independent parameters associated with the mean FDG uptake in VAT [$F(4, 151) = 632.95$, $p < 0.001$, $R^2 = 0.942$] and SAT [$F(8, 147) = 14.373$, $p < 0.001$, $R^2 = 0.439$] (Tables 4 and 6, respectively). We found that the abdominal circumference and the density of VAT had a positive predictive value in the mean FDG uptake in VAT. In SAT, higher BMI and maximum uptake in myocardium were independent and negatively associated with the mean FDG uptake. Density of SAT and VAT and mean uptake in muscle had a positive predictive value in the mean uptake in SAT.

DISCUSSION

Our study demonstrated a higher FDG uptake in VAT, comparatively to SAT, in both obese and non-obese patients. Similar findings were reported by other authors, and it is assumed to be correlated to a higher metabolic activity in VAT. Furthermore, this difference could reflect the different profile of inflammatory mediators secreted between the two adipose tissues, supporting the concept that VAT is more strongly correlated with adverse metabolic profile risk.[5,8–11]

Notwithstanding the known link between obesity and inflammation, there were no differences in FDG uptake in VAT between patients with or without obesity. This result is in conformity with Christen *et al*, but in contrast with the results of Oliveira *et al,* where obese patients had higher FDG uptake in VAT.[5,10]

We found a positive and independent association between abdominal circumference and mean FDG uptake in VAT. However, BMI was not associated with the mean FDG uptake in VAT. Those observations support the fact that adipose tissue distribution might have a more important role than excess adiposity per se in metabolic risk stratification.[12]

In concordance with Rosenquist *et al*, obese patients had lower density of VAT and SAT. It is known that the lower density is a marker of a more lipid dense and less vascularity of fat tissue. Rosenquist *et al* have also found that a lower CT attenuation (measured in HU) in VAT and in SAT was correlated with higher BMI. Moreover, the lower density of VAT and SAT was associated with a more adverse cardiometabolic risk.[13] Besides, our regression analysis demonstrated that density in VAT and in SAT were independent and positively associated with uptakes in VAT and in SAT, supporting the concept that higher density is associated with higher metabolic activity.

Remarkably, obese patients had higher maximum FDG uptake but lower mean FDG uptake in SAT. Also, in the regression analysis, higher BMI was independently associated with lower mean FDG uptake in SAT. As higher BMI is associated with lower density of adipose tissue, the lower density in obese patients could explain the lowering effect in the mean FDG uptake.

Similar to the study of Oliveira *et al*, we observed higher

Table 3 – Spearman correlations between mean uptake in VAT and the studied variables

Variables	FDG uptake in VAT (mean)	
	r	*p*
Age	-0.024	0.76
Glycaemia	0.021	0.79
BMI	-0.154	0.054
Abdominal circumference	-0.158	0.049
VAT density	0.487	< 0.001
SAT mean FDG uptake	0.450	< 0.001
SAT density	0.266	0.001
Muscle mean FDG uptake	0.117	0.146
Liver mean FDG uptake	-0.004	0.961
Myocardium maximum FDG uptake	-0.005	0.148

VAT: Visceral adipose tissue; FDG: ^{18}F-fluorodeoxyglucose; BMI: Body mass index; SAT: Subcutaneous adipose tissue

Table 4 – Linear regression analyses for the significant correlation of FDG uptake in VAT

Variables	FDG uptake in VAT (mean)		
	Linear regression analysis		
	B	t	*p*
Abdominal circumference	0.445	2.939	0.004
VAT density	0.885	49.344	< 0.001
SAT density	-0.183	-1.814	0.072
SAT mean FDG uptake	-24.844	-1.975	0.05

VAT: Visceral adipose tissue; FDG: ^{18}F-fluorodeoxyglucose; SAT: Subcutaneous adipose tissue

Table 5 – Spearman correlations between mean uptake in SAT and the studied variables

Variables	FDG uptake in SAT (mean)	
	r	*p*
Age	0.305	< 0.001
Glycaemia	0.198	0.013
BMI	-0.242	0.002
Abdominal circumference	-0.137	0.089
SAT density	0.478	< 0.001
VAT mean FDG uptake	0.450	< 0.001
VAT density	0.316	< 0.001
Muscle mean FDG uptake	0.207	0.009
Liver mean FDG uptake	0.106	0.189
Myocardium maximum FDG uptake	-0.203	0.011

SAT: Subcutaneous adipose tissue; FDG: ^{18}F-fluorodeoxyglucose; BMI: Body mass index; VAT: Visceral adipose tissue

Table 6 – Linear regression analyses for correlates of metabolic activity in SAT

Variables	FDG uptake in SAT (mean)		
	B	t	*p*
Age	0.001	1.899	0.06
Glycaemia	0.00067	0.273	0.785
BMI	-0.006	-2.185	**0.030**
SAT density	0.003	5.488	**< 0.001**
VAT mean FDG uptake	-0.001	-1.839	0.068
VAT density	0.001	2.104	**0.037**
Muscle mean FDG uptake	0.179	3.526	**0.001**
Myocardium maximum FDG uptake	-0.005	-2.310	**0.022**

SAT: Subcutaneous adipose tissue; FDG: ^{18}F-fluorodeoxyglucose; BMI: Body mass index; VAT: Visceral adipose tissue

FDG uptake in muscle of obese patients.[10] Although the muscle FDG uptake can increase with hyperglycemia, there were no differences in glycemia between the groups. So, further examinations under steady-state conditions with dynamic PET are warranted to determine the glucose flux.

Obese patients had higher FDG uptake in liver and this is consistent with the results of the study of Batallés *et al*. In that study, liver FDG uptake was independently associated with BMI, age and gender.[14] The higher FDG uptake in the liver might be a consequence of a chronic inflammatory response, probably steatosis. In our population, further correlation with CT attenuation could answer that question. Nevertheless, chemotherapy agents and concomitant liver disease were not evaluated and these variables are known to influence the FDG uptake.

Interestingly, the mean uptake in VAT was not correlated with uptake in other tissues such as muscle and myocardium. However, SAT mean uptake was independently associated with a lower myocardium uptake and a higher muscle uptake. Those findings may correspond to a different pattern of regulation, but further studies are needed to confirm that hypothesis.

Our retrospective study had some limitations to note.

An important limitation was the fact that our study population was not comprised of healthy subjects, as they underwent ^{18}FDG-PET/CT scanning for cancer diagnosis or staging. Also, the ongoing treatments and cancer staging were not controlled.

Another limitation was the FDG uptake measure in SUV. It is known that SUV can have inter and intra subject variability as a result of multiple factors, including glycemia, insulin concentrations and the time of image acquisition after FDG injection.

We lacked adipose tissue quantification that could help with better correlation and explanation of our findings.

Finally, this was a retrospective study and we lacked the fasting lipid profile, insulin levels and indices of inflammation that could complement the study.

CONCLUSION

A non-invasive ^{18}FDG-PET/CT scanning allowed us to demonstrate significant differences between SAT and VAT metabolic activity in both obese and non-obese patients.

According to our results, abdominal circumference is an important determinant in FDG uptake in VAT. We also demonstrated that obese patients had lower density which is a marker of a lipid-laden fat tissue and minor vascularity. Our findings reinforce the importance of the adipose tissue quality and distribution for metabolic risk stratification.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication. Informed consent was duly obtained from the patient.

CONFLICTS OF INTEREST

All authors report no conflict of interest.

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