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Effect of Coronavirus Disease 2019 on Fluorine-18 fluorodeoxyglucose Uptake of Endocrine Organs

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Research Article

History

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ABSTRACT

Objective: The new type of Coronavirus (SARS-CoV-2) damages cells by using the angiotensin converting enzyme-2 (ACE2) as a receptor to adhere and go through the cell membrane. It is known that some of the endocrine organs express ACE2 and these organs are potential targets for Coronavirus 2019 disease (Covid-19). This study aimed to investigate the effect of Covid-19 on Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) uptake of endocrine system organs.

Methods: Sixteen patients who had Covid-19 underwent ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) later, 77 patients who did not have Covid-19 underwent ^{18}F-FDG PET/CT between March 2020-October 2021 were included. SUVmax and SUVmean of the pituitary, thyroid, adrenal gland, pancreas, and testis measured from the PET/CT of the patients who had Covid-19 were compared with SUVmax, and SUVmean measured from the same organs in PET/CT images of the patients who had not Covid-19.

Results: Pancreatic mean SUVmax was significantly higher in patients who had Covid-19 than in patients who did not (p= 0.035). Pancreatic mean SUVmean was slightly higher in patients who had Covid-19 than in patients who did not, but this difference was not statistically significant (p= 0.072). No significant difference was found between the SUVmax and SUVmean values of the pituitary gland, thyroid gland, adrenal gland, and testis in patients who had Covid-19 and did not have.

Conclusion: It was thought that the pancreas might have been affected in the course of Covid-19 due to the higher mean SUVmean values of the pancreas in patients who had Covid- 19.

Keywords: Covid-19, endocrine system, FDG, PET/CT

Covid-19 Enfeksiyonu Sonrası Endokrin Organların F-18 Florodeoksiglukoz Tutulumundaki Değişiklikler

Araştırma Makalesi

Süreç

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ÖZET

Amaç: Yeni tip koronavirüs (SARS-CoV-2) anjiyotension dönüştürücü enzim-2'yi (ACE2)reseptör olarak kullanarak hücreye tutunur, hücre membranı geçer ve hücreye zarar verir. Bazı endokrin organların ACE2 eksprese ettiği bilinmektedir ve bu organlar Covid-19 için hedef olma potansiyeline sahiptir. Bu çalışmada Covid-19'un endokrin sistem organlarındaki F-18 florodeoksiglukoz (^{18}F-FDG) tutulumuna etkisini araştırmak amaçlanmıştır.

Yöntem: Mart 2020-Ekim 2021 arasında Covid-19 geçirip sonrasında ^{18}F-FDG PET/BT çekimi yapılan 16 hasta ile Covid-19 geçirmeyen 77 hastanın verileri analiz edildi. Covid-19 geçiren ve geçirmeyen hastaların hipofiz bezi, tiroid bezi, adrenal bez, pankreas ve testislerinden ölçülen SUVmax ve SUVmean değerleri karşılaştırıldı.

Bulgular: Covid-19 geçiren hastaların ortalama pankreas SUVmax değeri Covid-19 geçirmeyen hastalarınkinden daha yüksekti (p= 0.032). Covid-19 geçiren hastaların ortalama pankreas SUVmean değeri Covid-19 geçirmeyen hastalarınkinden daha yüksekti ancak bu fark istatistiksel olarak anlamlı düzeyde değildi (p= 0.072). Covid-19 geçiren ve geçirmeyen hastaların hipofiz bezi, tiroid bezi, sürrenal bez ve testislerinden ölçülen SUVmax ve SUVmean değerleri arasında anlamlı düzeyde farklılık saptanmadı.

Sonuç: Covid-19 geçiren hastalarda ortalama pankreas SUVmean değerinin daha yüksek olması nedeniyle pankreasın Covid-19 sürecinde etkilenmiş olabileceği düşünüldü.

Anahtar Kelimeler: Covid-19, endokrin sistem, FDG, PET/BT

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Introduction

The Coronavirus 2019 disease (Covid-19), which emerged in Wuhan, China, in December 2019, spread all over the world in a short time, and the World Health Organization (WHO) declared Covid 19 a pandemic on March 11, 2020. The new type of coronavirus (SARS-CoV-2), the causative agent of Covid-19 (1), has mutated, revealing new, more infectious variants (Alpha, Beta, Gamma, Delta, and Omicron, etc.) (2-4).

Covid-19 usually manifests itself with mild upper respiratory tract infections or is asymptomatic in people with a robust immune system and no severe comorbidities (5). The most frequently affected organ system in severe cases is the pulmonary system (5,6). However, many extrapulmonary manifestations have been reported (5). Hyperthyroidism and hypothyroidism are among the best-known effects of Covid-19 on the endocrine system (7,8). The effect of Covid-19 on other endocrine organs other than the thyroid gland has not yet been clarified. It was revealed in the severe acute respiratory syndrome (SARS) epidemic in 2003 that the coronavirus could affect the endocrine system (9). It is known that Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) has a high uptake in inflammatory pathologies. Therefore, in the presence of inflammation in endocrine organs, ^{18}F-FDG uptake of these organs may increase. This study aims to investigate the effect of Covid-19 on ^{18}F-FDG uptake/glucose metabolism of endocrine system organs.

Material and Method

All patients who underwent ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) in our hospital and applied to the Covid-19 pandemic outpatient clinic between March 2020 and October 2021 were identified. Among these patients, those who did not have a real-time polymerase chain reaction (RT-PCR) test were excluded. Finally, 93 patients who underwent ^{18}F-FDG PET/CT in our clinic and whose RT-PCR was studied from nasal and throat swabs for Covid-19 for any reason were included in the study. During this period, PET/CT was not performed on patients with symptoms such as fever, cough, sore throat that may be associated with Covid-19, unless the RT-PCR result was negative. Maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean) (threshold of 40% of SUVmax) were calculated by placing a circular region of interest (ROI) in the localization of the pituitary fossa, thyroid gland, pancreas, adrenal gland and testes of male patients on PET/CT fusion images (Figure 1). Patients with ^{18}F-FDG uptake suggest primary malignancy associated with the aforementioned endocrine organs or metastasis in these organs were excluded. Since four of 16 patients who had Covid-19 had pancreatic cancer, SUV measurements were not made from the pancreas of these patients. Since the hypothalamus, pineal gland, parathyroid glands, and ovaries could not be distinguished in ^{18}F-FDG PET/CT, SUV values of these organs could not be calculated.

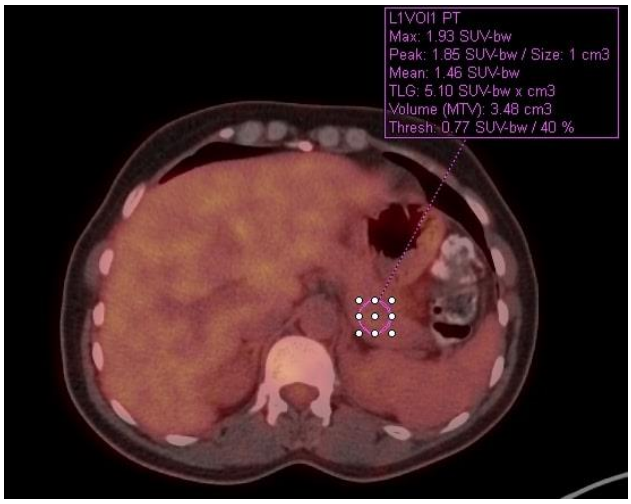

Figure 1. Calculation of the SUVmax and SUVmean from the endocrine organs using circular region of interest

^{18}F-FDG was injected intravenously at a 3.7 MBq/kg (0.1 mCi/kg) dose to patients with blood glucose levels below 200 mg/dl after fasting for at least 4-6 hours. Before PET/CT, the patients rested for 60 minutes in a single room. PET/CT images were obtained from the vertex to the upper thigh (Siemens Biograph mCT 20). First, low-dose CT images were acquired with 120 kVp, 50 mAs, iodine-containing oral contrast, and free-breathing protocol. Then, PET images were obtained with a 2 min/bed position in three-dimensional mode. A nuclear medicine physician with five years of oncological PET/CT experience evaluated images at the Siemens syngo.via workstation.

SUVmax and SUVmean values of the pituitary, thyroid, adrenal gland, pancreas, and testis measured from the first PET/CT performed in the post-Covid-19 period of patients had Covid-19 were compared with SUVmax, and SUVmean values measured from the areas mentioned earlier in PET/CT images performed during the staging phase of the diseases of the patients who had not Covid-19. The independent sample t-test was used to make this comparison. Only eight patients with Covid-19 had PET/CT images before Covid-19. The SUVmax and SUVmean values obtained from the previously mentioned endocrine organs from these patients' pre- and post-Covid-19 images were compared. The Wilcoxon test was used to make this comparison. In all statistical tests, $p < 0.05$ was considered statistically significant. All Statistical analyzes were performed with SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Post-infective PET/CT imaging of patients who had Covid-19 was performed median of 130 (45-284) days after nasal and throat swab RT-PCR results. Detailed demographic information is in Table 1.

Only six of 16 patients who had Covid-19 did not receive oncological treatment at the time of post-Covid-19 PET/CT, and imaging was performed for cancer staging in these patients; In the other ten patients, the imaging purpose was to evaluate treatment response. Pancreatic mean SUVmax value was slightly higher in patients who had Covid-19 (2.1 ± 0.3) than in patients who did not (1.9 ± 0.4) (p= 0.035) (Table 2). In addition, pancreatic mean SUVmean value was slightly higher in patients who had Covid-19 (1.6 ± 0.3) than in patients who did not (1.4 ± 0.3), but this difference was not statistically significant (p= 0.072). SUVmax and SUVmean values of the pituitary gland, thyroid gland, adrenal gland, and testis did not differ between the patients who had Covid-19 and who did not (Table 2).

Table 1. Patient characteristics

	Patients infected by Covid-19	**Patients not infected by Covid-19**	P value
Gender			
Female	6	22	0.479
Male	10	55	
Primary malignancy			
	Lung, 5 (31%)	Lung, 24 (31%)	
	Pancreas, 4 (25)	Unknown primary, 9 (11)	
	Breast, 3 (19)	Larynx, 6 (7)	
	Others, 4 (25)	Others, 39 (51)	
Age (years), Mean ± SD	65 ± 11	66 ± 13	0.737
Blood glucose level during FDG injection (mg/dL), Mean ± SD	104 ± 15	102 ± 18	0.624
Dose of FDG (MBq), Mean ± SD	274 ± 85 (7.4 ± 2.3 mCi)	285 ± 48 (7.7 ± 1.3 mCi)	0.416

Covid-19: Coronavirus disease 2019, FDG: Fluorodeoxyglucose

Table 2. SUVmax and SUVmean values of the endocrine organs

	Patients infected by Covid-19 (n=16)	**Patients not infected by Covid-19 (n=77)**	**p-value**
	Mean ± SD	Mean ± SD	
Pituitary gland			
SUVmax	2.6 ± 0.6	2.8 ± 0.7	0.506
SUVmean	1.8 ± 0.4	2.0 ± 0.5	0.361
Thyroid gland			
SUVmax	2.2 ± 0.8	2.0 ± 0.5	0.228
SUVmean	1.6 ± 0.7	1.6 ± 0.4	0.964
***Pancreas**			
SUVmax	2.1 ± 0.3	1.9 ± 0.4	**0.035**
SUVmean	1.6 ± 0.3	1.4 ± 0.3	0.072
Adrenal gland			
SUVmax	2.1 ± 0.4	2.3 ± 0.6	0.175
SUVmean	1.6 ± 0.4	1.6 ± 0.4	0.948
Testicle			
SUVmax	2.9 ± 0.8	3.2 ± 0.6	0.598
SUVmean	1.9 ± 0.6	2.5 ± 0.8	0.207

SUV: standardized uptake value, Covid-19: Coronavirus disease 2019, SD: Standard deviation

***** n=12 for postinfected group, because 4 patients had focal F-18 FDG uptake in pancreas due to pancreatic cancer.

No significant difference was found between the SUVmax and SUVmean values of the pituitary gland, thyroid gland, adrenal gland, pancreas, and testis before and after Covid-19 in 8 patients who had Covid-19 and had PET/CT examination both before and after infection (Table 3).

Table 3. SUVmax and SUVmean values of the endocrine organs befere and after Covid-19 (n=8)

	Before Covid-19		After Covid-19		p-value
	Mean ± SD	Median (min - max)	Mean ± SD	Median (min-max)	
Pituitary gland					
SUVmax	2.7 ± 0.6	2.7 (1.9 – 3.4)	2.6 ± 0.5	2.3 (2.0 – 3.2)	0.596
SUVmean	1.9 ± 0.4	1.9 (1.5 – 2.6)	1.8 ± 0.3	1.6 (1.5 – 2.2)	0.129
Thyroid gland					
SUVmax	1.8 ± 0.4	2.0 (1.2 – 2.4)	2.1 ± 0.6	2.3 (1.2 – 2.6)	0.416
SUVmean	1.6 ± 0.3	1.6 (1.1 – 1.9)	1.6 ± 0.4	1.7 (1.1 – 2.0)	0.414
Pancreas					
SUVmax	1.9 ± 0.5	1.9 (1.4 – 2.7)	2.1 ± 0.3	2.1 (1.6 – 2.5)	0.115
SUVmean	1.0 ± 0.6	1.2 (0.9 – 1.7)	1.6 ± 0.3	1.5 (1.3 – 2.1)	0.114
Adrenal gland					
SUVmax	2.1 ± 0.5	2.1 (1.4 – 2.8)	2.2 ± 0.4	2.2 (1.7 – 2.7)	0.734
SUVmean	1.7 ± 0.5	1.6 (1.2 – 2.5)	1.8 ± 0.4	1.7 (1.1 – 2.3)	1.000
Testicle					
SUVmax	3.5 ± 0.8	3.7 (2.4 – 4.3)	2.9 ± 0.7	3.0 (2.1 – 3.4)	0.068
SUVmean	2.3 ± 0.4	2.4 (1.8 – 2.7)	1.9 ± 0.4	2.0 (1.5 – 2.3)	0.144

SUV: standardized uptake value, Covid-19: Coronavirus disease 2019

Discussion

In the light of the information obtained from the SARS epidemic, the endocrine system was thought to be a potential target for SARS-CoV-2 (9). Findings of central adrenal insufficiency in some patients after SARS epidemic, thyroid follicular epithelial damage and decrease in TSH in some patients, presence of SARS-CoV in pancreatic tissue, increase in prolactin, luteinizing hormone and follicle-stimulating hormone, decrease in estrogen and progesterone after SARS in women, the demonstration of microscopic damage to the testicular tissue of patients who died from SARS and the high angiotensin converting enzyme-2 (ACE2) expression in the testis were the basis of this thought (9). Clinically, it has been shown in some retrospective studies that Covid-19 can cause endocrinological problems, especially thyroid dysfunction (10,11).

Considering this information, we examined whether there were changes in the glucose metabolisms of the endocrine system organs after Covid-19. Pancreatic SUVmax values of patients who had Covid-19 were slightly higher than those who did not (p= 0.035). Among these patients, SUV measurement was not performed in the pancreas of 4 patients with primary pancreatic cancer. None of the remaining 12 patients had focal or diffuse pathological ^{18}F-FDG uptake in their pancreas. Five of these patients had lung cancer, but none had a history of immunotherapy that could cause pancreatitis. Wang et al. reported elevated pancreatic enzymes in 17% of 52 patients hospitalized for Covid-19 pneumonia (12). Bruno et al. showed that 8.5% of the 70 patients hospitalized for Covid-19 who had pneumonia had elevated pancreatic enzymes (13). In the two studies mentioned, the patients had no acute pancreatitis clinically. Since the patients in our study applied to the hospital for cancer staging or oncological treatment response evaluation, amylase and lipase laboratory test results were not available in the routine clinical evaluation of the patients. Therefore, the relationship between pancreatic ^{18}F-FDG uptake after Covid-19 and pancreatic enzymes could not be examined. The expression of ACE2 messenger RNA in pancreatic tissue (14,15) and the presence of case reports about Covid-19-associated acute pancreatitis (16-18) suggest that the pancreas may be vulnerable to the attack of SARS-CoV-2. We think that the mild SUVmax elevation, which we detected after Covid-19 in the pancreas, may be related to mild inflammation.

Lania et al. detected thyrotoxicosis in 20.2% of the 287 Covid-19 patients who were hospitalized (10). They found overt thyrotoxicosis in 53.4% of the patients with thyrotoxicosis. They reported an inverse correlation between thyroid stimulatin hormone (TSH) and interleukin 6 (rho= −0.41; p < 0.001). The same study reported that 5.2% of the patients had hypothyroidism. Our study showed no difference between SUVmax and SUVmean of the thyroid glands of patients who had and did not have Covid-19. There was no difference between pre-Covid-19 and post-Covid-19 SUVmax and SUVmean of the thyroid glands of the eight patients who underwent PET/CT before and after Covid-19. The patients' history of hospitalization due to Covid-19, serum TSH, free T3 and free T4 hormones, and thyroid antibody levels during the PET/CT were unknown. The small number of patients in this study and perhaps the fact that most of the patients had mild Covid-19 may be the reason why there was no diffuse increase in ^{18}F-FDG uptake in the thyroid gland. Also, Albano et al. reported that the most common pathology in patients with diffuse ^{18}F-FDG uptake in the thyroid gland is thyroiditis (19). However, not all patients

with thyroiditis may show diffuse ^{18}F-FDG uptake. For this reason, we think that the presence of thyroiditis cannot be definitively excluded in the patients in our study who had Covid-19.

In their review, Frara et al. reported that cases of pituitary apoplexy, syndrome of inappropriate antidiuretic hormone, and hypophysitis associated with Covid-19 have not yet been proven (20). Similarly, Covid-19-related adrenal gland and testicular inflammation have not been proven. In our study, there was no difference between the SUVmax and SUVmean values of the pituitary, adrenal gland, and testis in patients who had and did not have Covid-19.

Study Limitations

Our study has some limitations. The small number of patients who had and did not have Covid-19 is is an important factor that may affect the results of statistical analysis. The high number of patients who had PET/CT scans both before and after Covid-19 could have enabled us to more accurately evaluate the effect of Covid-19 on ^{18}F-FDG uptake of endocrine organs. Because the laboratory test results associated with organs whose SUV values were measured were absent in our study, we could not evaluate the glucose uptake of these organs parallel to test results such as thyroid function tests, amylase, and lipase. In addition, among the patients included in our study, asymptomatic carriers who did not have a PCR test and the presence of patients with false negative or false positive PCR test results cannot be definitively excluded.

Conclusion

The pancreas, like many organs, is a possible target for SARS-CoV2 due to its expression of ACE2 mRNA. In our study, the slightly higher ^{18}F-FDG uptake in pancreas in the patients who had Covid-19 compared to those who did not have the disease suggested that the pancreas may have been affected in the course of Covid-19.

Ethics Committee Approval: This study was approved by Ethics Committee and conducted according to the principles of the Declaration of Helsinki (Decision date: 14.12.2021, approval number: 2021/213).

Informed Consent: The ethical committee waived the requirement for informed consent as the study was retrospective.

Authors' Contributions: Concept- O.B. ; Design- O.B., S.G., D.N. ; Supervision: O.B. ; Data Collection and Processing: O.B., S.G., D.N. ; Analysis and/or Interpretation: O.B, S.G., D.N. ; Literature Search: O.B., ; Writing: O.B.

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This article has an erratum in issue 45(3) because of a typo during layout. This is the corrected article.