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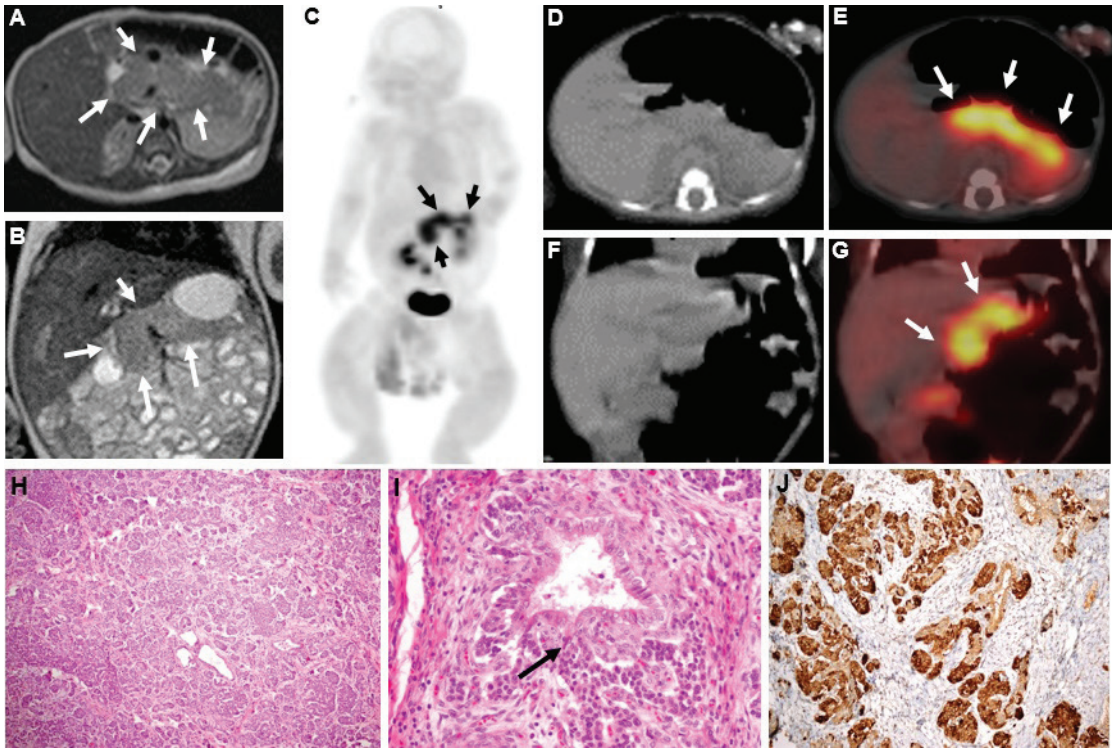

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Erselcan T, Hasbek Z, Tandogan I, Gumus C, Akkurt I. Modification of Diet in Renal Disease equation in the risk stratification of contrast induced acute kidney injury in hospital inpatients. Nefrologia 2009 doi: 10.3265/Nefrologia.2009.29.5.5449.en.full.

Article in a journal published ahead of print: Ludbrook J. Musculovenous pumps in the human lower limb. Am Heart J 2009;00:1-6. (accessed 20 February 2009).

Lang TF, Duryea J. Peripheral Bone Mineral Assessment of the Axial Skeleton: Technical Aspects. In: Orwoll ES, Bliziotes M (eds). Osteoporosis: Pathophsiology and Clinical Management. New Jersey, Humana Pres Inc, 2003;83-104.

Books: Greenspan A. Orthopaedic Radiology a Pratical Approach. 3th ed. Philadelphia, Lippincott Williams Wilkins 2000, 295-330.

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CONTENTS

Original Articles

Interesting Images

Original Article
Mol Imaging Radionucl Ther 2019;28:46-52 DOI:10.4274/mirt.galenos.2019.60352

Comparison of SUV_{max} Values Obtained from F-18 FDG PET/CT and Cell-free DNA Levels Measured from Plasma in Oncology Patients

Onkoloji Hastalarında F-18 FDG PET/BT'de Elde Edilen SUV_{maks} Değerleri ile Plazmadan Ölçülen Cell-free DNA Seviyelerinin Karşılaştırılması

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Abstract

Objectives: The aim of this study was to compare the quantitative value of standardized uptake value (SUV) SUV_{max} obtained from F-18 FDG positron emission tomography/computed tomography (PET/CT) imaging of oncology patients with the cell-free DNA (cfDNA) amounts measured in plasma of patients and thus investigate if cfDNA is a significant marker to identify the presence of malignancy in the early period.

Methods: A total of 184 patients were included in the study. The clinical, histopathologic, laboratory and treatment parameters were extracted from patient files. SUV_{max} and cfDNA quantities were assessed.

Results: There was no statistically significant difference in plasma cfDNA values between patient and control groups. The comparison of SUV_{max} and cfDNA values in the study showed that there was a weak correlation between SUV_{max} and cfDNA. There was a significant difference between tumor size and SUV_{max} values. However, there was no statistically significant difference between tumor size and cfDNA.

Conclusion: cfDNA measurements in the blood as a screening test have provided hope for early diagnosis and monitoring of cancer patients. Comparison of cfDNA levels obtained from plasma and quantitative parameters from PET/CT images of oncology patients in detailed advanced studies with larger patient series are required.

Keywords: F-18 FDG PET/CT, SUV_{max}, cell-free DNA

Öz

Amaç: Bu çalışmanın amacı, onkoloji hastalarında F-18 FDG pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) görüntülemelerinden elde edilen standart tutulum değeri (SUV) SUV_{maks}'ın, hastaların plazmalarında ölçülen serbest DNA (cfDNA) miktarları ile kantitatif değerini karşılaştırmak ve böylece cfDNA'nın erken dönemde malignitenin varlığını tanımlamak için önemli bir belirteç olup olmadığını araştırmaktır.

Yöntem: Çalışmaya toplam 184 hasta dahil edildi. Klinik durum, histopatolojik, laboratuvar ve tedavi parametreleri hasta dosyalarından araştırıldı. SUV_{maks} değeri ve cfDNA miktarları karşılaştırıldı.

Bulgular: Hasta ve kontrol grubu arasında plazma cfDNA değerleri arasında istatistiksel olarak anlamlı fark yoktu. Araştırmada SUV_{maks} ve cfDNA değerlerinin karşılaştırılmasının sonucunda SUV_{maks} ve cfDNA arasında zayıf bir korelasyon vardı. Tümör boyutu ve SUV_{maks} değerleri arasında anlamlı bir fark bulundu. Bununla birlikte, tümör boyutu ve cfDNA arasında belirgin bir istatistiksel farklılık saptanmadı.

Sonuç: Basit bir tarama testi olarak kullanılabilecek olan cfDNA ölçümleri kanser hastalarının erken tanı ve takiplerinde umut vaad etmektedir. Bu nedenle onkoloji hastalarının plazmalarından elde edilen cfDNA düzeyi ve PET/BT görüntülerinden elde edilen kantitatif parametrelerin karşılaştırıldığı daha büyük hasta serilerinde ve detaylı ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: F-18 FDG PET/BT, SUV_{maks}, serbest DNA

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Introduction

Cancer is an important health problem. It is the second most common cause of death in the world generally, after cardiovascular diseases. It is predicted that in future years the incidence will significantly increase (1).

Survival after cancer is linked to factors such as tumor stage at time of diagnosis, form of treatment, general state of the patient, and morphologic and molecular characteristics of the tumor. As a result, early detection of cancer has great importance in preventing mortality and morbidity linked to cancer. Though there are advances in the diagnosis and treatment of some cancer types, early diagnosis and treatment of cancer continues to be a significant problem.

In recent years, the importance of the nuclear medicine imaging method positron emission tomography/computed tomography (PET/CT) used for diagnosis, staging and monitoring the treatment of various cancers has increased worldwide (2).

PET/CT images are assessed qualitatively and semi-quantitatively. The most commonly used parameter in semi-quantitative evaluation is the standardized uptake value of F-18 FDG called "standardized uptake value" (SUV). The SUV value represents the amount of radioactivity accumulated per gram of tissue (3).

In addition to conventional imaging modalities, biological markers are being used to distinguish tumor cells from normal cells for early diagnosis (4).

During the last years, circulating cell-free DNA (cfDNA) in the blood of healthy and cancer patients gained increasing attention. It was understood in the late 1980s that the DNA in the circulation has neoplastic property and reflects the biological character of the tumor (5,6).

The study relies on physical and biological properties of DNA that differ in normal tissues as compared to tumors.

However, although tumor markers found in serum in patients and specific to some types of cancer are routinely used for early identification of oncologic diseases, due to limited specificity and sensitivity the desired results have not been reached for early diagnosis. Consequently, its routine application is still not recommended.

The aim of this study was to compare the quantitative value of SUV_{max} obtained from full body PET/CT imaging of oncology patients with cfDNA amounts measured in plasma of patients, and thus investigate whether cfDNA is a significant marker to identify the presence of malignancy in the early period.

The study was approved by Çanakkale University Ethics Committee (protocol number: 204-14). Informed consent was obtained from all participants.

Materials and Methods

Patient Selection

The study was prospective and was begun after receiving ethics committee approval. It included 184 oncology patients (87 females, 97 males) directed for F-18 FDG PET/CT imaging from January 2015-February 2016 and a control group of 92 people comprising 57 females and 35 males. Ninety-two people was enrolled as a control group. Patients who had no known oncological disease but were suspected to have laboratory and clinically were included in the study. Study patients did not have any comorbid diseases.

The clinical, histopathologic, laboratory and treatment parameters were extracted from patient files. The patients' age, gender, weight, height, smoking habit, accompanying diseases, date of diagnosis, diagnosis methods, histologic types, stages, tumor diameter, number and location of metastases, and chemotherapy and radiotherapy histories were investigated.

PET/CT Procedure

Imaging of patients was completed with a Biograph Duo LSO F-18 FDG PET/CT scanner (Siemens, Germany). All patients received routine PET/CT imaging protocol. According to this protocol, patients were requested to avoid excessive physical exercise and exposure to cold two days prior to imaging, and starve for at least six hours. Before imaging, all patients had glucose measurements from capillary blood and F-18 FDG PET/CT imaging was delayed in those with serum glucose levels above 180 mg/dL to allow blood sugar regulation. Patients with appropriate blood sugar levels were injected with 8-12 mCi F-18 FDG intravenously with the aid of an angiocath. After the injection, patients rested in a calm and comfortable environment without speaking or moving for 45-60 minutes to provide biodistribution of the radiopharmaceutical and ensure ideal tumor uptake. At the end of the waiting period, patients emptied their bladders and laid on the PET/CT scanner bed in the supine position with arms at the sides. Initial guideline topogram images were obtained, non-contrast CT images were taken for the body regions from the vertex to 1/3 proximal thigh followed by PET images. The patient's PET/CT images were taken with mean 7-8 bed positions and 2 mm slices and were completed in about 25 minutes.

The PET/CT images of all patients were reported within the framework of routine evaluation procedure by at least one nuclear medicine specialist and a senior nuclear medicine assistant. Within this procedure, multiplanar PET, CT and PET/CT fusion slices with and without attenuation correction and maximum intensity projection PET images were investigated on an LCD monitor using a computer

software program (esoft Workstation, Syngo MI, Siemens). Evaluation was made considering the clinical history obtained from patient files and direct interviews with the patient, current complaints, conventional imaging findings, biopsy results and previous operation history. Lesions identified on PET/CT were primarily visually assessed. For quantitative assessment, SUV_{max} values were used. SUV_{max} values were measured according to region of interest and automatically calculated by the computer. The SUV_{max} value was measured in the lesion with highest F-18 FDG uptake among all positive lesions.

cfDNA Measurement

Each case had 10 mL venous blood sample obtained from the forearm and taken in ethylene diamine tetra acetic acid tubes which were sent to the laboratory. Without delay, blood samples were centrifuged at 3800 rpm for 10 minutes. The supernatant was transferred to a new tube and centrifuged at 3000 rpm for 10 minutes. Later, plasma samples of 1 mL each were distributed to cryo tubes and stored at -20 C until use.

Automatic DNA isolation was completed with a MagNA pure nucleic acid isolation kit in accordance with total nucleic acid plasma protocol. Using 400 µL plasma samples the elution buffer amount was determined as 50 µL. The obtained samples were spectrophotometrically measured at 260 nm and 280 nm wavelengths and then DNA amount and DNA purity levels were measured as ng/mL with nanodrop.

Statistical Analysis

Analysis of the study data used SPSS for Windows 22.0 packet program. The Shapiro-Wilk test was used to test whether data had normal distribution or not. Data without normal distribution had the Kruskal-Wallis test used to compare more than two independent groups. If significant differences were found, the groups were compared in pairs with the Mann-Whitney U test. The Mann-Whitney U test was used for comparison of two independent groups without normal distribution. Variables without normal distribution are given as median (minimum-maximum) values. The significance level for statistical analysis was taken as $p<0.05$.

Results

Patient Characteristics

The patients in the study group were 87 females (47.3%) and 97 males (52.7%) with an age range for the total of 184 patients of 25 to 89 years and mean age of 53.38±17.98 years. The control group comprised 57 females (62.0%) and 35 males (38.0%) for a total of 92 patients with ages ranging from 19 to 86 years and mean age calculated as 36.5±12.98 years (Table 1).

When the study group and control group patients were divided into two groups as those below the age of 50 and above; there were 25 patients in the study group (13.6%) below the age of 50 with 159 patients (86.4%) above 50 years of age. In the control group, there were 64 cases (69.6%) below the age of 50 and 28 cases (30.4%) above the age of 50. In terms of age distribution above and below the age of 50 in the two groups, there was a statistically

Table 1. Patients characteristics-mean age and number of patients for each group

Variable		Patient (n=184)	Control (n=92)	p value
Mean age (year)#		62 (25-85)	36.5 (19-86)	p<0.001
Age (year)&	<50	25 (13.6%)	64 (69.6%)	p<0.001
	≥50	159 (86.4%)	28 (30.4%)	
Gender&	Female	87 (47.3%)	57 (62.0%)	0.030
	Male	97 (52.7%)	35 (38.0%)	
Smoking&	Yes	99 (53.8%)	40 (43.5%)	0.136
	No	85 (46.2%)	52 (56.5%)	

#The data are given as mean (minimum-maximum) or &fr equency (percent)

Table 2. Comparison of the patient and control group's demographic data with cell-free DNA quantities

Variable		Patient (n=184)	cfDNA (ng/dL)	p value	Control (n=92)	cfDNA (ng/dL)	p value
Age (year)#	<50	25	7 (0-30)	0.995	64	8 (0.5-16)	0.649
	≥50	159	8 (2.5-50)		28	7.5 (2-21)	
Sex	Female	87	9 (0-50)	0.426	57	8 (0.5-16)	0.885
	Male	97	8 (2.5-30)		35	7.5 (1.5-21)	
Smoking#	Yes	99	9 (0-50)	0.465	40	8.5 (0.5-21)	0.167
	No	85	8 (2.5-20)		52	7.5 (1.5-13)	

#The data are given as mean (minimum-maximum) or &frequency (percent).
cfDNA: Cell-free DNA

significant difference between patients in the control and study groups (p<0.001, Table 2).

When the patients were compared in terms of smoking habit, 99 cases in the patient group (53.8%) smoked while 40 cases in the control group (43.5%) smoked. There was no statistically significant difference between the two groups in terms of smoking history (p=0.136, Table 2).

cfDNA Measurements in Two Groups

Evaluation of the plasma cfDNA values identified the mean cfDNA value in the patient group as 8.8 ng/mL (0-50) and in the control group as 8 ng/mL (0.5-21). Comparison between the groups did not reveal a statistically significant difference (p=0.405, Table 3).

Comparison of Oncologic Subtypes According to cfDNA

When 184 patients are compared in terms of oncologic subtypes, operation history and treatment, there was no statistically significant difference between the two groups. When patients participating in the study had oncologic subtypes, operation and treatment histories compared with plasma cfDNA levels, there was no statistically significant difference (Table 4). Additionally, there was no statistically significant difference in terms of operation history, chemotherapy and radiotherapy treatment. However; lung, cervix, thyroid and pancreas cancers were identified to have higher cfDNA values as compared to other types (Table 4).

Comparison of Tumor and Metastatic Lesion SUV_{max} Values and cfDNA Measurements

SUV_{max} measured in tumor and metastatic lesions were compared along with plasma cfDNA values (Figure 1). There was no statistically significant difference between the two groups in terms of tumor and metastasis presence

Table 3. Comparison of cell-free DNA values of groups

	Patient group (n=184)	Control group (n=92)	p value
cfDNA mean (min-max)	8.8 (0-50)	8 (0.5-21)	0.405

cfDNA: Cell-free DNA, min: Minimum, max: Maximum

Table 4. Comparison of cell-free DNA amount according to tumor type

Variables[#]		Patients (n=184)	cfDNA (nd/dL)	p value
Tumor type	Lung carcinoma	62	8 (2.5-50)	0.440
	Thyroid carcinoma	5	12 (8-40)	
	Colon carcinoma	16	7.25 (3-18)	
	Ovarian carcinoma	7	8 (0-13)	
	Breast carcinoma	18	7.5 (2.5-17)	
	Endometrial carcinoma	19	7 (2.5-15)	
	Cervical carcinoma	6	11.5 (6.5-50)	
	Bladder carcinoma	7	8 (3.5-15)	
	Oral carcinoma	8	8.25 (4.5-20)	
	Malignant lymphoma	4	6 (3-20)	
	Pancreatic carcinoma	7	11 (4-14)	
	Other cancers*	10	8.25 (2.5-30)	
	Renal carcinoma	4	9.5 (8-15)	
	Testicular carcinoma	4	5.75 (2.5-12)	
	Primary-unknown carcinoma	7	9 (2.5-13)	
History of operation	+	67	8 (0-50)	0.982
	–	117	8 (2.5-50)	
History of treatment	Chemo	43	6.5 (0-50)	0.206
	RT	4	8.5 (5-18)	
	Chemo +RT	27	10 (2.5-30)	
	–	110	8 (2.5-30)	

[#]The data are given as median (minimum-maximum)

+: Yes, -: No, Chemo: Chemotherapy, RT: Radiation therapy

*Other cancers (hepatocellular carcinoma, gallbladder carcinoma, gastric carcinoma, esophageal carcinoma)

(p=0.497, Table 5). However, comparison between the groups in terms of presence of malignant lesions and metastasis with SUV_{max} values identified a statistically significant difference in patients with metastasis as compared to patients without metastasis (p=0.049, Table 5).

Comparison of SUV_{max} Value and cfDNA Measurements According to Tumor Size

The SUV_{max} values and cfDNA values of patients according to tumor size are presented in Table 6. Accordingly, the mean SUV_{max} values of lesions with tumor size <2 cm were identified as 2.4 (0-34.4), as 10.4 (3.20-53) for masses 2-6 cm and as 13.35 (3.3-34.2) for masses ≥6 cm. Statistically, there was a significant difference identified between tumor size and SUV_{max} values. There was no clear statistical difference identified between tumor size and cfDNA.

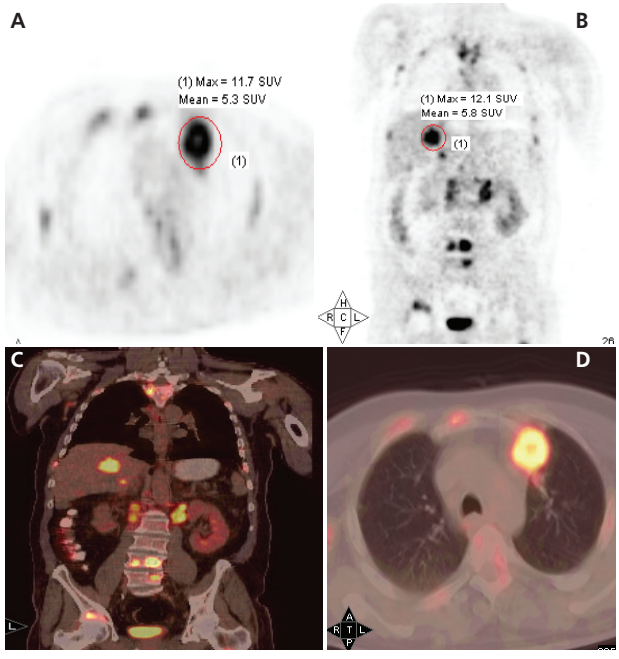

Figure 1. A patient with non-small cell lung carcinoma. The tumor in the left upper lobe shows F-18 FDG uptake (SUV_{max}: 11.7) as well as liver metastasis (SUV_{max}: 12.1). Coronal maximum intensity projection (A) and axial PET images (B) and axial PET/CT images (C), Coronal fused PET/CT images (D). The amount of cfDNA obtained from the patient's plasma was measured as 5 ng/mL. Primary tumor and liver metastasis lesions' SUV_{max} values and cfDNA values were compared. There was no significant difference between primary tumor and metastasis SUV_{max} and cfDNA values

Discussion

Several studies in the literature reported an increase of cfDNA in various types of cancer (7). A significant portion of these studies stated there were increased amounts of cfDNA in oncology patients as compared to normal patients healthy human beings (8). However, there are only a few comparative studies on cfDNA and tumor metabolic activity. We identified a weak correlation between SUV_{max} values and cfDNA. Furthermore, our results showed higher cfDNA values in lung, cervix, thyroid and pancreas cancers as compared to other type of malignancies.

A study on the correlation between ovarian cancer and cfDNA levels reported increase in cfDNA levels prior to epithelial ovarian cancer operations (9).

The 2005 study on cases with thoracic malignancy by Herrera et al. (10) is noteworthy as they did not observe a significant difference in the plasma cfDNA levels of healthy individuals, gastroesophageal reflux patients, esophageal and lung cancer patients. Similarly, in our study, there was no significant difference in cfDNA levels between the control and the patient groups. However, the results of this study identified that cfDNA levels were high in metastatic lung and cervix cancer.

Some studies on the correlations between cancer and risk factors have stated that cancer risk increases with age.

In a 2017 study on cfDNA amounts and mutations in cancer patients and healthy controls, Chen et al. (11) stratified the healthy controls according to gender and age (<50 - ≥50) and did not find a significant difference in cfDNA levels

Table 5. Comparison of tumor and metastasis presence with cell-free DNA and SUV_{max} values in oncologic patients

Variables	Patients (n=184)	cfDNA (ng/dL)*	p value	SUV_{max}**	p value
Tumor and metastasis	33	10 (2.5-20)	0.497	11.3 (2.6-34.4)	0.049
Tumor	67	9 (2.5-50)		8 (5-20)	
Metastasis	32	8 (2.5-30)		6 (4-11)	
No FDG¥ uptake tumor and metastasis	52	7.5 (0-40)		-	

The data are given as medians (minimum-maximum)
*cfDNA: Cell-free DNA
**SUV_{max}: Maximum standardized uptake value
¥FDG: Fludeoxyglucose

between groups. Similarly, in our study, age (<50 - ≥50) and gender were not observed to cause a difference in cfDNA amounts.

Kim et al. (12) reported that cfDNA amounts were higher in the non-smoking patient group as compared to smokers in a cohort of gastric carcinoma patients. In our study, comparison of smoking and non-smoking patients and control groups did not reveal a significant correlation between cfDNA levels with smoking in both groups.

Some literature studies have stated that cfDNA concentrations in healthy subjects ranged between 0 and 100 ng/mL, whereas in cancer patients the concentration in plasma or in serum ranged between 0 and 1000 ng/mL (13).

It is not known whether this broad range of cfDNA levels is linked to normal physiologic variability or to chronic or sub-clinical pathologic situations. It is likely that body mass index, presence of a sub-clinical disease at the time of measurements, and chronic disease may affect cfDNA levels. In our study, cfDNA levels were measured according to the current disease of the patient. Previous diseases and blood markers of these diseases were not measured. However, there was no significant difference between the oncologic patient and control group in terms of cfDNA levels.

A broad-scale study of oncology patients and healthy cases found a significant difference in cfDNA concentrations between the groups included in the study; however, no cut-off value could be determined for the use of cfDNA in cancer diagnosis screening (14). In our study, we did not determine a cut-off value between the patient and control groups. The measurements could not be standardized due to reasons such as sampling at different times, and including various operators although the same technique was used. There was also no access to broad patient-linked investigations, thus an appropriate reference interval could not b determined.

In a study by Heitzer et al. (15), cfDNA belonging to the tumor was not found in the plasma at measurable intervals in some of the metastatic cancer patients.

In our study, there was no statistically significant difference identified in terms of cfDNA between metastatic and nonmetastatic disease. Comparison of the groups in terms of SUV_{max} values in the presence of malignant lesions and metastatic disease identified a statistically significant difference between patients with metastasis and those without. As only a small portion of the total cfDNA in the circulation belongs to the tumor, identification of cfDNA at undetectably low levels in metastatic carcinoma patients appears possible, although it contradicts the literature. There are many studies indicating that plasma DNA levels correlate with tumor size, degree of tumor invasion, disease stage, survival and progression of disease with treatment.

Nygaard et al. (16), in a 2014 study evaluating the correlation between tumor load and cfDNA by using PET/CT in non-small cell lung cancers, did not find a correlation between metabolic tumor volume and tumor lesion glycolysis with cfDNA. Similarly, in our study, while there was an increase in SUV_{max} values linked to increased tumor volume, this increase did not appear to correlate with cfDNA.

Study Limitations

There are several problems in evaluating cfDNA such as standardization of assays, isolation technologies, standards, assay conditions, and specificity and sensitivity rates (17). Blood collection, transport time and storage conditions should be optimized during the study.

Firstly, the technique used to measure cfDNA and thus the determined cfDNA concentrations may be different. As a result, it is very difficult to define a cut-off value to distinguish benign and malignant diseases. Moreover, it is not known whether this broad interval of cfDNA levels is normal physiologic variability or linked to chronic or subclinical pathologic situations. It appears probable that body mass index, current subclinical diseases and chronic diseases may affect cfDNA levels during measurement. In our study, patients had cfDNA levels measured based on current diseases. Previous diseases and markers of these diseases in the blood were not measured. Nevertheless, there was no significant difference observed in cfDNA levels between the oncologic patient and control group.

Secondly, there are some difficulties related to how to determine the sensitivity and specificity of molecular tumor

Table 6. Comparison of tumor size, SUV_{max} and cell-free DNA values in oncologic patients

Variables		Patients	SUV_{max}	p value	cfDNA (ng/dL)	p value
Tumor size#	a.<2 cm	134	2.4 (1.3-34.4)	p<0.001	8 (0-50)	0.399
	b. 2-6 cm	38	10.4 (3.20-53)		10 (2.5-50)	
	c.≥6 cm	12	13.35 (3.3-34.2)		6.75 (2.5-16)	

#The data are given as minimum (minimum-maximum). cfDNA: Cell-free DNA

markers at clinical levels. It is difficult to compare different research groups due to the use of different nucleic acid isolation techniques for plasma and serum. Though this study used the same technique, we identified different values linked to different personnel. As a result, we believe it is necessary to obtain nucleic acid automatically with certain standards to provide common use of serum/plasma DNA in the future.

Conclusion

Currently, there is no diagnostic method that can be used for early diagnosis of cancer and evaluating response to treatment alone. Conventional imaging methods are extremely important in the diagnosis and treatment of oncology patients. However, a range of problems may be experienced due to ionizing radiation and assessment errors. As a result, there is a need for easy-to-use, simple additional screening methods. With this aim, cfDNA measurements in the blood for use as a simple screening test have provided hope for early diagnosis and monitoring of cancer patients in recent years. As a result, there is a need for comparison of cfDNA levels obtained from plasma and quantitative parameters from PET/CT images of oncology patients in more detailed advanced studies with larger patient series.

Ethics

Ethics Committee Approval: The study was approved by Çanakkale University Ethics Committee (protocol number: 204-14).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.Z.T., Design: Y.Z.T., F.Ç., Data Collection or Processing: F.Ç., F.S., Analysis or Interpretation: Y.Z.T., F.Ç., S.Ö., Literature Search: F.Ç., Writing: Y.Z.T., F.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of Myocardial Perfusion Imaging SPECT Parameters and Pharmacologic Stress Test with Adenosine Versus Coronary Angiography Findings: Are They Diagnostically Concordant?

Miyokardial Perfüzyon Görüntüleme SPECT Parametreleri ve Adenozin ile Yapılan Farmakolojik Stres Testinin Koroner Anjiyografi Bulguları ile Değerlendirilmesi, Tanı Uyumu Var mı?

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Abstract

Objectives: In this study our first aim was to evaluate the diagnostic concordance of myocardial perfusion scintigraphy (MPS) by pharmacological stress test with adenosine (APST) with coronary angiography (CAG). The secondary aim of this study was to evaluate the correlation between CAG findings and automated analysis parameters such as left ventricular ejection fraction, summed stress score (SSS), summed rest score, summed difference score (SDS), stress MPS defect percentage ratio (extent) and transient ischemic dilation (TID) obtained by myocardial perfusion imaging single-photon emission computed tomography (SPECT).

Methods: A total of 129 patients (62 male, 67 female, median age: 60.02) undergoing MPS due to suspicion of coronary ischemia who also underwent subsequent CAG in the last year were included in this study, their MPS data and CAG results were compared.

Results: There was no statistically significant diagnostic concordance when visual evaluation of MPS, quantitative MPS parameters and exercise treadmill test (ETT) electrocardiography results were used alone. In fact, diagnostic concordance was higher when automated analysis parameters like TID, SSS and extent values were added to MPS SPECT visual analyses. There was diagnostic concordance in 57.9% of APST patients and 41.7% of ETT patients. There was diagnostic concordance in 75.8% of APST patients and 52.6% of ETT patients who were older than 65 years of age.

Conclusion: In our study, we found that the use of APST during MPS increases diagnostic concordance with CAG. Therefore, we think that it would be appropriate to use APST in women and elderly patients with limited exercise habits. The CAG diagnostic mismatch is far above what it should be when MPS reporting is only done with visual data, and it is not supported by quantitative data such as TID, SSS, SDS and extent.

Keywords: Myocardial perfusion, SPECT, adenosine, stress test, quantitative parameters

Öz

Amaç: Bu çalışmada ilk amacımız, adenozin ile farmakolojik stres testinin (AFST), egzersiz treadmill teste (EST) göre koroner anjiyografi (KAG) ile uyumunu araştırmaktır. İkinci amacımız ise, miyokard perfüzyon tek-foton emisyon tomografisi bilgisayarlı tomografi SPECT (MPS) ile elde edilen sol ventrikül ejeksiyon fraksiyon, summed stres skoru (SSS), summed rest skoru, summed difference skoru (SDS), stres MPS defekt yüzde oranı (extent) ve transient iskemik dilatasyon (TID) gibi otomatik analiz parametrelerinin KAG ile uyumunu araştırmaktır.

Yöntem: Çalışmaya son 1 yıl içerisinde koroner arter hastalığı nedeniyle iskemi düşünülerek bölümümüzde MPS yapılan, sonrasında KAG uygulanan 129 hasta (62 erkek, 67 kadın, medyan yaş: 60,02) dahil edildi. MPS verileri ve KAG sonuçları karşılaştırıldı.

Bulgular: Tek başına vizüel değerlendirme, eforlu elektrokardiyografi sonuçları veya sayısal veriler kullanıldığında, KAG ve MPS bulguları arasında

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istatistiksel olarak anlamlı bir uyum bulunamadı. Oysa MPS vizüel analizine, otomatik analiz parametreleri eklendiğinde KAG ile tanı uyumunun TID, SSS ve extent verileri ile arttığı bulundu. EST yapılan hastaların %41,7'sinde ve AFST yapılan hastaların ise %57,9'unda KAG ile tanı uyumu vardı. Yaşı ≥65 olan hastalardan EST yapılan hastaların %52,6'sında, AFST yapılan hastaların %75,8'inde KAG ile tanı uyumu vardı.

Sonuç: Çalışmamızda MPS sırasında AFST kullanılmasının KAG ile tanı uyumunu artırdığını bulduk. Bu nedenle özellikle efor alışkanlığı kısıtlı olan kadın ve yaşlı hastalarda AFST kullanımının tercih edilmesinin uygun olacağını düşünmekteyiz. MPS raporlama sadece görsel verilerle yapılıp, TID, SSS, SDS ve extent gibi sayısal verilerle desteklenmediğinde KAG uyumsuzluğunun, beklenenin çok üstünde olduğu unutulmamalıdır.

Anahtar kelimeler: Miyokard perfüzyon, SPECT, adenozin, stres test, kantitatif parametreler

Introduction

Coronary artery diseases (CAD) is one of the most important causes of mortality and morbidity in the world. Coronary angiography (CAG) is the gold standard in diagnosing CAD. Nevertheless, myocardial perfusion scintigraphy (MPS) using single-photon emission computed tomography (SPECT) with radiopharmaceuticals is widely used for non-invasive diagnosis of obstructive CAD. MPS provides comprehensive information on myocardial perfusion, regional and global left ventricular function that provide incremental diagnostic and prognostic information. MPS evaluates regional myocardial perfusion as well as giving information about functional parameters such as transient ischemic dilation (TID), extent of perfusion defect, etc. (1). A normal stress MPS with adequate stress indicates a very good prognosis, with an annual myocardial infarction or death rate of less than 1-2%. Ischemic perfusion abnormalities usually remain undetected during rest, while stenosis of 50% or more are reliably identified with MPS under maximal myocardial stress. That is why MPS studies are performed with several stress test protocols. Exercise or pharmacological stress augment myocardial blood flow. Although with different mechanisms, myocardial blood flow in coronary vasculature without significant stenosis increases nearly 3-fold with exercise and 3- to 5- fold with vasodilator stressors (2). Exercise (treadmill or bicycle) is the preferred stress modality in patients who can exercise and achieve adequate exercise end-points. The most common mode of stress used in myocardial perfusion imaging is a multi-stage exercise treadmill test (ETT) based on a Bruce or modified Bruce protocol. Pharmacologic stress with adenosine, dobutamine and dipyridamole cause coronary hyperemia and increase myocardial workload allows a successful myocardial perfusion study in patients who cannot perform or tolerate adequate exercise, those with limited heart rate response due to -blockers or calcium-channel blockers, those with a pacemaker rhythm, Wolff-Parkinson-White syndrome, a transient ventricular pacemaker or with left bundle-branch block. This option is suggested for particular patients in guidelines. The sensitivity and specificity rates of MPS with pharmacological stress test study are reported to be comparable to that of maximal exercise studies, in the range of 85% to 90% (3). A meta-analysis determined the sensitivity and the specificity of adenosine SPECT imaging as 90% and 70%, respectively (4). However, treadmill exercise test is the primarily preferred method for MPS in most nuclear medicine clinics.

In general, SPECT studies are interpreted based on visual assessment of relative tracer uptake images. In clinical practice, imaging equipment, imaging protocols, stress protocols, reconstruction algorithm and filters, the patient's body habitus, age and gender, artifacts from patient motion, display monitor, the physician's vision and various other issues affect image evaluation by a nuclear medicine physician. However, automated analysis data from quantitative software tools can be used to assist visual analysis. Quantification is an extremely valuable tool in MPS, as it provides an objective assessment of the parameters under investigation.

Our first aim in this study was to evaluate the concordance of CAG and MPS findings with exercise stress test and pharmacological stress test with adenosine (APST). The second aim in this study was to investigate the correlation between CAG findings and automated analysis parameters such as left ventricular ejection fraction (LVEF), summed stress score (SSS), summed rest score (SRS), summed difference score (SDS), stress myocardial perfusion defect percentage ratio (extent) and TID obtained from MPS SPECT.

Materials and Methods

Study Population

This retrospective study was performed in accordance with the Helsinki Declaration. A total of 129 patients (67 female, 62 male, median age: 60.02) who underwent MPS due to suspicion of coronary ischemia and had CAG within the last one year were included in this study. Patients who had motion artifacts in MPS, who had high extra-cardiac activity during MPS, and those who had undergone previous coronary surgery were excluded.

Stress Protocols (Adenosine and ETT)

Patients were asked to stop taking nitrates for 6 h, calcium-channel blockers for 24 h, and ß-blockers for 48 h prior to ETT. Modified Bruce protocol was used in all patients in ETT. Tc-99m sestamibi was injected when the patient's heart rate reached 85% of predicted maximum heart rate and exercise was continued for two minutes after the injection.

Exercise Treadmill Test Procedures

Routine ETT was performed with the use of the standard Bruce protocol. The ETT was continued until the occurrence of marked ST-segment changes, worsening chest pain, sustained ventricular arrhythmias, or excessive fatigue. ST-segment changes, heart rate, and blood pressure measurements were recorded throughout testing. Exertional chest pain or excessive dyspnea was also documented. A normal ETT was defined as the lack of significant ST-segment changes with adequate exercise tolerance. An indeterminate ETT was defined as 0.5 to 1.0 mm of ST-segment changes, exertional chest pain, and/or submaximal exercise tolerance. An abnormal ETT was defined as ≥1 mm of ST-segment change generally occurring in ≥2 leads. The electrocardiography (ECG) was interpreted by site investigators.

This study was approved by the Local Ethics Committee of Sivas Cumhuriyet University (protocol number: 2018-03/06). Consent form was filled out by all participants.

Stress Testing Procedure with Adenosine

In APST, the adenosine dose was specified as 0.14 mg/kg/min in 100 cc 0.9% NaCl physiological saline solution administered in 6 minutes via intravenous infusion. The Tc-99m sestamibi was injected about halfway into the adenosine infusion (at 3 minutes), when maximal vasodilation and myocardial hyperemia occurred. Heart rate, blood pressure, and a 12-lead electrocardiogram were recorded at baseline and during the study, and for at least 2 minutes after completion of the study.

Gated SPECT Protocol

All patients underwent the two-day MPS protocol. A dose of ~20-30 mCi Tc-99m sestamibi was injected intravenously for the stress study and ~20 mCi Tc-99m sestamibi was injected for the rest study. All data acquisition was performed with double head SPECT system (DDD-CorCam, Denmark) equipped with a low-energy, high resolution collimator. A protocol consisting of a 64x64 matrix, 30 projections per head, 25-s projections over a 180° circular orbit and 8 frames per cycle was applied, with 140 keV energy photopeak. A rotational arc of 180 degrees was used, beginning at the 45-degree right anterior oblique position and ending at the 45-degree left posterior oblique position with 64 steps in every 3-6 degrees. Image acquisition was done 15-30 minutes after ETT and 45-60 minutes after APST. The gated images were used to assess left ventricle volumes and EF. Gated data acquisition was done with 16 frames per cardiac cycle for the R-R interval length by using the forward-backward gating method.

MPS images were interpreted based on a 17-segment model (5). Images were categorized as either normal or ischemic. Perfusion parameters were derived in an entirely automated fashion using commercially available software program [Cedars-Sinai quantitative perfusion score (QPS) SPECT and quantitative gated SPECT (QGS)]. This program can generate a surface contour even in the apparent absence of perfusion by using smoothness, the iso-contours of the coordinate system, and the geometry of the defect boundaries as constrains. The automatic computations were adjusted manually if left ventricular cavity segmentation was unsuccessful. Visual scan interpretation was performed by at least two experienced readers.

The total score at stress is called SSS that reflects the extent and severity of the abnormality including ischemia and infarction. The difference between the SSS and SRS is called SDS, which reflects a reversible defect.

Semi-quantitative parameters were classified as follows;

A SSS ≤3 was accepted as a normal result, while a score of 4-8 as a mild defect, 9-12 as a moderate defect and >12 as a severe defect (6).

A SDS of 1-3 represented mild ischemia, 4-7 moderate ischemia and >7 severe ischemia (6).

TID indicates a larger left ventricular cavity during stress than rest. TID values were calculated using a commercially available automated program (QPS, Cedars-Sinai). TID more than 1.22 was considered as abnormal (7).

The perfusion defect size correlates with the extent of CAD. Extent indicates perfusion defect area as percent of the mid-myocardial surface area. The perfusion defect extent is calculated as the percentage of the total surface area of the left ventricle, for which test-data are below 3.0 mean absolute deviations (approximately equivalent to 2.5 standard deviations) threshold. Perfusion defect size quantification by percentage size of the left ventricle was classified as (% terms, limits 0-100%): small (0-10%), medium (>10% to 20%), and large (>20%) (6).

LVEF and left ventricular volumes were measured by using QGS. LVEF was also calculated by estimation of end diastolic (EDV) and end systolic volumes (ESV) derived from short axis images [(EDV-ESV) / EDV] x 100. A LVEF <50% was considered as abnormal. CAG data were obtained from

cardiac catheterization reports within six months after MPS. Data from MPS and CAG results were compared. If there was an ischemic area in MPS with 50% or more stenosis of coronary arteries in CAG, this result was accepted as concordance in diagnosis. Similarly, if there was not any ischemic area in MPS along with <50% stenosis in coronary arteries in CAG, the result was accepted as concordant diagnosis.

Abbreviations used in the following tables represent;

MPS + (presence of ischemia), MPS - (absence of ischemia), TID + (TID ≥1.22), TID - (TID <1.22), extent (perfusion defect size by percentage size ≥10), extent - (perfusion defect size by percentage size <10), SSS + (SSS ≥4), SSS - (SSS <4), SDS + (SDS ≥4), SDS - (SDS <4).

Statistical Analysis

Analysis was performed by using SPSS Statistical Software program (SPSS version 23.0, SPSS Inc., Chicago). Diagnostic concordance with CAG was presented by gender, exercise type, MPS visual analysis result, and MPS gated SPECT data (SSS, SDS, extent, TID, LVEF) by using cross tabulations. The chi-square test was used to compare these proportions in different groups. Correlation between automated analysis parameters and stenosis percentage in CAG were evaluated via using Pearson correlation. All continuous variables were described as a mean ± SD. A p value <0.05 was considered as statistically significant.

Results

One hundred twenty-nine patients were included in the study. Patient demographic features and gated SPECT parameters are summarized in Table 1. There were 67 female patients (51.9%) and 62 male patients (48.1%) in our study. The median patient age was 60.02 years (range: 31-86). There was ≥50% stenosis in a coronary artery in 49 patients (38%), and there was no or <50% stenosis in a coronary artery in 80 patients (62%).

Table 1. Demographic characteristics and myocardial perfusion scintigraphy gated single-photon emission computed tomography parameters

Parameter	Median	Range
Age (years)	61	31-86
TID	0.97	0.63-1.37
Stress EF (%)	61	23-79
SSS	7	0-51
SDS	3	0-27
Extent	8	0-64

TID: Transient ischemic dilation, EF: Ejection fraction, SSS: Summed stres score, SDS: Summed difference score

There was diagnostic concordance between MPS and CAG in 57.9% of APST patients and 41.7% of ETT patients (p=0.067). There was diagnostic concordance between MPS and CAG in 67.3% of patients older than 65 years of age and in 36.4% of patients younger than 65 years of age (p=0.001). There was diagnostic concordance between MPS and CAG in 75.8% of APST patients and 52.6% of ETT patients who were older than 65 years of age (p=0.087). There was diagnostic concordance between MPS and CAG in 37.3% of female patients and 61.3% of male patients (p=0.006). Diagnostic concordance between MPS and CAG was significantly higher in APST group than in ETT group, although it was not statistically significant among male patients (p=0.173 for male patients; p=0.046 for female patients) (Table 2).

The mean (standard deviation ±) values of the quantitative MPS parameters of patients with ≥50% coronary artery stenosis in CAG were as follows; SSS: 14.59 (12.1), SDS: 5.86 (5.7), TID: 1.01 (0.14), stress extent 19.06 (16.2), and stress LVEF 55.13 (10). The SSS, SDS, TID and stress extent parameters were statistically significantly higher in patients

Table 2. Comparison of stress types, patient gender and age with diagnostic concordance of coronary angiography, p* <0.05

			Diagnostic concordance with CAG		p*
			Absent	Present	
			n (%)	n (%)	
Stress type	ETT		42 (58.3)	30 (41.7)	0.067
	APST		24 (42.1)	33 (57.9)	
Gender	Female		42 (62.7)	25 (37.3)	0.006*
	Male		24 (38.7)	38 (61.3)	
Age	<65		49 (63.6)	28 (36.4)	0.001*
	≥65		17 (32.7)	35 (67.3)	
Female	Stress type	ETT	24 (75)	8 (25)	0.046*
		APST	18 (51.4)	17 (48.6)	
Male	Stress type	ETT	18 (45)	22 (55)	0.170
		APST	6 (27.3)	16 (72.7)	
Age <65	Stress type	ETT	33 (62.3)	20 (37.7)	0.710
		APST	16 (66.7)	8 (33.3)	
Age ≥65	Stress type	ETT	9 (47.7)	10 (52.6)	0.087
		APST	8 (24.2)	25 (75.8)	

ETT: Exercise treadmill test, APST: Pharmacological stress test with adenosine administration, CAG: Coronary angiography, *: p<0.05

with ≥50% coronary artery stenosis than in patients with <50% coronary artery stenosis in CAG (p=0.037; 0.029; 0.050; 0.022 and 0.602, respectively.

ETT was performed in 33 female patients and exercise level was inadequate in 10 of those patients (30.3%). Within this group, the ECG result was (+) in 16 patients (48.5%) and was normal in seven patients (21.2%). ETT was performed in 41 male patients and exercise level was inadequate in five of these patients (12.2%). Within this group, ECG result was (+) in 22 patients (53.7%) and was normal in 14 patients (34.1%) (p=0.127).

There was no statistically significant diagnostic concordance between MPS and CAG when visual evaluation of MPS, quantitative MPS parameters and ETT ECG results were used alone. There was 47% diagnostic concordance between MPS and CAG if only visual evaluation of MPS was used. Diagnostic concordance between MPS and CAG was 66.7% when MPS was reported as normal (p=0.194). There was no statistically significant diagnostic concordance between MPS and CAG when SSS, SDS, extent, TID, LVEF and ETT ECG results were used alone (Table 3). In fact, diagnostic concordance was higher when automated analysis parameters like TID, SSS and extent values were added to MPS SPECT visual analysis. Diagnostic concordance between MPS and CAG was 54.1% in MPS + SSS + patients, 60.8% in MPS + extent + patients, and 85.7% in MPS + TID + patients. Moreover, diagnostic concordance between MPS and CAG was 100% in MPS - SSS - patients (only three patients), 83.3% in MPS - extent - patients, and 72.7% in MPS - TID - patients (p=0.021, 0.020 and 0.044, respectively). Although not statistically significant, diagnostic concordance between MPS and CAG was higher in patients with MPS + EF <50% and MPS + SDS + than in patients with MPS + on visual evaluation alone (p=0.055, 0.117, respectively). There was no statistically significant difference in diagnostic concordance between MPS and CAG when ETT results and visual MPS results were evaluated together (p=0.513) (Table 4).

There was low-intermediate or insignificant correlation between CAG and automated analysis parameters (Table 5).

Table 3. Comparison of automated analysis parameters derived from myocardial perfusion scintigraphy single-photon emission computed tomography and visual evaluation with diagnostic concordance of coronary angiography, *p<0.05

Variable	Grouping	Diagnostic concordance with CAG		
		Absent	Present	p
		n (%)	n (%)	
MPS result	MPS -	4 (33.3)	8 (66.7)	0.194
	MPS +	62 (53)	55 (47)	
SSS category	Normal (1-3)	23 (65.7)	12 (34.3)	0.174
	Mild defect (4-8)	20 (51.3)	19 (48.7)	
	Moderate defect (9-12)	11 (44)	14 (56)	
	Severe defect (>12)	12 (40)	18 (60)	
SDS category	Minor ischemia (1-3)	38 (55.1)	31 (44.9)	0.629
	Moderate ischemia (4-7)	18 (47.4)	20 (52.6)	
	Severe ischemia (>7)	10 (45.5)	12 (54.5)	
Extent	Small (0-9)	43 (59.7)	29 (40.3)	0.092
	Medium (10-19)	10 (40)	15 (60)	
	Large (>20)	13 (40.6)	19 (59.4)	
TID	<1.22	64 (52.9)	57 (47.1)	0.126
	≥1.22	2 (25)	6 (75)	
Stress LVEF (%)	<50	8 (34.8)	15 (65.2)	0.067
	≥50	57 (55.9)	45 (44.1)	
ECG results on ETT	Positive	20 (51.3)	19 (48.7)	0.108
	Negative	10 (47.6)	11 (52.4)	
	Suspicious	12 (80)	3 (20)	

SSS: Summed stres score, SDS: Summed difference score, Stress extent: Stress mid myocardial perfusion defect percentage, TID: Transient ischemic dilation, LVEF: Left ventricular ejection fraction, ECG: Electrocardiography, ETT: Exercise treadmill test, CAG: Coronary angiography

Discussion

MPS is frequently used for diagnosis and risk stratification in patients with CAD. The anatomical extent of stenosis is poorly correlated with flow reserve and the degree of ischemia. Factors that might impact the functional significance of an anatomical circumferential narrowing include the length, shape, and location of a stenotic lesion. Functional imaging with MPS is often needed to evaluate the clinical significance of a previously known stenosis, particularly in those within the range of 50-70% (8). MPS is a frequently used noninvasive imaging modality for the diagnosis and follow-up of CAD in our country and throughout the world.

Interpretation of MPS images is subjective since several technical and inter-personal features might affect the study. In addition, dilated cardiomyopathy, exercise-induced coronary spasm, mitral valve prolapse, and aortic stenosis have also been associated with various SPECT abnormalities (9).

Although specialists with expertise usually ignore image artifacts that mimic ischemia, false positive findings are still reported frequently because of patient's clinical situation which can cause image artifacts such as obesity, diaphragm attenuation, breast attenuation and etc. Taking quantitative parameters into consideration along with visual evaluation increases diagnostic accuracy of MPS. Also, artifacts on

Table 4. Comparison of automated analysis parameters derived from myocardial perfusion scintigraphy single-photon emission computed tomography and visual evaluation with electrocardiography results in exercise treadmill test with diagnostic concordance of coronary angiography, *p<0.05

Variable	Grouping	Diagnostic concordance with CAG		
		Absent	Present	p
		n (%)	n (%)	
MPS/SSS	MPS +, SSS +	39 (45.9)	46 (54.1)	0.021*
	MPS +, SSS -	23 (71.9)	9 (28.1)	
	MPS -, SSS +	4 (44.4)	5 (55.6)	
	MPS -, SSS -	0	3 (100)	
MPS/SDS	MPS +, SDS +	26 (45.6)	31 (54.4)	0.117
	MPS +, SDS -	36 (60)	24 (40)	
	MPS -, SDS +	2 (66.7)	1 (33.3)	
	MPS -, SDS -	2 (22.2)	7 (77.8)	
MPS/Extent	MPS +, extent +	20 (39.2)	31 (60.8)	0.020*
	MPS +, extent -	42 (63.6)	24 (36.4)	
	MPS -, extent +	3 (50)	3 (50)	
	MPS -, extent -	1 (16.7)	5 (83.3)	
MPS/TID	MPS +, TID +	1 (14.3)	6 (85.7)	0.044*
	MPS +, TID -	61 (55.5)	49 (44.5)	
	MPS -, TID +	1 (100)	0	
	MPS -, TID -	3 (27.3)	8 (72.7)	
MPS/EF	MPS +, EF +	7 (33.3)	14 (66.7)	0.055
	MPS +, EF -	54 (58.7)	38 (41.3)	
	MPS -, EF +	0	1 (100)	
	MPS -, EF -	3 (30)	7 (70)	
MPS/ECG	MPS +, ECG +	20 (54.1)	17 (45.9)	0.513
	MPS +, ECG -	9 (47.4)	10 (52.6)	
	MPS -, ECG +	0 (0)	2 (100)	
	MPS -, ECG -	1 (50)	1 (50)	

SSS: Summed stres score, SDS: Summed difference score, Stress extent: Stress mid myocardial perfusion defect percentage, TID: Transient ischemic dilation, ECG: Electrocardiography, CAG: Coronary angiography, *: p<0.05

MPS can cause false positive results. The reproducibility of quantitative analysis of MPS study is higher than visual analysis. Xu et al. (10) reported that quantitative measures of stress, rest and ischemic (stress-rest) defects were significantly more reproducible than visual scores.

Mazzanti et al. (7) determined a sensitivity rate for detection of severe and extensive CAD of 41% by visual analysis as compared to 71% by automatic analysis. Berman et al. (11) found that by perfusion assessment alone, high-risk disease with moderate to severe defects was identified in only 56% of patients visually and in 59% by quantitative evaluation. However, by combining visual perfusion data and nonperfusion variables, especially TID, 83% of patients were identified as high-risk (11). Slomka et al. (12) reported that delayed enhancement MR data and MPS quantitative defect extent percentage showed excellent concordance for detecting the infarct area and its extent. In our study, MPS concordance with CAG was higher than quantitative analysis by visual evaluation alone when the patient was reported as normal (66.7%). However, MPS concordance with CAG was lower than quantitative analysis by visual evaluation alone when the patient was reported as ischemic (47%) (Table 3). In their study with 1148 patients, Chavoshi et al. (13) stated that the incidence of total cardiac events was higher among patients with high SSS and SDS and in those with TID. It is also known that LVEF and left ventricular volumes are important prognostic factors in patients with CAD and left ventricular dysfunction. There is a strong correlation between gated MPI and reference standard measurements of quantitative LVEF, all of which are relatively independent of the isotope, protocol, standard, and algorithm used (14). In a similar manner, TID measured by all the algorithms notwithstanding with effort type is a specific indicator of severe and extensive coronary disease, and TID with positive MPS is accepted as a predictor of poor clinical outcome (15,16). Bourque (17) stated that normal MPS studies with SSS <4 and normal LV function and systolic volumes have a low likelihood of obstructive CAD and a low subsequent event rate in the absence of high-risk comorbidities even with positive TID, and that these patients can be observed with careful follow-up and do not need invasive CAG. However, Abidov et al. (18) indicated that a normal MPS study does not always predict excellent prognosis. TID is an important prognostic factor especially in elderly and diabetic patients. Isolated positivity of TID ratio can be related to diffuse, balanced and severe ischemia (18,19).

In our study, we found that the diagnostic concordance of MPS with CAG increases statistically significantly when TID, SSS and extent ratio (perfusion defect area as percent of the mid-myocardial surface area) were added to visual MPS evaluation. The diagnostic concordance between MPS and CAG was 47% if only visual evaluation of MPS was used. However, the diagnostic concordance was determined as 85.7% in MPS + TID + patients, as 54.1% in MPS + SSS + patients, and as 60.8% in MPS + extent + patients ($p<0.05$). Diagnostic concordance between MPS and CAG was higher but statistically not significant in patients with MPS + EF <50% and MPS + SDS + than in patients with MPS +, in visual evaluation alone ($p=0.055$ and 0.117, respectively).

Performing an appropriate and adequate stress test is an important factor that can influence the sensitivity and specifity of an MPS study. According to the EANM guideline, the diagnostic performance of an MPS study is statistically independent of stress agents or modalities (20). A meta-analysis that includes 24 studies and 14.918 patients showed that patients undergoing pharmacologic stress studies are at a higher risk for subsequent cardiac events like myocardial infarction and death from cardiac reasons (21). In contrast, in their prospective study including 266 exercise (bicycle) stress testing and 65 APST, Hochgruber et al. (22) stated that exercise stress but not adenosine stress results in an increase of cardiac wall stress, angina symptoms and ECG changes in patients with reversible ischemic changes on MPS. That is why the absence of these surrogates of

Table 5. Correlation of automated analysis parameters of myocardial perfusion scintigraphy single-photon emission computed tomography and coronary angiography findings

	LAD p (r)	RCA p (r)	LCX p (r)
SSS	0.001 (0.291)*	0.0001 (0.367)*	0.001 (0.292)*
SDS	0.001 (0.305)*	0.065 (0.165)	0.045 (0.179)*
TID	0.014 (0.218)*	0.074 (0.410)	0.101 (0.146)
Stress extent	0.0001 (0.326)*	0.0001 (0.380)*	0.0001 (0.323)*
LVEF	0.028 (-0.197)	0.001 (-0.303)*	0.002 (-0.272)*

SSS: Summed stres score, SDS: Summed difference score, Stress extent: Stress mid myocardial perfusion defect percentage, TID: Transient ischemic dilation, LVEF: Left ventricular ejection fraction, *: p<0.05

myocardial ischemia suggests that adenosine stress does not induce acute myocardial ischemia, but rather displays relative perfusion differences (22). According to American Heart Association data in a study on vasodilator stress in a cohort of 130 women who underwent APST imaging, there was a reported 91% sensitivity and 86% specificity for detecting significant coronary artery stenosis >50% (23). Nevertheless, the same study reported that the sensitivity of MPS with ETT was 78-88% and the specifity was 64-91% (24). In our study, we found that MPS with APST has higher but statistically not significant diagnostic concordance with CAG than MPS with ETT, when all patients were taken into consideration (Table 2). Additionally, we found that the diagnostic concordance with CAG was higher in MPS with APST in both male and female patients than in MPS with ETT (Table 2). This finding was attributed to the low exercise tolerance of patients who have been referred to MPS in our clinics. Interestingly, diagnostic concordance of APST with CAG was higher in patients older than 65 years of age than in ETT ($p>0.05$). It is the author's opinion that this situation was related to the fact that APST was the primarily preferred method for elderly patients instead of ETT and that adequate cardiac stress might have been created with APST. In the same patient group, patients did not complete an ETT that can generate adequate cardiac stress. In their WOMEN trial study (The What Is the Optimal Method for Ischemia Evaluation in Women) in low-risk, exercising women, Shaw et al. (25) reported that a diagnostic strategy that uses ETT versus exercise MPS yielded similar two-year post-test outcomes and similar prognosis. In this study, the 85% of predicted maximal heart rate was achieved in 88.4% and 88.1% of patients with MPS and ETT, respectively. However, in our study, 48.5% of female patients performed adequate exercise. Daily life activity and social sports habits may vary depending on country and geographical settlement. Unfortunately, daily sports activities are not routine in our country, especially among women. In addition, exercise capacity decreases significantly in the elderly. According to our study, there was no correlation between ETT and CAG alone. Moreover, ETT did not provide additional contribution in terms of diagnostic concordance with CAG and MPS in our study.

Conclusion

In our study, we found that the use of APST during MPS increased diagnostic concordance with CAG. Therefore, we think that it would be appropriate to use APST in women and elderly patients with limited exercise habits. However, ETT should be preferred in patients who are thought to be able to perform the test properly and who have a high likelihood of coronary artery stenosis. Evidently, MPS and CAG cannot be expected to comply fully with both physiological (existing collateral circulation, false positive ischemic cardiac pathologies, etc.) and non-physical (due to imaging artifacts, inadequate exercise, etc.) causes. Nevertheless, it should be kept in mind that MPS reporting is based on visual data alone and that CAG diagnostic mismatch is higher than acceptable rates when it is not supported by quantitative data such as TID, SSS, SDS and extent.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Sivas Cumhuriyet University (protocol number: 2018-03/06).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.H., S.A.E., A.Ç., İ.G., A.Y., Concept: Z.H., S.A.E., İ.G., A.Y., Design: Z.H., S.A.E, İ.G., A.Y., Data Collection or Processing: Z.H., S.A.E., A.Ç., Analysis or Interpretation: Z.H., S.A.E, A.Ç., Literature Search: Z.H., S.A.E., A.Ç., İ.G., A.Y., Writing: Z.H., S.A.E., A.Ç., İ.G., A.Y.

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Original Article
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Significance of Microalbuminuria in Predicting Silent Myocardial Ischemia in Patients with Type 2 Diabetes Using Myocardial Perfusion Imaging

Miyokard Perfüzyon Sintigrafisi ile Sessiz Miyokard İskemisi Saptanan Tip 2 Diyabetik Hastalarda Mikroalbuminürinin Önemi

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Abstract

Objectives: In light of increased risk of cardiovascular events and the poor prognosis of coronary artery disease (CAD) in diabetic versus non-diabetic patients and also with respect to the importance of early diagnosis of CAD in this status, the study was aimed to assess the importance of microalbuminuria in predicting silent myocardial ischemia (SMI) in patients with type 2 diabetes using myocardial perfusion imaging (MPI).

Methods: This study included 120 patients with diabetes type 2, but without previously known CAD or any cardiac symptoms that were stratified into two groups based on presence/absence of microalbuminuria. All participants underwent CAD evaluation using gated myocardial perfusion single-photon emission computed tomography (MPS) imaging. Other clinical and laboratory indices were also recorded.

Results: Studied population consisted of 84 males (70%) and 36 females (30%), totally 120 patients with mean age of 58.61±9.90). In total, asymptomatic ischemia was detected in 78 (65%) of the included diabetic patients. Stress induced ischemia was found in 56 patients (87.5%) of albumin+ (Alb) group and in 22 patients (39.3%) of Alb- group. The frequency of stress induced ischemia was 10.81 times higher in the patients with microalbuminuria compared to Alb- ones [p<0.001, Odds ratio: 10.81, 95% confidence interval: 4.33-26.99]. On the other hand, no relationship was found between the presence of stress induced ischemia and therapy type, diabetes duration, history of evident retinopathy, history of hypertension and also serum levels of hemoglobin A1c (p>0.05).

Conclusion: The current study showed that abnormal MPI findings are significantly more common in diabetic patients with microalbuminuria. With respect to low cost and availability of urine Alb detection tests, it might be as a biomarker for prediction of SMI in diabetic population.

Keywords: Microalbuminuria, silent myocardial ischemia, type 2 diabetes, myocardial perfusion imaging

Öz

Amaç: Bu çalışmada diyabetik olgularda diyabetik olmayanlara göre kardiyovasküler olay riskinin yüksek ve koroner arter hastalığı (CAD) prognozunun kötü olmasından yola çıkarak tip 2 diyabette CAD'nin erken tanısında mikroalbuminürinin önemi miyokard perfüzyon sintigrafisinde (MPS) saptanan sessiz miyokard iskemisi (SMİ) bulguları ile birlikte değerlendirilmektedir.

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Yöntem: Önceden bilinen CAD ve kardiyak semptomu bulunmayan tip 2 diyabetli 120 olgu çalışmaya dahil edilerek mikroalbuminüri varlığına/yokluğuna göre iki gruba ayrılarak incelendi. Tüm hastalara CAD'yi değerlendirmek üzere miyokard perfüzyon tek-foton emisyonlu bilgisayarlı tomografi ile görüntüleme yapıldı. Ayrıca diğer klinik ve laboratuvar verileri toplandı.

Bulgular: Çalışma grubu 84 erkek (%70) ve 36 kadından (%30) oluşan, yaş ortalaması 58,61±9,90 olan 120 hastalık bir gruptur. Gruba dahil edilen diyabetik olguların 78'inde (%65) asemptomatik iskemi saptandı. Albumin+ (Alb) olguların 56'sında (%87,5), Alb- olguların 22'sinde (%39,3) stres iskemisi bulundu. Mikroalbuminüri bulunan olgularda stres iskemisi sıklığı diğerlerine göre 10,81 kez fazlaydı [p<0,001, Odds oranı: 10,81, %95 güven aralığı: 4,33-26,99]. Öte yandan, stres iskemisi ile tedavi tipi, diyabetin süresi, bariz retinopati öyküsü, hipertansiyon ve serum hemoglobin A1c düzeyi arasında ilişki bulunmadı (p>0,05).

Sonuç: Bu çalışma mikroalbuminürisi bulunan diyabetik olgularda MPS'sinde anormal bulguların daha sık olduğunu göstermektedir. Düşük maliyeti ve kolay temini nedeniyle idrarda albumin ölçümü diyabetik popülasyonda SMİ'yi öngörmede bir biyobelirteç olarak kullanılabilir.

Anahtar kelimeler: Mikroalbuminüri, sessiz miyokard iskemisi, tip 2 diyabet, miyokard perfüzyon sintigrafisi

Introduction

Type 2 diabetes is defined as impairment of the ability to produce or respond to the insulin hormone, leading to abnormal metabolism of carbohydrates and increasing in levels of blood glucose. The risk of type 2 diabetes increases with age specifically over 50 years old.

Globally about 400 million adults are living with diabetes mellitus around the world and it is predicted that this number will be increased to more than 640 million until year 2040 (1).

About 4 million deaths per year are attributable to diabetes side effects, which is 9% of all deaths worldwide. These side effects include cardiovascular and cerebrovascular attacks, retinopathy, nephropathy, neuropathy and non-traumatic limbs amputations (2,3,4,5).

Cardiovascular events including coronary artery disease (CAD) 40% and other cardiac disorders like chronic heart failure 15% are the leading cause of morbidity and mortality of patients with diabetes, and death will occur 14.6 years earlier in type 2 diabetic patients compared to non-diabetics (5).

Microalbuminuria, defined as urinary albumin excretion of 20-200 mg/day, is a marker of systemic vascular damage, renal functional impairment and CAD (2).The prevalence of microalbuminuria is estimated 19% in diabetic patients as a marker of renal, cardiac and cerebral vascular damage (6).

Clinically patients with diabetes are more likely to be without chest pain in the setting of unstable angina, myocardial infarction or during exercise testing, and thus late presentation contributes to late CAD diagnosis and a higher mortality in these patients (7).

Silent myocardial ischemia (SMI) is classically described as an objective document of myocardial ischemia in patients without subjective ischemia symptoms. Now, there are different clinical methods in the diagnostic evaluation of CAD. Coronary artery angiography (CAG) is the gold standard for distinguishing of asymptomatic CAD. Computed tomography coronary angiography (CTCA) can depict anatomy, trend and extent of coronary stenosis. Myocardial perfusion imaging (MPI) uses to diagnose whether anatomical stenosis yields to myocardial dysfunction, to assess the risk estimation and prognosis of myocardial disease and also is frequently applied in clinical evaluation of CAD (8,9,10,11,12,13).

In view of increased risk of cardiovascular events and the poor prognosis of CAD in diabetic versus non-diabetic patients and also with respect to the importance of early diagnosis of CAD in this status, the study was aimed to assess the importance of microalbuminuria in predicting SMI in patients with type 2 diabetes using MPI.

Material and Methods

Study Population

Our study was designed as a non-randomized cross sectional clinical study. The study evaluated 120 patients with known and established diabetes type 2, but without previously known CAD or any cardiac symptoms.

The patients with past history of acute coronary syndrome, myocardial ischemia, abnormal electrocardiogram, previous myocardial infarction, percutaneous CTCA, coronary artery bypass graft surgery, peripheral vascular disease, established predisposing malignancy, chronic inflammatory disorders (vasculitis, rheumatoid arthritis, systemic lupus erythematosus), severe systemic illnesses and renal diseases were excluded from the study.

Evaluation for CAD was performed using MPI gated single-photon emission computed tomography (SPECT) imaging in the department of nuclear medicine of a university affiliated hospital. MPI findings were compared to the microalbuminuria status. Other clinical indices like presence of retinopathy, hypertension, systolic and diastolic blood pressure, liver function tests (aspartate aminotransferase,

alanine aminotransferase, alkaline phosphatase), serum lipid profile (high density lipoprotein, low density lipoprotein, thyroglobulin), hemoglobin A1c (HbA1c) and blood urea nitrogen/serum creatinine were also recorded. It should be mentioned that all eligible patients signed an inform consent. This study complies with the Declaration of Helsinki, and it was approved by the Institutional Ethics Committee of Bushehr University of Medical Sciences.

Microalbuminuria Assessment: Microalbuminuria was measured after 24 h urine collection and the patients were divided into two groups with microalbuminuria [renal albumin excretion between 20-200 mg/day, albumin$^+$ (Alb)] and without microalbuminuria (renal albumin excretion less than 20 mg/day, Alb$^-$). The patients with more than 200 mg/day were excluded.

Gated-SPECT MPI: Patients were instructed to refrain from caffeine-containing beverages for at least 12 hours, nitrates for 24 hours and beta-blockers for 48 hours before the study.

A two-day stress/rest MPI protocol was carried out for all patients. At stress phase, weight –adjusted doses of 10 MBq/kg of Tc-99m methoxyisobutylisonitrile (at least 700 MBq) was injected at peak pharmacologic stress and the similar dose was injected at rest for each patient on the next day.

Pharmacologic stress was obtained by 0.56 mg/kg of body weight of dipyridamole in 20 mLnormal saline which was injected intravenously during 5 minutes under electrocardiographic monitoring. Four minutes later, Tc-99m MIBI was injected.

SPECT acquisition was performed almost 30 minutes later. At the rest phase, almost 45 minutes after injection of Tc-99m MIBI, SPECT acquisition was performed for each patient.

SPECT Imaging Protocol: Images were done over a 180º orbit from right anterior oblique 45º to left posterior oblique 45º using a dual-head γ-camera (ADAC, USA) equipped with ultra-high resolution collimator. Acquisition was carried out in 32 steps at 30 seconds per stepusing the step- acquisition mode. For image acquisition, a 20% acceptance window around the 140 keV photopeak was applied. A 64x64 matrix was applied for all acquisitions. The prefilteration of projection datasets was performed by a Butterworth filter and images were reconstructed by filtered back-projection. For all images, a technologist experienced in nuclear cardiology reconstructed the raw data.

Interpretation of MPIs: All images were assessed qualitatively by two experienced practitioners, who reached an agreement on the results. The physicians were blind to the patient's data. Segmental perfusion defect in the stress phase images, which revealed filling-in (more uptake) in the rest phase study was considered as ischemia or reversible perfusion defect. Segment with perfusion defect in the stress phase scan with no alteration in size or amount of uptake (perfusion score) in the rest phase images were considered as irreversible perfusion defect or scar tissue.

Statistical Analysis

The continuous variables are presented as the mean ± standard deviation, and categorical variables as the absolute values and percentages. Categorical variables were compared using chi-square test and continuous variables using unpaired Student's t-test. Statistical analysis was performed with the use of the SPSS Statistical Package (version 20). A p value <0.05 was considered statistically significant.

Results

Studied population consisted of 84 males (70%) and 36 females (30%), totally 120 patients with mean age of 58.61±9.90 years old. In terms of duration of diabetes, 39 patients (32.5%) had more than 10 years, 39 patients (32.5%) had between 5-10 years and 42 patients (35%) had less than five years diabetes history. Anti-diabetic therapy used by the patients were as follow: 44 patients (36.7%) metformin, 33 patients (27.5%) metformin and glibenclamide combination, seven patients (5.8%) glibenclamide, six patients (5%) metformin and insulin combination, three patients (2.5%) insulin and one patient (0.8%) metformin, glibenclamide and insulin combination (Table 1). In addition, 87 patients were using aspirin. The type of antidiabetic therapy in our participants, did not show any significance in neither group Alb$^+$ nor Alb$^-$ (p>0.05).

Totally, 64 patients (53.3%) had the history of microalbuminuria, 30 patients (25%) had the history of established retinopathy and 76 patients (63.3%) had the history of hypertension.

Comparison of Diabetic Patients with and without Microalbuminuria: From 64 patients with established microalbuminuria (group Alb$^+$), 25 (39.1%) were male and

Table 1. Patient's data according to the use of antidiabetic medication

Therapy type	Group Alb$^+$	Group Alb$^-$	p value
Insulin	8 (12.5%)	2 (3.6%)	0.07
Sulfonylureas	20 (31.3%)	21 (37.5%)	0.47
Metformin	45 (70.3%)	39 (69.6%)	0.93
Aspirin	47 (73.4%)	40 (71.4%)	0.80

Alb: Albumin

39 (60.9%) were female, and from 56 patients without evident microalbuminuria (group Alb^-), 11 (19.6%) and 45 (80.4%) were male and female respectively. The abundance of microalbuminuria incidence was 2.62 times higher in males compared to female patients [Odds ratio (OR): 2.62, 95% confidence interval (CI): 1.14-6.00, p=0.02].

Average age of the patients with and without microalbuminuria was 59.37±9.42 years old and 57.75±10.43 years old, respectively which showed no statistical significance (p=0.37).

From 64 patients in group Alb^+, 41 (64.1%) and 23 (35.9%) cases had evident diabetes more and less than five years, respectively. Likewise, from 56 patients in group Alb^-, 25 (44.6%) and 31 (55.4%) cases had evident diabetes more and less than five years, respectively.

Among all diabetic patients in our study, the risk of developing microalbuminuria was 2.21 times higher in patients with the history of over five years diabetes disease compared to the patients with the history of less than five years evident diabetes (OR: 2.21, 95% CI: 1.06-4.60, p=0.03).

The average of the duration of diagnosed diabetes were 9.21±6.56 years in group Alb^+ and 6.66±4.84 years in group Alb^- and showed statistically significance (p=0.01).

Among the patients with microalbuminuria, 20 (31.3%) and among the patients without microalbuminuria, 10 (17.9%) had the history of retinal vascular surgery but it didn't show statistically significance (p=0.09).

Likewise, in group Alb^+, 41(64.1%) patients and in group Alb^-, 35 (62.5%) patients had the history of diagnosed hypertension (p=0.85).

Table 2. The presentation of overall laboratory tests

Laboratory results	Group Alb^+	Group Alb^-	p value
TG (mg/dL)	191.23±23.96	192.58±20.57	0.74
LDL (mg/dL)	86.03±7.18	86.17±7.29	0.91
HDL (mg/dL)	31.89±4.58	32.64±4.22	0.35
HbA1c (average):	7.01±0.54	7.16±0.56	0.14
<7%	37 (57.8%)	36 (64.3%)	0.46
≥7%	27 (42.2%)	20 (35.7%)	
BUN (mg/dL)	16.92±8.73	15.63±8.61	0.41
SCr (mg/dL)	1.05±0.63	0.87±0.41	0.07
AST (U/L)	23.67±6.52	23.17±6.72	0.68
ALT (U/L)	26.42±9.56	24.26±7.40	0.17
ALP (U/L)	168.23±32.77	172.46±28.55	0.45

Alb: Albumin, TG: Thyroglobulin, BUN: Blood urea nitrogen, SCr: Serum creatinine, LDL: Low density lipoprotein, HDL: High density lipoprotein, HbA1c: Hemoglobin A1c, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase

The average of systolic and diastolic blood pressures was 126.17±4.77 mmHg and 84.68±4.16 mmHg, as well as in group Alb^+, 125.98±4.90 mmHg and 84.10±4.27 mmHg in group Alb^- (p=0.83, p=0.45), respectively.

Laboratory test results are shown in Table 2 and showed no significance between group Alb^+ and Alb^- (p>0.05).

Myocardial Gated SPECT Findings: In total, SMI was detected in 78 (65%) of the included diabetic patients. Stress induced ischemia was found in 56 patients (87.5%) of Alb^+ group and in 22 patients (39.3%) of Alb^- group. As described, the frequency of stress induced ischemia was 10.81 times higher in the patients with microalbuminuria compared to Alb^- patients (p<0.001, OR: 10.81, 95% CI: 4.33-26.99). Likewise, this ischemic status was also correlated to the gender and occurred 2.95 times more in males than females. From 36 male cases, 29 (80.55%) and from 84 female cases, only 49 (58.33%) showed stress induced myocardial ischemia (OR: 2.95, 95% CI: 1.16-7.51, p=0.019). No correlation was found among the presence of stress induced ischemia and therapy type, diabetes duration, history of evident retinopathy, history of hypertension and serum levels of HbA1c (p>0.05). In addition, cardiac SPECT findings revealed presence of septal hypertrophy in 40 patients (62.5%) of group Alb^+ and in 37 patients (66.1%) of group Alb^- without any statistically significance (p=0.684).

Average ejection fraction (FE) was estimated 53.51±3.17% for Alb^+ patients and 56.07±3.77% for Alb^- ones and EF was significantly higher in Alb^- patients compared to the other group (p=0.001) (Table 3).

Discussion

Diabetes mellitus is one of the major disabling diseases around the world. Prevalence and incidence of type 2 diabetes is increasing over time especially in under developed countries. Increasing diabetes prevalence will lead to increasing the side effects of this disease as well as patient's morbidity and mortality. Diabetes is accompanied with 2 to 4 times increased risk of the CAD development and progression (14). The mortality resulted from any

Table 3. Myocardial perfusion single-photon emission computed tomography findings

MPI findings	Group Alb^+	Group Alb^-	p value
Septal hypertrophy	40 (62.5%)	37 (66.1%)	0.68
Ejection fraction	53.51±3.17%	56.07±3.77%	<0.00
Ischemia (+)	56 (87.5%)	22 (39.3%)	<0.00
Ischemia (-)	8 (12.5%)	34 (60.7%)	

Alb: Albumin, MPI: Myocardial perfusion imaging

cause including CAD likely will be more in younger patients who have also higher serum glucose levels and suffer from diabetic nephropathy (15,16).

SMI is the most common manifestation of CAD in diabetic patients and can be manifested as myocardial infarction or death in some patients. The reported prevalence of SMI in diabetic patients ranges between 6 to 57% (17,18), but it was estimated 65% in our recent study which could be related to the use of different methodologies through the studies. Diabetic neuropathy is the most common underlying cause of silent ischemia in about 22-42% of asymptomatic diabetic patients (19,20,21). Furthermore, about 19% of diabetics have renal protein excretion and most studies found the increased risk of cardiovascular events in the patients with overt microalbuminuria (22,23). Microalbuminuria is the first sign of renal involvement and incoming diabetic nephropathy (10), likewise it could be taken as an accurate and sensitive predictive indicator of end stage renal disease in diabetic patients (6). Microalbuminuria is also a marker of cardiac and cerebral vascular damage in addition to renal damage (2).

Accordingly, this study was designed to show the correlation between microalbuminuria and the presence of CAD in asymptomatic diabetic patients by evaluation of myocardial perfusion scan findings. Our study showed that, although the duration of diabetes is not correlated to patient's gender, the frequency of the development of microalbuminuria is 2.62 times higher in males. Probability of microalbuminuria development in diabetic patients was 2.21 times higher in patients with the history of diabetic disease more than five years.

In the evaluation of MPI findings, average FE was lower in patients with microalbuminuria and also prevalence of ischemia was 10.81 times higher than the patients without microalbuminuria. This result is contrary to the results of The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study by Wackers et al. (18), which showed no significant association between microalbuminuria and perfusion defects on myocardial perfusion scan.

Ischemia was also correlated with patient's gender and we found ischemia 2.95 times more in males than females as in DIAD study by Wackers et al. (18). We also found no association between myocardial ischemia and therapy type, diabetes duration, history of retinopathy, history of hypertension and serum levels of HbA1c.

Salehi et al. (11) evaluated the MPI findings in diabetic patients, and they found a relationship between diabetes duration and abnormal MPI findings, so that patients with longer diabetes duration showed 2.27 times more MPI abnormalities. These results were contrary to our findings. They indicated that performing myocardial perfusion SPECT in asymptomatic diabetic patients will lead to early CAD diagnosis and should be considered as a screening tool in cases with diabetes.

Shmendi et al. (24) evaluated the findings of myocardial perfusion scan in diabetic patients with a suspicion of myocardial ischemia. They found that abnormal MPI findings, including stress inducible ischemia, were seen more in diabetic patients compared to non-diabetics. On the other hand, HbA1c >7% was related to more abnormal myocardial perfusion SPECT (MPS) findings and ischemia risk in diabetic patients. The results of this study are not in agreement with our current results as we did not find any correlation between myocardial ischemia and HbA1c level >7%. Finally, they showed that the frequency of abnormal MPS findings and myocardial ischemia is higher in diabetic patients versus non-diabetics. Likewise poorer control of serum glucose level resulted more probability of ischemia in diabetics.

In another study, Al-Humaidi et al. (10) worked on myocardial perfusion scan abnormalities in asymptomatic patients with type 2 diabetes. They found abnormal MPI findings in 22 (37%) of 59 patients. In their study, abnormal MPI was found to be correlated well with diabetes duration, insulin therapy, diabetic nephropathy and neuropathy. However in the current study, only gender and microalbuminuria were correlated with abnormal MPS results. They also represent that abnormal MPI results are more prevalent in asymptomatic diabetic patients and they should be screened with MPI if they have high CAD pre-test probability.

Potier et al. (14) assessed the correlation between cardiac microvascular dysfunction and microalbuminuria in diabetics with ^{82}Rubidium-positron-emission tomography scan. In their study, myocardial flow reserve (MFR) was significantly lower in diabetic patients versus non-diabetics. On the other hand, MFR was progressively declined parallel to increasing albumin secretion in urine. Whereas MFR as a marker of myocardial ischemia, the results of their study are consistent with our results. MFR was not significantly different in patients with or without retinopathy but micro and macroalbuminuria was associated with abnormal MFR. They finally emphasized that abnormal MFR is strongly related to diabetes and the severity of albumin secretion in urine.

In a study by Giovacchini et al. (25) the frequency of CAD in diabetic patients was evaluated and in similar to our study, their results showed that microalbuminuria is the only predicting factor for silent ischemia in asymptomatic diabetic patients and the incidence of ischemia is 4.42 times higher in patients with microalbuminuria.

Furthermore, it has been shown that microalbuminuria and left ventricular hypertrophy are both associated with increased cardiovascular morbidity and mortality, especially in diabetic patients. Therefore, it has been recommended that patients with type 2 diabetes and increased urinary albumin excretion should be check for increased left ventricular mass as an important and potentially reversible cardiovascular risk factor (26,27,28).

Additionally, it has been demonstrated that increased septal perfusion observed on MPI is the signal of asymmetrical septal hypertrophy which can be graded based on its severity (29). In our study, although the septal hypertrophy was shown in 76 patients, it was not statistically significant between two Alb^+ and Alb^- groups (p value >0.05).

Study Limitations

It should also be mentioned that our study has some limitations. The most important limitation is the lack of follow-up to assess the patient's clinical outcome; although in our prior experience, about 50% of the patients with abnormal MPI findings demonstrated abnormal CAG (13) and also should be considered the point that CAG does not reflect myocardial perfusion at the terminal coronary circulation and in cases with SMI, false negative findings may happen. The small sample size and lack of quantitative evaluation of myocardial ischemia on MPS are other limitations that should be underlined. Further well-designed studies with large number of patients using quantitative analysis of myocardial perfusion SPECT will be required to validate its clinical role.

Conclusion

The current study showed that abnormal MPI findings are significantly more common in diabetic patients with microalbuminuria. With respect to low cost and availability of urine albumin detection tests, it might be as a biomarker for prediction of SMI in diabetic population.

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Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Bushehr University of Medical Sciences.

Informed Consent: Consent forms were filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.E., Z.N., M.A., Design: T.E., A.S., M.K., D.I., Data Collection or Processing: T.E., A.S., E.J., M.A., E.J., Analysis or Interpretation: A.S., T.E., Z.N., M.A., A.G., E.J., D.I., Literature Search: Z.A., A.G., M.A., Writing: Z.A., A.G., M.A.

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Risk Factors for Predicting Osteoporosis in Patients Who Receive Thyrotropin Suppressive Levothyroxine Treatment for Differentiated Thyroid Carcinoma

Diferansiye Tiroid Kanserli Tirotropin Süpresif Levotiroksin Tedavisi Alan Hastalarda Osteoporozu Öngören Risk Faktörleri

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Abstract

Objectives: Endogenous hyperthyroidism accelerates bone *turnover* and shortens the normal bone *remodeling* cycle, which results in reduced bone density. It is estimated that suppressive levothyroxine (LT4) therapy also decreases bone density. The aim of this study was to define risk factors for osteoporosis development in patients under thyrotropin-stimulating hormone (TSH) suppressive treatment for differentiated thyroid cancer (DTC).

Methods: Patients with a diagnosis of low or intermediate risk group DTC according to the American Thyroid Association 2015 guidelines and who have been receiving LT4 suppression therapy and were physically fit to undergo femur and lumbar vertebra bone density study were included in the study. Patients lacking information on demographic data, medical history, preoperative thyroid hormone status, or routine follow-up data were excluded from the study. A study form consisting of patient information on possible risk factors for osteoporosis such as gender, age, menopausal status, smoking, family history of osteoporosis, preoperative thyroid hormone status, postoperative hypoparathyroidism history, mean serum TSH levels, and duration of TSH suppression was created and filled out for each participant. Bone mineral densitometries of the femur and lumbar vertebrae were measured along with serum vitamin D and parathyroid hormone levels.

Results: During TSH suppression (mean 7.2±4.5 years, range: 1-26), osteoporosis was detected in 89 (9.6%) patients. The mean time to develop osteoporosis was significantly different in patients with or without a family history of osteoporosis (15.3±0.4 versus 20.3±0.6 years; p=0.002). Similarly, the mean time to develop osteoporosis for was found to be significantly shorter in postmenopausal patients than that for premenopausal women (18.6±0.7 versus 20.4±0.4 years; p<0.001). Male gender (p<0.001), a family history of osteoporosis (p=0.001) and menopausal state (p<0.001) were identified as independent predictive factors for developing osteoporosis.

Conclusion: Postmenopausal women, men, and patients with a family history who receive TSH-suppression treatment have a tendency to develop osteoporosis.

Keywords: Differentiated thyroid carcinoma, osteoporosis, thyroid-stimulating hormone suppression treatment

Öz

Amaç: Endojen hipertiroidi kemik *turn-overini* hızlandırır ve normal kemik *remodeling* döngüsünü kısaltır, bu da azalmış kemik yoğunluğuyla sonuçlanır. Süpresif levotiroksin (LT4) tedavisinin de kemik yoğunluğunu azalttığı düşünülmektedir. Bu çalışmada, diferansiye tiroid kanseri (DTK) için tirotropin-stimüle edici hormon (TSH) süpresif tedavi altındaki hastalarda osteoporoz gelişimi için risk faktörlerinin tanımlanması amaçlanmıştır.

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Yöntem: Amerikan Tiroid Derneği 2015 rehberine göre düşük veya orta riskli DTK tanısı ile takipli, LT4 süpresyon tedavisi alan; bazal tedavi sonrası rutin klinik takip bilgilerine ulaşılan; hasta dahil etme formu doldurmak için gerekli ve yeterli demografik ve medikal takip bilgileri bulunan; genel durumu femur ve lumbal vertebra kemik dansitometri çalışması yapılması için uygun olan hastalar çalışmaya dahil edildi. Osteoporoz için olası risk faktörleri olan cinsiyet, yaş, menopoz durumu, sigara, ailede osteoporoz hikayesi, preoperatif tiroid hormon durumu, postoperatif hipoparatiroidi hikayesi, ortalama serum TSH düzeyi ve TSH süpresyon süresini içeren bir hasta dahil etme formu dolduruldu. Dahil edilen hastalara bu aşamada femur boynu ve lumbal vertebralardan kemik mineral dansitometrisi yapıldı, serum D vitamin ve parathormon düzeylerine bakıldı.

Bulgular: Ortalama TSH süpresyon süresi 7,2±4,5 (aralık: 1-26) yıl idi, hastaların 89'unda (%9,6) osteoporoz saptandı. Postmenopozal olgularda osteoporoz gelişmesine kadar geçen ortalama süre premenopozal olgulardan anlamlı şekilde kısaydı (18,6±0,7'ye karşın 20,4±0,4 yıl; p<0,001). Erkek cinsiyet (p<0,001), aile hikayesi (p=0,001) ve menopoz durumu (p<0,001) osteoporoz gelişimi için bağımsız risk faktörleri olarak saptandı.

Sonuç: TSH süpresyon tedavisi alan postmenopozal kadınlar, erkek ve aile öyküsü olan hastalar osteoporoz gelişimine eğilim göstermektedir.

Anahtar kelimeler: Diferansiye tiroid karsinomu, osteoporoz, tiroid-stimüle edici hormon süpresyon tedavisi

Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine neoplasia. Although the incidence of DTC is increasing its mortality rate remains stable (1,2). After initial treatment with a thyroidectomy with/without radioiodine treatment, patients are treated with levothyroxine (LT4) therapy to suppress thyrotropin-stimulating hormone (TSH) since suppression of serum TSH levels reduces tumor recurrence rates (3).

Endogenous hyperthyroidism has been shown to reduce bone density because hyperthyroidism accelerates bone turnover and shortens the normal bone remodeling cycle (4). For this reason, suppression LT4 therapy might cause a decrease in bone density. Considering the long life expectancy for DTC patients, treatment related comorbidities could affect their quality of life.

Although several studies have been designed to explore the correlation between bone density changes and LT4 treatment, conflicting findings have been reported (4,5). Most of the reported studies have included small number of patients, and despite this limitation bone density seems to decrease in at least some DTC patients. In this large series, we analyzed DTC patients' bone density after considering several demographic features, comorbidities, and treatment-related risk factors. In our analysis, we aimed to define additional risk factors for developing osteoporosis in patients who received TSH-suppressive LT4 treatment for DTC.

Materials and Methods

Patients

This study included prospective and retrospective components and was approved by the Institutional Ethical Committee of Ankara University Medical Faculty (approval number: 11-489-16). After receiving informed consent for the prospective component, patient inclusion was continued for the period between June 2016 and Jan 2018. All patients had received radioiodine treatment for DTC in Ankara University Medical Faculty Department of Nuclear Medicine. Patient inclusion criteria were based on several parameters: (1) low or intermediate risk group DTC diagnosis according to the American Thyroid Association (ATA) 2015 guidelines; (2) receiving LT4 suppression therapy after initial treatment; (3) available routine follow-up data after initial therapy; (4) known preoperative thyroid hormone status; (5) sufficient and available demographic and medical history data to fill-in the study form; and (6) be physically fit enough to undergo a femur and lumbar vertebra bone density study (6).

Data Generation

A study form including information on possible risk factors for osteoporosis such as gender, age, menopausal status, smoking, family history of osteoporosis, preoperative thyroid hormone status, postoperative hypoparathyroidism history, mean serum TSH levels, and duration of TSH suppression was created and filled out. Mean serum TSH levels were calculated from at least two serum TSH measurements per year, excluding endogenous or exogenous short duration stimulated TSH levels. The duration of TSH suppression was calculated as the interval between TSH-suppression LT4 treatment initiation and the date of patient inclusion. After selection of patients, bone mineral densitometries of the femur and lumbar vertebrae, serum vitamin D, and parathyroid hormone measurements were performed. T and Z scores of the femur and lumbar vertebrae were used for analysis. The presence of osteoporosis was accepted as T scores <-2.5. In patients who already had osteoporosis at the time of study initiation, the date of osteoporosis diagnosis was retrospectively obtained from patient files.

Statistical Analysis

The differences in proportions between groups were compared by using chi-square test. The survival estimations were performed using the method of Kaplan-Meier algorithm, and the comparison between groups was evaluated with the log-rank test. Multiple Cox regression proportional hazard model was used to determine independent predictors of osteoporosis development (7). p value less than 0.05 was considered as significant. SPSS version 20.0 (IBM, Chicago, Illinois, USA) was used for statistical analyses.

Results

Patients

A total of 929 patients (813 female, 116 male, mean age: 52.33±7.2) who received TSH suppression therapy for DTC were included. Patient descriptive data are presented in Table 1.

Risk Factors to Development of Osteoporosis

During TSH suppression (mean 7.2±4.5 years, range: 1-26), osteoporosis was detected in 89 (9.6%) patients. The rate of osteoporosis in patients with and without a family history of osteoporosis was 13% and 8%, respectively. Osteoporosis detection rates were calculated as 0.6%, 15%, and 12% in premenopausal and postmenopausal women and men, respectively. Preoperative hyperthyroidism was found to be significantly correlated with the presence of osteoporosis based on chi-squared analysis with 15% versus 8% (p=0.003); however, this significance was lost in multivariate Cox regression analysis. Although mean serum TSH levels were not significant factors for the presence of osteoporosis, osteoporosis detection rates seem to decrease in patients with TSH levels >0.4 mIU/L. Osteoporosis rates for different risk groups are summarized in Table 2.

The mean time to develop osteoporosis for patients with and without a family history of osteoporosis was significantly different (15.3±0.4 versus 20.3±0.6 years; p=0.002). Similarly, the mean time to develop osteoporosis

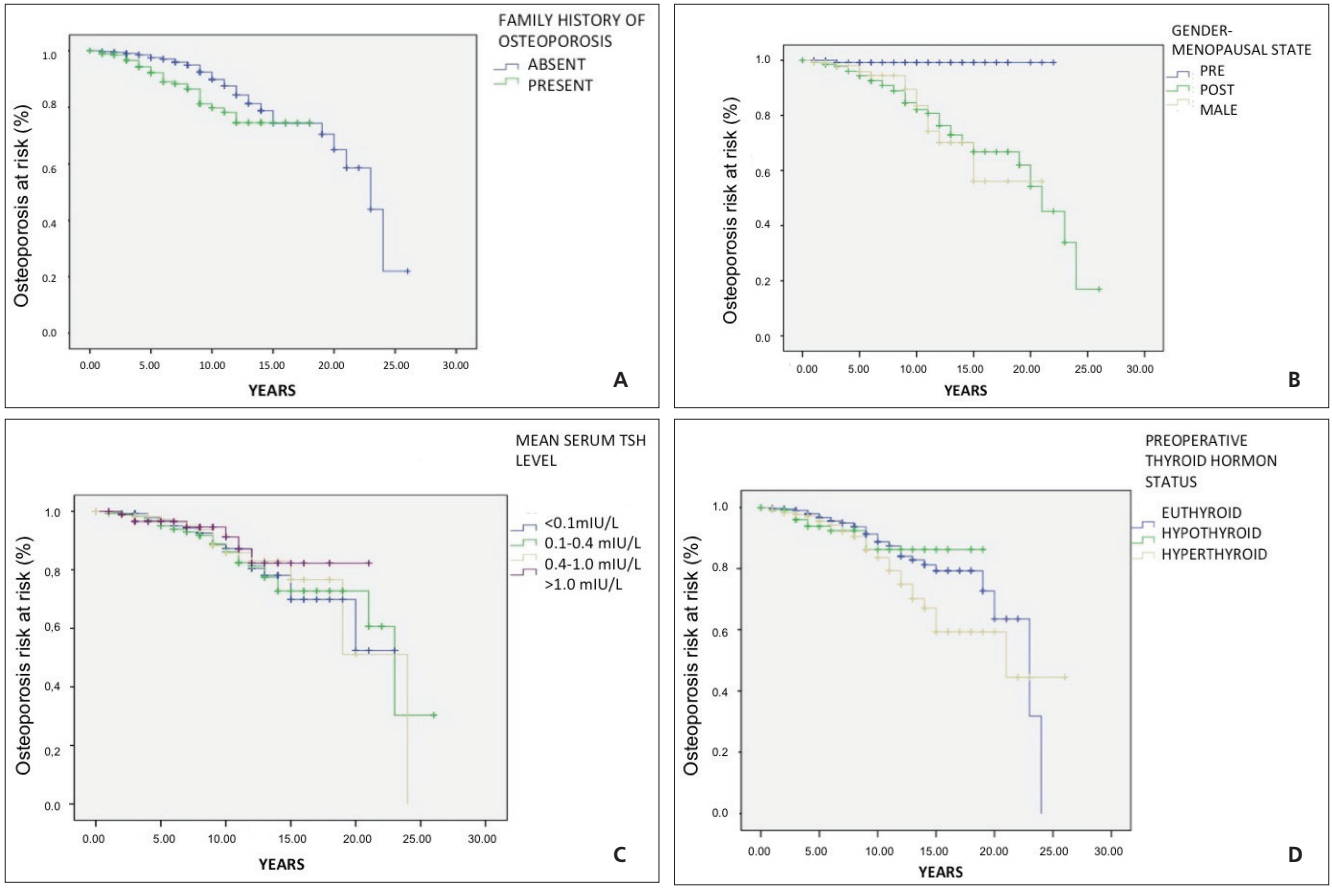

Figure 1. A, B, C, D) Kaplan-Meier curve for developing osteoporosis according to different risk groups
TSH: Thyrotropin-stimulating hormone

Table 1. Descriptive data of patients

Parameter	n (%)
Gender	
F	813 (87.5)
M	116 (12.5)
Menopausal state	
Premenopausal	321 (39.0)
Postmenopausal	492 (61.0)
Smoking	
Smoker	268 (28.8)
Nonsmoker	661 (71.2)
Family history of osteporosis	
Present	266 (28.6)
Absent	663 (71.4)
Preoperative thyroid hormone status	
Hypothyroid	114 (12.3)
Euthyroid	581 (62.5)
Hyperthyroid	234 (25.2)
Postoperative hypoparathyroidism	
Present	343 (36.9)
Absent	586 (63.1)
Mean serum TSH level (mIU/mL)	
<0.1	270 (29.1)
0.1-0.4	276 (40.5)
0.4-1.0	178 (19.2)
>1.0	105 (11.3)

F: Female, M: Male, n: Number, TSH: Thyrotropin-stimulating hormone

Table 2. Osteoporosis rates of different groups

Parameter	Osteoporosis rate, (n)	p value
Gender		
F	9% (74)	0.330
M	12% (15)	
Menopausal state		
Premenopausal	0.6% (2)	0.001
Postmenopausal	15% (72)	
Smoking		
Smoker	11% (29)	0.287
Non-smoker	9% (60)	
Family history of osteporosis		
Present	18% (61)	0.036
Absent	8% (28)	
Preoperative thyroid hormone status		
Hypothyroid	8% (9)	
Euthyroid	8% (45)	0.012
Hyperthyroid	15% (35)	
Postoperative hypoparathyroidism		
Present	9% (30)	0.667
Absent	10% (59)	
Mean serum TSH level (mIU/mL)		
<0.1	10% (25)	
0.1-0.4	11% (28)	0.559
0.4-1.0	8% (29)	
>1.0	7% (17)	

F: Female, M: Male, n: Number, TSH: Thyrotropin-stimulating hormone

was found to be significantly shorter in postmenopausal patients as compared to premenopausal women (18.6±0.7 versus 20.4±0.4 years; p<0.001). The mean time to develop osteoporosis according to patient characteristics is shown in Table 3. The mean time to develop osteoporosis among patient groups according to risk factors was not significant in Kaplan-Meier analysis (p>0.05). Kaplan-Meier curves for different groups are presented in Figures 1A, 1B, 1C, 1D.

Using the Cox proportional hazards regression analysis, male gender [hazard ratio (HR): 20.510, 95% confidence interval (CI): 4.644-90.579, p<0.001], family history of osteoporosis (HR: 2.215, 95% CI: 1.365-3.308, p=0.001) and menopausal state (post menopausal: HR: 18.488, 4.534-75.389, p<0.001; HR: 20.510, 4.644-90.579, p<0.001) were identified as independent predictive factors for developing osteoporosis (Table 4). According to multiple Cox regression proportional hazard analysis, other risk factors were not found to be significant (p>0.05).

Discussion

It is considered that remnant DTC cells behave in a manner similar to benign thyrocytes from which they originated. TSH stimulates the number, size and activity of thyrocytes (8). The rationale for this approach was based on observations that the incidence of thyroid cancer is correlated with serum TSH levels in the normal population (9). Hence, the primary aim of TSH suppression therapy is to lower endogenous TSH levels to reduce the risk of disease recurrence.

In the literature, different outcomes have been reported concerning the benefits of long-term TSH suppression in DTC patients. Lower serum TSH levels have been shown to be an independent predictor for disease progression in patients with a high risk of tumor recurrence. Interestingly, a similar effect has not been demonstrated on patients with stage 1 or 2 disease (10). Moreover, a meta-analysis including 10 studies did not demonstrate any benefits

Table 3. The mean time to develop osteoporosis according to patient characteristics

Parameter		Time to develop osteoporosis (years, mean±SD, 95% CI)	p value
Gender	F	20.2±0.7, 18.9-21.6	0.2
	M	16.7±1.0, 14.5-18.8	
Menopausal state	Pre	20.4±0.4, 19.6-21.2	<0.001
	Post	18.6±0.7, 17.2-20.2	
Smoking	No	20.7±0.8, 19.2-22.3	0.27
	Yes	18.9±0.9, 17.1-20.6	
Family history	No	20.3±0.7, 18.9-21.7	0.002
	Yes	15.3±0.4, 14.4-16.1	
Preoperative thyroid hormone status	Euthyroid	23.0±2.2, 18.7-27.3	0.09
	Hypothyroid	22.2±2.3, 17.2-25.5	
	Hyperthyroid	21.0±1.9, 19.2-26.8	
Postoperative hypoparathyroidism	No	23.0±2.0, 18.9-27.0	0.9
	Yes	22.3±1.8, 16.5-24.2	
Mean serum TSH level	<0.1	21.0±1.2, 18.6-23.3	0.43
	0.1-0.4	21.5±2.1, 19.2-22.5	
	0.4-1.0	23.0±2.2, 18.6-27.3	
	>1.0	23.0±1.9, 19.1-26.8	

CI: Confidence interval, TSH: Thyrotropin-stimulating hormone, SD: Standard deviation

Table 4. Independent predictive factors of developing osteoporosis

	B	SE	p	HR	95% CI for HR
Menopausal state					
Post menopausal	2.917	0.717	<0.001	18.488	4.534-75.389
Male	3.021	0.758	<0.001	20.510	4.644-90.579
Family history	0.754	0.226	0.001	2.125	1.365-3.308

HR: Hazard ratio, SE: Standard error, CI: Confidence interval

from TSH suppression (11). The National Thyroid Cancer Cooperative Study Group Registry published a study including 1548 patients. In contrast to our study, in their analysis, TSH suppression improved overall survival in stage 2 patients (12). Similarly, Hovens et al. (13) have reported results of 366 patients treated with total thyroidectomy followed by radioiodine treatment. They found that serum TSH levels >4.5 mU/L was an independent predictor for death, and TSH levels >2 mU/L were also associated with DTC-related deaths and recurrence in patients with T1-3, M0 tumors. Also, Pujol et al. (14) reported that suppressed serum TSH levels were associated with an increase in relapse-free survival in patients with DTC.

Controversial results based on these analyses have led to discussions about optimal TSH level and duration of suppression for low-intermediate risk group patients with respect to therapy-related side effects. Thyroid hormones act directly on the skeleton, and endogenous hyperthyroidism is known to be related with a high risk of osteoporosis (15). Known risks of iatrogenic overt or subclinical hyperthyroidism are osteoporosis, osteopenia, and/or atrial fibrillation. For this reason, slightly subnormal or normal TSH levels are recommended for long term periods (16). Two cohort studies have demonstrated that postmenopausal DTC patients with fully suppressed TSH levels have a high risk of osteoporosis (17,18). In our study, we aimed to analyze additional risk factors for developing osteoporosis in a large cohort. A family history of osteoporosis and menopausal status were found to be significant factors favoring osteoporosis development. The presence of preoperative hyperthyroidism could also be another risk factor. Interestingly, we could not find any significant correlation between mean serum TSH levels and presence of osteoporosis. However, osteoporosis detection rates tend to decrease in patients with mean TSH levels >0.4 mIU/L.

Another interesting finding of our analysis was that male patients who received TSH suppression therapy were found to have a 20-fold increase in developing osteoporosis as compared to premenopausal women. Most studies have included only female patients for osteoporosis analysis. Reverter et al. (19) analyzed bone mineral densities and bone fractures in male patients receiving long-term TSH suppressive therapy. They compared bone mineral density and bone turnover parameters from 33 DTC patients with age- and body mass index-matched control groups. They did not find any significant differences between bone turnover parameters, including the T and Z scores, between groups. We could not compare our study parameters with an age-matched group. However, the number of included male patients in this study was higher than that in the previous study. A total of 66 patients and 67 controls were included in a recent meta-analysis on the effects of TSH suppression in men. The authors did not find any significant correlation between TSH suppression and lower BMD values in men (20). For this reason, the osteoporosis rate in male patients receiving TSH suppression therapy needs further clarification with prospective randomized control studies.

The ATA 2015 guidelines recommend 0.1-0.5 mU/L levels as an initial TSH goal for low-risk group patients with indeterminate or incomplete response as well as for intermediate risk group patients based on data on this subject. The guide recommends continuation therapy with 0.5-2.0 mU/L levels for low and intermediate risk group patients with excellent response. It is reasonable for clinicians to consider disease stage, response to initial treatment, and personal risk factors to develop osteoporosis in order to personalize a patient's TSH suppression therapy. The risk of disease recurrence and TSH suppression-related risks should be balanced. Postmenopausal women, men, and patients with a family history of osteoporosis have a high rate of osteoporosis under TSH-suppression LT4 treatment. Preoperative hyperthyroidism and mean serum TSH levels seem to be possible predictors of developing osteoporosis, although not statistically significant.

Conclusion

The current data suggest that personalized TSH suppression treatment, based on DTC risk group and patient-related risk factors to develop osteoporosis, might be beneficial.

Postmenopausal women, men, and patients with a family history who are under TSH-suppression treatment have a high rate of osteoporosis. Thus, male or postmenopausal female patients with low/intermediate risk DTC and a family history of osteoporosis should be closely followed-up.

Ethics

Ethics Committee Approval: This study included prospective and retrospective components and was approved by the Institutional Ethical Committee of Ankara University Medical Faculty (approval number: 11-489-16).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.S., D.N., E.Ö., M.K.K., Concept: Ç.S., Design: Ç.S., M.K.K., E.Ö., N.Ö.K., Data Collection or Processing: D.N., Ç.S., A.H.E., Analysis or Interpretation: A.H.E., Ç.S., Literature Search: D.N., Ç.S., Writing: Ç.S., D.N., E.Ö.

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Giant Abdominal Aortic Aneurysm in Bone Scan

Kemik Sintigrafisinde Dev Abdominal Aort Anevrizması

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Abstract

Abdominal aortic aneurysm (AAA) may be incidentally detected in three-phased bone scintigraphy. AAA should be diagnosed prior to the development of symptoms to perform elective repair surgery. We present a rare case who presented with back pain and underwent a 3-phase bone scan with Tc-99m methylene diphosphonate, which revealed a giant AAA on blood-flow and blood-pool phases in addition to bone metastases. F-18-fluorodeoxyglucose positron emission tomography/computed tomography (CT) identified hypermetabolic liver, lung, and bone lesions, and CT component of the study confirmed the diagnosis of AAA with a maximum diameter of 92 mm. The initial two phases of a 3-phase bone scintigraphy are decisive to identify vascular pathologies that may be life-threatening, if left untreated.

Keywords: Whole body scan, Tc-99m methylene diphosphonate, abdominal aortic aneurysm, metastases, PET/CT

Öz

Abdominal aort anevrizması (AAA), 3-fazlı kemik sintigrafisinde insidental olarak saptanabilmektedir. Semptomlar ortaya çıkmadan elektif cerrahi uygulanabilmesi için, AAA tanısının doğru olarak konulması önemlidir. Burada, sırt ağrısı şikayeti ile başvuran bir olguda, Tc-99m metilen difosfonat 3-fazlı kemik sintigrafisinde kemik metastazlarının yanı sıra kan akımı ve kan havuzu fazlarında dev AAA saptanan nadir bir olgu sunuyoruz. F-18 florodeoksiglukoz pozitron emisyon tomografi/bilgisayarlı tomografide (BT) hipermetabolik karaciğer, akciğer ve kemik lezyonları görüldü ve çalışmanın BT bileşeninde maksimum çapı 92 mm olan AAA tanısı doğrulandı. 3-fazlı kemik sintigrafisinde, tedavi edilmediği takdirde yaşamı tehdit edebilecek vasküler patolojileri tanımlamak için ilk iki faz belirleyicidir.

Anahtar kelimeler: Tüm vücut kemik sintigrafisi, Tc-99m metilen difosfonat, abdominal aort anevrizması, metastaz, PET/BT

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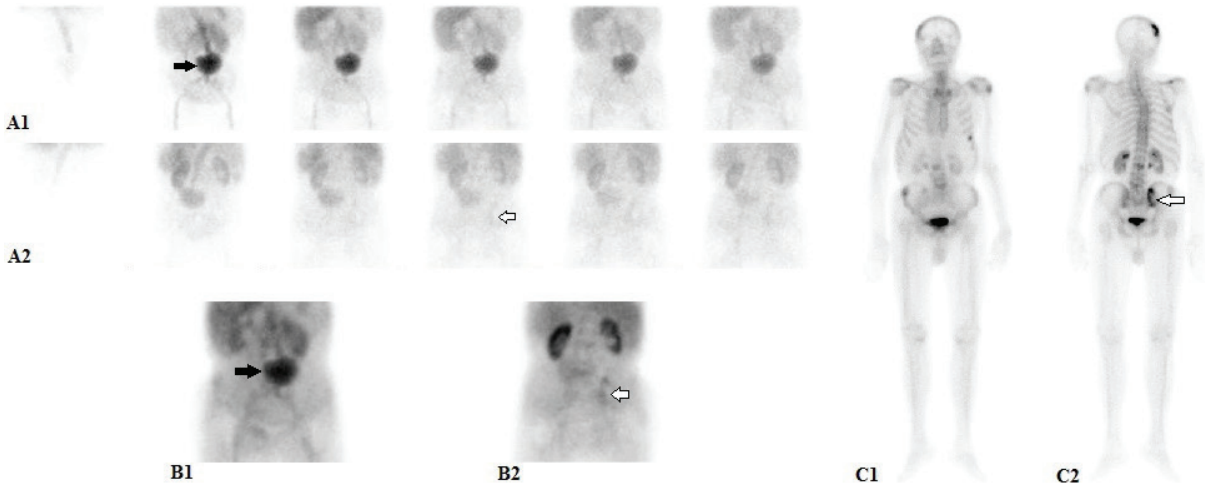

Figure 1. An 84-year-old man presented with low back pain since two months. Lumbar magnetic resonance imaging revealed hypointense lesions in the vertebral column on T1- and T2-weighted images. The patient was referred to 3-phase bone scan for evaluation of suspected bone metastasis of unknown origin. Dynamic blood-flow and static blood-pool images were obtained following intravenous bolus injection of 740 MBq (20 mCi) Tc-99m methylene diphosphonate. Blood-flow and blood-pool phase images demonstrated tracer accumulation in the left side of the mid-abdominal portion of the infrarenal area (blood-flow phase, anterior: A1; posterior: A2, black arrows), and tracer activity consistent with hyperemia in the right sacroiliac joint (blood-pool phase, anterior: B1; posterior: B2, white arrows). Late phase images showed abnormal tracer uptakes in the right parietal bone of the skull, right scapular spine, anterior side of the left 6th costa, posterior aspect of the left 12th costa, L2 and L5 vertebrae, as well as the right sacroiliac joint (late phase, anterior: C1; posterior: C2, white arrow)

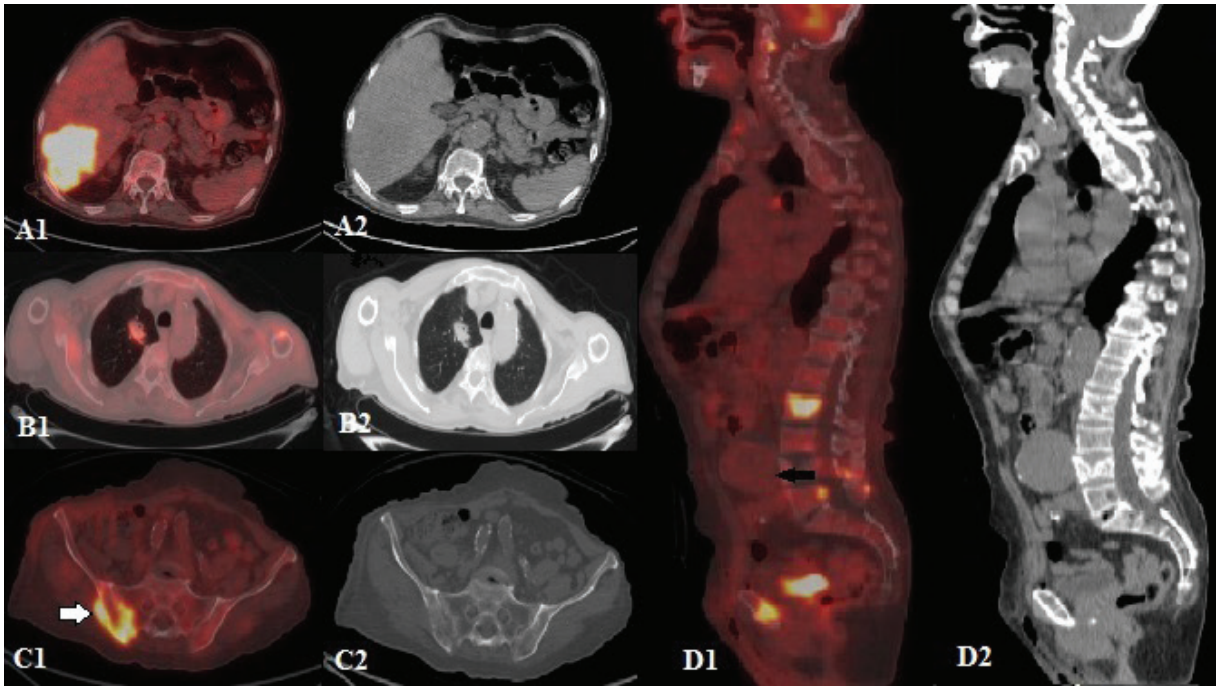

Figure 2. An F-18-fluorodeoxyglucose positron emission tomography/computed tomography was performed to identify the primary tumor site and revealed a mass lesion (86x74x120 mm) in the right lobe of the liver (SUV_{max}: 21.2) (A1, A2), an irregularly contoured right lung upper lobe anterior segment mass (27x35 mm, SUV_{max}: 4.6) (B1, B2), right hilar and subcarinal lymph nodes, and bone lesions in right iliac crest (SUV_{max}: 14.5) (C1, C2, white arrow) which were hypermetabolic, along with a hypometabolic giant abdominal aortic aneurysm (AAA) (65x92x79 mm) (D1, D2, black arrow). The patient did not have a history of trauma or infection, therefore the lesion was diagnosed as a true aneurysm. The patient was referred to cardiovascular surgery for surgical intervention and interventional radiology for liver biopsy

AAA is dilation of the abdominal aorta greater than 50% of the normal aortic diameter (1). For most adults, an infrarenal aorta with a maximum diameter of ≥3.0 cm is considered an aneurysm (1,2,3). AAA is more likely found among men, and only 1-2% of male patients are older than 50 years (4,5). More than 90% of patients with AAA are current or past smokers, and smoking is more closely associated with AAA than atherosclerotic diseases (6). AAA should be identified accurately prior to development of symptoms and elective repair is the mainstay of treatment to prevent rupture and sudden death, especially for patients who have AAA with a maximum diameter >5.5 cm, a saccular aneurysm, or an abdominal or back pain that can be attributable to AAA. Immediate repair is recommended for patients who present with a ruptured aneurysm (1).
In three-phase bone scans, vascular pathologies (AAA, iliofemoral occlusive arterial abnormalities, and lower extremity varicose veins) that could not be detected in conventional bone scintigraphy, may be detected incidentally in blood-flow and blood-pool phases, depending on lesion vascularity (7). False AAAs in three-phase bone scan has been reported previously (8,9). However, to the best of our knowledge, our case is the first reported true AAA that was shown in a three-phase bone scan.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Ç., M.B., Concept: D.Ç., Design: D.Ç., M.B., Data Collection or Processing: D.Ç., Ö.E., Analysis or Interpretation: D.Ç., Ö.E., A.Ö.K., Literature Search: D.Ç., M.B., S.S.G., Writing: D.Ç., M.B.

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Detection of Squamous Cell Carcinoma Foci in a Patient with Dystrophic Epidermolysis Bullosa in ^{18}F-FDG PET/CT

Distrofik Epidermolizis Bülloza Tanısı Alan Bir Olguda Skuamöz Hücreli Karsinom Odağının ^{18}F-FDG PET/BT Yöntemi ile Saptanması

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Abstract

Dystrophic epidermolysis bullosa (DEB) is a rare, inherited skin fragility disorder characterized by blister formation in the sublamina densa. DEB is associated with aggressive squamous cell carcinoma (SCC) that has increased risk of metastases and poor prognosis. A 41-year-old woman with DEB underwent ^{18}F-fluoro-2-deoxy-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/BT). PET/CT showed increased ^{18}F-FDG uptakes in multifocal cutaneous lesions in both lower extremities. The patient was diagnosed with SCC via skin biopsy from the left lateral lower thigh. Ten months later, PET/CT showed increased FDG uptakes in the primary tumor area as well as the left inguinal and left supraclavicular lymph node regions. ^{18}F-FDG PET/CT seems to be useful for re-staging and planning appropriate therapeutic strategy in DEB-patients with SCC.

Keywords: ^{18}F-FDG PET/CT, dystrophic epidermolysis bullosa, squamous cell carcinoma

Öz

Distrofik epidermolizis bülloza (DEB), sublamina densada veziküler ve yaygın bül oluşumu ile karakterize nadir görülen kalıtsal bir deri frajilite bozukluğudur. DEB bilhassa artmış metastaz riski ve kötü prognostik özellikler gösteren agresif skuamöz hücreli karsinom (SHK) oluşumu ile ilişkilendirilmiştir. DEB tanısı konulan 41 yaşındaki kadın olgu ^{18}F-floro-2-deoksi-glukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (^{18}F-FDG PET/BT) taraması ile deri malignitesi açısından incelenmiştir. PET/BT taraması ile her iki alt ekstremitede multifokal kutanöz lezyonlarda artmış ^{18}F-FDG tutulumu gösterilmiş ve sol lateral alt uyluk bölge derisinden elde edilen biyopsi materyali ile SHK tanısı konulmuştur. On ay sonra yapılan ikinci PET/BT taraması sonucunda primer tümör alanı, sol inguinal ve sol supraklaviküler lenf nodu alanında artmış ^{18}F-FDG tutulumu gösterilmiştir. SHK'li DEB hastalarında ^{18}F-FDG PET/BT yönteminin özellikle uygun terapötik stratejinin belirlenmesi adına hastalığın yönetimi ve yeniden evrelendirilmesinde faydalı olacağı kanaatindeyiz.

Anahtar kelimeler: ^{18}FDG-PET/BT, distrofik epidermolizis bülloza, skuamöz hücreli karsinom

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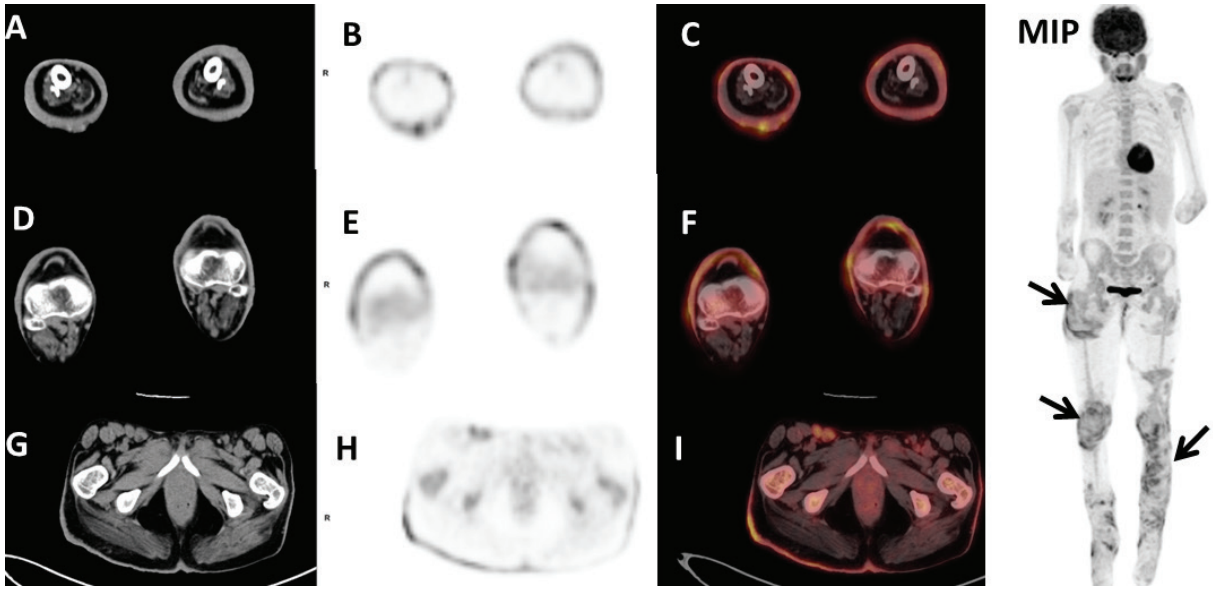
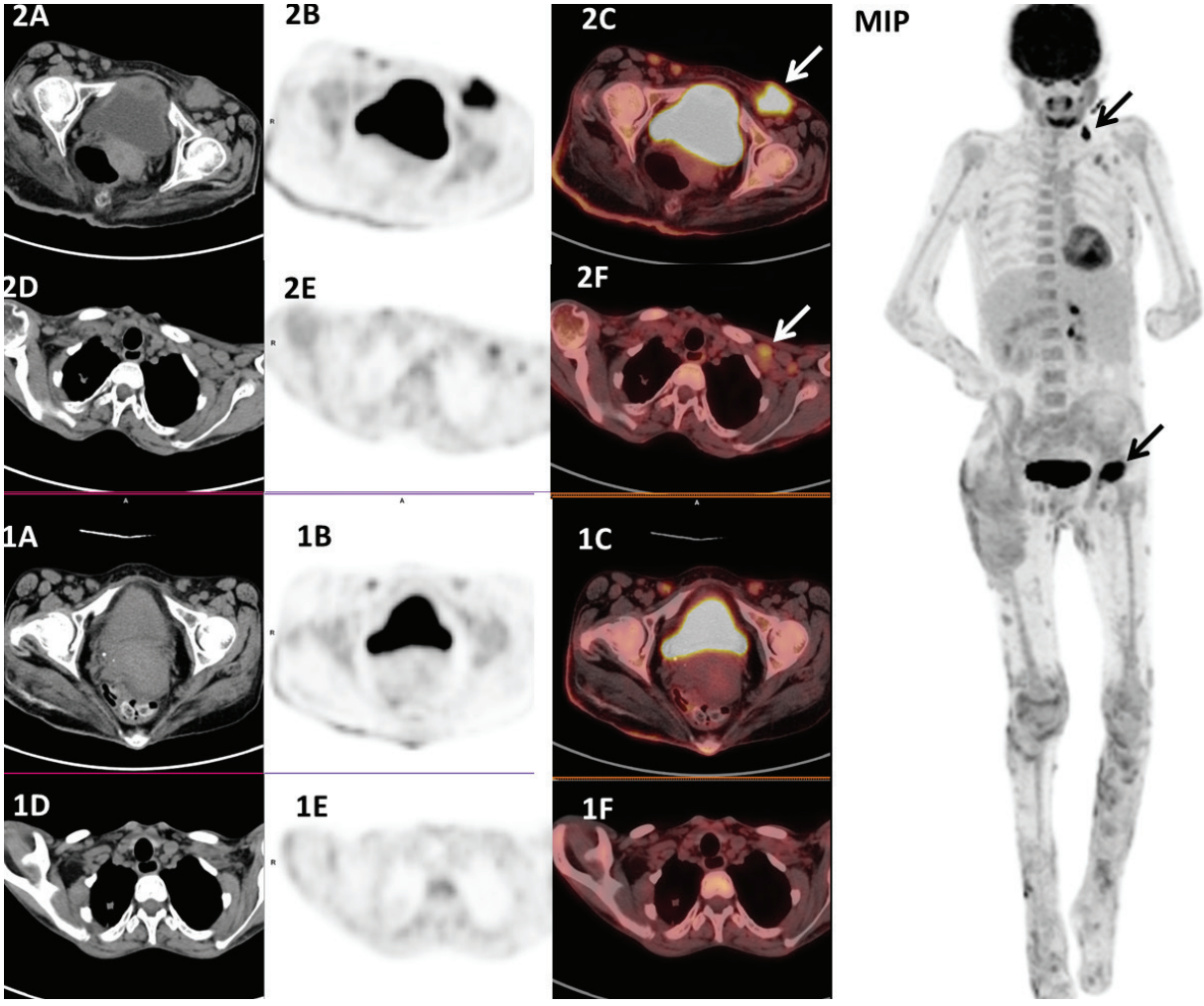


A, D, G: CT, B, E, H: PET, and C, F, I: Fusion slices.
MIP: Maximum intensity projection

Figure 1. Epidermolysis bullosa (EB) is a clinically heterogeneous group of inherited blistering disorders characterized by increased skin fragility, while the dystrophic variant of EB (DEB) is a clinically more severe subtype of EB (1,2). Patients with DEB are at high risk of developing squamous cell carcinoma (SCC), which particularly arise from areas of poorly healing wounds, and lead to metastasis and death (3). A 41-year-old female patient with DEB underwent ^{18}F-fluoro-2-deoxy-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in the follow-up period. PET/CT showed increased metabolic activity in multifocal cutaneous lesions in both lower extremities. The incisional biopsy performed from the skin of the left lateral lower thigh where one of the increased ^{18}F-FDG uptakes was observed revealed invasive SCC (black arrows). There was no other increased pathologic metabolic activity in any part of the skin, lymph nodes or organs



1: First PET/CT images, 2: Second PET/CT images. A, D: CT, B, E: PET and C, F: Fusion slices.
MIP: Maximum intensity projection

Figure 2. Ten months later, a second PET/CT scan was performed for re-staging purposes due to clinical detection of suspicious inguinal lymph nodes on physical examination. The second PET/CT showed a lymph node with increased FDG uptake in the left inguinal region (SUV_{max}: 12.9) as well as additional unexpected lymph nodes in the left supraclavicular region (SUV_{max}: 11.0) consistent with local and distant nodal metastasis (black arrows). Due to the multifocal or multiclonal onset of SCC, it is difficult to identify nodal and visceral spread of the tumor (4). Despite the high sensitivity of CT and PET/CT to detect subclinical nodal spread, false-positive results are still common. (5) By Jennings and Schmults 18F-FDG PET is reported to be beneficial to differentiate disease involvement and areas of necrosis and fibrosis. Cho et al. (6) have examined 12 SCC patients (nine cases with high-risk SCC) by ^{18}F-FDG/PET. The authors have identified lymph node metastases in three cases (25.0%), distant organ involvement in one case (8.3%) and primary lesions in nine cases (83.3%). Mahajan et al. (7) reported that ^{18}F-FDG PET/CT achieved overall sensitivity and accuracy of 100% and 92%, respectively, in 13 patients with primary SCC. It was emphasized that ^{18}F-FDG detected four previously unknown secondary lesions and changed management schedule in three of these. Supportively, Mackie and Avram (8) evaluated a 34-year-old woman with EB with soft tissue thickening in the left foot showing an increased ^{18}F-FDG uptake, which was confirmed histopathologically as SCC. In conclusion, ^{18}F-FDG PET/CT seems to be useful in re-staging and management of follow-up to plan appropriate therapeutic strategy in DEB patients with SCC

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., T.F.Ç., A.E.K.A., M.S.G., C.L., Concept: E.A., T.F.Ç., A.E.K.A., M.S.G., C.L., Design: E.A., T.F.Ç., A.E.K.A., M.S.G., C.L., Data Collection or Processing: E.A., T.F.Ç., A.E.K.A., M.S.G., C.L., Analysis or Interpretation: E.A., T.F.Ç., A.E.K.A., M.S.G., C.L., Literature Search: E.A., T.F.Ç., A.E.K.A., M.S.G., C.L., Writing: E.A., T.F.Ç., A.E.K.A., M.S.G., C.L.

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Interesting Image
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Striking Visualization of Diffuse Congenital Nesidioblastosis on Ga-68 DOTATATE PET/CT

Diffüz Konjenital Nesidioblastosisin Ga-68 DOTATATE PET/BT'de Çarpıcı Olarak Görüntülenmesi

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Abstract

"Nesidioblastosis", later renamed as "persistent hyperinsulinemic hypoglycemia of infancy" presents as either focal or diffuse neo-differentiation of pancreatic Langerhans islet cells from the ductal epithelium. Differentiation of focal disease from diffuse involvement is crucial for optimal disease management. The current methods used to differentiate the two forms pre-operatively are invasive techniques. The definite role of imaging modalities to differentiate diffuse versus focal form has not yet been proven. Herein, we report a 15 day-old infant having diffuse nesidioblastosis, successfully demonstrated by Ga-68 DOTATATE positron emission tomography/computed tomography imaging that was histopathologically confirmed.

Keywords: Nesidioblastosis, hyperinsulinemic hypoglycemia, differential diagnosis, Ga-68 DOTATATE PET/CT

Öz

Pankreasın Langerhans ada hücrelerinin duktus epitelinden yeniden farklılaşması olan "nesidioblastosis", yeni adlandırılmasıyla "yenidoğanın inatçı hiperinsülinemik hipoglisemisi", fokal ya da diffüz olarak iki şekilde görülebilir. Fokal formun diffüz olandan ayırt edilmesi hastalığın doğru yönetimi için son derece önemlidir. Bu iki formun cerrahi öncesi ayrımında kullanılan güncel metodlar invaziftir. Görüntülemenin diffüz formu fokal olandan ayırt etmedeki rolü tam olarak ortaya konamamıştır. Burada, Ga-68 DOTATATE pozitron emisyon tomografi/bilgisayarlı tomografi görüntüleme ile başarılı bir şekilde gösterilen ve histopatolojik olarak da doğrulanan diffüz nesidioblastosis hastası 15 günlük bir infant olgusunu sunduk.

Anahtar kelimeler: Nesidioblastosis, hiperinsülinemik hipoglisemi, ayırıcı tanı, Ga-68 DOTATATE PET/BT

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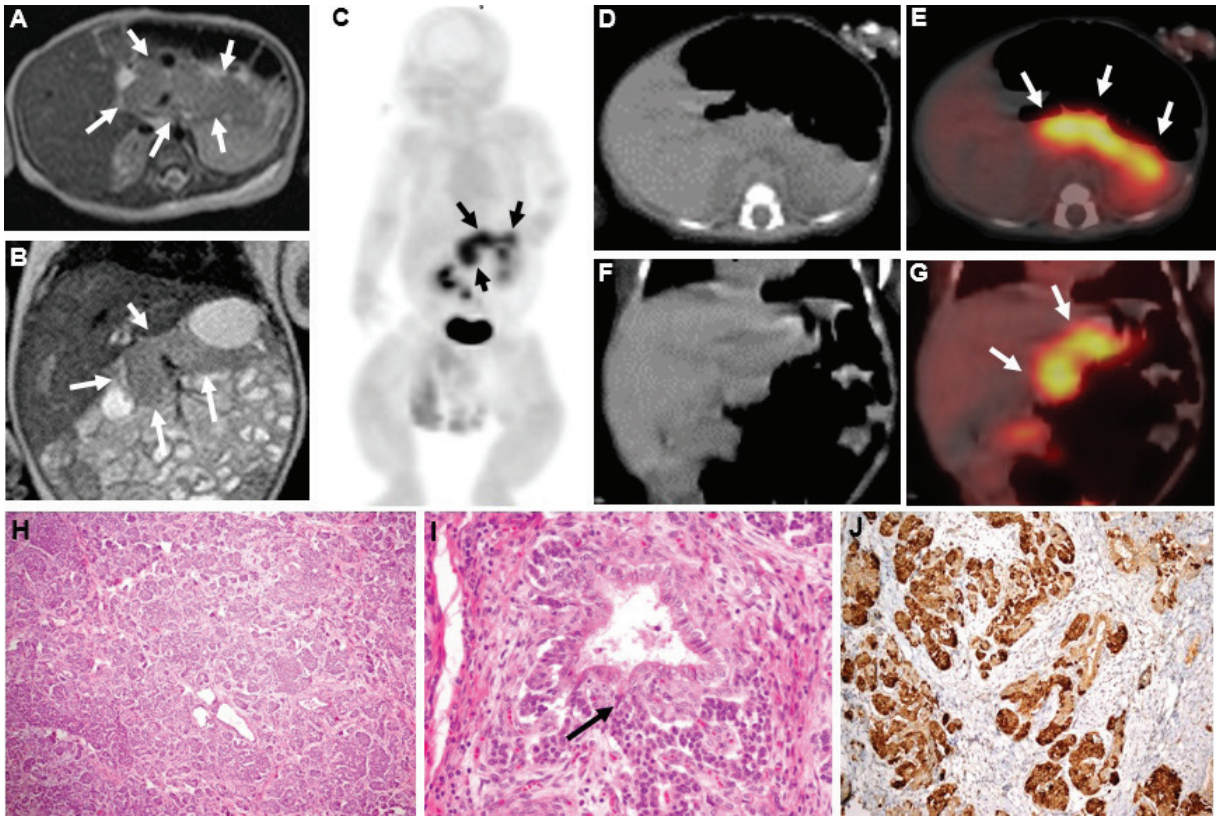

Figure 1. A 15-day-old infant presented with hyperinsulinemic hypoglycemia suffering from hypotonia, apnea and poor feeding. On physical examination, the abdomen was distended. The laboratory investigations revealed hypoglycemia (12 mg/dL, normal range: 70-110 mg/dL) and hyperinsulinemia with serum insulin levels of 55 IU/mL (normal range: 2,42-13 IU/mL). The baby was administered intravenous glucose infusion up to 20 mg/kg/min and oral feeding was supported with glucose to maintain euglycemic state. After intravenous diazoxide (15 mg/kg/day) and octreotide therapy (30-45 mcg/kg/day), no sufficient response could be obtained. Axial (A) and coronal (B) T2-weighted magnetic resonance images demonstrated diffuse enlargement of the pancreas with normal parenchymal signal without any focal lesion. Ga-68 DOTATATE positron emission tomography/computed tomography (PET/CT) imaging [maximum intensity projection anterior (C), axial CT (D), fused PET/CT (E), coronal CT (F) and fused PET/CT (G)] showed diffusely increased tracer uptake (SUV_{max}: 4,84; 3,99 and 3,99 for head, corpus and tail of the pancreas, respectively) in the entire enlarged pancreas (arrows) (with physiological radiotracer distribution throughout the rest of the body) suggesting a diffuse variant of nesidioblastosis. Due to the persistent hyperinsulinemic hypoglycemia and considering the findings in the Ga-68 DOTATATE PET/CT somatostatin receptor imaging, the patient underwent near total pancreatectomy. Histopathologic findings confirmed the diagnosis of diffuse nesidioblastosis, demonstrating diffuse enlargement of pancreatic lobules composed of solid endocrine cell clusters without a tumor. The disarray of lobular architecture with diffuse and irregular hyperplasia of endocrine cells (H: H&E, x100), the continuity between the duct epithelium and endocrine cells (the ductulo-insular complex, arrow) (I: H&E, x200) and immunohistochemistry with chromogranin A staining endocrine cells (J: x200) are demonstrated. Congenital hyperinsulinism is the most common cause of persistent hypoglycemia in infancy, existing in two forms of either focal or a diffuse adenomatous hyperplasia of insulin secretion in the pancreas. The pre-operative differentiation of these two conditions is crucial for disease management (1,2). Focal type can be treated by selective surgical resection in contrast to the diffuse form which requires near total pancreatectomy when resistant to medical treatment (3). No clinical or biological features are typical in determining disease type in affected infants. The current methods used for pre-operative differentiation are invasive techniques and do not always provide differential diagnosis (4,5,6). The definite role of imaging modalities to differentiate diffuse versus focal form has not yet been proven. F-18-fluoro-dihydroxyphenylalanine PET scan has been used in case of hyperinsulinemia with a reported accuracy of 96% in diagnosing focal or diffuse disease, and of 100% in localizing the focal lesion (3,7). To the best of our knowledge, only few case reports have been published regarding the role of somatostatin receptor imaging to distinguish focal disease from diffuse involvement, where Ga-68 DOTATATE PET scan had been applied successfully in one case and Ga-68 DOTATOC PET scan has been reported to have limited success in another report (1,8). The presented case is evident with an enlarged pancreas showing diffuse increased Ga-68 DOTATATE uptake and indicates somatostatin receptor imaging as a valuable option to guide the type of pancreatectomy in patients with persistent hyperinsulinemic hypoglycemia

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., H.M.A., Concept: F.C., Design: F.C., Data Collection or Processing: F.C., Analysis or Interpretation: F.C., B.C.M., M.C.B., Literature Search: F.C., Writing: F.C.

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Interesting Image
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Incidental Hydroxyapatite Ocular Implant Uptake on Bone Scan Done for Prostate Cancer Staging: Case Report and Brief Review

Prostat Kanseri Evrelemesi için Yapılan Kemik Sintigrafisinde Oküler İmplantta İnsidental Hidroksiapatit Tutulumu: Olgu Sunumu ve Kısa Özet

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Abstract

A 74-year-old man recently diagnosed with high-risk prostate cancer with high serum prostate specific antigen was referred to nuclear medicine for a technetium-99m-methylene diphosphonate (Tc-99m MDP) bone scan. On delayed three-hour anterior planar image, an unexpected round focus of intense uptake was found overlying the right orbit. Single-photon emission computed tomography/computed tomography localized the uptake to an ocular prosthesis. The hydroxyapatite composition of the ocular implant can be recognized by its bone-like density and its intense accumulation of Tc-99m MDP. Review of the patient's history revealed remote right eye evisceration secondary to a complication of cataract surgery, consistent with the findings.

Keywords: Tc-99m MDP, bone scan, ocular implant, artificial eye, eye prosthesis, hydroxyapatite

Öz

Yakın zamanda yüksek riskli prostat kanseri tanısı almış, serum prostat spesifik antijen seviyesi yüksek 74 yaşında bir erkek hasta teknesyum-99m-metilen difosfonat (Tc-99m MDP) kemik sintigrafisi için nükleer tıp bölümüne yönlendirildi. Gecikmiş üç saatlik anterior planar görüntüde sağ orbita üzerinde beklenmeyen yuvarlak ve yoğun tutulum odağı saptandı. Tek-foton emisyon bilgisayarlı tomografi/bilgisayarlı tomografi tutulumu oküler protezde lokalize etti. Oküler implantın hidroksiapatit bileşeni kemiğe benzer dansite ve yoğun Tc-99m MDP tutulumu ile tanınabilir. Hastanın özgeçmişinde, bulgularla uyumlu şekilde, katarakt cerrahisi komplikasyonuna sekonder sağ göz eviserasyonu saptandı.

Anahtar kelimeler: Tc-99m MDP, kemik sintigrafisi, oküler implant, yapay göz, göz protezi, hidroksiapatit

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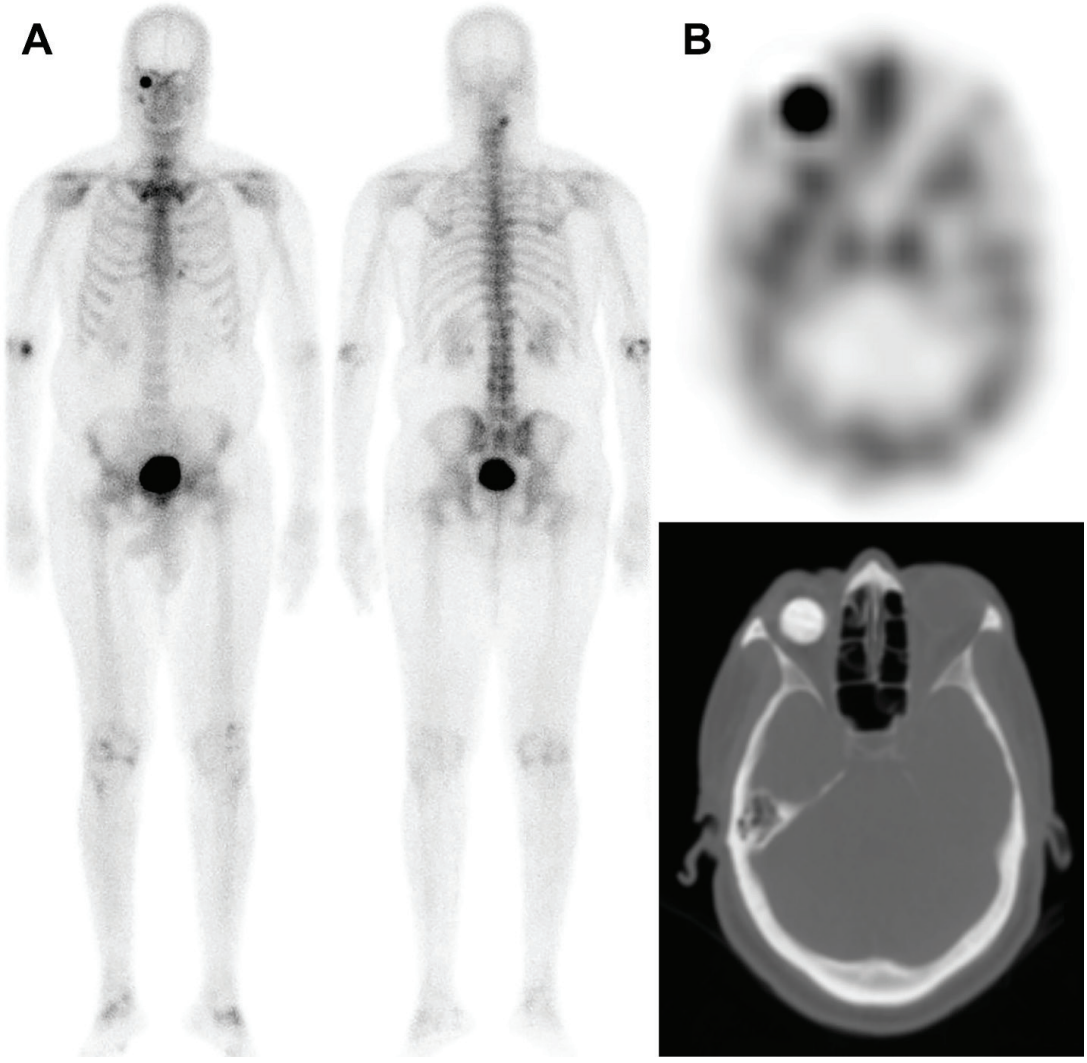

Figure 1. A 74-year-old man recently diagnosed with high-risk prostate cancer with high serum prostate specific antigen was referred to nuclear medicine for a technetium-99m-methylene diphosphonate (Tc-99m MDP) bone scan. As per institutional protocol, whole-body blood pool images were acquired, which were unremarkable (not shown). A) On delayed three-hour planar images, an unexpected round focus of intense uptake was found overlying the right orbit. B) Selected axial slice of Tc-99m MDP single-photon emission computed tomography/computed tomography showing intense uptake throughout a right hydroxyapatite ocular prosthesis. The hydroxyapatite nature of the ocular implant can be recognized by its bone-like density and its accumulation of bone scan agent. Review of the patient's history revealed right eye evisceration 20 years prior secondary to a complication of cataract surgery, consistent with the findings.

Although they are more costly, hydroxyapatite ocular implants offer many advantages over non-integrated implants. Thanks to their porous surface and organic composition, they allow in-growth of tissue, are lighter and allow insertion of a peg-a small pin-like device that improves coupling of the eyeball to the overlying artificial eye (1). A painful blind eye, cosmetics or trauma are reasons for their use. Evisceration, a process by which the inner content of the eyeball is removed by preserving the sclera, is then followed by insertion of the hydroxyapatite implant. Fibrovascular in-growth provides minimal risk of rejection, infection or migration (1). Radionuclide bone scan has been used to assess vascularization of eye prosthesis, an essential prerequisite prior to the drilling of the peg hole. Civelek et al. (2) demonstrated that semi-quantitative measurement by means of implanted to non-implanted eye ratios of uptake on bone scan identifies proper vascularization with high specificity. However, it seems that distribution of activity throughout the whole implant, rather than simply the intensity of the uptake, predicts greater likelihood of success (2,3). The peg hole must be conjunctivized, and therefore requires complete vascularization of the implant before being drilled. As uptake on bone scan is proportional to the vascularization of the implant, it can be used to assess the timing of complete vascularization, which usually occurs at around four months post-implantation (4). Counterintuitively, bone scan early phase "flow" studies and blood pool image analysis are not useful in this regard, and only delayed-phase imaging reliably correlates with vascularization; it is hypothesized that fibrovascular tissue lacks sizeable arteries to be detected by such means (5). Our case illustrates interesting but normal incidental ocular prosthetic uptake which is infrequently seen. Bone scan can be used to guide early implant management, but this finding can be encountered 20 or more years after hydroxyapatite ocular implant insertion

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.C., J.L., G.A., S.P., Concept: G.C., J.L., G.A., S.P., Design: G.C., J.L., G.A., S.P., Data Collection or Processing: G.C., J.L., G.A., S.P., Analysis or Interpretation: G.C., J.L., G.A., S.P., Literature Search: G.C., J.L., G.A., S.P., Writing: G.C., J.L., G.A., S.P.

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