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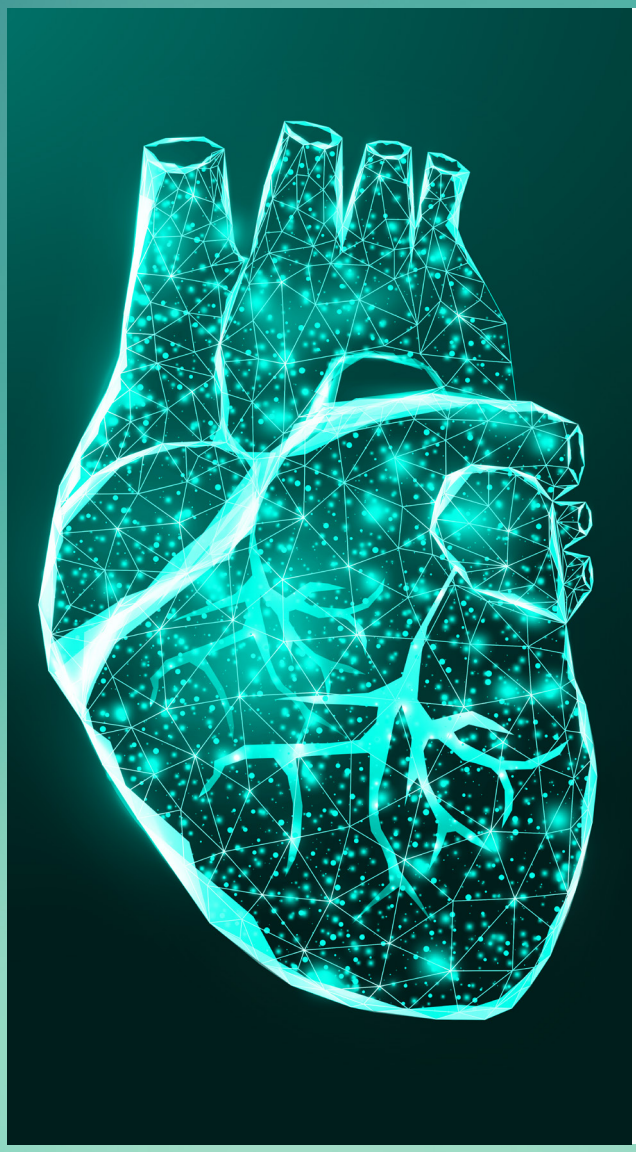

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RESEARCH ARTICLE

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Role of Speckle Tracking Echocardiography in Differentiating between Ischemic and Non-ischemic Cardiomyopathy

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Abstract

Background and Aim: Cardiovascular imaging plays an essential role in the early detection of cardiac injury and left ventricular (LV) function subclinical alterations. Non-invasively, speckle-tracking imaging provides objective and quantitative assessment of global and regional cardiac function. We investigated whether speckle tracking echocardiography (STE) can be used to distinguish between ischemic cardiomyopathy (ICM) and non-ischemic dilated cardiomyopathy (NICM) based on the pattern of cardiac deformation.

Materials and Methods: This research involved cases of dilated cardiomyopathy during the period from January 2022 to December 2022 in 100 patients separated into two groups. Baseline clinical data were evaluated. Conventional and STE were done. The cases were separated into two groups: Group A involved 50 cases with a history of ischemia confirmed by coronary angiography and group B involved 50 cases with NICM who had normal coronary angiography.

Results: Patients with NICM had significantly greater LV volumes, lower LV systolic function, and lower global longitudinal and circumferential strain. Basal longitudinal strain over the sum of mid and apical longitudinal strain was significantly lower in NICM (0.42 ± 0.03 vs. 0.49 ± 0.03, $P < 0.001$). Moreover, regional longitudinal strain decreased from apical to basal in NICM and was homogeneous throughout all segments in ICM.

Conclusion: Two-dimensional-STE can help differentiate ICM from NICM. Patients with NICM had a specific strain pattern as basal worsening of LV systolic strain with relative apical sparing.

Keywords: Speckle tracking echocardiography, ischemic, non-ischemic cardiomyopathy

INTRODUCTION

Left ventricular (LV) dilatation with reduced systolic performance characterizes dilated cardiomyopathy (DCM), a condition of the cardiac muscle that is considered a common characteristic of ischemic and non-ischemic heart disorders. Different approaches are taken for treating and prognosing ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM) because they are distinct disorders. Cases diagnosed with ICM survived worse in the long term than those diagnosed with NICM.[1]

Advances in management, earlier diagnosis, and careful follow-up significantly enhanced the prognosis of patients with DCM. In the past few years, DCM prognosis and survival have significantly improved, with decreased need for cardiac transplantation.[2]

Coronary angiography is the most reliable method for identifying ischemic etiology and is recommended by heart failure (HF) guidelines to exclude ischemic etiology.[3] NICM can be diagnosed if there is no evidence of coronary artery disease (CAD) or if the myocardial impairment does not explain

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the degree of ischemic involvement. However, the diagnostic benefits of coronary angiography should be weighed against the risk and cost. According to a previous study, ICM caused newly diagnosed HF in 15% of patients only,[4] and the use of coronary angiography in this setting was unnecessary. Thus, non-invasive methods could be of value in the diagnosis of ICM and should be thoroughly investigated.[5]

Two-dimensional speckle tracking echocardiography (2D-STE) plays a crucial and useful role in the estimation of global and regional myocardial function and can aid in the diagnosis of ischemic etiology.[6] Our research assessed the role of the myocardial deformation pattern evaluated by STE in the differentiation between ICM and NICM.

MATERIALS AND METHODS

Cases with DCM admitted to the cardiology department, Benha University Hospital, Egypt between January 2022 and December 2022 were evaluated. DCM was defined as LV dilatation (LV end-diastolic dimension >57 mm) and decreased LV systolic function [ejection fraction (EF) <45%].[6] Exclusion criteria were the existence of valvular heart disease, atrial fibrillation, permanent pacemaker use, the presence of chronic kidney disease, and poor echo window. The study cases were separated into two groups: Group A, 50 cases with a history of ischemia confirmed with coronary angiography and Group B, 50 cases with NICM who had normal coronary angiography. All patients were of matched age, gender, and risk factors (diabetes mellitus, hypertension). Informed written permission was obtained, and the research was approved by Benha University Faculty of Medicine Research Ethics Committee (study no: 29.9.2020).

Conventional transthoracic echocardiography

A 1.7-4 MHz transducer (Philips IE33 Ultrasound Machine) was used to acquire echocardiographic images while electrocardiogram signals were captured concurrently. The left lateral position of the patient was used for all examinations. During a breath hold, a series of 2D pictures were taken and preserved in cine-loop format for three consecutive heartbeats. The frame rate ranged from 40 to 60s. The apical four- and two-chamber views were used to evaluate LV systolic function using a modified Simpson's approach.[7]

2D speckle tracking echocardiography

We recorded three consecutive cardiac cycles in each apical view and stored the data as grayscale harmonic images in digital format for further analysis. Among forty and sixty frames per second were shown. Apical images were taken near the end of systole, and three sites were marked off: Two on either side of the mitral annulus and one at the apex of the left ventricle. Each of the 17 LV segments from American Heart Association's 17-segment LV model had its peak systolic longitudinal strain values automatically calculated by the algorithm. Global longitudinal strain (GLS) was estimated by averaging the strain measurements taken at each of the 17 segmental strain values. Strain values were measured at levels of strain in each of the six segments [five segments for the apical regional longitudinal strains (RLS)], and the mean of those values was used to determine RLS, including basal, mid, and apical RLS (Figure 1).[8]

The end-systolic period was used to manually establish sample sites together with the endocardial layers to determine the global circumferential strain (GCS) using parasternal short-axis views at the mitral, mid, and apical levels. The software then detected tissue speckles and followed their motion during the cardiac cycle frame by frame.[9]

Coronary angiogram

All patients underwent coronary angiography, and ICM was considered if luminal diameter stenosis ≥50% of the left main (LM) artery or ≥75% of the epicardial coronary artery. Conversely, NICM was considered when the luminal stenosis <50 percent of LM artery or <75 percent of epicardial coronary artery.[10]

Statistical analysis

Statistical analysis was performed with the assistance of the IBM SPSS 19.0 software package. Quantitative data are given as the mean ± standard deviation. An analysis of variance with a totally randomized design was used to conduct a comparative analysis of the variables of the two groups. A post hoc analysis was performed on the findings, and the findings that showed significant differences among the groups were compared. The receiver operator characteristic (ROC) was used to determine the degree to which the echocardiographic data accurately differentiated ICM from NICM. Contrasting the respective diagnostic accuracies required estimation of the area under the curve (AUC). Every statistical test consisted of two parts. *P*-value greater than 0.05 was statistically insignificant.

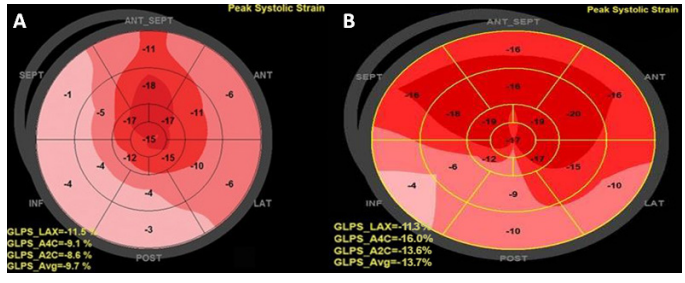

Figure 1: Bull's eye view of LV longitudinal strain of a patient with (A) NICM and (B) ICM

LV: Left ventricular, NICM: Non-ischemic cardiomyopathy, ICM: Ischemic cardiomyopathy

RESULTS

A total of 208 patients with DCM admitted to our cardiology department were evaluated. One hundred and eight patients were excluded because of the presence of valvular heart disease (n = 25), atrial fibrillation (n = 39), poor echo window (n = 24), and 20 patients were not matched. Finally, this study included 100 patients who were divided into two groups. The baseline characteristics of the research groups are provided in Table 1. Cases in the ICM group had more complaints of chest pain (41 patients 82% vs. 31 patient 62%, P = 0.026). However, there were no significant statistical variances between the two groups concerning the New York Heart Association functional classification, heart rate, and systolic and diastolic blood pressure (Table 1).

Both LV end-diastolic and end-systolic volumes were significantly greater in NICM patients. However, LVEF was significantly lower in NICM (P < 0.001).

The mean GLS and circumferential strains were significantly lower in NICM (-10.34 ± 0.97 vs. -11.83 ± 0.84 % and -7.55 ± 1.33 vs. -11.52 ± 1.61% respectively, P < 0.001). Regarding the regional strain, the average basal longitudinal strain (BLS) was significantly lower in NICM (-9.14 ± 1.21 vs. -11.60 ± 1.03%, P < 0.001). Moreover, it was significantly lower in NICM in anterior, inferior, anteroseptal, inferoseptal, inferolateral, and anterolateral segments (P < 0.001). In addition, the average mid and apical segmental longitudinal strain was significantly lower in NICM. Moreover, the mid and apical longitudinal stain of each segment was significantly lower in NICM (Table 2).

The mean BLS over the sum of the mean mid and apical longitudinal strain was significantly lower in NICM (0.42 ± 0.03 vs. 0.49 ± 0.03, P < 0.001). Moreover, the RLS decreased from apical to basal in NICM and was homogeneous throughout all segments in ICM.

ROC curve

The ROC curve was used to test the diagnostic value of the mean GLS, mean GCS, LVEF, and basal over sum of mid and apical longitudinal strain to differentiate between NICM and ICM. The mean GLS cut off value ≤-11 was revealed to have acceptable diagnostic accuracy (sensitivity =86%; specificity =70%) in differentiation between NICM and ICM. Also, the average basal over sum of mid and apical longitudinal strain cut-off value >0.449 was found to have acceptable diagnostic accuracy (sensitivity =90%; specificity =86%) in differentiation between NICM and ICM with higher AUC compared with mean GLS, mean GCS, and LVEF (0.937 vs. 0.894, 0.680, and 0.638) (Figure 2).

Table 1: Baseline clinical and conventional echocardiographic data

	Group A (ICM) (n = 50)	Group B (NICM) (n = 50)	*P*-value
Age, years	51.74±5.98	50.10±6.42	0.189
Gender			
Male, *n* (%)	29 (58)	25 (50)	0.422
Female, *n* (%)	21 (42)	25 (50)	
HTN, *n* (%)	31 (62)	29 (58)	0.683
DM, *n* (%)	39 (78)	29 (58)	0.32
Smoking, *n* (%)	23 (46)	23 (46)	1.0
NYHA functional class			
NYHA I, *n* (%)	12 (24)	15 (30)	0.545
NYHA II, *n* (%)	22 (44)	20 (40)	
NYHA III, *n* (%)	16 (32)	13 (26)	
NYHA IV, *n* (%)	0 (0)	2 (4)	
Heart rate (bpm)	94.92±11.16	97.32±10.03	0.261
SBP (mmHg)	125.7±22.6	127.5±20.5	0.501
DBP (mmHg)	70.9±11.5	72.6±10.9	0.561
Conventional echocardiography			
LVEDV (mL)	225.94±29.27	271.72±43.84	<0.001
LVESV (mL)	134.9±23.91	173.6±37.97	0.005
LVEF (%)	40.22±2.99	35.36±3.94	<0.001

ICM: Ischemic cardiomyopathy, NICM: Non-ischemic cardiomyopathy, HTN: Hypertension, DM: Diabetes mellitus, NYHA: New York Heart Association, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end systolic volume, LVEF: Left ventricular ejection fraction

Table 2: Speckle tracking echocardiographic data

	Group A (ICM) (n = 50)	Group B (NICM) (n = 50)	*P*-value
GLS	-11.83±0.84	-10.34±0.97	<0.001
GCS	-11.52±1.61	-7.55±1.33	<0.002
Basal/(mid + apical) GLS	0.49±0.03	0.42±0.03	<0.001
BLS			
Average BLS, %	-11.6±1.03	-9.14±1.21	<0.001
Anterior, %	-11.39±1.44	-8.86±1.18	<0.001
Inferior, %	-11.78±1.79	-9.0±1.46	<0.001
Anteroseptal, %	-12.0±1.52	-8.94±1.67	<0.001
Anterolateral, %	-11.59±1.65	-9.46±1.54	<0.001
Inferoseptal, %	-11.37±1.6	-9.04±1.85	<0.001
Inferolateral, %	-11.49±1.36	-9.52±1.58	<0.001
MLS			
Average MLS, %	-11.79±0.83	-10.71±1.08	<0.001
Anterior, %	-11.81±1.3	-10.56±1.42	<0.001
Inferior, %	-11.94±1.27	-10.66±1.24	<0.001
Anteroseptal, %	-11.72±1.44	-10.92±1.37	0.006
Anterolateral, %	-11.70±1.29	-10.74±1.66	0.002
Inferoseptal, %	-11.52±1.66	-10.6±1.71	0.008
Inferolateral, %	-12.01±1.5	-10.74±1.72	<0.001
ALS			
Average ALS, %	-12.11±1	-11.19±0.93	<0.001
Anterior, %	-12.25±1.27	-11.46±1.07	<0.001
Inferior, %	-12.51±1.37	-11.22±1.15	<0.001
Lateral, %	-12.15±1.48	-11.20±1.55	0.002
Septal, %	-11.53±1.57	-10.84±1.45	0.024
Apex, %	-12.08±1.58	-11.22±1.62	0.009

ICM: Ischemic cardiomyopathy, NICM: Non-ischemic cardiomyopathy, GLS: Global longitudinal strain, GCS: Global circumferential strain, BLS: Basal longitudinal strain, MLS: Mid longitudinal strain, ALS: Apical longitudinal strain

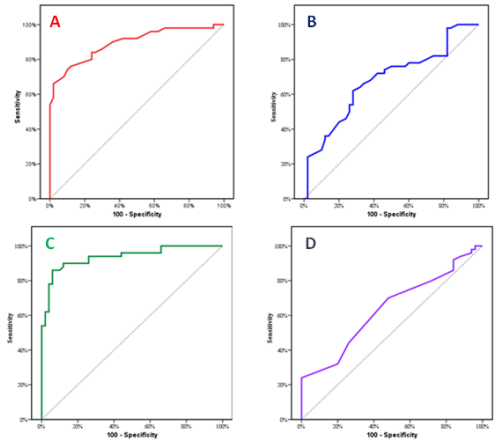

Figure 2: ROC curve for differentiating NICM from ICM using (A) mean GLS; (B) mean GCS; (C) basal over summation of mid and apical longitudinal strain; (D) LVEF

NICM: Non-ischemic cardiomyopathy, ICM: Ischemic cardiomyopathy, GLS: Global longitudinal strain, GCS: Global circumferential strain, LVEF: Left ventricular ejection fraction, ROC: Receiver operator characteristic

Univariate and multivariate regression analyses

Univariate and multivariate regression analyses were used to detect the predictors of ICM (Table 3). Multivariate analysis identified the average basal over sum of mid- and apical longitudinal strain as the only independent predictor of ICM (OR: 184.214, 95% CI: 10.311-3291.173, $P < 0.001$).

DISCUSSION

The most reliable method for diagnosing CAD is invasive coronary angiography. Therefore, it is used in patients with DCM to detect the ischemic etiology of lower LV systolic function. This research aimed to determine whether we can depend on non-invasive measures as STE to differentiate ICM from NICM.

This study showed that we can use echocardiography, especially STE, to differentiate between ICM and NICM. Conventional echocardiographic parameters showed that both LV end-diastolic and end-systolic volumes were significantly greater in NICM patients with significantly lower LVEF. These findings were similar to prior researches by Tymińska et al.[11] and Melichova et al.[12], who revealed that LV volumes and dimensions were significantly higher in NICM patients along with lower LVEF.

Moreover, STE revealed that the mean global LV longitudinal and circumferential strains were significantly lower in NICM ($P < 0.001$). In addition, segmental strain was significantly lower in NICM with a lower mean BLS over the sum of the mean mid- and apical longitudinal strains ($P < 0.001$). The RLS for each individual wall decreased from apical to basal segments in NICM (basal worsening) and was homogeneous throughout all affected segments in the distribution of the diseased vessel in patients with ICM.

Similarly, Abdelkarim et al.,[13] revealed that the global LV longitudinal strain was significantly lower in NICM (-10.29 ± 1.46 vs. -12.40 ± 1.35, $P < 0.001$). Zuo et al.[10] showed that both GCS and global radial strain were significantly lower in NICM than in ICM (-5.4 ± 2.6% vs. -7.0 ± 2.5%, $P = 0.006$; and 7.5 ± 4.5% vs. 10.7 ± 4.7%, $P = 0.019$), respectively.

In addition, Ilov et al.,[14] revealed that in cases with ICM, the worst features were discovered in the apical segments of the LV ($P = 0.008$), whereas in cases with NICM, the worst characteristics were discovered in the basal segments of the LV ($P = 0.046$). The LV peak systolic longitudinal strain was used to make this determination.

In the present study, we used the ROC curve to test the diagnostic value of the mean GLS, mean GCS, LVEF, and basal over sum of mid and apical longitudinal strain to differentiate between NICM and ICM. The cutoff value was ≤-11% for the mean GLS and >0.449 for the ratio between average basal over sum of mid and apical longitudinal strain with higher AUC compared to mean GLS, mean GCS, and LVEF.

Zuo et al.[10] showed that according to ROC analysis, the ratio of BLS to the total of apical and mid-level strains could accurately predict NICM with a sensitivity of 63.4% and a specificity of 88.4% (the cut-off value was 0.47, and the AUC was 0.792). GCS at cut-off >-6.67% was revealed to have acceptable diagnostic accuracy (sensitivity= 65%; specificity= 68%) in the differentiation between NICM and ICM. However, GLS and LVEF were not reliable in differentiating NICM from ICM.

Study limitations

There are some drawbacks to this research. First, there was a relatively small sample size and it was a single-center research. Moreover, the cases included in the study were referred for coronary angiography; therefore, we cannot exclude selection bias. Intraobserver and interobserver variability could not be excluded. Finally, patients with single-vessel disease (SVD) in an artery other than the LM or proximal left anterior descending artery (LAD) were judged to have NICM and were thus excluded from the study. As a result, the impact of SVD with 75% stenosis in an artery other than the LM or proximal LAD on myocardial

Table 3: Univariate and multivariate logistic regression analyses for predicting ICM

	Univariate		#Multivariate	
	P-value	OR (LL - UL 95% CI)	*P*-value	OR (LL - UL 95% CI)
LVESV	0.007	0.921 (0.868-0.978)	0.545	0.875 (0.568-1.348)
LVEDV	<0.001	0.964 (0.949-0.979)	0.193	1.172 (0.923-1.487)
Mean MLS	<0.001	0.275 (0.152-0.499)	0.832	0.833 (0.154-4.516)
Mean GLS	<0.001	0.140 (0.064-0.308)	0.059	0.127 (0.015-1.078)
Mean GCS	0.009	0.724 (0.568-0.923)	0.727	1.097 (0.653-1.841)
Basal / (mid + apical) GLS	<0.001	731.266 (61.79-8655.0)	<0.001	184.214 (10.311-3291.173)

#All variables with p<0.05 was included in the multivariate

ICM: Ischemic cardiomyopathy, LVESV: Left ventricular end systolic volume, LVEDV: Left ventricular end diastolic volume, MLS: Mid longitudinal strain, GLS: Global longitudinal strain, GCS: Global circumferential strain, CI: Confidence interval, UL: Upper limb, LL: Lower limb, OR: Odds ratio

dysfunction could not be determined. Intraobserver and interobserver variability could not be excluded.

CONCLUSION

2D-STE can help differentiate between ICM and NICM. Cases with NICM have strain patterns that include relative apical sparing and basal worsening of LV longitudinal strain. In addition, the mean GLS cutoff value ≤-11 and was shown to have acceptable diagnostic accuracy with average sensitivity and specificity. Moreover, the ratio between the basal over sum of the mid and apical longitudinal strains is more specific.

Ethics

Ethics Committee Approval: The research was approved by Benha University Faculty of Medicine Research Ethics Committee (study no: 29.9.2020).

Informed Consent: Informed consent was obtained from the participants.

Authorship Contributions

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

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

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RESEARCH ARTICLE

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Does Increased Fructose Consumption Increase Atherosclerosis Burden in Patients with NSTEMI?

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Abstract

Background and Aim: The pathophysiological process of coronary artery disease is not completely understood. According to some studies, fructose consumption is associated with coronary artery diameter change and blood flow; however, the relationship between fructose consumption and coronary atherosclerotic burden has not been adequately studied, and the purpose of our study was to investigate this relationship.

Materials and Methods: One hundred and fifty patients with non-ST-elevation myocardial infarction (NSTEMI) who underwent coronary angiography were divided into two groups: low (<23) and high (≥23) synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) scores. Fructose consumption was calculated for both groups, and the calculated fructose consumption was compared between the groups.

Results: Fructose consumption was higher in patients with a high SYNTAX score than in those with a low SYNTAX score (10.75 ± 2.04 and 6.86 ± 1.54, $P < 0.001$). Receiver operating characteristic curve analysis showed that the cut-off value of fructose consumption was 41.50 (g) for the prediction of high SYNTAX score (area under the curve: 0.891, sensitivity: 94%, specificity: 73%, $P < 0.001$). Fructose consumption was determined to be a predictor of high SYNTAX score in patients with NSTEMI (odds ratio: 1,239; 95% confidence interval: 1,146-1,339; $P < 0.001$).

Conclusion: Patients with high SYNTAX scores consumed a higher amount of fructose than those with low SYNTAX scores. High intake of fructose may play a role in coronary atherosclerotic burden score in patients with NSTEMI.

Keywords: NSTEMI, fructose, coronary atherosclerotic burden, SYNTAX score

INTRODUCTION

Globally, acute coronary syndromes (ACS) are the leading cause of death.[1,2] A sedentary lifestyle may increase risk factors for heart diseases in industrialized and developing countries because their calorie consumption is imbalanced with their needs.[3] Furthermore, industrially produced foods are also important risk factors for heart disease.[4] Several studies have demonstrated that consuming fructose, a natural sugar found in fruits, which is widely used in foods as a sweetener, is associated with cardiometabolic diseases such as difficulty regulating insulin, type 2 diabetes, hyperlipidemia, hyperuricaemia, gout, and metabolic syndrome.[5-7]

Excessive fructose consumption may lead to vascular deterioration due to endothelial dysfunction and atherosclerosis.[8] This can cause cardiac dysfunction and damage to important systems such as the kidneys and brain.[9]

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The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score is derived from answering consecutive questions on a computer program. It provides important information, such as angiographic lesion number determination, functional significance, and lesion location, about coronary artery disease (CAD).[10] In addition, with the use of the SYNTAX score, coronary atherosclerosis burden can be evaluated.[11]

There in no evidence regarding fructose consumption and CAD. We aimed to investigate the role of fructose consumption in the pathophysiology of coronary atherosclerotic burden in patients with non-ST-elevation myocardial infarction (NSTEMI).

MATERIALS AND METHODS

Target population

We screened all consecutive patients who underwent coronary angiography with a diagnosis of NSTEMI at a tertiary health center. The Çanakkale Onsekiz Mart University Clinical Research Ethics Committee approved the study (decision no: 2022-09, date: 18.05.2022). The Declaration of Helsinki guided all study procedures. We obtained informed consent from the participants.

A total of 381 patients were screened. A total of 150 patients were included because of the presence of the exclusion criteria. We categorized the patients into two groups based on their SYNTAX scores: low SYNTAX score (group 1; n = 40) and high SYNTAX score (group 2; n = 110). A computer program calculates the SYNTAX score based on a series of sequential, interactive questions (www.syntaxscore.com). To determine the severity of CAD, the SYNTAX scoring system, which uses features such as the number of lesions, functional importance, and location of the lesions, provides important information. As part of the scoring process, vessels with a diameter of at least 1.5 mm and lesions with at least 50% stenosis were enrolled. SYNTAX score <23 was evaluated as a low SYNTAX score, while SYNTAX score ≥23 was assessed as a high SYNTAX score.

NSTEMI was diagnosed according to the following criteria:[12]

1. Symptoms of angina or angina equivalents (such as dyspnea) that persist for more than 30 min.

2. When cardiac troponin (cTn) levels are above the 99th percentile of the cut-off value for each assay, they typically increase rapidly and decrease slowly, which is typical for high-sensitivity (hs) cTn levels.

3. Absence of STEMI criteria as defined in the fourth universal definition of myocardial infarction.

Exclusion criteria included history of ACS, chronic renal disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2), peripheral vascular disease, stroke, coronary artery bypass graft, active infection, chronic inflammatory disease, malignant disease, thyroid dysfunction, reduced left ventricular dysfunction [left ventricular ejection fraction LVEF) ≤40%], regular alcohol consumption (>20 g/day), or if they were aged <18 years.

Calculation of fructose consumption and blood samples

Blood drawn from the antecubital vein was used for simultaneous blood test measurements. Blood samples for the above-mentioned tests were collected within 6 h of admission. The literature commonly uses three-day (3 weekdays and 1 weekend) and seven-day diet records.[13,14] According to our study, fructose consumption was calculated based on food records for three days (2 weekdays, 1 weekend). In this study, fructose and other nutrient consumption were calculated by an expert dietician using the Nutrition Information System (BeBiS) 9 program (BeBiS, İstanbul, Turkey). An important advantage of the program is that it is a scientific and professional computer program that calculates the nutritional value of more than 20,000 foods, 130 nutrients including fructose, and the Turkish diet.

Angiographic assessment

Coronary imaging was performed by an omniscient cardiologist. Two experienced cardiologists reviewed the angiographic images. Two interventional cardiologists who were unaware of the study evaluated the angiographic images. Automated systems (GE Medical Systems) were used to analyze the angiographic images. Significant stenosis is defined as at least 50% of the coronary artery lumen in vessels at or above 1.5 mm.

Statistical analysis

G-Power 3.1.9.7 was used for power analysis. According to the researchers, a sample size of 134 subjects would be required, with an effect size of 0.50, a margin of error of 0.05, and a power of 0.80 (80%). The study data were statistically analyzed using SPSS 19.0 software (SPSS Inc. in Chicago, IL, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Depending on the sampling distribution, data are expressed as mean (standard deviation) or median (interquartile range). Numbers (n) and percentages (%) were used to express categorical variables. In the case of normal distributions, Student's t-tests were used, and in the case of non-normal distributions, Mann-Whitney U tests were used. Fisher's exact test or chi-squared test were used to compare categorical variables. To estimate the high SYNTAX score, possible confounding independent variables were

included in the univariate analysis. Data with a non-adjusted *P*-value of less than 0.1 were deemed possible risk factors in univariate analysis and were incorporated into the multivariate analysis based on them. The independent predictors of high SYNTAX scores in patients with NSTEMI were investigated using multivariate analysis. The Hosmer-Lemeshow test was used to interpret model sufficiency. $P < 0.05$ was considered statistically significant.

RESULTS

Our study evaluated the data of 150 patients. The baseline clinical, laboratory, and angiographic data of the patients are summarized in Table 1. Groups 1 and 2 differed significantly in terms of some of the laboratory parameters, namely, Hs C-reactive protein (CRP) [1.77 (1.00-2.20) and 2.14 (1.07-1-0.60), $P = 0.019$], and LVEF (49.75 ± 6.15 and 47.24 ± 5.91, $P = 0.029$) (Table 1). Multivessel disease was more prevalent in the high SYNTAX group (Table 1).

Table 1: Baseline clinical, laboratory, and angiographic data of the study patients

	Low SYNTAX score (n=40)	High SYNTAX score (n=110)	*P*-value
Age (years)	60.73±12.57	61.53±13.08	0.734
Gender (M/F)	30/10	87/23	0.755
Body mass index (kg/m^2)	25.77±2.13	26.49±2.82	0.147
Smoking, n (%)	13 (32.5)	24 (21.8)	0.202
Diabetes mellitus, n (%)	9 (22.5)	20 (18.2)	0.641
Hypertension, n (%)	12 (30)	22 (20)	0.269
Hypercholesterolemia, n (%)	8 (20)	14 (12.7)	0.299
SBP (mmHg)	130.70±22.95	129.93±21.68	0.854
DBP (mmHg)	82.20±17.21	80.67±16.27	0.628
Laboratory data			
Glucose, mg/dL	106.70±27.28	109.45±26.29	0.584
Creatinine, mg/dL	0.89±0.18	0.92±0.19	0.325
Uric acid, mg/dL	5.00±1.18	5.00±1.15	0.991
Hemoglobin (g/dL)	12.89±1.95	12.99±1.94	0.774
WBC count 10^9/L	8.52±3.02	8.47±2.92	0.931
Platelet count, 10^9/L	228.90±55.4	224.65±53.74	0.677
LDL-cholesterol, mg/dL	110.07±40.60	119.52±40.55	0.212
HDL-cholesterol, mg/dL	40.48±8.75	40.13±8.31	0.824
Triglyceride, mg/dL	174.72 (132.0-214.25)	162.00 (128.0-215.0)	0.978
Cardiac Tn, ng/L	172.85 (46.55-497.15)	334.0 (71.77-740.05)	0.108
TSH (uIU/mL)	2.12 (1.55-3.14)	2.27 (1.56-3.19)	0.688
HbA1C (%)	7.07±0.95	7.12±0.97	0.790
Hs-CRP, mg/L	1.77 (1.00-2.20)	2.14 (1.07-10.60)	0.019
LVEF, %	49.75±6.15	47.24±5.91	0.029
Angiographic data			
Number of vessels diseased			<0.001
1	23 (57.5)	17 (15.5)	
2	14 (35.0)	48 (43.6)	
3	3 (7.5)	45 (40.9)	
Chronic occlusion	3 (7.5)	27 (24.5)	0.021
Multi-vessel disease	18 (45)	77 (70)	0.009
SYNTAX score	12.75±4.55	26.09±1.48	<0.001
Decision, n (%)			<0.001
Stent implantation	31 (93.9)	40 (36.4)	
CABG	2 (6.1)	70 (63.6)	

CABG: Coronary artery bypass graft, DBP: Diastolic blood pressure, HbA1C: Glycated hemoglobin, Hs-CRP: High-sensitivity C-reactive protein, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, LVEF: Left ventricle ejection fraction, SBP: Systolic blood pressure, Tn: Troponin, WBC: White blood cell count, M/F: Male/female, TSH: Thyroid stimulating hormone, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery

When the daily dietary energy and fructose consumption of the patients were compared, total energy (2646.68 ± 333.83 and 2813.90 ± 393.27, $P = 0.018$), carbohydrate (255.35 ± 47.36 and 283.38 ± 74.48, $P = 0.008$), and fructose consumption (10.75 ± 2.04 and 6.86 ± 1.54) were higher in the high SYNTAX score group (Table 2).

Univariate analysis identified LVEF, Hs-CRP, total carbonhydrate consumption, total energy consumption, and fructose consumption as significant predictors of high SYNTAX score in patients with NSTEMI. Multivariate analysis identified LVEF [odds ratio (OR): 0.912, 95%; confidence interval (CI): 0.831-1.000, $P = 0.049$] and fructose consumption (OR: 1.239, 95%; CI: 1.146-1.339, $P < 0.001$) as significant predictors of high SYNTAX score in patients with NSTEMI (Table 3). The Hosmer-Lemeshow test results show that the model was well fitted, as indicated by the positive results of the test (χ^2=6.12; $P = 0.380$).

The predictive value of fructose consumption for predicting high SYNTAX score was confirmed using receiver operating characteristic curve analysis. The cut-off value of fructose consumption was 41.50 (g) (area under the curve: 0.891; 95% CI: 0.830-0.951; $P < 0.001$; sensitivity, 94%, specificity, 73%; positive predictive value, 94.55% and negative predictive value, 72.50%) (Figure 1).

DISCUSSION

To date, no research has been conducted on fructose consumption and coronary atherosclerotic burden in patients with NSTEMI. Our study showed an association between fructose consumption and coronary atherosclerotic burden.

Atherosclerosis is a chronic inflammatory disease of the vascular system that occurs when laminar flow is disrupted, leading to the accumulation of lipid particles and immune cells in the subendothelial space.[15] When reactive oxygen species

Table 2: Comparison of fructose consumption with daily dietary energy

	Low SYNTAX score	High SYNTAX score	*P*-value
Energy (kcal)	2646.68±333.83	2813.90±393.27	0.018
Carbohydrate (g)	255.35±47.36	283.38±74.48	0.008
Carbohydrate (TE %)	51.74±15.47	60.37±25.95	0.015
Protein (g)	81.18±35.68	85.26±37.75	0.543
Protein (TE %)	16.44±8.25	17.80±8.55	0.381
Lipid (g)	153.63±13.66	157.17±16.48	0.188
Lipid (TE %)	30.84±5.56	32.93±7.73	0.072
Fructose (g)	34.25±6.56	51.82±6.36	<0.001
Fructose (TE %)	6.86±1.54	10.75±2.04	<0.001

TE: Total energy, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery

Table 3: Predictors of high SYNTAX scores in patients with non-ST elevation myocardial infarction

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Current smoking	1.725	0.774-3.846	0.182			
Gender	1.261	0.539-2.951	0.593			
LVEF	0.898	0.844-0.956	0.001	0.912	0.831-1.000	0.049
Hypertension	1.714	0.754-3.900	0.199			
Diabetes mellitus	1.306	0.538-3.170	0.554			
Triglyceride	1.000	0.996-1.004	0.985			
Hs-CRP	1.193	1.052-1.351	0.006	1.087	0.918-1.288	0.332
Cardiac Tn	1.001	1.000-1.002	0.063			
Creatinine	2.698	0.369-19.721	0.328			
Uric acid	1.002	0.733-1.370	0.990			
Total carbonhydrate consumption	1.009	0.982-1.017	0.031	1.004	0.994-1.015	0.401
Total energy consumption	1.001	0.967-1.002	0.020	0.998	0.994-1.001	0.757
Fructose consumption	1.250	1.165-1.341	<0.001	1.239	1.146-1.339	<0.001

LVEF: Left ventricularventricle ejection fraction, Hs-CRP: High-sensitivity C-reactive protein, Tn: Troponin, CI: Confidence interval, OR: Odds ratio

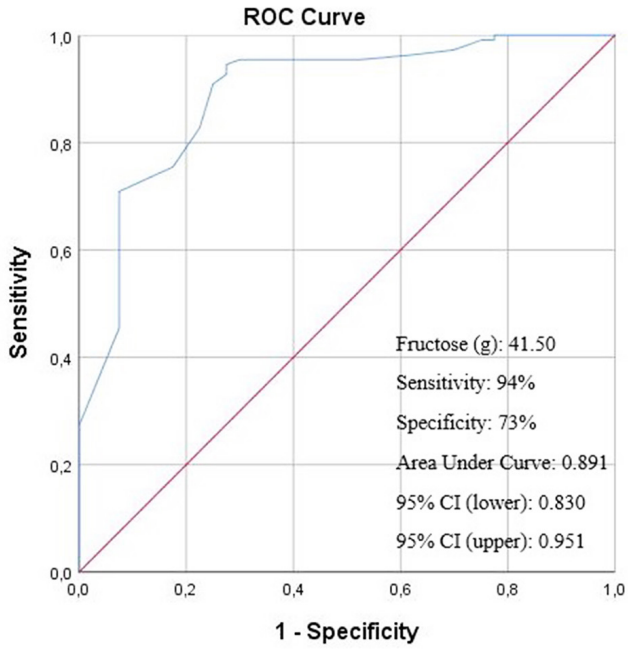

Figure 1: ROC curve analysis for fructose consumption in predicting high SYNTAX scores

ROC: Receiver operator characteristic, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery, CI: Confidence interval

(ROS) oxidize lipid molecules and immune cells, inflammatory responses result and the atherosclerotic cycle begins.[16] Adenine dinucleotide phosphate oxidase in endothelial cells and ROS originating from mitochondria are the most important free oxygen radicals in vascular beds[17], and oxidative stress and lipid metabolism play an important role in atherosclerosis in vascular structures as well as in the onset and severity.[16,18] Fructose transporter (GLUT)-5 facilitates the transport of fructose to the intestinal cell, which is then metabolized via the glycolytic pathway, unlike glucose.[19] Fructose consumption increases lipid particles, such as fatty acids, and increases the risk of endothelial damage caused by ROS.[20] According to these data, fructose consumption may promote endothelial damage and oxidative stress, which may lead to the initiation and progression of atherosclerosis. In our study, no difference was observed in lipid parameters or glucose levels between the groups. Perhaps an important reason for this is that our number of patients was small and we calculated fructose consumption differently methodologically.

Conventional risk factors, such as advanced age, gender, dyslipidemia, and smoking, have been associated with CAD severity.[21] In addition, the relationship between coronary atherosclerotic burden and fructose consumption was investigated in our study. Fructose consumption has been previously classified as moderate (0-50 g/day), high (50-100 g/day), and very high (100-150 g/day).[22] In our study, more fructose consumption was found in the group with a high SYNTAX score.

There is a strong relationship between inflammation and atherosclerosis.[23] Hs-CRP is an important inflammatory marker.[24] In our study, Hs-CRP and increased fructose consumption were found to be higher in the high SYNTAX score group.

Animal experiments have shown that fructose consumption causes inflammation and may contribute to various diseases.[25,26] In humans, its clinical effects remain unclear. Studies have shown that excessive fructose consumption may cause coronary slow flow and coronary ectasia.[27,28] CAD development is influenced by inflammation, oxidative stress, and endothelial injury. All these pathogenetic processes are closely related to high fructose consumption, as observed in our study, and increased fructose consumption was found to be associated with coronary atherosclerotic burden. Atherosclerosis is continuous, and one of the factors that can accelerate this process is fructose consumption. As a matter of fact, as seen in our study, fructose consumption may affect the spread of atherosclerosis.

Study limitations

Our study was conducted in only one center with some patients. There are limitations to the study due to food. Although consumption records are a practical method for detecting daily fructose, measuring the amount of fructose in 24 h urine is a more reliable method; however, there are no study examples comparing both methods. In our study, we used the most commonly used method to calculate fructose consumption, but it is less effective than direct measurement. Because of the lack of follow-up, we couldnot determine whether fructose consumption was associated with significant adverse cardiac events. To address these shortcomings, prospective multicenter studies are needed. Until then, these results should be interpreted cautiously due to the limitations of this study.

CONCLUSIONS

It is unclear how fructose consumption affects the cardiovascular system. Increasing fructose consumption may trigger atherosclerosis in the vascular structures. Finally, we demonstrated that increased fructose consumption can play a role in the mechanisms of coronary atherosclerotic burden in patients with NSTEMI.

Ethics

Ethics Committee Approval: The Çanakkale Onsekiz Mart University Clinical Research Ethics Committee approved the study (decision no: 2022-09, date: 18.05.2022).

Informed Consent: Informed consent was obtained from the participants.

Authorship Contributions

Surgical and Medical Practices: U.K., B.T., K.P., Concept: U.K., B.T., K.P., Design: U.K., B.T., K.P., Data Collection or Processing: U.K., B.T., K.P., Analysis or Interpretation: U.K., B.T., K.P., Literature Search: U.K., B.T., K.P., Writing: U.K., B.T., K.P.

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CASE REPORT

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An Interesting Association with Pulmonary Hypertension: Swyer-James-Macleod Syndrome

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Abstract

Pulmonary hypertension (PH) is a chronic disease that has increased awareness in recent years and has high morbidity and mortality. There are many unexplained points outside the current PH classification. Congenital heart diseases and lung pathologies are important causes of PH. Swyer-James-Macleod syndrome is a syndrome characterized by unilateral pulmonary arterial flow reduction due to involvement mostly in childhood and contralateral lung hyperlucency in imaging methods. It is rare for this syndrome to be observed together with congenital heart diseases and to be defined in a patient with PH.

Keywords: Atrial septal defect, congenital heart disease, pulmonary hypertension, Swyer-James-Macleod syndrome

INTRODUCTION

Pulmonary hypertension (PH) is a disease that can include more than one clinical condition and is closely related to cardiovascular and respiratory system diseases. The definition of PH is made by right heart catheterization. In right heart catheterization measurements, the disease is diagnosed when the mean pulmonary artery pressure is >20 mmHg. Pulmonary vascular resistance (PVR) and pulmonary artery wedge pressure measurements are also essential for disease classification.[1]

In the 2022 European Society of Cardiology (ESC) PH guidelines, the disease was evaluated in 5 groups. Cardiovascular diseases are the most common in the etiology of the disease. In addition, lung pulmonary obstructive, and systemic diseases are among the causes of PH. However, isolated pulmonary arterial hypertension is the focus of PH treatment. Congenital heart diseases are also included in the group 1 PH classification according to the ESC 2022 PH guidelines. Swyer-James-Macleod syndrome (SJMS), which we have diagnosed, is a disease that is generally thought to be related to childhood infections and is evaluated within the classification of developmental lung diseases and group 3 PH related to it.[2] The coexistence of SJMS and congenital heart diseases is rare.

In our study, we present a case of a patient with SJMS who was diagnosed with PH and had a history of atrial septal defect (ASD) closure.

CASE REPORT

A 22-year-old female patient presented to us with increasing difficulty in breathing for the last two years. In addition to breathing difficulties, the patient had long-standing stabbing chest pains. There was no sputum or cough complaint. In the patient's history, it was learned that she had undergone ASD closure surgery 11 years ago. The patient had no history

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of recurrent lung infections. Physical examination of the patient revealed that blood pressure was 110/60 mmHg, heart rate was rhythmic 65 beats/min, oxygen saturation was 96%, and cardiac auscultation had a 2/6 systolic murmur. On the chest X-ray of the patient, increased vascularity in the right lung, heart, and mediastinal structures were directed to the left (Figure 1). Sinus rhythm and incomplete right bundle branch block morphology were observed on electrocardiography.

The ejection fraction was evaluated as 60% in the patient's echocardiography. No serious pathology was observed in the left-sided valves. The RV basal diameter was measured as 4.2 cm, RV FAC: 50%, TAPSE: 19 mm, and RV SM: 10.9 cm/s. The patient's systolic pulmonary artery pressure was 55 mmHg, TR velocity was 3.8 m/s, and the TAPSE/sPAP ratio was 0.34 mm/mmHg. It was also noted that the patient did not have a serious lung infection during childhood. The 6-min walking test was found to be 460 m. On the patient's complaints, he was hospitalized for right heart catheterization and medical treatment. The patient's laboratory parameters were found to be normal. The N-terminal pro-brain natriuretic peptide (NT-proBNP) level was measured as 174 ng/L. In the right heart, the mean pulmonary artery pressure was measured as 32 mmHg. The vasoreactivity test was negative. Cardiac output: 4 lt/min, PVR was calculated as 5.4 wood units, Qp/Qs: 1.1. The pulmonary capillary wedge pressure was measured as 8 mmHg. Then, ventilation-perfusion scintigraphy was performed with Tc99m. Because of scintigraphy, a hypoplasic left lung with subsegmental hypoperfusion was observed, and a compensatory hypertrophic right lung with normal perfusion was observed (Figure 2). Pulmonary computed tomography angiography of the patient revealed a hypoplastic left main pulmonary artery (Figure 3, 4) Our patient was diagnosed with SJMS. Our patient, who also had a history of ASD closure, was evaluated as group 1 PH in the low-risk group, and sildenafil 20 mg 3*1 treatment was started. During the follow-up of the patient, systolic pulmonary artery pressure was measured as 35 mmHg on transthoracic echocardiography, and functional capacity was evaluated according to NYHA 1.

Informed consent was obtained from the patient.

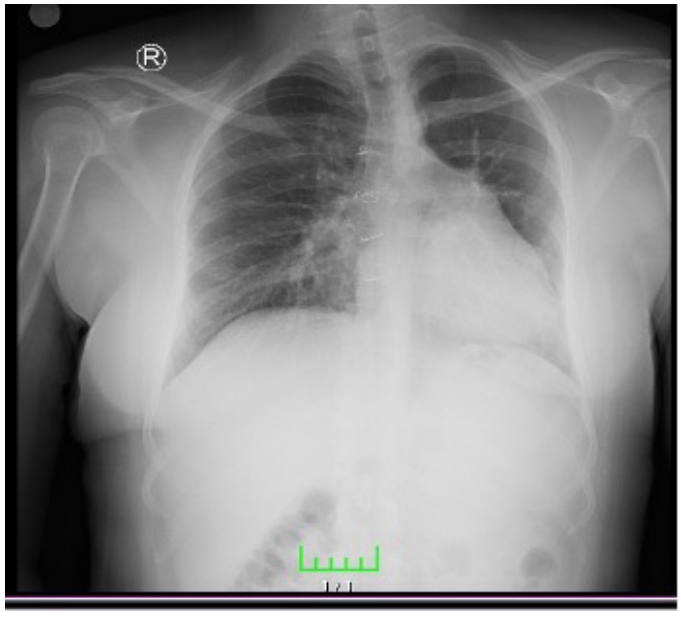

Figure 1: On chest X-ray, the vascularity of the right lung was increased, and the heart and mediastinal structures were observed to be deviated to the left

Discussion

PH is a chronic disease that can affect all age groups, and its prevalence is estimated to be 1% in the global population. Cardiovascular diseases are the most common causes of PH. The second most common is chronic obstructive pulmonary disease.[3] Although the prevalence of PH increases with age, it is seen especially in the younger patient group due to congenital heart diseases. It would also be useful to investigate systemic diseases in young patients with PH, human immunodeficiency virus, and infective diseases such as schistosomiasis in endemic areas.[4]

The diagnosis of PH is made by right heart catheterization. After the diagnosis is made, the etiology is clarified using catheter measurements and different imaging methods. Clarification of

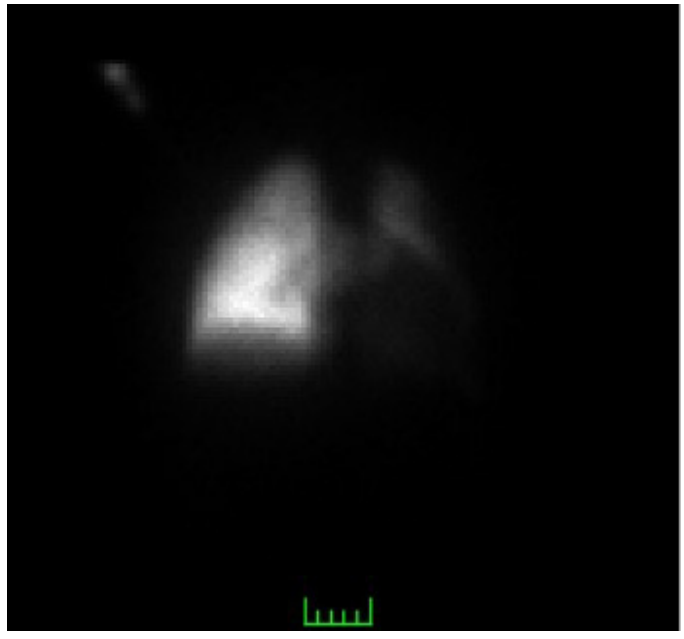

Figure 2: In the scintigraphy images, hypoplastic left lung with subsegmental hypoperfusion and compensatory hypertrophic right lung with normal perfusion were observed

the etiology and evaluation of hemodynamic measurements play a role in arranging the treatment plan, as classification and risk assessment play an important role for treating PH. In the follow-up of the patients, treatment arrangements are made with a four-stage evaluation system, including World Health Organization functional classification, 6-min walk test, and BNP or NT-proBNP levels.

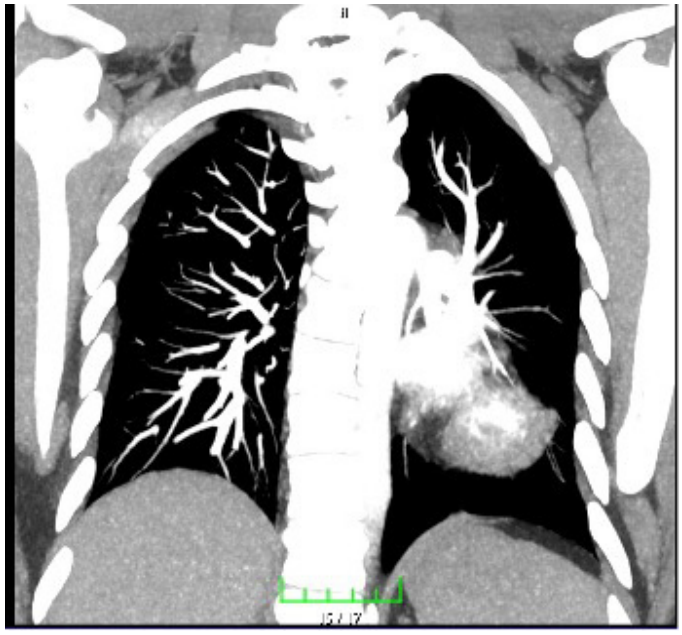

Figure 3: Compensatory increase in the right air spaces was observed in the patient's pulmonary computed tomography angiography

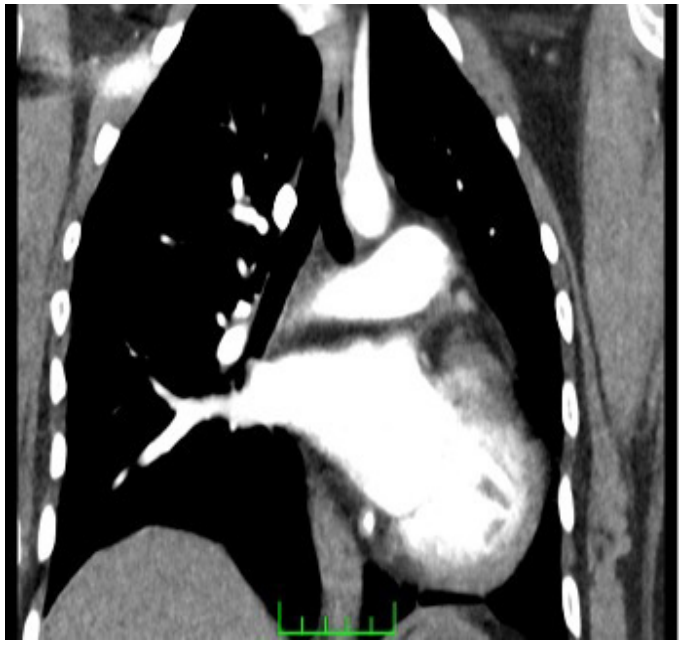

Figure 4: Pulmonary computed tomography angiography of the patient showed hypoplasia of the left main pulmonary artery

SJMS is a rare clinical condition. Although adult patients are generally asymptomatic, some patients may develop exertional dyspnea, cough, sputum production, and hemoptysis.[5] It is thought that the most likely mechanism causing the disease is the underdevelopment of bronchioles and terminal branches secondary to bronchiolitis obliterans, which occurs in early life.[6] There are rare reports of its association with SJMS and congenital heart diseases. The association between coronary outflow anomaly and ventricular septal defect has been shown previously.[7] It remains a mystery whether it causes PH together with these. It is important to prevent and treat recurrent infections during the follow-up of the disease. However, there are no definitive data on the clinical follow-up of patients with PH and their prognosis.

SJMS can be evaluated within the scope of developmental lung diseases and can be evaluated in group-3 PH class.[8] The presence of ASD as a congenital heart disease in our patient and its correction, the absence of echocardiographic measurements because the patient had no complaints for 10 years after the repair and did not come to follow-ups, weakens our ability to reveal the etiology. In our patient, who also had a history of ASD closure, it can be thought that the mechanism of PH development combined group 1 and group 3, depending on the underlying lung disease. Measurements of lung functional capacity in our patient could guide us in the differentiation. Our patient had no history of recurrent lung infections. There was no evidence of bronchiectasis in the lung evaluation. Diffusing capacity of the lung for carbon monoxide measurements are a useful test in this sense, and it is a shortcoming that it could not be performed in our patient.

In case our patient had a combination of group 1 and group 3 PH, it was decided to start monotherapy first because he had dyspnea complaints, had a mean pulmonary artery pressure of 32 mmHg, and was in the low-risk group. However, because the patient was known to have persistent PH after possible congenital heart disease and the prognosis in this case was worse, combination therapy was considered in the follow-up. Endothelin receptor antagonists were considered to be added to the treatment if the patient's complaints continued during the follow-up. In this patient, considering the pathogenesis of group 4 PH and flow-limiting obstructive pulmonary disease, adding riociguat to the treatment may also be beneficial.

Conclusion

In this case report, a patient with SJMS and ASD coexistence, which is rare in the etiology of PH, and our treatment management are presented.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.T.Ş., Concept: Y.A., Design: A.T.Ş., A.A., Data Collection or Processing: Y.A., M.A.D., Analysis or Interpretation: M.A.D., Literature Search: A.T.Ş., C.K., Writing: A.T.Ş.

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

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CASE REPORT

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An Unprecedented Association; Coronary Artery Disease and Sagliker Syndrome

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Abstract

Sagliker syndrome (SS) develops in chronic kidney disease patients because of insufficiently treated secondary hyperparathyroidism (SHPT) at an early stage. Studies indicating the potential association of the pathophysiology of the syndrome with genetic mutations are available. Phenotypic characteristics such as Brown tumors, lytic non-neoplastic bone lesions resulting from abnormal bone metabolism, deformities in the mandible and maxilla, irregularly spaced teeth, hypertrophic prominence of the lips, short neck, and slender upper and lower extremities are prominent in these patients. Brown tumors are often found in the metaphyses of the long bones, pelvis, maxilla, and costae, with significant involvement observed in our patient's bilateral costae. The facial deformities in our patient were consistent and similar to the phenotype findings in other cases reported in the literature. In patients with chronic kidney disease (CKD), anemia is frequently observed because of increased SHPT, with a direct toxic effect on erythropoietin synthesis and erythropoietin progenitors in bone marrow. While anemia is common, bone marrow fibrosis and pancytopenia are much rarer. Although hyperparathyroidism is considered to be the responsible factor in the pathophysiology of SS, the literature does not report an association between SS and bone marrow fibrosis, making our case the first presentation of such an association. The high prevalence and early onset of coronary artery diseases (CAD) in patients with CKD are associated with a combination of systemic inflammation, oxidative stress, hypertension, vascular calcification, and disruptions in bone metabolism. In the patient's medical history, there was no presence of hypertension, diabetes, smoking, or a family history of these conditions. SHPT in end-stage renal disease has been shown to accelerate vascular calcification and subclinical atherosclerosis. The presence of early-onset CAD in our patient, despite the absence of traditional risk factors, raises the question of whether hyperparathyroidism, a prominent factor in this syndrome, played a significant role in its etiology.

Keywords: Renal osteodystrophy, secondary parathyroidism, hypercalcemia, brown tumor, angina, coronary angiography

INTRODUCTION

Sagliker syndrome (SS) is a rare condition in which secondary hyperparathyroidism (SHPT) and chronic renal failure (CKD) co-exist. First described in 2004, this syndrome is typically seen in young women (18-39 years), and its association with CKD is very rare (0.05%).[1,2] While the pathophysiologic factor responsible for SS has been shown to be hyperparathyroidism secondary to CKD, *GNAS1* gene mutation has been demonstrated in 40% of SS patients.[3] Although renal transplantation may halt the progression of musculoskeletal deformities, it may not reverse SS-related deformities.[4] Patients frequently present with deformities of the upper and lower jaw, dental abnormalities, marked lip hypertrophy, short neck, short stature, bone deformities, deformities of the hands and fingertips, and psychiatric disorders. Although patients with CKD are at high risk for coronary artery disease (CAD), cases of bone marrow myelofibrosis secondary to hyperparathyroidism in CKD have been reported in the literature, but no case of co-existence of SS, CAD, and bone marrow fibrosis has been reported. In this case

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report, we present the case of a patient with SS who continued to exhibit persistent deformities in long-term follow-up despite undergoing two parathyroidectomies, with the comorbidity of existing CAD and severe pancytopenia.

CASE REPORT

A 39-year-old woman presented to the outpatient clinic with exertional dyspnea, joint pain, and leg weakness. She had been on hemodialysis for 5 years because of end-stage renal failure. Her medical history revealed that she underwent kidney transplantation in 2012 and had a history of rejection 2.5 years after transplantation. Two years earlier, coronary imaging of the patient showed 80-90% stenosis after lymphadenectomy D2, 30-40% stenosis after CX OM1, and 20-30% stenosis in the middle segment of the right coronary artery with anterior origin. She had undergone 2.75x16 mm Promus Premier (Boston Scientific) stent implantation for a critical lesion in the left anterior descending artery (Figure 1, 2). There was also no known history of diabetes, family history, or smoking. Physical examination revealed a dialysis fistula in the right arm (Figure 3), dental deformities, malocclusion, caries, protruding lips, enlargement of the mandible and maxilla, short neck, short stature (Figure 4), finger deformities (Figure 5), and weakened lower extremities, with distinct phenotypic features consistent with SS, which is rare in patients with CKD compared with cases in the literature. Blood pressure and pulse rate were within the normal range. Cardiac auscultation revealed a 2/6 diastolic murmur in the mesocardia focus, and abdominal palpation revealed splenomegaly. In the medical history of the patient, it was reported that parathyroidectomy was performed 8 years ago and weakness, fatigue, and serum parathyroid hormone level was 1,989 ug/L three years after the operation. The patient underwent a second parathyroidectomy. However, despite two parathyroidectomies, the deformities persisted in the long-term follow-up. At the last nephrology clinic evaluation, fluorodeoxyglucose (FDG) positron emission tomography-computed tomography was ordered because of diffuse bone pain and revealed a 44 mm enlarging sclerotic lesion in the right 9th rib (An Unprecedented Association; CAD and SS ure 6), a similar lesion with 37 mm FDG uptake in the left 10th rib, a 1 cm lytic lesion in the right femoral neck, and a l (Figure 6, 7). Brown tumors were reported on tru-cut biopsy of lytic bone lesions. Simultaneous parathyroid evaluation revealed minimal FDG uptake in a paratracheal location, and

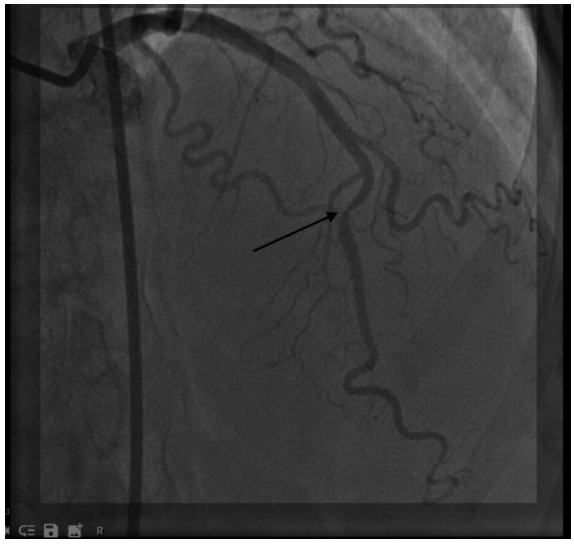

Figure 1. Coronary angiography revealed 80-90% stenosis in the left anterior descending coronary artery (lymphadenectomy)

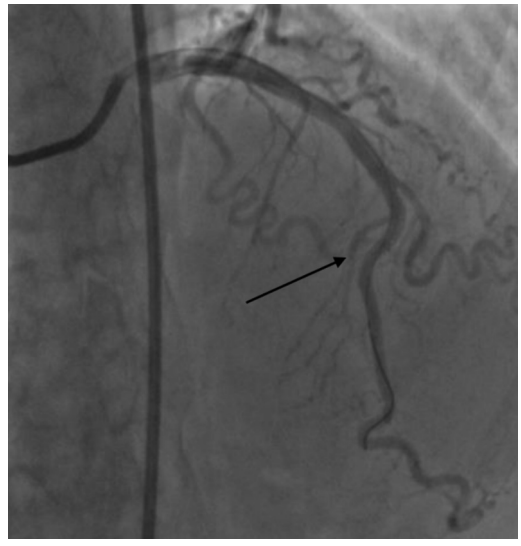

Figure 2. After lymphadenectomy D2, a 2.75x16 16 mm Promus stent was implanted

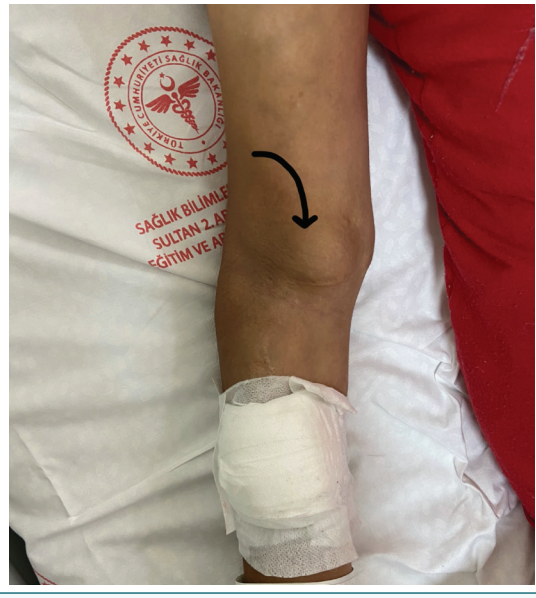

Figure 3. Dialysis fistula was observed in the patient's arm

methoxy-isobutylisonitrile (MIBI) scintigraphy revealed focal increased MIBI uptake in the upper level of the left thyroid lobe. In the last laboratory findings in our clinic, parathyroid level was 277 ng/L, alkaline phosphatase level was 116 U/L, Ca level was 8.18 mg/dL and p=2.07 mg/dL. Although CAD remained stable, the patient's white blood cell count was 1.69 mm^3, hemoglobin was 8.8 g/dL, hematocrit was 19.8, and platelet count was 61 mm^3. Hematologic evaluation was requested but the patient refused. The patients history revealed two bone marrow biopsies resulting in myelofibrosis. Medical treatment included cinacalcet, acetylsalicylic acid 100 mg, clopidogrel 75 mg, bisoprolol 12.5 mg, atorvastatin 40 mg, pantoprazole 40 mg, sevelamer carbonate, trimethazidine 80 mg, doxazosin 8 mg xl, folic acid, nifedipine 30 mg. Transthoracic echocardiography revealed an ejection fraction of 60%, moderate aortic valve regurgitation, mild to moderate tricuspid valve regurgitation, calcified mitral and aortic valves with adequate patency, and pulmonary artery pressure of 45 mmHg. The patient did not have a detected mutation associated with the *GNAS1* gene (Table 1). Informed consent of the patient was obtained.

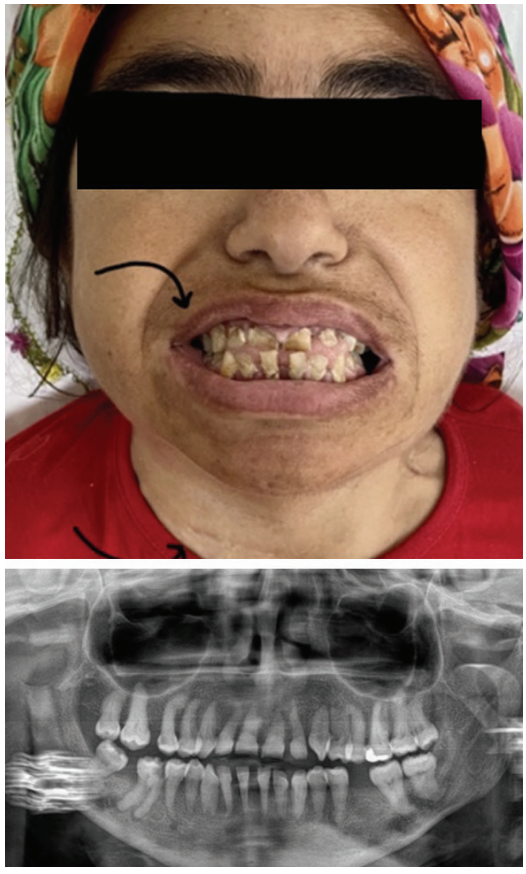

Figure 4. The patient exhibits dental deformities, gaps, decay, protruding lips, and widening of the mandible and maxilla, along with a short neck

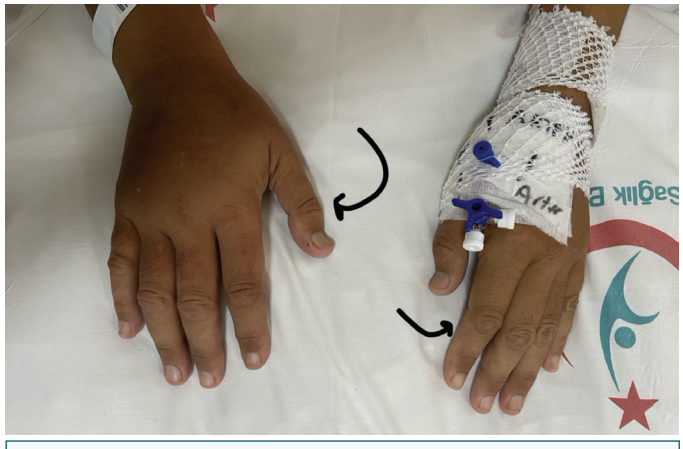

Figure 5. The patients fingers show deformities

DISCUSSION

SS is a syndrome that develops because of inadequately treated SHPT in the early stages of chronic kidney disease (CKD). Studies also suggest an association between the pathophysiology of SS and genetic mutations. Missense mutations in exons 1, 4, 5, 7,10 and 13 of the *GNAS1* gene are the most common mutations associated with SS. In addition, cytogenetic chromosomal abnormalities and calcium-sensing receptor mutations have been described.[5] Abnormal bone metabolism in these patients leads to lytic non-neoplastic bone lesions known as brown tumors, deformities of the mandible and maxilla, irregularly spaced teeth, hypertrophic lips, short stature, and thin upper and lower extremities, all of which present as distinct phenotypic features. Brown tumors frequently occur in the metaphysis of the long bones, pelvis, maxillae, and ribs; in our patient, they were prominently present in the bilateral ribs. The facial deformity observed in our patient is compatible with the phenotypic findings of other cases reported in the literature.[6]

Anemia in patients with CKD frequently occurs due to increased SHPT and leads to direct toxic effects on erythropoietin synthesis and erythropoietin progenitors in the bone marrow. However, bone marrow fibrosis and pancytopenia are much rarer conditions.[7] Although hyperparathyroidism is accepted as a responsible factor in the pathophysiology of SS, the association between SS and bone marrow fibrosis has not been reported in the literature, which makes our case the first

Table 1. Biochemical parameters

Parathyroid	277 ng/L
Alkaline phosphatase	116 U/L
Calsiyum	8.18 mg/dL
Phosphor	2.07 mg/dL
Hemoglobin	8.8 g/dL
Hematocrit	19.8
Platelet	61 mm^3
White blood cell	1.69 mm^3

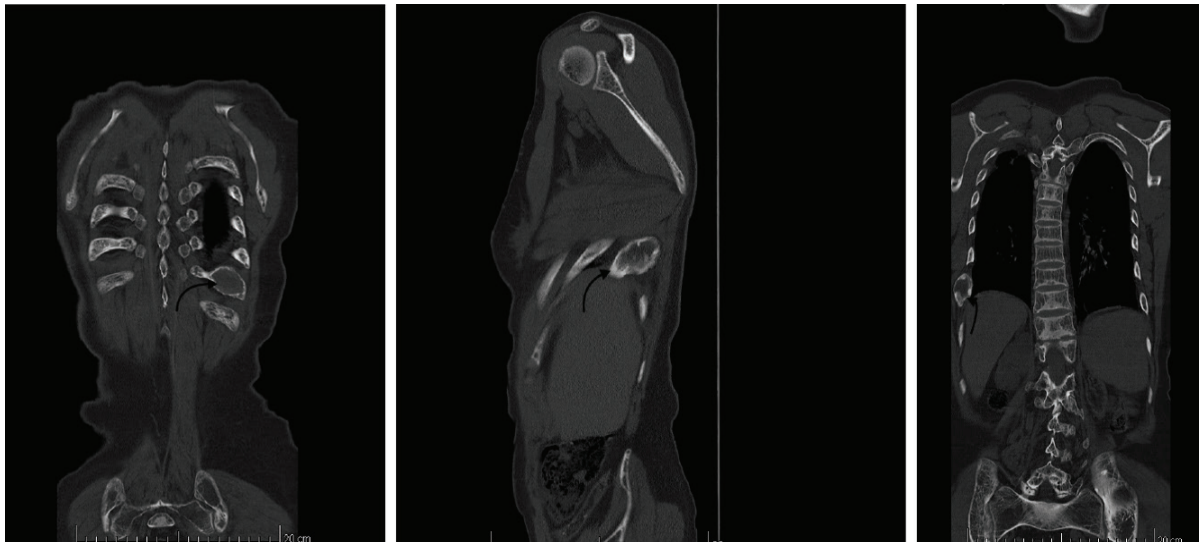

Figure 6. CT scan of the patient reveals an expansive sclerotic lesion with a width of 44 mm and a thickness of 20 mm at the posterolateral aspect of the right 9th rib

CT: Computed tomography

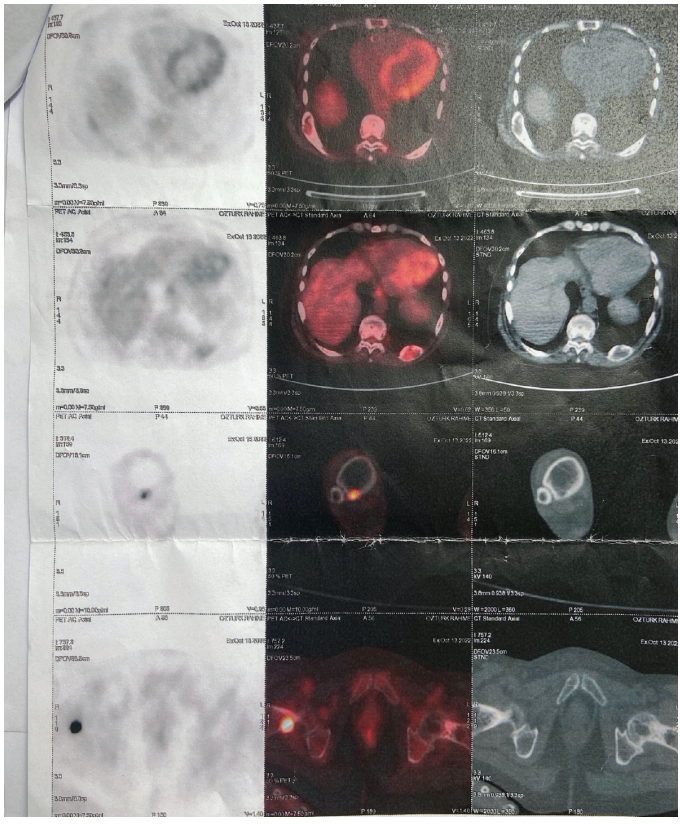

Figure 7. The patient was found to have a lesion in the intramedullary area with mild FDG uptake, and based on the trucut biopsy of lytic bone lesions, the lesions present in the left 10th and right 9th ribs appear to be consistent with brown tumors

FDG: Fluorodeoxyglucose

report of such an association. The high prevalence and early onset of CAD in patients with CKD have been associated with a combination of systemic inflammation, oxidative stress, hypertension, vascular calcification, and disturbances in bone metabolism.[6]

Our patient did not have risk factors such as hypertension, diabetes, smoking, or a positive family history of anemia. In patients with end-stage renal disease, SHPT accelerates vascular calcification and subclinical atherosclerosis in addition to renal osteodystrophy.[8] Although our patient did not have traditional risk factors, the onset of CAD at an early age raises the question of whether hyperparathyroidism, which is an important factor in the etiology of this syndrome, is the primary contributing factor. Our patient's coronary lesion was non-calcific lesion. The reason why the lesion does not appear calcific in our patient coronary angiography may be that the patient is a premenopausal female patient at a relatively young age. It has been stated that vascular inflammation may be less in women than in male patients in CKD patients[9], but if we had the opportunity to evaluate the coronary lesion under intravascular ultrasound images, we could clarify the characteristic findings of the lesion. SHPT can lead to abnormal functions of various organs, such as ectopic calcification of blood vessels and tissues and pathological fractures, which increase the disability rate and the incidence of cardiovascular events.[10] The main treatment of SS involves lowering serum phosphorus levels; therefore, treatment modalities such as the use of phosphorous binders and dialysis may be used. Vitamin D and calcium replacement or parathyroid surgery may be used.[10]

CONCLUSION

SS is a rare complication observed in patients with CKD. Our patient contributed to the literature with his clinical history, extensive systemic involvement, and genetic analysis of SS. In particular, in young patients with CKD, the risk of SS, CAD, and bone marrow fibrosis due to hyperparathyroidism may increase. It is crucial to raise awareness for the regular control and follow-up of such cases. Increased vigilance and awareness can significantly impact prognosis, leading to early diagnosis and appropriate treatment options.

Ethics

Informed Consent: Informed consent of the patient was obtained.

Authorship Contributions

Surgical and Medical Practices: N.E.D., M.U., Concept: İ.Y., N.E.D., M.U., Design: İ.Y., Data Collection or Processing: İ.Y., Analysis or Interpretation: İ.Y., N.E.D., M.U., Literature Search: İ.Y., N.E.D., M.U., Writing: İ.Y., N.E.D., M.U.

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

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