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Comparison of the Effects of Paricalcitol and Calcitriol on Vascular Calcification in Patients Undergoing Chronic Hemodialysis

Kronik Hemodiyaliz Hastalarında Parikalsitol ve Kalsitriolün Vasküler Kalsifikasyon Üzerine Etkilerinin Karşılaştırılması

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ABSTRACT

Introduction: Secondary hyperparathyroidism is considered an unconventional risk factor of vascular calcification in hemodialysis patients (HPs). An important factor of vascular calcification is vitamin D receptor activator used in the treatment of secondary hyperparathyroidism. This study aimed to investigate the change in pulse wave velocity (PWV) and fibroblast growth factor-23 (FGF-23), Klotho, and 25-hydroxyvitamin D [25(OH)D] levels as a result of 1-year treatment with paricalcitol or calcitriol among patients undergoing chronic dialysis.

Methods: Eighty HPs were included in the study, and PWV measurements were obtained at the beginning and after 1 year of treatment. Serum Klotho and 25(OH)D levels were evaluated at the end of 1-year treatment with paricalcitol or calcitriol.

Results: At the end of 1 year, FGF-23 levels in the paricalcitol group were significantly lower than those in the calcitriol group. Klotho and 25(OH)D levels were significantly higher in the paricalcitol group. The PWV at the beginning of the study was statistically similar between the two groups; in contrast, PWV at 1 year was significantly lower in the paricalcitol group than in the calcitriol group ($p=0.002$). When the PWV change was considered as the dependent variable, the most powerful determinant in multiple regression analysis was the FGF-23 level.

Conclusion: In HPs, paricalcitol has a protective effect against vascular calcification compared with calcitriol treatment, owing to its positive effects on both parathyroid hormone and calcium-phosphorus balance. Therefore, paricalcitol should be the first choice in the treatment of secondary hyperparathyroidism.

Keywords: Paricalcitol, calcitriol, vascular calcification, pulse wave velocity, FGF-23

ÖZ

Amaç: Sekonder hiperparatiroidizm, hemodiyaliz hastalarında (HH) vasküler kalsifikasyon gelişiminde geleneksel olmayan bir risk faktörü olarak kabul edilir. Vasküler kalsifikasyon üzerinde etkili olan önemli bir faktör, sekonder hiperparatiroidizmin tedavisinde kullanılan D vitamini reseptör aktivatörleridir. Bu çalışmada, kronik diyaliz hastalarında 1 yıllık parikalsitol veya kalsitriol tedavileri sonucunda nabız dalga hızındaki (NDH) değişimi ve fibroblast büyüme faktörü-23 (FGF-23), Klotho ve 25 hidroksivitamin D [25(OH)D] düzeylerini araştırmayı amaçladık.

Yöntemler: Seksen HH çalışmaya dahil edildi ve tedavinin başlangıcında ve bir yıl sonra PWV ölçümleri yapıldı. Parikalsitol veya kalsitriol ile bir yıllık tedavinin sonunda serum FGF-23, Klotho ve 25(OH)D düzeyleri değerlendirildi.

Bulgular: Parikalsitol grubundaki FGF-23 düzeyleri, bir yıl sonunda kalsitriol grubuna göre istatistiksel olarak anlamlı derecede düşüktü; Klotho ve 25(OH)D düzeyleri istatistiksel olarak anlamlı derecede yüksek bulundu. Çalışmanın başındaki NDH iki grup arasında istatistiksel olarak benzerdi; bir yılın sonundaki NDH değeri parikalsitol grubunda kalsitriol grubuna göre istatistiksel olarak anlamlı derecede yavaştı ($p=0,002$). NDH değişimi bağımlı değişken olarak alındığında çoklu regresyon analizinde en güçlü belirleyicinin FGF-23 düzeyleri olduğu bulundu.

Sonuç: HH'lerde kullanılan parikalsitol tedavisi, hem paratiroid hormonu hem de kalsiyum-fosfor dengesi üzerindeki olumlu etkileri nedeniyle kalsitriol tedavisine göre vasküler kalsifikasyondan koruyucu etkileri vardır. Bu nedenle, sekonder hiperparatiroidi tedavisinde parikalsitol ilk tercih olmalıdır.

Anahtar Kelimeler: Parikalsitol, kalsitriol, vasküler kalsifikasyon, nabız dalga hızı, FGF-23



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Introduction

The most important cause of cardiovascular mortality in both the general population and hemodialysis patients (HPs) is calcification occurring in the vessels. Uremia-related factors might play an important role in the development of vascular calcification in HPs. Secondary hyperparathyroidism is considered an unconventional risk factor of vascular calcification and is associated with increased mortality for patients in the predialysis stage and undergoing maintenance hemodialysis (MHD) (1).

All processes in the development of vascular calcification mainly involve systemic/local activator and inhibitory factors. In addition to parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D [1,25(OH)₂D₃], which play a role in phosphorus metabolism, fibroblast growth factor-23 (FGF-23) and Klotho have been identified as two important factors. These two factors, which plays an important role in phosphorus and vitamin D regulation, have been shown to be associated with vascular calcification including atherosclerosis and soft tissue calcification (2,3). Currently, pulse wave velocity (PWV) measurement is a simple, non-invasive, reliable, and reproducible method for measuring arterial stiffness. PWV is associated with increased mortality in populations with and without kidney disease (4). In addition, PWV has been associated with total calcification scores as measured using electron-beam computed tomography (5).

An important factor affecting vascular calcification is vitamin D receptor activators used in the treatment of secondary hyperparathyroidism in HPs. In this study, we aimed to investigate the change in PWV as well as FGF-23, Klotho, and 25-hydroxyvitamin D [25(OH)D] levels following 1-year treatment with paricalcitol or calcitriol among patients undergoing chronic dialysis.

Methods

This single-center randomized study was conducted at a university teaching hospital. After approval of the study protocol by Başkent University Faculty of Medicine Local Ethics Committee (approval number: KA12/83, date: 12.05.2012), 300 patients undergoing MHD were evaluated, of which 80 met the inclusion criteria. Written informed consent was obtained from all participants. The inclusion criteria was as follows: Patients receiving dialysis treatment for chronic renal failure since at least 1 year, for 4 hours 3 times per week at our hemodialysis unit and those with PTH levels 300-1000 pg/mL, corrected Ca level of 8.5-9.5 mg/dL, phosphorus level ≤5.5 mg/dL, calcium-phosphorus product (CaxP) <55, and albumin ≥3 g/dL. The exclusion criteria were as follows: Kt/V <1.4, chronic inflammatory disease, malignancy, chronic liver disease, a change in vitamin D receptor activator treatment during follow-up, receiving calcimimetic therapy or addition of this therapy during follow-up, hospitalization during follow-up, a diagnosis of peripheral arterial disease or patients who underwent stenting/operation for this diagnosis, allergy to paricalcitol or calcitriol, pregnancy or breastfeeding, history of parathyroidectomy, mean hemoglobin <10.5 g/dL, doxercalciferol treatment or unresponsiveness to erythropoietin treatment, severe cardiac arrhythmia, uncontrolled hypertension, and use of warfarin.

The demographic data were extract from patient files, and the results of tests that were performed monthly (phosphorus, calcium, albumin,

sodium, potassium alanine aminotransferase, and complete blood count) and every 3 months [PTH and alkaline phosphatase (ALP)] were extracted for a year. Data on phosphorus binders (calcium acetate and/or sevelamer by calculating the amount of contained elemental calcium) and vitamin D receptor activators (paricalcitol or calcitriol) that were used monthly, were recorded for 1 year.

At the end of the first year, blood samples were obtained from all patients to evaluate FGF-23, Klotho, and 25(OH)D levels and were stored at -80 °C. Serum FGF-23 and Klotho levels were measured using enzyme-linked immunosorbent assay using Uscn Life Science Inc. kits (Wuhan, P.R. China). The reference range for FGF-23 was 15.6-1000 pg/mL. Intra and inter-assay variations were <10% and <12%, respectively. The reference range for Klotho was 0.156-10 ng/mL, and the intra and inter-assay variations were <10% and <12%, respectively.

PWV was measured at the beginning of the study and at the first year. A SphygmoCor (AtCor Medical Instruments) tonometry device was used for PWV measurements using the method reported by Kelly et al. (6).

Statistical Analysis

The data were analyzed using the SPSS for Windows 21.0 program, and study results are reported as means ± standard deviations and percentages. Between the two groups, Student's t-test was used for comparing quantitative variables when the data were normally distributed, and Mann-Whitney U test was used for non-parametric cases. Group comparisons for categorical variables were analyzed using crosstab statistics, for which the chi-square test was used. The Fisher's exact test was used for 2x2 tables that did not meet the required condition. Kruskal-Wallis variance analysis was used for more than two independent group comparisons for quantitative variables, and the Mann-Whitney U test was used for subgroup comparisons. Bonferroni correction was applied to the alpha significance level, and p<0.017 was considered statistically significant for these comparisons. Relationships among quantitative variables were evaluated using Spearman's correlation analysis. The statistical significance level was accepted at p<0.05.

Results

Eighty patients undergoing MHD were included in the study and were categorized into two groups according to the vitamin D treatment they received: paricalcitol (n=40; mean age: 51.6±12.6 years; female/male: 14/26) and calcitriol groups (n=40; mean age: 53.9±16.8 years; female/male: 16/24). Age, sex, hemodialysis duration, etiologies of chronic kidney disease, and Charlson Comorbidity Index values were statistically similar in both the groups (p>0.05 for all). The descriptive characteristics of all enrolled patients are shown in Table 1.

Patients were followed up for 1 year without any changes in vitamin D treatment. Results revealed no differences between baseline PTH, calcium, phosphorus, CaxP, and ALP values in both the groups (p>0.05 for all). The increase in PTH from baseline to 1 year was not significant in the paricalcitol group (from 573.4±180.7 pg/mL to 598.5±191.3 pg/mL; p=0.461). In the calcitriol group, the increase in PTH from baseline (515.2±176.6 pg/mL) to 1 year (681.9±371.4 pg/mL; p=0.002)

was statistically significant. In addition, calcium values were similar in both the groups; however, phosphorus and CaxP values were lower in the paricalcitol group than in the calcitriol group at every 3-month

assessment ($p < 0.05$ for all) (Table 2). There was no statistically significant difference between ALP values in both the groups ($p > 0.05$) (Table 2).

Table 1. Demographic characteristics of patients

Mean \pm SD, median (IR)	Paricalcitol group (n=40)	Calcitriol group (n=40)	p-value
Age (years)	51.6 \pm 12.6	53.9 \pm 16.8	0.492
Sex (female, %)	14 (35)	16 (40)	0.644
Hemodialysis duration (years)	11 (4-12)	6 (6-9)	0.626
Etiology of CKD (n, %)			
DM	7 (17.5)	10 (25)	0.881
HT	9 (22.5)	11 (2.5)	
GN	4 (10)	3 (7.5)	
ADPKD	4 (10)	2 (5)	
Other	10 (25)	8 (20)	
Unknown	6 (15)	6 (15)	
CCI (score)	5.2 \pm 2.4	4.9 \pm 2.9	0.648

CKD: Chronic kidney disease, DM: diabetes mellitus, GN: glomerulonephritis, HT: hypertension, ADPKD: autosomal dominant polycystic kidney disease, CCI: Charlson Comorbidity Index, IR: interquartile range, SD: Standard deviation

Table 2. One-year parathyroid hormone, calcium, phosphorus, calcium-phosphorus product, and alkaline phosphatase levels in both groups

Mean \pm SD, median (IR)	Paricalcitol group (n=40)	Calcitriol group (n=40)	p-value
Basal PTH (pg/mL)	573.4 \pm 180.7	515.2 \pm 176.6	0.148
PTH at 4 th month (pg/mL)	577.5 \pm 247.1	484.3 \pm 290.3	0.126
PTH at 7 th month (pg/mL)	591.7 \pm 240.7	581.4 \pm 293.4	0.863
PTH at 10 th month (pg/mL)	595.1 \pm 247.0	632.5 \pm 293.1	0.640
PTH at 13 th month (pg/mL)	598.5 \pm 191.3	681.9 \pm 371.4	0.210
% PTH change	+10.3%	+35.0%	0.085
Basal Ca (mg/dL)	8.6 \pm 0.7	8.4 \pm 0.7	0.261
Basal P (mg/dL)	5.1 \pm 0.9	5.4 \pm 1.2	0.163
Basal CaxP	44.3 \pm 8.3	46.1 \pm 10.2	0.383
Ca at 1 st -3 rd month (mg/dL)	8.7 \pm 0.6	8.6 \pm 0.6	0.248
P at 1 st -3 rd month (mg/dL)	5.1 \pm 0.8	5.9 \pm 0.9	0.001
CaxP at 1 st -3 rd month	44.8 \pm 8.3	50.6 \pm 8.4	0.003
Ca at 4-6 th month (mg/dL)	8.5 \pm 0.7	8.8 \pm 0.5	0.039
P at 4-6 th month (mg/dL)	5.4 \pm 1.1	5.9 \pm 1.1	0.068
CaxP at 4-6 th month	46.6 \pm 10.2	52.3 \pm 10.4	0.016
Ca at 7-9 th month (mg/dL)	8.6 \pm 0.7	8.9 \pm 0.4	0.052
P at 7-9 th month (mg/dL)	5.4 \pm 1.1	6.0 \pm 1.1	0.004
CaxP at 7-9 th month	46.8 \pm 10.9	54.6 \pm 10.9	0.002
Ca at 9-12 th month (mg/dL)	8.6 \pm 0.6	8.8 \pm 0.5	0.145
P at 9-12 th month (mg/dL)	5.3 \pm 0.9	5.9 \pm 1.1	0.010
CaxP at 9-12 th month	46.6 \pm 9.5	53.2 \pm 11.1	0.006
Basal ALP (U/L)	82 (66.5-112.5)	97.5 (65-149.5)	0.288
ALP at 4 th month (U/L)	98 (77-125.5)	99.5 (77.5-164.5)	0.570
ALP at 7 th month (U/L)	92 (74-137)	101.5 (81-154.5)	0.189
ALP at 10 th month (U/L)	132.5 (96-181.5)	143.5 (97-232)	0.465
Hypercalcemia frequency (months)	0.5 (0-3.5)	0 (0-2)	0.511
Hyperphosphatemia frequency (months)	4.4 \pm 3.4	7.3 \pm 3.8	0.001
Frequency of CaxP >55 (months)	2 (0-4.5)	4 (1-7)	0.036

PTH: Parathyroid hormone, Ca: calcium; P: phosphorus, ALP: alkaline phosphatase, CaxP: calcium-phosphorus product, IR: interquartile range, SD: standard deviation

The frequency of hyperphosphatemia and CaxP being >55 in 1 year were statistically lower in the paricalcitol group than in the calcitriol group ($p < 0.001$ and $p = 0.036$, respectively). In addition, hypercalcemia frequency was significantly different between the groups ($p = 0.511$) (Table 2). Examination of the elemental calcium load in patients for 1 year revealed that the paricalcitol group received less calcium than the calcitriol group, but this difference only reached statistical significance between the 4th and 6th months ($p = 0.022$). There were no statistically significant differences between the sevelamer doses received by both the groups ($p > 0.05$). The doses of vitamin D receptor activator received by the patients over 1 year were statistically significantly higher in the paricalcitol group than in the calcitriol group ($p < 0.05$). The frequency of discontinuation of vitamin D receptor activator treatment due to any reason was statistically significantly lower in the paricalcitol group than in the calcitriol group ($p < 0.001$) (Table 3). The mean systolic and diastolic blood pressures during hemodialysis sessions as well as the rate of angiotensin-converting enzyme inhibitor and angiotensin II receptor antagonist use was statistically similar in the groups ($p > 0.05$).

FGF-23 levels in the paricalcitol group were significantly lower than those in the calcitriol group at 1-year ($p = 0.036$); however, Klotho and 25(OH) D levels were significantly higher ($p = 0.044$ and $p = 0.044$ respectively)

(Table 4). FGF-23 levels had a positive correlation with mean phosphorous ($r = 0.275$; $p = 0.014$) and mean CaxP ($r = 0.278$; $p = 0.013$). In addition, a positive correlation was noted between 25(OH)D and the annual mean dose of vitamin D receptor activator drug ($r = 0.252$; $p = 0.024$).

The PWV at the beginning of the study was statistically similar in the two groups ($p = 0.399$); however, at 1 year, this value was statistically significantly lower in the paricalcitol group than in the calcitriol group ($p = 0.002$) (Table 5). Considering PWV change as the dependent variable, FGF-23 level was found to be the most powerful determinant in multiple regression analysis ($p = 0.004$). When the patients were divided into two groups according to the PWV values at the beginning and end of the study, the demographic and baseline laboratory values of 45 patients with baseline PWV measurements < 7 m/sec and 35 patients with PWV values > 7 m/sec after 1 year were statistically similar ($p > 0.05$ for all) (Table 6). At the end of the first year, the PWV of 36 patients was < 7 m/s and of 44 patients was > 7 m/s, with the annual PWVs being statistically similar in both these groups ($p > 0.05$ for all). At the end of the year, 63.9% of patients with PWV < 7 m/s were receiving paricalcitol, which was statistically significantly higher than the proportion of patients receiving calcitriol (36.1%) ($p < 0.05$) (Table 7).

Table 3. Annual phosphorus binder, vitamin D receptor activator doses, vitamin D/PTH index, and vitamin D skipping times in both groups

Mean \pm SD, median (IR)	Paricalcitol group (n=40)	Calcitriol group (n=40)	p-value
Elemental Ca dose of 1 st -3 rd months (g)	1.8 (0-6.7)	5.3 (0-8.8)	0.120
Elemental Ca dose of 4-6 th months (g)	2.3 (0-7.5)	6.1 (1.8-11.4)	0.022
Elemental Ca dose of 7-9 th months (g)	5.0 \pm 5.2	7.2 \pm 5.3	0.079
Elemental Ca dose of 10-12 th months (g)	4.7 (0-8.8)	7.9 (2.3-12.3)	0.058
Dose of sevelamer 1 st -3 rd months (g)	8.4 (0-24.3)	11.2 (0-23.3)	0.956
Dose of sevelamer 4-6 th months (g)	14 (0-28)	5.6 (0-22.4)	0.383
Dose of sevelamer 7-9 th months (g)	22.4 (0-33.6)	22.4 (0-33.6)	0.933
Dose of sevelamer 10-12 th months (g)	22.4 (0-33.6)	30.8 (0-33.6)	0.353
Dose of vitamin D equivalent 1 st -3 rd month (μ g/week)	5 (4.2-6.7)	2 (1.3-4)	0.001
Dose of vitamin D equivalent 4-6 th month (μ g/week)	5 (3.3-7.5)	2 (0.7-4)	0.003
Dose of vitamin D equivalent 7-9 th month (μ g/week)	5 (1.9-5)	2 (1.3-4)	0.024
Dose of vitamin D equivalent 10-12 th month (μ g/week)	4.2 (2.3-5)	2 (1.7-4)	0.010
Frequency of treatment discontinuation (month)	0 (0-3)	3.5 (2-5.5)	0.001

Ca: Calcium, PTH: parathyroid hormone, IR: interquartile range, SD: standard deviation

Table 4. Protective and accelerator markers of vascular calcification levels of both groups

Mean \pm SD, median (IR)	Paricalcitol group (n=40)	Calcitriol group (n=40)	p-value
FGF-23 (pg/mL)	18.7 (15.6-38.4)	36.4 (16.7-75.6)	0.036
Klotho (ng/mL)	0.9 (0.3-2)	0.3 (0.2-1.1)	0.044
25-hydroxyvitamin D (μ g/L)	25 (20-29)	21 (18-24.5)	0.044

FGF-23: Fibroblast growth factor-23, IR: interquartile range, SD: standard deviation

Table 5. Pulse wave velocity in both groups at baseline (PWV1) and the end of study (PWV2) and 1-year variation

Mean \pm SD, median (IR)	Paricalcitol group (n=40)	Calcitriol group (n=40)	p-value
PWV1 (m/sec)	7.67 \pm 3.01	8.21 \pm 2.64	0.399
PWV2 (m/sec)	7.07 \pm 2.02	8.97 \pm 3.26	0.002
PWV variation (%)	-1.56 \pm 39.6	+18.6 \pm 59.4	0.135

PWV: Pulse wave velocity, IR: interquartile range, SD: standard deviation

Discussion

Secondary hyperparathyroidism caused by chronic renal failure in HPs is considered an unconventional risk factor in the development of vascular calcification and is associated with increased mortality for both predialysis patients and patients undergoing dialysis (1). In our study, baseline PTH values were similar in both the groups, but 1-year PTH values non-significantly increased by 10.3% in the paricalcitol arm and by 35% in the calcitriol arm. Accordingly, paricalcitol treatment might be considered more effective in PTH control.

Phosphorus plays a key role in the pathogenesis of vascular calcification and is associated with its prevalence and progression in HPs. In the general population, phosphorus levels in the upper limit of normal were associated with increased cardiovascular and all-cause mortality (7). In *in vitro* experiments, phosphorus was shown to increase vascular calcification in vascular smooth muscle cells in a dose-dependent manner (8). In our study, we observed that patients in the paricalcitol group achieved significantly better control of phosphorus for a year than patients in the calcitriol ($p < 0.05$). Similarly, there was a close relationship between high serum calcium levels and the development of vascular calcification in patients undergoing MHD (9). Especially

the use of calcium-containing phosphorus binders has been shown to cause vascular calcification by inducing a positive calcium balance (10). Calcium alone can cause vascular calcification *in vitro* (11). In our study, basal serum calcium levels were similar in both the groups, and the tendency to develop hypercalcemia was more frequently observed in the calcitriol group, albeit non-significantly. One aspect of calcium-phosphorus balance is the synergistic effect induced by calcium and phosphorus in the calcification of vascular smooth muscle cells, which is called CaxP (12). In an aortic culture model, increasing the doses of calcium and phosphorus in vascular smooth muscle cells resulted in calcification via a synergistic effect; in addition, calcium was found to be a more potent stimulant than phosphorus (13,14). Similarly, in our study, CaxP value was significantly controlled during the follow-up in the paricalcitol group than in the calcitriol group ($p < 0.005$). Therefore, in the treatment of secondary hyperparathyroidism, we believe that reducing the frequency of hypercalcemia and hyperphosphatemia and maintaining within normal values should be the main focus, rather than PTH suppression. In view of all these findings, it is possible that paricalcitol treatment causes hyperphosphatemia and hypercalcemia less frequently; therefore, it is superior to calcitriol in terms of treatment sustainability.

Table 6. Baseline laboratory values according to baseline PWV (PWV1)

Mean ± SD, median (IR)	PWV1 <7 m/sec (n=37)	PWV1 >7 m/sec (n=43)	p-value
Basal PTH (pg/mL)	558.6±148.4	494.4±168.3	0.074
Basal Ca (mg/dL)	8.6±0.6	8.5±0.4	0.138
Basal P (mg/dL)	5.2±0.9	5.4±1.2	0.563
Basal CaxP	45.9±8.9	44.3±9.8	0.442
Basal ALP (U/L)	96 (73-127)	78 (63-123)	0.065
Basal hemoglobin (g/dL)	11.0±1.4	10.9±1.3	0.757
Basal albumin (g/dL)	3.6±0.3	3.6±0.3	0.593
Basal CRP (mg/L)	6.2 (3.1-15.3)	7.3 (2.7-14.2)	0.930

ALP: Alkaline phosphatase, Ca: calcium, CaxP: calcium-phosphorus product, CRP: C-reactive protein, P: phosphorus, PTH: parathyroid hormone, IR: interquartile range, SD: standard deviation

Table 7. Patients results according to last PWV (PWV2) values (annual average laboratory values, vitamin D receptor activator usage distributions, protective and activator markers of vascular calcification levels)

Mean ± SD, median (IR)	PWV2 <7 m/sec (n=36)	PWV2 >7 m/sec (n=42)	p-value
PTH (pg/mL)	592.6±224.8	573.7±189.1	0.685
Ca (mg/dL)	8.8±0.4	8.7±0.4	0.188
P (mg/dL)	5.6±0.8	5.6±0.9	0.934
CaxP (mg ² /dL ²)	49.8±8.4	49.2±9.2	0.754
ALP (U/L)	111.1 (91.6-177.1)	97.1 (78.3-168.5)	0.095
Hemoglobin (g/dL)	10.9±1.1	10.9±1.1	0.697
Albumin (g/dL)	3.8±0.26	3.7±0.25	0.468
CRP (mg/L)	9.8 (4.0-17.5)	6.4 (3.4-11.8)	0.376
Ratio of patients using paricalcitol (%)	23 (63.9)	17 (38.6)	0.025
Ratio of patients using calcitriol (%)	13 (36.1)	27 (61.4)	
FGF-23 (pg/mL)	23.8 (15.6-54.6)	29.2 (15.6-75.6)	0.816
Klotho (ng/mL)	1.1 (0.3-2.6)	0.4 (0.2-1)	0.044
25-hydroxyvitamin D (µg/L)	24 (18-29.5)	22.5 (19-26)	0.405

ALP: Alkaline phosphatase, Ca: calcium, CRP: C-reactive protein, FGF-23: fibroblast growth factor-23, P: phosphorus, PTH: parathyroid hormone

Studies suggest that the main point for FGF-23 elevation in patients undergoing MHD is the presence of secondary hyperparathyroidism. PTH has been shown to increase FGF-23 expression in *in vivo* and *in vitro* environments (15). In addition, calcium itself directly increases FGF-23 mRNA levels, which consequently increases the serum FGF-23 level independently from serum phosphorus and vitamin D levels (16). Klotho, which is known as the cofactor of FGF-23, is significantly reduced in HPs (17). Klotho deficiency can aggravate impaired mineral metabolism in patients undergoing MHD and increase non-renal complications (18). Reportedly, Klotho deficiency is associated with secondary hyperparathyroidism, cardiac hypertrophy, and vascular calcification and mortality (19,20). In our study, consistent with that in the literature, FGF-23 levels were significantly lower and Klotho levels were significantly higher in the paricalcitol group than in the calcitriol group ($p < 0.036$ and $p < 0.044$, respectively). In addition, FGF-23 levels correlated positively with mean phosphorous and mean CaxP.

In HPs, the synthesis of 1,25(OH)₂D₃ decreases owing to chronic kidney failure. The presence of vitamin D receptors in vascular smooth muscle cells may explain the role of vitamin D in vascular calcification pathogenesis (21). In HPs, decreased vitamin D has been associated with arterial stiffness (22). Lee et al. (23) showed that low vitamin 25(OH)D levels correlated with vascular calcification in both predialysis patients and in those undergoing dialysis. In addition, although the patients were receiving active vitamin D treatment, a deficiency of vitamin D was noted in both the groups; however, 25(OH)D levels in the paricalcitol group were significantly higher than those in the calcitriol group ($p < 0.044$). In addition, there was a positive correlation between 25(OH)D levels and the average daily dose of vitamin D ($r = 0.252$; $p = 0.024$).

In HPs, the two most commonly used vitamin D receptor activators are calcitriol and paricalcitol that maintain PTH within the recommended limits for the treatment of secondary hyperparathyroidism. At therapeutic doses, both drugs have hypercalcemic and hyperphosphatemic effects, but these effects are known to be less with paricalcitol than with calcitriol (24). Although vitamin D receptor activation, particularly at high doses, has been shown to cause vascular calcification, in addition to the anti-calcification effects of active vitamin D therapy, drug selection may have a role in this opposite effect. Mizobuchi et al. (25) showed that calcitriol and doxercalciferol caused calcification in uremic rats, whereas similar doses of paricalcitol did not cause vascular calcification. This effect of paricalcitol has been linked to its lower hypercalcemia-inducing and hyperphosphatemia-inducing properties than those of calcitriol. A study comparing patients receiving paricalcitol and calcitriol suggested that paricalcitol offered life advantage over the later (26). All these studies revealed that vitamin D receptor activators had effects on vascular calcification via different mechanisms. The fact that the effects on vascular calcification are different is explained by the stimulation of the same vitamin D receptor with different activators, triggering different events at the cellular level.

PWV measurement the most commonly used non-invasive method for determining arterial stiffness and thus vascular calcification (27). Carotid-femoral pulse wave measurement, the method used in our study for central arterial stiffness measurement, is the gold standard

(28). In our study, PWV tended to decrease at 1 year in the paricalcitol group and tended to increase in the calcitriol group. In addition, although the initial PWV in both the groups was similar, the PWV at 1 year in the paricalcitol group was statistically significantly lower than that in the calcitriol group ($p = 0.002$). The absence of an annual increase in PWV in the paricalcitol group may be attributed to the sustainability of treatment and less frequent observation of hyperphosphatemia and CaxP increase in this group, as well as higher levels of calcification inhibitors. Likewise, the fact that FGF-23 level was an independent variable of annual PWV change in our study, and that this value was lower than the calcitriol group, suggests that paricalcitol has positive effects on PWV change.

Study Limitations

As a limitation of our study, the number of patients enrolled was slightly low; however, this type of follow-up study, finding eligible patients is difficult. In addition, the findings could have been more informative if FGF-23 and Klotho levels were also studied at the beginning of the study.

Conclusion

We believe that paricalcitol use in HPs has greater protective effects against vascular calcification than calcitriol use owing to its positive effects on both the PTH and calcium-phosphorus balance as well as calcification markers. Therefore, we believe that paricalcitol should be the first choice for the treatment of secondary hyperparathyroidism.

Ethics Committee Approval: This study was approved by the Başkent University Faculty of Medicine Ethical Committee (approval number: KA12/83, date: 12.05.2012).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - Z.B.; Design - S.K., Z.B., S.S.; Data Collection or Processing - Z.B.; Analysis or Interpretation - S.K., Z.B., S.S.; Literature Search - S.K., Z.B.; Writing - S.K., Z.B.

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Radiological Assessment of Dysbaric Osteonecrosis as a Part of Fitness-to-dive Examinations

Dalışa Uygunluk Muayenelerinin Bir Parçası Olarak Disbarik Osteonekroz Değerlendirmeleri

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ABSTRACT

Introduction: It is important for professional divers and candidates to be medically and physically fit to undertake their underwater work safely. This study aimed to review the screening of dysbaric osteonecrosis (DON) using conventional radiography, which has been stated in the legislation as part of fitness-to-dive examinations, in terms of international standards and scientific facts.

Methods: Data on clinical, demographic, laboratory, and radiological evaluations were retrospectively collected for 46 professional divers or candidates who were referred for fitness-to-dive examinations between 2018 and 2020. The approach of the Professional Divers Regulation to DON was compared with that of the Military Health Regulation for the Turkish Armed Forces and the Turkish Underwater Sports Federation Equipped Diving Instruction, as well as that of the legislation of United Kingdom and European Diving Technology Committee standards.

Results: Forty-six divers (males: n=45; female: n=1) were enrolled in the study. Their median age was 34 (range: 18-63) years, and the mean body mass index was 25.42 kg/m². The prevalence of DON was 2.17% in the study group. Compared with the national and international legislations, Professional Diver Regulation was the only regulation that mandated radiological evaluation for DON in both the initial and periodic fitness-to-dive examinations.

Conclusion: One of the aims of regulations is that medical fitness-to-dive standards should be evidence-based and compatible with contemporaneous clinical practice. By the 2000s, attitudes toward DON, fitness to continue diving, and compressed air work have changed in Europe. In light of the findings of the present study, we believe that it is time for a critical reappraisal of the Professional Divers Regulation.

Keywords: Dysbaric osteonecrosis, fitness-to-dive examinations, radiology

ÖZ

Amaç: Profesyonel dalgıç ve dalgıç adaylarının sualtı çalışmalarını güvenli bir şekilde gerçekleştirebilmeleri için dalışa, tıbbi, mental ve fiziksel açıdan uygun olmaları önemlidir. Bu çalışmada, dalışa uygunluk muayenelerinin bir parçası olarak mevzuatta belirlenmiş haliyle radyolojik disbarik osteonekroz (DON) değerlendirmelerinin uluslararası standartlar ve bilimsel gerçekler açısından gözden geçirilmesi amaçlanmıştır.

Yöntemler: 2018-2020 yılları arasında dalışa uygunluk muayeneleri için başvuran 46 profesyonel dalgıç veya adayının klinik, demografik, laboratuvar ve radyolojik değerlendirmeleri retrospektif olarak incelendi. Profesyonel Sualtıadamları Yönetmeliği'nin DON yaklaşımı, Türk Silahlı Kuvvetleri Sağlık Yeteneği Yönetmeliği, Türkiye Sualtı Sporları Federasyonu Donanımlı Dalış Talimatı, Birleşik Krallık Mevzuatı ve Avrupa Dalış Teknolojisi Komitesi standartları ile karşılaştırıldı.

Bulgular: Çalışma süresi boyunca kırk altı dalgıç (erkek: n=45; kadın: n=1) başvurmuştu. Ortanca yaş 34 (18-63 aralığında) ve ortalama vücut kitle indeksi 25,42 kg/m² idi. Çalışma grubumuzda DON prevalansı %2,17 tespit edildi. Profesyonel Sualtıadamları Yönetmeliği, bu çalışma kapsamında incelenen ulusal ve uluslararası mevzuatla karşılaştırıldığında hem başlangıç hem de periyodik dalışa uygunluk muayenelerinde DON açısından radyolojik değerlendirmeyi zorunlu kılan tek yönetmeliktir.

Sonuç: Yönetmeliklerin düzenleme amaçlarından biri de, dalış için tıbbi uygunluk standartlarının kanıta dayalı ve çağdaş klinik uygulamalarla uyumlu olmasıdır. 2000'li yıllarla birlikte, DON, dalışa ve basınçlı hava çalışmalarına devam edebilme kriterlerine yönelik bakış açısı ve tutumlar tüm Avrupa'da değişmiştir. Bu çalışmadan elde ettiğimiz veriler ışığında, Profesyonel Sualtıadamları Yönetmeliği'nin eleştirel bir şekilde yeniden değerlendirme zamanının geldiğini düşünüyoruz.

Anahtar Kelimeler: Disbarik osteonekroz, dalışa uygunluk muayeneleri, radyoloji



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Introduction

It is important for professional divers and candidates to be medically and physically fit to participate in the underwater work safely. Being unfit to dive is a risk to the divers themselves as well as to other members involved in conducting the activity underwater. Health and safety considerations in professional diving are specified by the regulations in Turkey, as in all other countries globally. The regulations aim to enhance the quality and reduce any unnecessary variability of fitness-to-dive assessments, thereby establish national standards. International standardization of fitness-to-dive examinations is an issue declared and studied by the European Diving Technology Committee (EDTC), since 1999 (1). In our country, these examinations are conducted in accordance with the Professional Divers Regulation issued in 1997 by the Ministry of Transportation, Maritime Affairs and Communication. Aspects that are to be considered while evaluating the musculoskeletal system in the aforementioned regulation have been stated as follows: "All extremities of professional divers should be in integrity and extremity movements within normal limits. It is mandatory to perform radiological assessments in terms of dysbaric osteonecrosis (DON) during the initial and periodical examinations" (2). X-rays of hips, shoulders, and knees have been used as a standard for these mandatory radiological assessments since the introduction of the regulation. Furthermore, these radiological examinations are repeated biennially since the interval of medical assessments is determined as two years.

In this study, we aimed to review DON screening performed using X-rays as determined in the legislation, as part of the fitness-to-dive examinations in our country, from the point of view of international standards and scientific facts.

Methods

This was a retrospective cross-sectional study. After approval from the Clinical Research Ethics Committee of Çanakkale Onsekiz Mart University (approval number: 2020/12, date: 09.23.2020), data extraction was performed by retrospectively assessing the medical records of all professional divers and candidates who were referred for the fitness-to-dive examination to Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Underwater and Hyperbaric Medicine, between June 2018, and September 2020. Informed consent was not obtained owing to the retrospective nature of the study. The following data were evaluated: Demographic characteristics, body mass index (BMI), past and current diseases, medications, steroid use, tobacco use, alcohol intake, diving experience (years of diving and total diving time), maximum diving depth, history of omitted decompression and decompression sickness (DCS), blood profile (complete blood counts, erythrocyte sedimentation rate, serum cholesterol, triglyceride, aspartate transaminase, alanine transaminase, urea, creatinine, and fasting blood glucose), urine analysis, radiologic evaluations [X-rays of hips, shoulders, and knees and (if performed) magnetic resonance imaging (MRI)].

The approach of the national legislation to DON, as part of fitness-to-dive examinations for professional divers (2), was compared with the Military Health Regulation for the Turkish Armed Forces (3) and the Turkish Underwater Sports Federation Equipped Diving Instruction (4),

as well as the legislation of Health and Safety Executive (HSE) in UK (5) and EDTC standards (1).

Statistical Analysis

The IBM SPSS Statistics for Windows, Version 19.0, (IBM Corp, Chicago, IL, USA) was used to analyze data. Quantitative variables were expressed as means \pm standard deviations, whereas categorical variables were expressed as numbers and percentages.

Results

In total, 46 individuals (males: n=45, female: n=1) were referred during the study period. The median age of participants was 34 (range: 18-63) years, and their mean BMI was 25.42 kg/m². The mean diving time was 2736 hours, and besides participating in scuba and using hookah or surface supplied diving systems, 28 divers (60.8%) were also performing freediving. The breathing mixture used was air; however, four individuals had also performed dives using trimix and nitrox. The average of maximum dive depth was 39.4 m (range: 15-80) seawater, and the average bottom time was 11.6 min. Three divers had a history of musculoskeletal DCS, of which two reported the disease twice. Twenty-two divers (47.8%) had been screened for DON once or more than once during previous fitness-to-dive examinations via X-ray imaging of the hips, shoulders, and knees. Biochemical examinations revealed high levels of serum/plasma cholesterol and/or triglycerides in 18 (39.1%) divers. Oral glucose tolerance test revealed that four divers had impaired fasting glucose (fasting plasma glucose values between 100 to 125 mg/dL); for these, a change in diet was recommended. After 6 months, fasting glucose levels measured for these divers were within the normal range. In addition, 52.1% divers reported that they did not consume alcohol. Two divers who reported using alcohol had a habit of regular alcohol consumption. Only one diver had a history of short-term, high-dose steroid use. The demographic, clinical, and laboratory characteristics of divers are summarized in Table 1.

Bilateral anteroposterior radiographs of the shoulders, hips, and knee joints revealed DON lesions at the humeral head and neck in only one of the 46 divers. The diver had a history of acute DCS and 40 years of diving career, when factors associated with the occurrence of lesions were evaluated, including age, diving experience, and physical factors (6). The prevalence of DON was 2.17% in our study.

When the approach of Professional Divers Regulation for medical surveillance of DON (2) was compared with that of other regulations, the following results were determined. 1) According to the Military Health Regulation for the Turkish Armed Forces, Item 59 (3); "in divers and frogmen, screening for DON disease, which can develop related to diving, is performed at the discretion of the underwater and hyperbaric medicine specialist" (3). 2) TSSF Equipped Diving Instruction, Sixth Section, Health Conditions, Item 20e states that "since DON is an occupational disease, it is recommended that a skeletal survey (X-ray or MRI) be performed at the first examinations for the detection of DON because these images will provide a baseline for future reference; however, it is not mandatory. Screening for DON is not mandatory in cases where there are no complaints or signs of physical examination in control examinations. However, according to the results of the physical

examination, additional examinations for diseases of the skeletal system may be requested at the discretion of the underwater and hyperbaric medicine specialist" (4). 3) According to the Medical Examination and Assessment of Professional Divers (MA1) that meets HSE standards and guidelines for the MA1 in UK, "the diver must have the appropriate degree of mobility, strength and dexterity for the diving activities and work undertaken. Musculoskeletal problems require a careful and individual risk assessment. Routine long-bone X-rays are not required for surveillance of divers. Long-bone radiography and/or MRI is indicated

in cases of suspected DON" (5). 4) The recommendations of EDTC — in which our country is represented in the medical category — on the DON are as follows: "As a standard, screening is needed only for divers with more than 20 hours per week underwater or diving of over 30 m. Bone X-rays were standard for many years, but they will be replaced in the future by MRI as this technique allows screening without the use of ionizing radiation, which makes it ethically more acceptable (in spite of the increased costs)." "... all new entrants on graduating should be considered for baseline long-bone imaging." "These records must be stored longer than the lifetime career of the diver." "Those found to have bone necrosis are not necessarily unfit for diving. If the lesion is in the shaft of a bone (B lesion), the diver is not at risk from joint collapse and the condition has no effect on underwater safety. A juxta-articular (JA) lesion is more serious but, again, is unlikely to affect underwater safety and so medical disqualification cannot be for that reason alone. The strong advice to give up diving is based on the need for the individual to avoid excessive weight bearing at that joint" (1).

Table 1. Summary of demographic, clinical, and laboratory characteristics of 46 divers

Age, years (mean ± SD)	34.4±10.8
Sex, n (%)	
Male	45 (97.8%)
Female	1 (2.1%)
Body mass index, kg/m ² (mean ± SD)	25.4±3.0
Diving experience, years (mean ± SD)	11.4±10.6
Total diving time, hours (mean ± SD)	2736.6±4420
≤100	11 (23.9%)
100-1000	14 (30.4%)
>1000-5000	15 (32.6%)
≥5000	6 (13.0%)
History of musculoskeletal DCS, n (%)	3 (6.5%)
Maximum diving depth, m seawater (mean ± SD)	39.4±22.4
Type of diving activity, n (%)	
Professional inshore/offshore diver	21 (45.6%)
Sea harvesting diver	21 (45.6%)
Directorate general of coastal safety diver	2 (4.3%)
Fish farm diver	2 (4.3%)
Smoking	27 (58.6%)
Alcohol consumption	22 (47.8%)
Biochemical parameters	
Fasting blood glucose, mg/dL (mean ± SD)	95.1±9.3
Erythrocyte sedimentation rate, mm/h (mean ± SD)	6.8±4.2
Total cholesterol, mg/dL (mean ± SD)	183.1±48.0
Triglyceride level, mg/dL, (mean ± SD)	148.6±180.6
Urea, mg/dL (mean ± SD)	27.5±7.3
Creatinine, mg/dL (mean ± SD)	0.9±0.1
Alanine transaminase, U/L (mean ± SD)	23.4±9.3
Aspartate transaminase, U/L (mean ± SD)	28.1±19.2
White blood cell count, 10 ⁹ /L (mean ± SD)	7.2±1.8
Hemoglobin, gr/dL (mean ± SD)	15.6±1.1
Hematocrit, % (mean ± SD)	44.7±2.9
History of previously been performed DON screening using X-ray, n (%)	n
Yes	22 (47.8%)
Once	6 (13.0%)
More than once	16 (34.7%)
No	24 (52.1%)
DCS: Decompression sickness, DON: dysbaric osteonecrosis, SD: standard deviation	

Discussion

DON is recognized as an important occupational health hazard in individuals who regularly exposed to hyperbaric environments in their professions, such as commercial divers and compressed air workers, despite adherence to recognized decompression procedures. Thus, it is a condition that deserves compensation in some way; however, it is not, on its own, an outcome of employer negligence. It is more common in those with a record of DCS treatment and can occur after a single exposure to pressure alone. Although omitted decompression after prolonged hyperbaric exposure is the major etiologic factor, the precise pathogenesis of DON is still unclear (1,7). In this context, the main findings of this study were as follows: 1) overall, the incidence of DON was 2.17% in our study which included 46 divers with different professional goals; 2) the Professional Diver Regulation (2) is the only regulation that mandates radiological evaluation for DON in both initial and periodic fitness-to-dive examinations when compared with the national and international legislations reviewed in this study; 3) according to the aforementioned regulation, the presence of DON lesions alone, whether localized in JA or head, neck, and shaft (HNS), cannot be a reason for medical disqualification; and 4) although conventional radiography has been used as the standard for many years, MRI is now the preferred initial screening technique to detect abnormalities in the long bone, which could be indicative of DON as with other aseptic necrosis of bone.

Imaging is crucial for diagnosing DON as the ischemic episode is painless, or because deep throbbing joint pain with or without passive and active range of motion occur weeks, months, or even years following exposure (8). Conventional radiography is the simplest, most readily available, and generally accepted means of confirming lesion diagnosis. A radiological description of the lesions and their classification have been provided by Davidson (9). According to this classification, JA lesions are more important than HNS lesions, because JA lesions, which occur relatively less frequently in divers and much more commonly in compressed air workers result in the collapse of the articular surface and the development of secondary osteoarthritis. The incidence and contributing factors of the disease have been

reviewed with X-rays by the British Medical Research Council (MRC) Decompression Sickness Central Registry in commercial divers. The registry's guidance notes for radiological skeletal surveys, which include the proximal ends of humerus and femur and the shafts of femur and tibia, are still being used in the diving medicine routine, as it was first prepared (6,9). However, unfortunately, is not sensitive for early stages of osteonecrosis (6-11). The time from dysbaric insult to the earliest radiological sign, characterized by an absolute increase in radiological density could take at least 6 months (9). MRI is the leading candidate against the decades-long throne of X-rays, as it allows scanning without the use of ionizing radiation, which makes it more ethically acceptable despite the increased costs. Although doses are as low as about 0.06 mSv, limb joints radiographs along with chest and teeth constitute a significant part of the annual individual and collective effective doses from diagnostic medical X-rays. This value has been estimated as 0.5 mSv and 130,000 person-Sv (12,13). MRI is the leading candidate against the decades-long throne of X-rays, as it allows scanning without the use of ionizing radiation, which makes it more ethically acceptable despite the increased costs. Contrast may be increased by the combination of T1 sequences with fat-suppressed short tau inversion recovery sequences as well as with the use of high-resolution surface coils (7). However, the fact that a number of early changes detected on MRI turn out to be false positives which then disappear -since some lesions probably heal without leaving a necrotic infarct- may raise the question of the timing of the imaging. EDTC recommends that all new entrants should be considered for baseline long-bone imaging on graduating; in addition, all those who dive regularly for >30 meters and >4 hours under pressure should undergo routine health surveillance along with those who have clinical symptoms, those with referable to a joint, and for those who have had a DCS (1). It has been also suggested that divers treated for musculoskeletal DCS should be routinely screened using MRI for the initial findings of DON (11).

Although many studies have determined the prevalence of DON among those who dive for different professional purposes, there are no data on the prevalence among divers examined in accordance with the professional diver regulation in our country. The prevalence of 2.17% observed in our study is higher than that observed in navy divers, who strictly follow the decompression rules and undergo periodic medical examinations (14). However, it is considerably lower than the prevalence of 70.6% in another study enrolling Turkish sponge divers who were not subjected to a proper training program for diving, did not use any particular decompression table, and among whom most had a history of DCS (15). These high figures are neither unique to our country nor to sponge divers. Similar rates have been also observed among Yucatán Mexican artisanal diving fishermen (16). Whatever the sponge, fish or sea snails, collection strategies are inevitably influenced by economic pressures, which implies that individuals diving for such commercial purposes subjects themselves to more risky and provocative dive profiles. In contrast, the prevalence of 2.17% obtained in our study is lower than the prevalence of 4.2% reported by British MRC Decompression Sickness Central Registry, which evaluated 4980 commercial divers (6). This may be attributed to the fact that our study included a relatively smaller cohort.

Undoubtedly, one of the aims of regulations is that medical fitness standards are evidence-based and compatible with contemporaneous clinical practice. By the 2000s, attitudes toward DON and fitness to continue diving and compressed air work have changed all around Europe. EDTC took the lead to give diving medicine physicians the competence to perform a differentiated assessment according to diving task-based criteria and abandon the rigid assessment style. The perspective that was being attempted to be instilled in the fitness-to-dive examinations was that a strong reason must be adduced before a diver is deprived of his/her jobs and before his/her experience is lost from the industry (1,17).

Conclusion

On the basis of these considerations, we propose the following topics for reconsideration by regulatory authorities. For the reasons of feasibility described above, conventional radiography has been used as a standard method for many years. However, even if deemed advantageous, it would be difficult to scientifically explain biennial exposure to ionizing radiation, and the delay from the known first hyperbaric exposure to the appearance of the first radiological findings. Thus, we suggest that such screening may be neither necessary nor advisable and therefore should be reconsidered. Despite the increased costs, MRI allows screening without using ionizing radiation, which makes it ethically more acceptable. In light of the above considerations, we believe that it is time for a critical reappraisal of the Professional Divers Regulation.

Ethics Committee Approval: The approval form the the Clinical Research Ethics Committee of Çanakkale Onsekiz Mart University was obtained (approval number: 2020/12, date: 09.23.2020).

Informed Consent: Informed consent was not obtained owing to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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Renal Glomerular Hyperfiltration is Associated with Poor Prognosis in Acute ST-Elevation Myocardial Infarction

Renal Glomerüler Hiperfiltrasyon Akut ST-Yükselmeli Miyokard İnfarktüsünde Kötü Prognoz ile İlişkilidir

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ABSTRACT

Introduction: Glomerular hyperfiltration is related to several clinical conditions, such as prediabetes and prehypertension, and associated with poor prognosis in long-term follow-up. This study aims to elucidate the relationship between glomerular hyperfiltration and short-term prognosis in patients with ST-segment elevation myocardial infarction (STEMI) treated by percutaneous coronary intervention (PCI).

Methods: A total of 1,402 patients (24% women, n=338) who had been diagnosed with STEMI and treated by primary PCI were enrolled in the present study. Glomerular hyperfiltration was defined as an estimated glomerular filtration rate (GFR) above the 95th percentile based on age- and sex-specific distributions, and a low-filtration rate was defined as an estimated GFR below the 5th percentile. GFR was assessed using the Chronic Kidney Disease Epidemiology Collaboration equation. The major adverse cardiovascular events (MACE) considered in this work included acute stent thrombosis, re-infarction, cardiogenic shock, and cardiac death within 30 days.

Results: MACE was observed in 178 patients (12.6%). High and low GFRs led to higher risks of developing major cardiovascular events [odds ratio (OR): 1.92, 95% confidence interval (CI): 1.19-3.08, p<0.01 and OR: 2.50, 95% CI: 1.50-4.17, p<0.01, respectively] compared with normal GFRs. Low ejection fraction, atrial fibrillation, previous coronary artery disease, and low systolic blood pressure were other independent risk factors influencing MACE rates in the multivariable regression models.

Conclusion: Glomerular hyperfiltration is independently correlated with short-term MACE rates in patients with acute STEMI treated by primary PCI.

Keywords: Glomerular hyperfiltration, acute myocardial infarction, prognosis

ÖZ

Amaç: Glomerüler hiperfiltrasyonun pre-diabetes, prehipertansiyon gibi birçok klinik durumla ilişkili olduğu ve uzun dönem takipte daha kötü prognoz ile ilişkili olduğu bilinmektedir. Amacımız perkütan koroner girişimlerle (PKG) tedavi edilen ST-segment yükselmeli miyokard enfarktüsü (STYME) hastalarda glomerüler hiperfiltrasyon ile kısa dönem prognoz arasındaki ilişkiyi aydınlatmaktır.

Yöntemler: STYME tanısı alan ve primer PKG ile tedavi edilen toplam 1.402 hasta (%24 kadın n=338) bu çalışmaya dahil edildi. Glomerüler hiperfiltrasyon, yaşa ve cinsiyete göre dağılımda 95. persentilin üzerindeki değerler olarak tanımlanırken, düşük filtrasyon hızı 5. persentilin altındakiler olarak tanımlandı. Glomerüler filtrasyon oranı Chronic Kidney Disease Epidemiology Collaboration equation formülüne göre hesaplandı. Majör kardiyovasküler olaylar 30 gün içerisindeki akut stent trombozu, re-İnfarkt, kardiyojenik şok ve kardiyak ölümden oluştu.

Bulgular: Yüz yetmiş sekiz hastada (%12,6) majör kardiyovasküler olaylar gelişti. Hem düşük hem de yüksek glomerüler filtrasyon oranı, majör kardiyovasküler olay gelişiminde [olasılık oranı (OR): 1,92 %95 güven aralığı (CI): 1,19-3,08, p<0,01 ve OR: 2,50 %95 CI: 1,50-4,17, p<0,01 sırası ile] normal glomerüler filtrasyon oranı ile karşılaştırıldığında daha yüksek riskliydi. Düşük ejeksiyon fraksiyonu, atriyal fibrilasyon, önceki koroner arter hastalığı ve düşük sistolik kan basıncı multivariante regresyon analizinde kötü prognoz için diğer bağımsız risk faktörleri idi.

Sonuç: Glomerüler hiperfiltrasyonun, primer PKG ile tedavi edilen STYME hastalarında 30 günlük kısa dönemde majör kardiyovasküler olaylar ile bağımsız bir şekilde ilişkili olduğu saptandı.

Anahtar Kelimeler: Glomerüler hiperfiltrasyon, akut miyokard enfarktüsü, prognoz



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Introduction

Chronic kidney disease (CKD) is a health problem of increasing prevalence that affects millions worldwide (1). Besides causing kidney complications, such as end-stage renal disease, and requiring expensive treatments, such as hemodialysis and renal replacement therapy, the disease is a well-known independent risk factor for cardiovascular morbidity and mortality (2). Emerging data indicate that abnormally elevated glomerular filtration rates (GFRs), also called glomerular hyperfiltration, may be a predictor of adverse cardiovascular outcomes (3). Glomerular hyperfiltration is often observed in diabetic patients; however, it is also hypothesized to be related to prehypertension (4), metabolic syndrome, obesity (5), and various renal diseases (6).

Despite the wide availability of potent anti-thrombotic therapies and utility of percutaneous coronary interventions (PCI), acute myocardial infarction (AMI) continues to be a substantial cause of morbidity and mortality. The predictors of short- and long-term outcomes of AMI have been investigated extensively. Vicent et al. (7), for example, demonstrated that older age, female sex, diabetes, multivessel disease, anemia, anterior infarct, prior heart failure, and CKD are related to a higher Killip class and in-hospital mortality in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary PCI (7). A study including 194 acute coronary syndrome patients, 41.2% of whom had STEMI, indicated that estimated GFR levels below 30 mL/min/1.73 m² could be correlated with unfavorable short- and long-term results (8). However, whether high GFR levels can be used to estimate major adverse cardiovascular outcomes (MACE) in patients with STEMI is unknown.

The characteristics of glomerular hyperfiltration have long been recognized, but its role in cardiovascular diseases has only been recently reported (9). Thus, the present study aims to predict the short-term MACE rates of hyperfiltrators diagnosed with STEMI and treated by primary PCI.

Methods

Study Population

Patients diagnosed with STEMI and treated by pPCI between the years 2014 and 2017 were consecutively enrolled in this study. Patients who underwent emergency surgery or had incomplete data were excluded. Patients were classified into the low, normal, or high-filtration groups according to age- and sex-matched GFR levels (Figure 1). Clinical and demographic characteristics and laboratory parameters were obtained from medical records. Short-term MACE rates were the primary outcome, and outcome assessment measures were acquired from hospital records. Informed consent was obtained from all patients, and the study protocol was approved by the İstanbul Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital Local Ethics Committee (approval number: 28001928-604.01.01, date: 25.12.2020).

Definitions and Adverse Outcomes

ST-segment elevation in at least two contiguous leads of >2 mm in men and >1.5 mm in women accompanied by typical chest pain was defined as STEMI according to the European Society of Cardiology guidelines (10). Stent thrombosis, cardiogenic shock, re-infarction, and cardiac

death during index hospitalization and within 30 days were regarded as short-term MACE. Stent thrombosis was defined as definite thrombosis confirmed angiographically within 30 days after first implantation. Cardiogenic shock was defined as persistent hypotension indicated by systolic blood pressure <90 mmHg or requiring vasopressor support to maintain a level of >90 mmHg despite adequate filling pressures and evidence of end-organ damage. Acute MI occurring within 28 days after the index event was considered as re-infarction.

GFR levels were estimated via the CKD-EPI equation according to the KDIGO guidelines (11) for white males and females. We referred to previous studies (3) and used the 5th and 95th percentiles as cut-off values produced from age- and sex-specific distributions of eGFR values.

Revascularization Procedure

All patients underwent invasive evaluation with standard angiographic techniques according to established guidelines. A loading dose of 600 mg of clopidogrel and 300 mg of acetylsalicylic acid was administered on admission. Then, 100 u/kg heparin or 1 mg/kg low-molecular weight heparin were given after the coronary anatomy was identified. The choice of stent type (i.e., bare metal or drug-eluting stents), use of adjunctive therapies (e.g., thrombus aspiration or bailout glycoprotein IIb/IIIa receptor antagonist infusion), and adoption of pre/post-dilatation was left to the discretion of the operator. All participants were recommended 75 mg of clopidogrel and acetylsalicylic acid at hospital discharge; other therapies, such as β blockers, angiotensin converting enzyme inhibitors, or statins, were also given as necessary unless contraindicated.

Laboratory Parameters and Echocardiography

Venous blood samples were obtained upon admission to the emergency department before primary PCI. Complete blood counts and biochemical tests were performed using a Beckman Coulter LH 750 and Beckman Coulter LX20, respectively. Serum creatinine levels were measured by the Jaffe method. After primary PCI, all patients underwent two-dimensional and Doppler echocardiographic evaluation to determine their LV ejection fraction; evaluations were conducted by an experienced operator using the Vivid-5 System (General Electric Company, Milwaukee, WI, USA).

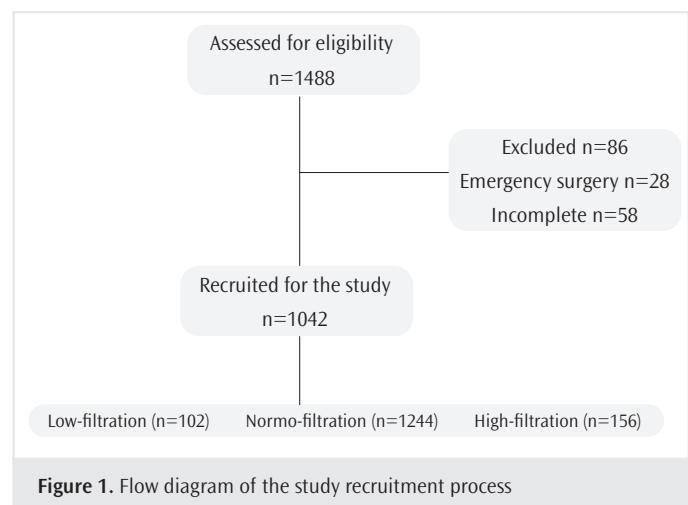


Figure 1. Flow diagram of the study recruitment process

Statistical Analysis

All data were presented as mean ± standard deviation for variables with a normal distribution or median (inter-quantile range) for variables with a non-normal distribution. Categorical variables were reported as numbers and percentages. Continuous variables were checked for the normal-distribution assumption by using Kolmogorov-Smirnov statistics. Categorical variables were tested by Pearson’s χ^2 test and Fisher’s exact test. Differences between MACE (+) and MACE (-) patients were evaluated using the Mann-Whitney U test or Student’s t-test when appropriate. Univariable and multivariable binary logistic regression analyses were performed to investigate independent correlations with MACE. Variables determined to have $p < 0.10$ by univariable regression analysis were included in the multivariable regression analyses. All p-values were two sided, and values of < 0.05 were considered statistically significant. All statistical studies were conducted using Statistical Package for Social Sciences software (SPSS 22.0 for Windows, SPSS Inc., Chicago, IL, USA).

Results

A total of 1402 patients [mean age: 57.5±11.8 years, 75.8% male (n=1064)] who had been diagnosed with STEMI were included in this study. The majority of the study population (81.6%) was included in the normo-filtration group. The frequencies of patients with hyperfiltration and low filtration were 11% and 7.3%, respectively. The MACEs observed included acute stent thrombosis (n=40, 2.8%), re-infarction (n=61, 4.3%), cardiogenic shock (n=44, 3.1%), and cardiac death (n=33, 2.3%). Comparisons of the clinical and demographic characteristics of the two groups are depicted in Table 1, 2. The frequencies of smoking, coronary artery disease, atrial fibrillation (AF), and anterior infarct were higher in

the MACE (+) group than in the MACE (-) group (p-values of 0.03, < 0.01 , < 0.01 , 0.03, respectively). Mean LV ejection fraction and systolic blood pressure values were lower in the MACE (+) group than in the MACE (-) group ($p < 0.01$ for both comparisons). The groups were statistically comparable in terms of other parameters.

A comparison of the laboratory parameters of the study groups is provided in Table 3. Compared with those of the MACE (-) group, mean white blood cell, alanine aminotransferase, and aspartate aminotransferase AST levels were higher whereas hemoglobin and low-density lipoprotein levels were lower in the MACE (+) group.

We performed univariable and multivariable binary logistic regression analyses for all variables to determine the independent predictors of short-term MACE. During univariable regression analysis, systolic blood pressure, anterior infarct location, LV ejection fraction, heart rate, AF, previous coronary artery disease (CAD), and low and high-filtration rates were found to be correlated with in-hospital and 30-day MACEs. When these parameters were entered into the multivariable regression model, systolic blood pressure (OR: 0.97, 95% CI: 0.96-0.98, $p < 0.01$), LV EF (OR: 0.96, 95% CI: 0.95-0.97, $p < 0.01$), AF (OR: 2.62, 95% CI: 1.21-5.63, $p < 0.01$), previous CAD (OR: 1.60, 95% CI: 1.07-2.39, $p < 0.01$), low-filtration rate (OR: 2.50, 95% CI: 1.50-4.17, $p < 0.01$), and high-filtration rate (OR: 1.92, 95% CI: 1.19-3.08, $p < 0.01$) were confirmed to be independent predictors of in-hospital MACE. A normal filtration rate was selected as the reference value when low and high-filtration rates were entered into the regression model (Table 4).

We assessed the tolerance and variance inflation factor (VIF) of all parameters included in the regression model to prevent multicollinearity.

Table 1. Demographic properties of the MACE (+) and MACE (-) groups

Variable	Total (n=1402)	MACE (+) (n=178)	MACE (-) (n=1224)	p-value
Age, years	57.5±11.8	58.6±13.5	57.3±11.5	0.17
Sex (men), n (%)	1064 (75%)	134 (75%)	930 (76%)	0.83
Diabetes mellitus, n (%)	332 (23%)	52 (29%)	280 (22%)	0.06
Hypertension, n (%)	624 (44%)	82 (46%)	542 (44%)	0.65
Smoking, n (%)	922 (66%)	130 (73%)	792 (65%)	0.03
Hyperlipidemia, n (%)	262 (18%)	28 (16%)	234 (19%)	0.27
Family history, n (%)	262 (19%)	32 (18%)	230 (19%)	0.79
Previous CAD, n (%)	244 (17%)	48 (27%)	196 (16%)	< 0.01
Previous HF, n (%)	20 (2%)	6 (3%)	14 (1%)	0.05
Atrial fibrillation, n (%)	38 (3%)	12 (7%)	26 (2%)	< 0.01

CAD: Coronary artery disease, HF: heart failure, LV: left ventricular, MACE: major adverse cardiovascular events

Table 2. Clinical characteristics of the MACE (+) and MACE (-) groups

Variable	Total (n=1402)	MACE (+) (n=178)	MACE (-) (n=1224)	p-value
Body mass index, kg/m ²	23.7±2.2	23.5±2.1	23.7±2.3	0.24
LV ejection fraction, (%)	44.3±10	40±10.6	45±9.6	< 0.01
Heart rate, bpm	80.4±18.4	82.7±19.7	80.1±18	0.08
Systolic blood pressure, mmHg	123±21.9	111±28.1	124.8±20.2	< 0.01
Anterior infarct, n (%)	606 (43.2%)	92 (51.7%)	514 (42%)	0.03
Multivessel disease	598 (43%)	78 (44%)	520 (43%)	0.73

LV: Left ventricular, MACE: major adverse cardiovascular events

All parameters revealed tolerance values >0.1 and VIF values <10 according to multicollinearity statistics. Thus, no multicollinearity exists between each of the variables in the regression model.

We plotted the relationship between the predicted probability of short-term MACE and filtration status according to our regression model (Figure 2). The graphic demonstrates that high and low-filtration rates indicate a higher probability of in-hospital MACE compared with normo-filtration rates. The mean probabilities of short-term MACE were 31% in the low-filtration rate group, 18% in the high-filtration rate group, and 10% in the normo-filtration rate group.

Discussion

The major finding of our study is that glomerular hyperfiltration is an independent predictor for short-term MACE in patients with STEMI treated by PCI. We also found an independent association between low GFRs and short-term MACE, as described in previous studies (7,8). To

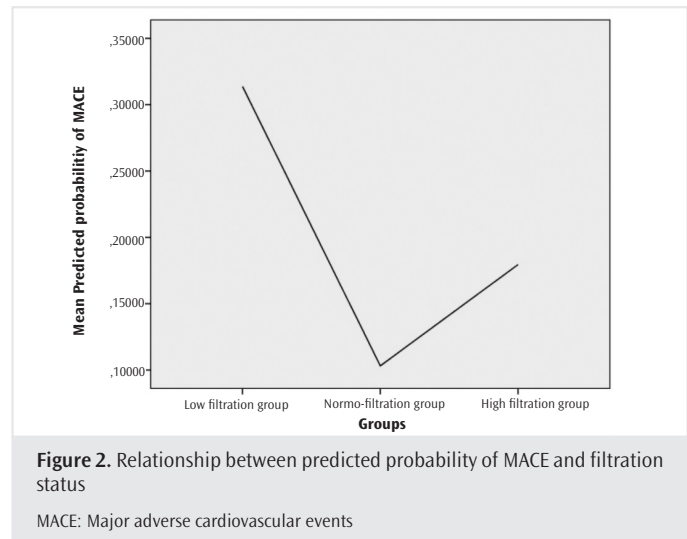


Table 3. Comparison of laboratory parameters between the MACE (+) and MACE (-) groups

Variable	Total (n=1402)	MACE (+) (n=178)	MACE (-) (n=1224)	p-value
White blood cell, $10^3/\mu\text{Lt}$	12.9 \pm 3.8	13.2 \pm 4.7	12.8 \pm 3.7	0.04
Hemoglobin, g/L	13.8 \pm 1.6	13.5 \pm 1.9	13.9 \pm 1.6	0.04
Platelet, /mm ³	245.7 \pm 74	246.1 \pm 91.3	245.6 \pm 71.3	0.93
First troponin, ng/mL	6.4 (38.8)	7.2 (48.2)	6.3 (36.9)	0.89
C-reactive protein, mg/L	3.9 (16.8)	12 (17.3)	3.4 (16.8)	0.18
HbA1c, mmol/L	6.2 \pm 3.5	6.4 \pm 2.6	6.1 \pm 3.6	0.35
Total cholesterol, mg/dL	190.5 \pm 45.7	190.6 \pm 50.3	190.5 \pm 45.1	0.98
LDL cholesterol, mg/dL	119.6 \pm 36.1	114.1 \pm 36.2	120.3 \pm 36	0.03
HDL cholesterol, mg/dL	37.8 \pm 10.6	37.6 \pm 12.5	37.5 \pm 10.3	0.80
Triglyceride, mg/dL	162.3 \pm 90.5	161.1 \pm 94.9	162.5 \pm 88	0.84
Sodium, mEq/L	137.1 \pm 6.6	137.5 \pm 5.1	137.1 \pm 6.7	0.35
Potassium, mEq/L	4.1 \pm 0.5	4.2 \pm 0.6	4.1 \pm 0.5	0.05
AST, IU/L	35 (72)	76 (128)	34 (63)	0.03
ALT, IU/L	31 (37)	56 (75.5)	29.5 (31.7)	0.04
Uric acid, mg/dL	6.2 \pm 1.6	6.2 \pm 1.8	6.2 \pm 1.6	0.97
Serum glucose, mg/dL	135.3 \pm 80.6	164 \pm 90.4	131.1 \pm 74.3	0.05
GFR, mL/min/1.73 m ²	92.5 \pm 22.6	87.2 \pm 28.8	93.2 \pm 21.4	<0.01
Normo-filtration	1244 (81.6%)	118 (66.3%)	1026 (83.8%)	<0.01
Hyperfiltration	156 (11%)	28 (15.7%)	128 (10%)	<0.01
Low filtration	102 (7.3%)	32 (18%)	70 (5.7%)	<0.01

AST: Aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, MACE: major adverse cardiovascular events, HbA1c: hemoglobin A1c

Table 4. Independent predictors of short-term MACE in multivariate regression analysis

Variable	Adjusted OR (%95 CI)	p-value
Systolic blood pressure	0.97 (0.96-0.98)	<0.01
LV ejection fraction	0.96 (0.95-0.98)	<0.01
Atrial fibrillation	2.62 (1.21-5.63)	<0.01
Previous CAD	1.60 (1.07-2.39)	<0.01
Low filtration	2.50 (1.50-4.17)	<0.01
Hyperfiltration	1.92 (1.19-3.08)	<0.01

MACE: Major adverse cardiovascular events, CAD: coronary artery disease, OR: odds ratio, CI: confidence interval, LV: left ventricular, CAD: coronary artery disease

the best of our knowledge, the present study is the first to demonstrate increased short-term MACE in patients with acute STEMI and glomerular hyperfiltration.

Glomerular hyperfiltration can occur as a physiological consequence of pregnancy or high protein consumption, and it is hypothesized to be the initiating event of GFR decline and progression to end-stage renal disease in many conditions, especially diabetes mellitus (12). Glomerular hyperfiltration could be identified in 70% and 50% of type 1 and 2 diabetes mellitus patients, respectively, in the early course of the disease (6). Glomerular hyperfiltration has been also shown to be related to hypertension (4,13) and smoking and obesity (5,14). Interestingly, the condition has been demonstrated to be an independent predictor of all-cause mortality and cardiovascular events in low-risk populations or healthy subjects (9,15). Dupuis et al. (16) concluded that glomerular hyperfiltration is associated with increased cardiovascular events, with a risk profile similar to that of stage 3a CKD, in healthy middle-aged subjects. In addition, subclinical cardiovascular indicators, such as left ventricular hypertrophy, coronary artery calcium score, and carotid artery atherosclerosis, are relatively high in glomerular hyperfiltration (17-19).

The exact mechanism of glomerular hyperfiltration and its relation to cardiovascular events has not been well examined. Increased activity of the RAAS and sympathetic nervous system have been shown to be related to glomerular hyperfiltration due to glomerular hypertension (20,21). Persistent activation of neurohormonal systems and their role in ventricular remodeling and left ventricular functions in the acute phase of MI are well known. This mechanism may help explain why patients with glomerular hyperfiltration are more susceptible to low ejection fraction and cardiogenic shock in the context of STEMI than those without. Increased adrenergic tone has been demonstrated to cause glomerular hyperfiltration by increasing renal plasma flow (22) and is known to be a risk factor for arrhythmic complications and death during the course of AMI (23). On the other hand nitric oxide (NO), a significant vasodilator, has been associated with glomerular hyperfiltration in an experimental model (24). However, while increases in the activity and expression of NO have been observed in the renal microcirculation, only low levels of the substance are detected in the systemic circulation, resulting in endothelial dysfunction. Decreased vasodilatation due to low NO levels in the ischemic myocardium may lead to increases in infarct size and short-term MACE rates. Finally, decreases in the plasma levels of some renally excreted drugs, such as clopidogrel, low-molecular weight heparin, and glycoprotein IIb/IIIa receptor antagonists, may promote the development of acute stent thrombosis or re-infarction.

Mortality and morbidity remain high despite improvements in the treatment of patients with STEMI. A recent meta-analysis showed MACE rates ranging between 4.2% and 51% (25). In our study, the MACE rate was 12.6%. Compared with patients with normal filtration rates, patients with glomerular hyperfiltration had a 1.9-fold increased risk while those with low filtration had a 2.5-fold increased risk of developing short-term MACE. These results agree with a previous study that demonstrated a 2.2-fold increase in risk for short-term MACE whom eGFR <60 mL/min/1.73 m² presented with AMI compared with patients had eGFR >60 mL/

min/1.73 m² (26). Our data demonstrate that glomerular hyperfiltration is a significant risk factor for adverse events, such as CKD, in patients with STEMI. Specifically, a U-shaped relationship was observed between GFR levels and short-term MACE rates.

A major confounding factor for research on this topic is the vague definition of glomerular hyperfiltration in the literature. Despite growing evidence, no clear cut-off value has yet been identified to quantify glomerular hyperfiltration. While the majority of the available trials tend to use a single threshold value, other works adopt age- and sex-specific thresholds to define glomerular hyperfiltration. Indeed, 30% of the related studies in the literature report no clear cut-off values (27). Thus, in this work, our definition of glomerular hyperfiltration depended on age- and gender-specific adjusted cut-offs, as proposed by Cachat et al. (27). This approach allowed us to avoid categorizing older patients into the renal insufficiency group inappropriately on account of the remarkable decline in GFR that often accompanies aging. Similarly, younger patients are not misclassified as hyperfiltrators solely on the basis of their GFR. Most of the studies in the literature use estimated GFR values, rather than objective measurements, because of the latter technique is time-consuming and expensive. Overall, our results indicate that glomerular hyperfiltration rates based on estimated age- and gender-specific distributions could predict short-term MACE rates in patients diagnosed with STEMI and treated by primary PCI.

Study Limitations

Our study includes several limitations. While our findings suggest that glomerular hyperfiltration is independently correlated with short-term MACE in STEMI patients, we could not establish a causal relationship between these parameters. We estimated GFRs using a predefined formula rather than direct measurement. Our data were acquired from a Turkish population and may not be generalizable to other ethnic groups. In addition, we could not assess the protein and salt consumption and muscle mass of the patients, all of which could alter filtration rates. Finally, our study is only a single-center retrospective study.

Conclusion

Our findings indicate that glomerular hyperfiltration may be a significant predictor of short-term MACE in patients with STEMI treated by primary PCI. Identifying patients with hyperfiltration may be of great value in efforts to manage this patient subgroup. Further studies are needed to confirm our findings.

Ethics Committee Approval: The study protocol was approved by the İstanbul Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital Local Ethics Committee (approval number: 28001928-604.01.01, date: 25.12.2020).

Informed Consent: Informed consent was obtained from all patients.

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Biomechanical Comparison of Three Treatments for Medial Malleolar Fractures

Medial Malleol Kırıklarının Tedavisinde Kullanılan Üç Farklı Yöntemin Biyomekanik Olarak Karşılaştırılması

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ABSTRACT

Introduction: Ankle fractures are relatively common, accounting for 10% of all fractures in the skeletal system, and are the second most common lower extremity fractures after hip fractures. Here, we conduct a biomechanical comparison of three approaches—medial malleolar plate, handy tension band, and malleolar screw—for the treatment of transverse fractures of the medial malleolus.

Methods: Forty-two cow tibias, cut for human consumption and free from soft tissues, were procured from the butcher. In the medial malleoli, transverse fractures were created using a bone saw, and the bones were categorized into three equal groups: bones with fractures fixed using handy tension bands, malleolar screws, and medial malleolar plates. The samples were analyzed biomechanically using equipment prepared in the laboratory, including a test device that could apply tensile and transverse forces. The data collected were interpreted after conversion into force-displacement curves.

Results: When tensile force was applied, the medial malleolar plate demonstrated the greatest resistance to 2 mm displacement force and catastrophic damage force. No difference in resistance was found between the medial malleolar plate and handy tension band methods. When a transverse force was applied, the medial malleolar plate method demonstrated the greatest resistance to 2 mm displacement force.

Conclusion: The medial malleolar plate is an appropriate method for the treatment of transverse fractures of the medial malleolus, although further research is required to identify any potential disadvantages of this method.

Keywords: Medial malleolus, medial malleolar plate, handy tension band, malleolar screw

ÖZ

Amaç: İskelet sistemine ait tüm kırıklar içerisinde %10 gibi bir oranla nispeten sık görülen ayak bileği kırıkları kalça kırıklarından sonra alt ekstremitenin en sık görülen ikinci kırık türüdür. Bu çalışmada, medial malleolün transvers kırıklarında medial malleol plağı, hazır gergi bandı, malleol vidası yöntemlerinin biyomekanik olarak karşılaştırılması amaçlanmıştır.

Yöntemler: Kasaptan, insan tüketimi için kesilmiş, yumuşak dokularından arındırılmış 42 adet inek tibiası temin edildi. Çalışma kapsamına alınan kemiklerin medial malleollerine kesici motor yardımıyla transvers kırıklar oluşturuldu ve her biri 14 kemikten oluşan 3 gruba ayrıldı. Bu 3 gruptaki oluşturulmuş olan medial malleol kırıkları hazır gergi bandı, malleol vidası, medial malleol plağı kullanılarak usulüne uygun tespit edildi. Örnekler laboratuvarında çekme kuvveti ve transvers kuvvet uygulayan test cihazında hazırlanmış aparatlar yardımıyla biyomekanik analize tabi tutuldu. Alınan veriler kuvvet-deplasman eğrilerine dönüştürülerek yorumlandı.

Bulgular: Çekme kuvvetinde medial malleol plağı yöntemi, 2 mm deplasman kuvveti ve katastrofik hasar kuvveti açısından diğer yöntemlere göre daha yüksek kuvvetlere dayanırken, dayanıklılık açısından hazır gergi bandı yöntemiyle arasında fark bulunamamıştır. Medial malleol plağı yönteminin çekme kuvvetinde malleol vidası yöntemine göre daha dayanıklı olduğu görülmüştür. Transvers kuvvet uygulanan gruplarda 2 mm deplasman kuvvetinde medial malleol plağı yöntemi, hazır gergi bandı ve malleol vidası yöntemlerine göre daha yüksek kuvvetlere dayanabilmiştir. Transvers kuvvetlerde medial malleol plağı yöntemi, hazır gergi bandı ve malleol vidası yöntemlerine göre daha dayanıklı bulunmuştur.

Sonuç: Medial malleol plağı medial malleolün transvers kırıklarında uygulanabilecek bir yöntem olup bu yöntemin olası dezavantajları için yapılacak başka çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Anahtar Kelimeler: Medial malleol, medial malleol plağı, gergi bandı, malleol vidası



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Introduction

Advances in and studies on fixation methods, secondary to the efforts to better understand ankle biomechanics, have helped change the treatment strategies for ankle fractures. The ultimate goal of treatments is to ensure a painless and functional ankle with the achievement of union. Surgical treatment is indicated when the anatomical integrity of the joint cannot be preserved using closed methods. Notably, studies have reported better functional outcomes with anatomical reduction (1,2).

Medial malleolar fractures might either be isolated fractures or accompany other (bimalleolar or trimalleolar) fractures of the ankle. The fracture pattern is transverse in 57%, oblique in 26%, and vertical in 6% of all medial malleolar fractures. Transverse fractures are mostly associated with supination-external rotation type fractures, which are the most common type of fractures based on the Lauge-Hansen classification, as well as with trimalleolar fractures and syndesmosis injuries. In addition, these are injuries that cause instability in the ankle. Transverse fractures are usually located at the level of the tibial plafond (3,4). Reportedly, open reduction-internal fixation is considered the standard treatment for unstable and displaced medial malleolar fractures (5,6).

Currently, several fixation methods are being used for the surgical treatment of medial malleolar fractures. The present study makes a biomechanical comparison of three such fixation methods, handy tension band, malleolar plate, and malleolar screw approaches, for the treatment of transverse fractures of the medial malleolus.

Methods

This study was financially supported by the university scientific research project. It used 28 malleolar screws (TST, İstanbul, Turkey), 14 handy tension band implants (TST, İstanbul, Turkey), and 14 medial malleolar anatomic plates (TST, İstanbul, Turkey) as well as and 84 screws (TST,



Figure 1. Implants used to fix fractures (left to right: malleolar screw, malleolar plate, and handy tension band)

İstanbul, Turkey) (Figure 1). The study was approved by Firat University Faculty of Medicine Non-Interventional Research Ethics Committee (approval number: 16, date: 03.10.2019). In total, 42 tibias from cows bred for human consumption were procured from a butcher and were cleared of soft tissue. Subsequently, the tibias were cut at 15 cm proximal to the tibial plafond, and the proximal segments were discarded. Then, transverse fractures were created on the medial malleoli of the bones using a bone saw, and the fractured bones were divided into three groups: Bones fixed using handy tension bands (n=14), malleolar screws (n=14), and medial malleolar plates (n=14). All samples were then analyzed biomechanically using a test device (Shimadzu AG-X 50kN, Japan) that could apply tensile and transverse forces. For this, we used an equipment designed specially to allow the attachment of the bones to the device and to provide axial loading in the metallurgical and materials engineering laboratory (Figure 2, 3). Tests were performed at 1 mm/min for tensile force and 5 mm/min for transverse force, with a preload of 20 N for the transverse force tests. Data from the test device were interpreted after being converting into force-displacement curves using the Trapezium X software (Shimadzu, Kyoto, Japan).

Statistical Analysis

The data were statistically analyzed using the IBM SPSS Statistics version 22.0 software package. Shapiro-Wilk test was used to determine whether the continuous measurements were normally distributed, and the data were presented as means \pm standard deviations. One-Way analysis of



Figure 2. Application of tensile forces to the prepared samples

variance was used to conduct an overall comparison of the continuous measurements of more than two groups. Among the groups, pairwise comparisons were made using Tukey's, Scheffe, and Tamhane tests, depending on the homogeneity of the within-group variance. The level of statistical significance was accepted as 0.05 for all analyses.

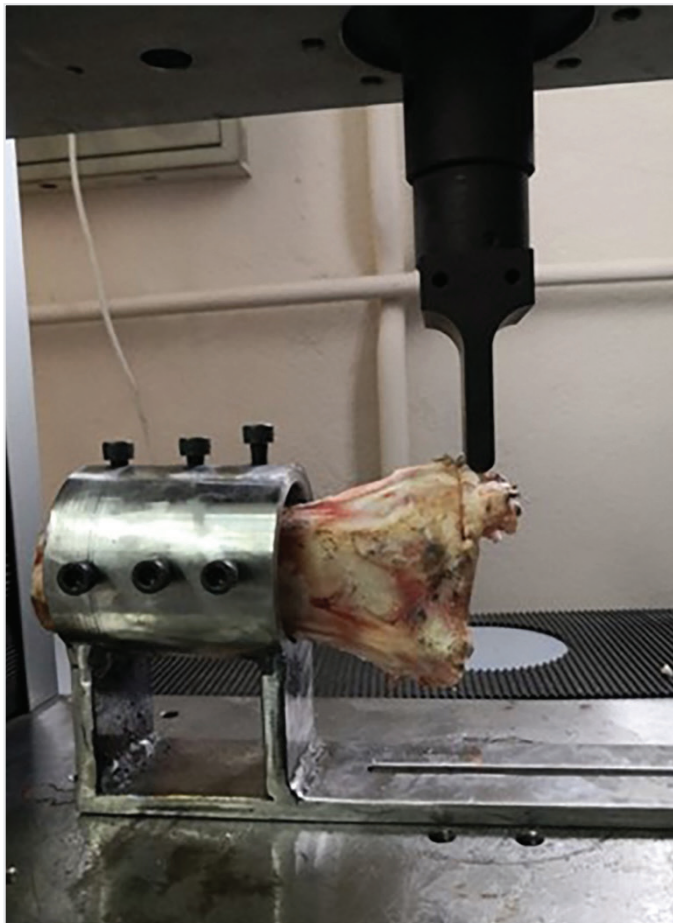


Figure 3. Application of transverse forces to the prepared samples

Results

Following application of transverse force, all three methods—malleolar screw, handy tension band, and medial malleolar plate—showed statistically significant differences in terms of such parameters as 2 mm displacement, catastrophic damage force, and resistance. Results of post-hoc analyses that were used to identify the relationship among the results of these three methods are provided in Table 1.

After the application of transverse force, the mean force required to create a 2 mm displacement was statistically significant in the malleolar plate group than the other fixation groups ($p < 0.001$). In addition, the 2 mm displacement force in the handy tension band group was significantly higher than that in the malleolar screw group ($p < 0.001$) (Table 1).

After the application of transverse force, the force required to create catastrophic damage was significantly higher in the medial malleolar plate group than in the malleolar screw group ($p < 0.001$). In addition, the mean force required to create irreversible damage was higher in the medial malleolar plate group than in the handy tension band group, albeit without statistical insignificance ($p = 0.051$). Under the same conditions, the handy tension band method was found to be superior to the malleolar screw method ($p = 0.001$) (Table 1).

After the application of transverse force, the malleolar plate group demonstrated significantly more resistant than the other two groups ($p < 0.001$), while the handy tension band group demonstrated greater resistance than the malleolar screw group ($p < 0.02$) (Table 1).

As with transverse force, application of tensile force also resulted in statistically significant differences in the parameters, and these differences were evaluated using post-hoc analyses (Table 1).

The medial malleolar plate group was compared with the malleolar screw and handy tension band groups in terms of the 2 mm displacement force. The medial malleolar plate group had significantly different 2 mm displacement force than the malleolar screw and handy tension band groups ($p < 0.001$). However, this parameter did not significantly

Table 1. Relationship between 2 mm displacement force, catastrophic damage force, and resistance following application of transverse and tensile forces*

		Transverse force					Tensile force				
		Mean	SD	Min.	Max.	p	Mean	SD	Min.	Max.	p
2 mm displacement, N	Malleolar screw	168.542 ^a	24.496	132.90	199.40	<0.001	1192.307 ^a	193.022	829.40	1392.00	<0.001
	Tension band	328.157 ^b	30.096	287.70	372.40		1188.571 ^a	158.774	916.60	1342.10	
	Malleolar plate	758.628 ^c	89.497	616.40	860.00		1789.214 ^b	205.869	1481.90	2048.30	
Catastrophic damage, N	Malleolar screw	3186.200 ^a	438.212	2458.70	3852.10	<0.001	1390.457 ^a	248.503	980.40	1620.90	<0.001
	Tension band	4705.985 ^b	713.471	3842.70	5651.80		1726.642 ^b	223.046	1361.20	1983.20	
	Malleolar plate	5574.757 ^b	724.822	4549.30	6457.80		2958.385 ^c	222.162	2648.00	3285.40	
Resistance, N/mm	Malleolar screw	103.057 ^a	12.524	87.40	122.20	<0.001	582.142 ^a	65.558	473.40	654.70	0.001
	Tension band	143.414 ^b	10.628	127.50	156.00		694.771 ^{ab}	135.242	509.20	847.00	
	Malleolar plate	457.071 ^c	40.346	387.40	512.10		815.085 ^b	57.941	752.80	914.10	

*One-Way analysis of variance was performed, ^{a,b,c}: shows that it is significantly different, *SD: standard deviation, Min.: minimum, Max.: maximum, N: Newton, mm: millimeter, $p < 0.05$ indicates statistical significance

differ between the handy tension band group and the malleolar screw group ($p=0.999$). The tensile force required for catastrophic damage was significantly higher in the medial malleolar plate group than in the malleolar screw and tension band groups ($p<0.001$).

Following the application of tensile force, a mean difference of 120.3 N/mm in resistance was noted between the medial malleolar plate and handy tension band groups, although the difference was not statistically significant ($p=0.065$). In contrast, the medial malleolar plate method was found to be significantly more resistant than the malleolar screw method ($p=0.001$).

Discussion

Several fixation methods have been reported for the surgical treatment of medial malleolar fractures. One of the most common methods involves the use of two 4 mm partially-threaded cancellous screws, inserted parallel to each other, and perpendicular to the fracture line. However, in case of small fragment fractures, which cannot be fixed with screws, the tension band method may be preferred. The buttress plates used for vertical fractures of the medial malleolus are not an appropriate implant option in transverse fractures (7,8). Mini-fragment plates might be an alternative approach for the surgical treatment of small fragment non-vertical fractures (9).

Locking plates may be promising for treating medial malleolar fractures owing to the angular stability they provide and the conversion of shear forces into compression forces (10). Previous studies have reported on the superiority of supporting plates over other methods for use in vertical fractures of the medial malleolus; however, studies regarding the use of locking plates in medial malleolar fractures are limited in number (11,12).

Amanatullah et al. (13) used composite synthetic bone models (Sawbones) to create medial malleolar osteotomies in such models, with fixation provided by malleolar screws, a traditional tension band, and properly contoured, mini-fragment T-plates. The malleolar screw group was divided into parallel and divergent subgroups to examine the two types of fixation. After fixation, all groups were exposed to tensile force, and then, resistance and 2 mm displacement forces were measured. The plate-fixation group demonstrated significantly more resistance than the other group in terms of resistance and 2 mm displacement forces. The authors identified no significant difference in the 2 mm displacement and resistance forces among the other groups. The present study found that the medial malleolar plate approach was significantly superior to other methods in terms of 2 mm displacement forces after the application of tensile force; however, the difference in resistance between the medial malleolar plate and handy tension band groups was not statistically significant. The medial malleolar plate approach was more resistant than the malleolar screw method.

Amanatullah et al. (13) used a traditional tension band and contoured mini-fragment T-plates; however, in the present study, we used a handy tension band system and a medial malleolar plate. The plate used in the present study was manufactured for compatibility with the medial malleolar area and therefore did not require contouring. Amanatullah et al. (13) suggested that the plate used in their study would not cause

skin irritation, as it was small and shaped to be fully compatible with the medial malleolar area. However, clinical studies are required to support this claim.

In their study, Wegner et al. (14) conducted transverse medial malleolar osteotomies on Sawbones models, with tensile force applied to the handy tension band and malleolar screw to evaluate resistance, 2 mm displacement, and catastrophic damage forces, similar to the present study. The authors found that the handy tension band system was significantly superior to the malleolar screw system in all three parameters. After the application of tensile force, the screws remained in the distal tibial area and with no screws in the malleolar area in the malleolar screw group. However, the screws broke loose from the distal tibia, and the malleolar area remained in the system in the handy tension band group. In the present study, the screws remained stable, while the malleolar area parted from the system in both the groups.

Implant irritation after the surgical treatment of medial malleolar fractures is a relatively common problem owing to the small amount of soft tissue coverage in this area (15,16). It is vital that in addition to providing stability, the material used to fix the fracture does not cause skin problems. Jiang et al. (17) designed a locking compression plate that was anatomically appropriate for the medial malleolar area. It featured a thinner profile on the distal side than on the proximal side (proximal thickness: 2 mm, distal thickness: 1 mm) and conducted a biomechanical study to compare the system with the malleolar screw approach. To this end, the authors created transverse, oblique, and vertical medial malleolar fractures through cuts at various angles on synthetic bones. Subsequently, they fixed such fractures with their plate and the malleolar screw system. Forces of 300-500 N and 700 N were applied to groups, and the plate was found to have a superior resistance in all fracture types compared with the malleolar screw, and this superiority was observed to be more apparent in vertical fractures than in the other fracture types. The authors further fixed the stress points on the plate and screw under loading but observed no increased stress density in the thinner distal part of the plate, and reported this finding a positive outcome for implant failure. The plate used in the present study was a medial malleolar curved locking compression plate with similar proximal and distal thickness (2 mm). Similar to the study by Jiang et al. (17), the present study found that the malleolar plate provided significantly greater resistance than the screw when transverse force was applied. Jiang et al. (17) assumed that transverse fractures could be fixed by adequate stabilization with screws, while suggesting plates in oblique and vertical fractures; however, their study was limited by the application of only adduction forces.

Owing to implant irritation, implant-related pain, and the associated need for secondary surgery requiring implant removal, researchers have been investigating various available implant models. Clyde et al. (18) conducted a biomechanical study on their knotless tension band to compare their method with the traditional tension band; they concluded that the knotless tension band was superior regarding certain criteria, such as 2 mm displacement, catastrophic damage force, and resistance. In a study by Fowler et al. (19), the bicortical screw, unicortical screw, traditional tension band, and fiber-wire tension band systems were compared. The screw groups were exposed to axial, transverse, and

tensile forces, whereas the tension band groups were exposed only to tensile forces to evaluate the 2 mm displacement force, catastrophic damage force, and resistance, in line with the present study. Among the bicortical and unicortical screw groups, the former was significantly superior in terms of 2 mm displacement force and catastrophic damage force when both transverse and tensile forces were applied. In the tension band groups, the traditional tension band was superior in resistance-catastrophic damage force, while there was no difference in 2 mm displacement force between the two groups. Regarding resistance against tensile force, the bicortical screw method was the most resistant, while the unicortical screw group had the lowest resistance. The present study compared the unicortical screw and handy tension band, but identified no significant difference in resistance against tensile forces between the two methods.

Few previous studies have suggested that the tension band implant is more appropriate for avulsion fractures that cannot be fixed with osteoporotic bones and screws (20,21). Nevertheless, the traditional tension band application may result in complications, such as skin problems and painful implants, which would require implant removal. In such cases, Fowler and Clyde indicate using fiber-wire tension bands, suggesting that this will minimize complications. The present study found the plate-fixation approach to be superior for most parameters examined, although there were no findings supporting the ability of this method to minimize complications.

A retrospective study by Maniar et al. (22) enrolled 85 patients and evaluated the outcomes of medial malleolar fractures treated with handy tension bands (n=21) and malleolar screws (n=64), examining parameters such as the time of union, radiological solid union, implant failure, implant removal, and visual analog scale (VAS) score. However, they found no significant differences between the two groups. Based on this finding, the authors suggested that the malleolar screw method was more appropriate considering cost, recovery rates, and complications, although they reported the low number of patients as a limitation and expressed the need for a similar study involving a larger population. A retrospective study conducted in our country by Bulut and Gursoy (23) with 32 patients assessed the outcomes of treatment with tension bands, malleolar screws, and fully threaded headless compression screws among patients with medial malleolar fractures. The authors evaluated parameters such as medial sensitivity, time of union, VAS score, American Orthopaedic Foot and Ankle Society (AOFAS) score, and implant removal. The authors found no significant differences between the two groups regarding the time of union and AOFAS scores. Implant removal resulting from implant irritation was not observed in the headless cannulated screw group. However, two patients in the malleolar screw group and three in the tension band group underwent implant removal.

A previous study evaluating the bicortical screw method for treating medial malleolar fractures discussed the importance of fixation among patients with risk factors for fracture union as well as underlined the target of early mobilization through bone stabilization (24). Reportedly, comorbidities such as advanced age, diabetes, renal failure, osteoporosis, and peripheral artery diseases can negatively affect surgical outcomes, can increase the rate of revision surgeries, and can

prolong immobilization time, with associated increases in treatment costs (25,26). Notably, a limited number of studies have assessed the use of plates for fixing medial malleolar fractures.

Under transverse force, the medial malleolar plate method was superior to the malleolar screw and handy tension band methods in terms of 2 mm displacement force and resistance, although there was no significant difference in the catastrophic damage force between the medial malleolar plate and handy tension band methods. The medial malleolar plate method was resistant to greater catastrophic damage forces than the malleolar screw.

Under tensile force, the medial malleolar plate method proved significantly superior to the malleolar screw and handy tension band methods in terms of 2 mm displacement and catastrophic damage forces. Although there was no significant difference in resistance between the plate and the handy tension band methods, the medial malleolar plate was more resistant than the malleolar screw.

Study Limitations

One limitation of our study is the *in vivo* design, which prevented the evaluation of complications. Another limitation is that the variables relating to the sourced animal bones (e.g., age and sex) could not be identified.

Conclusion

We concluded that the medial malleolar plate approach is appropriate for transverse fractures of the medial malleolus; however, further research is needed to identify the potential disadvantages of this method. Although our study demonstrated the biomechanical superiority of fixation with a plate compared with fixation with handy tension bands and malleolar screws in several parameters, we believe that clinical studies are needed to investigate complications related to the use of this fixation method in ankle fractures with comorbidities.

Ethics Committee Approval: The study was approved by Firat University Faculty of Medicine Non-Interventional Research Ethics Committee (approval number: 16, date: 03.10.2019).

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Histogram Analysis of Computed Tomography Images for Quantitative Assessment of Gastric Cancer Invasiveness

Mide Kanseri İnvazifliğinin Kantitatif Değerlendirmesinde Bilgisayarlı Tomografi Histogram Analizi

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ABSTRACT

Introduction: To explore the role of computed tomography (CT) texture analysis in predicting T-stage of gastric cancers (GC).

Methods: Preoperative enhanced CT images of 110 patients (men: 84, women: 26) with GC were reviewed retrospectively. Regions of interest were manually drawn along the margin of the lesion on the section where it appeared largest on the portal venous CT images, which yielded texture parameters (1, 10, 50, 90, and 99% percentiles; minimum, mean, and maximum norm; variance; skewness, and kurtosis). Correlations between texture parameters and pathological stage were analysed with Spearman's correlation test. The distributions of all variables were checked with the aid of the Kolmogorov-Smirnov test. The Independent-Samples t-test and the Mann-Whitney U test were used (as appropriate) to compare quantitative data. The chi-squared test was employed to compare qualitative data. The diagnostic performance of CT texture parameters in differentiating different stages was evaluated using receiver operating characteristic analysis.

Results: The T4 variance was significantly greater than that of the T1-to-T3 group ($p<0.05$). The T4 skewness was significantly lower than that of the T1-to-T3 group ($p<0.05$) but the T4 kurtosis significantly higher ($p<0.05$).

Conclusion: The histogram parameters of CT-TA, especially skewness and kurtosis derived from portal, venous phase CT images, may serve as biomarkers stratifying the risk of serosal invasion (stage-T4) by locally advanced GC. Thus, histogram analysis can be used preoperatively to evaluate serosal invasion.

Keywords: Gastric cancer, T-staging, CT, histogram analysis

ÖZ

Amaç: Mide kanserlerinin (MK) T-evresini tahmin etmede bilgisayarlı tomografi (BT) doku analizinin rolünü keşfetmektir.

Yöntemler: MK'li 110 hastanın (erkek: 84, kadın: 26) ameliyat öncesi geliştirilmiş BT görüntüleri retrospektif olarak incelendi. İlgili bölgeleri, doku parametreleri (1, 10, 50, 90 ve %99 persentiller; minimum, ortalama ve maksimum norm; varyans; çarpıklık ve basıklık). Doku parametreleri ile patolojik evre arasındaki ilişkiler Spearman korelasyon testi ile analiz edildi. Tüm değişkenlerin dağılımları Kolmogorov-Smirnov testi yardımıyla kontrol edildi. Niceliksel verileri karşılaştırmak için Independent-Samples t-test ve Mann-Whitney U testi (uygun şekilde) kullanıldı. Nitel verileri karşılaştırmak için ki-kare testi kullanılmıştır. Farklı aşamaları ayırt etmede CT doku parametrelerinin tanısal performansı, alıcı işletim karakteristiği analizi kullanılarak değerlendirildi.

Bulgular: T4 varyansı, T1-T3 grubuna göre anlamlı derecede daha yüksekti ($p<0,05$). T4 çarpıklığı, T1-T3 grubuna göre anlamlı derecede düşüktü ($p<0,05$), ancak T4 basıklığı anlamlı derecede yüksekti ($p<0,05$).

Sonuç: BT doku analizi histogram parametreleri, özellikle portal, venöz faz BT görüntülerinden türetilen çarpıklık ve basıklık, lokal olarak ilerlemiş mide tümörlerinde serozal invazyon riskini (evre-T4) katmanlandıran biyobelirteçler olarak hizmet edebilir. Bu nedenle, histogram analizi, serozal invazyonu değerlendirmek için preoperatif olarak kullanılabilir.

Anahtar Kelimeler: Mide tümörü, T-evreleme, BT, histogram analizi



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Introduction

Although the incidence of, and mortality from, gastric cancer (GC) have decreased recently, GC remains the fifth most common cancer and the third leading cause of cancer deaths worldwide (1). Treatment options are limited because many patients exhibit locally advanced cancer at diagnosis (stages T4a, 4b, and N1,2,3). New diagnostic options for locally advanced GC and identification of patient subgroups who can benefit from personalised treatments have become prime research topics (2-4). Multidetector computed tomography (MDCT) is often the primary method used for preoperative GC staging and shows promise in terms of detecting intra-tumour heterogeneity and, thus, variations in differentiation, angiogenesis, and the extracellular matrix (5). Textural analysis (TA) is a new non-invasive technique that can be applied to various images such as those of radiography, ultrasound, MDCT, magnetic resonance imaging, and positron emission tomography; TA assesses spatial changes in tumoural gray level densities (5). TA has attracted particular attention in the context of malignant tumour imaging, and may be used to estimate tumour stage, grade, treatment response, and prognosis (6-9). The diagnostic accuracy of MDCT in terms of T-staging improves from early to advanced stages, but remains unsatisfactory because it is difficult to evaluate all gastric wall layers, particularly the minor curvature (10). However, to the best of our knowledge, no previous report has explored whether TA can detect stage T4 locally advanced GC. Therefore, we retrospectively analysed whether first-order histogram analysis of the preoperative computed tomography "CT" textural features of locally advanced GC patients could be used to predict stage T4 disease.

Methods

Ethics

This single-centre retrospective study adhered to all relevant tenets of the Helsinki Declaration and the Good Clinical Practice Guidelines and was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Medical Ethics Committee (approval number: 1750, date: 15.03.2019). All patients were included after their informed consent was obtained.

We retrieved images taken from January 2017 to December 2019 from our archiving system.

Patients

A total of 148 consecutive patients who underwent radical gastrectomy with standard D1+/D2 lymph node dissection to treat locally advanced GC between January 2017 and December 2019 in our hospital were retrospectively analysed. The inclusion criteria were: the availability of contrast-enhanced CT images taken in our institution within 4 weeks before surgery and histologically confirmed GC. We excluded patients who were very weak because they lacked adequate adipose tissue in the perigastric region in which regions of interest (ROIs) were drawn for TA (n=21), and also those whose images afforded only poor tumour visualisation because of inadequate distension or peristalsis (n=17) We finally included 110 GC patients who underwent CT.

CT image acquisition

CT was performed using a 128-detector scanner (Philips Ingenuity, the Netherlands) or a 64-detector scanner (Aquilion, Canon Medical Systems, Japan). The usual MDCT scan parameters were: 1) 120 kVp; 2) 80-500 mA; 3) slice thickness 2 mm; 4) pitch 0.797-1.5; 5) field-of-view 50x50 cm; 6) rotation time 0.5-0.75 s; 7) window level 400 (200-600); 8) window width 40 (30-60); 9) matrix 512x512; and, 10) reconstruction interval 0.4 mm for 128-detector CT and 0.5 mm for 64-detector CT. A nonionic intravenous contrast agent (2 mL/kg iopromide (maximum: 150 mL); Ultravist 370: Bayer, Berlin, Germany) was delivered via an automatic injector (Optivantage) (Mallinckrodt, 2010); the volume varied by patient weight. Patient drank 1000-1500 mL of water and was injected with a hypotonic agent (20 mg of scopolamine) to distend the stomach before CT scanning.

Image preprocessing

All CT images were labelled, anonymised, and recorded in Digital Imaging and Communication in Medicine format. Pixel gaps were resized and synchronised to a 1x1 mm² in-plane resolution using free 3D-Slicer software (ver. 4.10.2). To minimise the effects of differences between the two CT devices, image normalisation and grey level discretisation were performed by assigning a gray level range between 1 and 2 kbits/pixel (termed K-values); the MaZda software (see below) analysed only images with K-values of 6. All images were normalised using the ± 3 -sigma technique (11,12).

Texture analysis

Preoperative CT images were retrieved from our archive and loaded onto an independent workstation for TA in random order. CT-TA was performed with the aid of MaZda software (ver. 4.6, P.M. Szczypiński, Institute of Electronics, Technical University of Lodz), which is free for research purposes (12). The first line of each region of interest (ROI) was drawn parallel to the gastric wall via the consensus of two radiologists (Aytül Hande Yardımcı and İpek Sel with 12 and 4 years of experience respectively, blinded to histopathological data). When expanding the ROI, the radiologists were careful to avoid large vessels and adjacent organs. In the section exhibiting the greatest portion of the tumour, a line was drawn to the outer tumour boundary. Three-fold dilatation was then performed using MaZda, and the area of perigastric area invasion within the ROI expanded toward that area. All tumour masses were evaluated separately (Figure 1a-c). The software automatically calculated all pixel attenuations within the ROI and generated 275 feature variables including first-, second-, and higher-order statistics for each patient (<http://www.Eletel.p.lodz.pl/programy/MaZda>). We used only the histogram features (1, 10, 50, 90, and 99% percentiles; minimum, mean, and maximum norm; variance; skewness, and kurtosis). All images were from the portal venous phase. The cases were divided in to two groups by tumour T-stage [T 4 (a, b) and T1-to-3]; calculations were performed separately for each group.

Statistical Analysis

The descriptive statistics include the mean, median, standard deviation, minimum, maximum, and percentage. The distributions of all variables

were checked with the aid of the Kolmogorov-Smirnov test. The Independent-samples t-test and the Mann-Whitney U test were used (as appropriate) to compare quantitative data. The chi-squared test was employed to compare qualitative data. Receiver operator curve analysis was performed to assess whether various features were of diagnostic utility. SPSS ver. 26.0 software was used for all statistical analyses.

Surgical resection

All GC resections was performed according to the Japanese Gastric Cancer Society guidelines (13). Radical gastrectomy and standard D1/D2 lymph node dissection were performed by surgeons expert in gastrointestinal system procedures; all cases had pathologically confirmed GC.

Pathological analysis and the reference standard

Specimens were evaluated by reference to edition 8 of the Tumour, Node, Metastasis staging system by two pathologists with 5 and 10 years of experience.

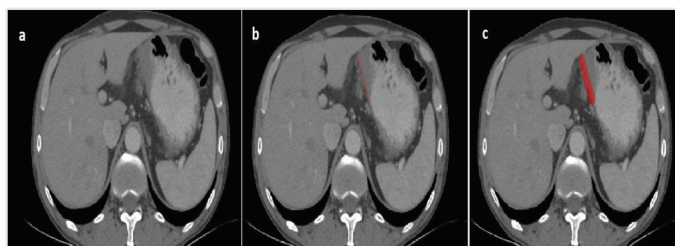


Figure 1. In picture (a), the single largest segment showing the perigastric tumor extension was selected and the tumor margins were determined, then a line showing the largest portion of the tumor (b) was drawn using Mazda software. Then, using the program, three-fold dilatation was performed sequentially (c) and a standard perigastric area to be analyzed within the ROI boundaries was provided

ROI: Regions of interest

Results

Patient data

A total of 110 patients with histopathologically proven GC were enrolled, of whom 10 had stage T1, 9 T2, 28 T3, and 63 T4 a,b disease. Eighty-four (76.4%) patients were male and 26 (23.6%) female. Histologically, 50 tumours were tubular adenocarcinomas; four papillary adenocarcinomas; three mucinous adenocarcinomas; 13 poorly cohesive carcinomas (including signet ring cell carcinomas and other variants); and 40 mixed adenocarcinomas (tubular, papillary, mucinous, medullary and poorly cohesive GCs).

Histogram analysis

Neither age nor gender differed significantly between the T1-to-T3 and T4 groups (both p>0.05). Stage T4 tumours were significantly larger in size than stage T1-to-T3 tumours (p<0.05). In the T4 group, the min, max, and mean norms; and the 1, 10, and 50% percentiles were significantly lower than in the T1-to-T3 group (all p<0.05). Neither the 90 nor 99% percentiles differed between the two groups (both p>0.05). The T4 variance was significantly greater than that of the T1-to-T3 group (p<0.05). The T4 skewness was significantly lower than that of the T1-to-T3 group (p<0.05) but the T4 kurtosis significantly higher (p<0.05) (Table 1, 2). The mean AUCs and classification accuracies with 95% confidence intervals are listed in Table 3.

Discussion

Locally advanced GC is defined as stage T4 disease in which the tumour perforates the serosa (T4a) or invades adjacent structures (T4b), and often has a poor prognosis because of the presence of peritoneal seeding, liver metastasis, and/or distant lymph node involvement (14). CT-TA has recently been considered a promising tool; CT-TA evaluates gray level

Table 1. Tumor size, age, gender distribution and histogram analysis findings among the T4 and T1,2,3 groups of the patients are summarized

		Grade T1-T2-T3		Grade T4		p
		Mean ± SD/(n, %)	Median	Mean ± SD/(n, %)	Median	
Age		62.7±11.2	64.5	60.5±10.2	60.0	0.289 ^t
Gender	Female	14 (29.2%)	-	12 (19.4%)	-	0.230 ^{χ2}
	Male	34 (70.8%)	-	50 (80.6%)	-	
Tumor size		4.88±2.21	4.50	6.89±3.35	6.00	0.001 ^m
Minimum norm		32,663±225	32,607	32,148±4,028	32,677	0.001 ^m
Maximum norm		32,957±199	32,922	32,402±4,040	32,905	0.012 ^m
Mean		32,811±210	32,765	32,425±2,854	32,789	0.001 ^m
Percentile 01%		32,717±215	32,673	32,170±4,032	32,694	0.002 ^m
Percentile 10%		32,743±216	32,695	32,209±4,030	32,737	0.001 ^m
Percentile 50%		32,819±209	32,779	32,285±4,034	32,798	0.001 ^m
Percentile 90%		32,868±205	32,826	32,320±4,034	32,834	0.105 ^m
Percentile 99%		32895±207	32,845	32,341±4,035	32,855	0.273 ^m
Variance		3,196±1,739	2,876	3,240±2,744	1,911	0.031 ^m
Skewnes		-0.26±0.38	-0.22	-0.64±0.43	-0.55	0.001 ^m
Kurtosis		-0.78±1.09	-1.14	0.03±1.14	-0.26	0.001 ^m

^t: t-test, ^m: Mann-Whitney U test, ^{χ2}: chi-square test, SD: standard deviation

Table 2. Stage T4 tumors were significantly larger in size than stage T1-to-T3 tumors ($p < 0.05$) in the left graphics on Table 2. All histogram parameters between stages 4 and stages 1-3 are listed in Table 2 and the right graphics

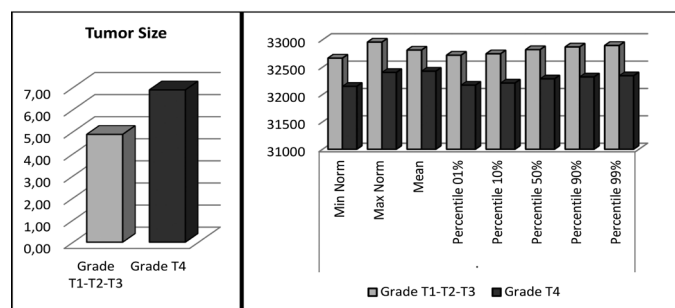


Table 3. The mean AUCs and classification accuracies with 95% confidence intervals are listed in Table 3

	AUC	95% CI	p
Skewnes	0.798	0.711-0.885	0.000
Kurtosis	0.776	0.684-0.868	0.000
Minimum norm	0.743	0.645-0.841	0.000
Mean	0.715	0.614-0.817	0.000
Percentile 10%	0.718	0.617-0.819	0.000
Percentile 50%	0.715	0.614-0.816	0.000
Tumor size	0.681	0.582-0.779	0.001
Percentile 01%	0.669	0.564-0.774	0.002
Maximum norm	0.640	0.535-0.746	0.012
Variance	0.620	0.513-0.727	0.031
Percentile 90%	0.590	0.482-0.699	0.105
Percentile 99%	0.561	0.451-0.671	0.273

Receiver operating characteristic curve.
AUC: Area under the curve, CI: confidence interval

distributions and spatial intratumoural heterogeneities (15). Earlier studies suggested that CT-TA might usefully evaluate GC clinical stage, pathological grade, and prognosis (16,17). However, CT-TA has not previously been used to detect serosal invasion (stage-T4) GC. We found significant differences in tumour size; the minimum, maximum, and mean norms; the 1, 10, and 50% percentiles; variance; skewness; and kurtosis between the T4 and T1-to-T3 stages. Skewness derived from portal venous phase images most accurately (AUC: 0.798) distinguished T4 from T1-to-T3 disease. CT attenuation reflects tumour enhancement (18); higher attenuation probably reflects the higher vascularity of more aggressive tumours.

We found that lower skewness and higher kurtosis were significantly associated with T4 status and serosal invasion. Higher skewness and lower kurtosis were significantly associated with the presence of a K-ras mutation in non-small cell lung cancer patients in the study of Weiss et al. (19). Feng et al. (20) showed that volumetric CT textural features, particularly entropy, could potentially serve as biomarkers for risk stratification of small intestinal/gastrointestinal stromal tumours. Here, we performed first-order histogram analysis of single slices; thus,

not entire tumours. Previous studies found that CT-TA predicted GC histopathological characteristics (16-20). Liu et al. (17) reported that the invasiveness of tumours of different grades depended principally on the extent of neovascularisation, reflected by attenuation of contrast-enhanced CT.

Study Limitations

Our work had several limitations. First, this was a retrospective single-centre study, with an inevitable patient selection bias. Second, we did not evaluate arterial phase data; this would aid determination of gastric wall invasion depth, especially early in disease progression.

Thirdly, when the perigastric area invasion of the tumor was evaluated after 3-fold dilatation using the MaZda program, both the perigastric and the area towards the tumor fell within the limits of the analysis. Considering different tumor types, this creates a limitation since it is analyzed in the tumor with the perigastric area, and in the next studies, the analysis by removing the tumor margin will give more successful results in evaluating the actual perigastric area invasion.

Finally, in weak patients, the absence of perigastric adipose tissue rendered it difficult to draw ROIs and perform CT-TA; we excluded such patients.

Conclusion

The histogram parameters of CT-TA, especially skewness and kurtosis derived from portal, venous phase CT images, may serve as biomarkers stratifying the risk of serosal invasion (stage-T4) by locally advanced GC. Thus, histogram analysis can be used preoperatively to evaluate serosal invasion.

Ethics Committee Approval: This single-centre retrospective study adhered to all relevant tenets of the Helsinki Declaration and the Good Clinical Practice Guidelines and was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Medical Ethics Committee (approval number: 1750, date: 15.03.2019).

Informed Consent: All patients were included after their informed consent was obtained.

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Diminutive Polyposis Coli: Should All Polyps be Removed during a Colonoscopy?

Diminütif Polipozis Koli: Kolonoskopi Sırasında Bütün Polipleri Çıkartmalı mıyız?

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ABSTRACT

Introduction: Colorectal cancer (CRC) is the second most common cause of cancer-related death. Most CRCs arise from colorectal polyps or adenomas. Colonoscopy with polypectomy offers a real-time management of benign adenomas, which breaks the adenoma-carcinoma sequence. In this study, the following question is discussed: should each polyp be excised in patients with more than three diminutive polyps?

Methods: The study was conducted in Yedikule Surp Pırgıç Ermeni Hospital between January 2012 and October 2020. The medical records of 2,222 patients who underwent colonoscopy were retrospectively examined. The patients were divided into two groups. The first group included patients with three or fewer polyps, whereas the second group included patients with four or more polyps. In the first group, all polyps were excised regardless of the polyp's diameter. In the second group, all polyps larger than 5 mm in diameter were excised. A maximum of three polyps were excised in patients who had more than three diminutive polyps. Student's t-test, chi-square test, and Fisher's exact test were used for the statistical analysis. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., USA). P<0.05 was considered statistically significant.

Results: The total number of performed colonoscopies was 2,222. Colorectal polyps were detected in 501 (22.5%) patients. The number of total polypectomies was 728. Five hundred eighty-nine (81.0%) polyps had a diameter of 1 cm or less. Diminutive polyps were detected in 352 (48.4%) patients. The most common histopathological diagnosis in patients with diminutive polyps was tubular adenoma with mild dysplasia (60.8%) and inflammatory polyp (31.0%).

Conclusion: It is concluded that excising all polyps encountered during colonoscopy is appropriate, whether they are diminutive or not. Further studies with a larger case series are needed in this area.

Keywords: Colorectal, diminutive polyp, adenomatous polyp, polypectomy

ÖZ

Amaç: Kolorektal kanserler, kanserden ölüm nedenleri arasında ikinci sırada yer almaktadır. Bu hastalığın poliplerden geliştiği göz önüne alındığında, düzenli yapılan kolonoskopi ve polipektomi, adenom-karsinom sekansını kırarak hastalığın önlenilebilir olduğunu ortaya koymaktadır. Bu çalışmada "üçten fazla diminütif polipe sahip hastada her polipe eksizyon uygulanmalı mıdır?" sorusu literatür verileri ve istatistiksel sonuçlarımız doğrultusunda tartışılmıştır.

Yöntemler: Çalışma Yedikule Surp Pırgıç Ermeni Hastanesi'nde Ocak 2012 ve Ekim 2020 yılları arasında kolonoskopi yapılmış olan 2.222 hastanın dosyalarının retrospektif olarak gözden geçirilmesi ile yapıldı. Hastalar, üç ve daha az polipi olanlar ile dört ve daha fazla polipi olan hastalar olmak üzere iki guruba ayrılarak incelendi. Birinci grup hastalarda, polip çapına bakmaksızın tüm polipler eksize edildi. İkinci grup hastalarda ise çapları 5 mm'den büyük olan tüm polipler eksize edildi. Eğer sadece diminütif polipozis saptanmışsa 3 adet polipe polipektomi yapıldı, diğer diminütif polipler yerinde bırakıldı. İstatistiksel analizlerde Student's t-test, ki-kare test, Fisher's exact test kullanıldı. Bütün istatistiksel analizler SPSS version 18.0 (SPSS Inc., USA) software programı kullanılarak gerçekleştirildi. İstatistiksel anlamlılık p<0,05 olarak kabul edildi.

Bulgular: Toplam kolonoskopi sayısı 2.222 olgudur ve 501 (%22,5) olguda kolorektal polip saptandı. Toplam polipektomi sayısı 728 olarak gerçekleşti. Polip çapı 589 (%81,0) polipte 1 cm ve daha küçüktü. Toplam 352 (%48,4) olguda diminütif polip saptandı. Diminütif polipli olgularda en sık karşılaşılan patolojik tanı tübüler adenom-hafif displazi (%60,8) ve enflamatuvar polip (%31,0) idi.

Sonuç: Diminütif olsun veya olmasın, kolonoskopide karşılaşılan tüm poliplere eksizyon uygulanmasının uygun olacağı kanaatindeyiz. Bu alanda daha geniş olgu serilerine sahip çalışmalara ihtiyaç olduğunu düşünüyoruz.

Anahtar Kelimeler: Kolorektal, diminütif polip, adenomatöz polip, polipektomi



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Introduction

Colorectal cancers (CRCs) are among the top causes of death from cancer in many western countries, ranking second in the USA (1). Since CRC develop from polyps, due to its diagnostic and therapeutic properties, colonoscopy has a crucial role in following up patients with colon polyps. It is evident that when colonoscopy is performed at regular intervals with classical guideline recommendations, it prevents CRC, which arise from preexisting adenomatous polyps, which represent one-half to two-thirds of all colorectal polyps (2,3). Total colonoscopy, with polypectomy of neoplastic polyps, has been associated with a reduced incidence of CRC and decreased mortality (4,5).

More than 90% of colorectal polyps had a diameter less than 1 cm (2,3). Polyps with a diameter of 5 mm or less are called diminutive polyps (1,4). Only 1.7% of the diminutive polyps are histologically advanced (high-grade dysplasia, villous, tubulovillous, and serrated adenoma) and have the risk of developing CRC (2,5). This statistical result may give an impression that removing all diminutive polyps at first glance is unnecessary. Besides, the excision of many diminutive polyps prolongs the colonoscopy procedure, and it is known that complications can result from invasive procedures.

In this study, considering our statistical results and literature data, the following question is discussed: should each polyp be excised in patients with more than three diminutive polyps?

Methods

This is a retrospective study, and all the procedures performed were part of routine care. Ethical approval was obtained from İstanbul Esenyurt University (approval number: E-12483425-199-748). Written and oral consent were obtained from the patients included in the study, and their data were evaluated within the scope of the study. This study retrospectively reviewed the medical files of patients who underwent colonoscopy in Yedikule Surp Pirgiç Ermeni Hospital between January 2012 and October 2020.

The age, gender, indications of colonoscopy, number and diameter of polyps detected on colonoscopy, number of polypectomies, and complications were recorded. The histopathological result of each polypectomy was evaluated. Both diameters of the polyp specified in the pathological report and the colonoscopic diagnosis were compared, and in case of any discordance, the polyp diameter specified in the pathological diagnosis was considered. All histopathological results of polyps were recorded.

Patients were divided into two groups. The first group included patients with three or fewer polyps, whereas the second group included patients with four or more polyps. In the first group, all polyps were excised regardless of the diameter. In the second group, a maximum of three polyps were excised in patients where only diminutive polyps were detected; the location of diminutive polyps, which were not excised, was described in detail in the colonoscopy report. These patients underwent regular colonoscopic follow-up examinations. Alternatively, in the second group, polyps found on colonoscopy with a diameter greater than 5 mm were excised.

Statistical analysis

Student's t-test, chi-square test, and Fisher's exact test were used for statistical analysis. The patients were divided into four groups for age-stratified analysis. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., USA). $P < 0.05$ was considered statistically significant.

Results

Total colonoscopies performed within the specified period were 2,222, and colorectal polyps were found in 501 patients (22.5%).

One thousand one hundred twenty-six (50.7%) patients were men and 1096 were women (49.3%). A total of 317 (28.2%) and 184 (16.8%) polyps were detected in men and women, respectively. The polyp detection rate was significantly higher in men ($p < 0.001$). No complications were encountered in any patient during colonoscopy.

The major clinical indications of colonoscopy were abdominal pain, obstipation or meteorism (40.5%), and hematochezia (29.8%). 11.1% of the patients underwent colonoscopy for routine control or screening. There was a significant difference between men and women ($p < 0.001$) in terms of the indications of colonoscopy. The most common indication of colonoscopy in men was hematochezia (35.2%), whereas, in women, it was iron-deficiency anemia (42.8%).

The age-stratified analysis revealed that polyps were most frequent in men over 60 years of age and women over 75 years of age ($p < 0.001$) (Table 1).

The total number of polypectomies performed in 501 patients was 728. When the numbers and diameters of polyps were compared, no statistical significance was found in terms of the distribution ($p = 0.610$) (Table 2).

Diminutive polyps were detected in 352 patients. The rate of diminutive polyp detection was significantly higher in women ($p = 0.003$) (Table 3).

The most common histopathological diagnosis of diminutive polyps was tubular adenoma with mild dysplasia (60.8%) and inflammatory polyp (31.0%). Fifteen polyps were reported as serrated adenoma with mild dysplasia (4.3%), whereas only one patient was diagnosed with tubulovillous adenoma with mild dysplasia (0.3%). The histopathological results of all patients (with and without diminutive polyps) are given in Table 4.

Discussion

Colonoscopy is a crucial diagnostic tool for detecting colon polyps, which plays an important role in preventing the development of CRC resulting from polypectomy. There is a consensus on the necessity to excise polyps with a diameter of 1 cm or more, especially when they have a high malignant potential (6). However, the management of polyps with a diameter of 5 mm or less, called diminutive polyps, is still controversial.

Recent technological developments in endoscopic imaging techniques have allowed the diagnosis of very small lesions and at the same time help distinguish between low-risk and high-risk lesions by performing simultaneous histopathological evaluations during colonoscopy. These

technologies are high definition white light, narrow band resolution colonoscopy (NBI), and other narrow band resolution technologies (7,8).

The potential effectiveness of these technologies is that they shorten the duration of colonoscopy, eliminate unnecessary histopathological

Table 1. Distribution of polyps by gender and age

Men		Polyp		Total	Women		Polyp		Total		
		Non	Yes				Non	Yes			
Age	<40	n	250	23	273	Age	<40	n	239	7	246
		%	91.6%	8.4%	100.0%			%	97.2%	2.8%	100.0%
	40-49	n	338	143	481		40-49	n	361	77	438
		%	70.3%	29.7%	100.0%			%	82.4%	17.6%	100.0%
	50-74	n	152	106	258		60-74	n	221	53	274
		%	58.9%	41.1%	100.0%			%	80.7%	19.3%	100.0%
	≥75	n	69	45	114		75+	n	91	47	138
		%	60.5%	39.5%	100.0%			%	65.9%	34.1%	100.0%
Total		n	809	317	1126	Total		n	912	184	1096
		%	71.8%	28.2%	100.0%			%	83.2%	16.8%	100.0%

Table 2. Polyp diameters and numbers of polypectomies

			Polyp size (mm)					Total
			<5	6-10	11-15	16-20	>20	
Polypectomy	1 polyp	n	162	105	40	13	19	339
		%	47.8%	31.0%	11.8%	3.8%	5.6%	100.0%
	2 polyps	n	90	70	23	6	5	194
		%	46.4%	36.1%	11.9%	3.1%	2.6%	100.0%
	≥3 polyps	n	100	62	17	9	7	195
		%	51.3%	31.8%	8.7%	4.6%	3.6%	100.0%
Total		n	352	237	80	28	31	728
		%	48.4%	32.6%	11.0%	3.8%	4.3%	100.0%

Table 3. Diminutive polyps in both genders

			Diminutive polyp		Total
			Non	Yes	
Gender	Men	n	261	218	479
		%	54.5%	45.5%	100.0%
	Women	n	115	134	249
		%	46.2%	53.8%	100.0%
Total		n	376	352	728
		%	51.6%	48.4%	100.0%

Table 4. Histopathological results

		Histopathology							Total	
		Polyp diameter inflammatory polyps	Tubular adenoma mild dysplasia	Tubulovillous adenoma mild dysplasia	Serrated adenoma mild dysplasia	Tubular adenoma high dysplasia	Hyperplastic polyps	Tubulovillous adenoma high dysplasia		
Other polyps	n	27	271	24	6	29	3	16	376	
	%	7.2%	72.1%	6.4%	1.6%	7.7%	0.8%	4.3%	100.0%	
Diminutive polyps	n	109	214	1	15	0	13	0	352	
	%	31.0%	60.8%	0.3%	4.3%	0%	3.7%	0%	100.0%	
Total		n	136	485	25	21	29	16	16	728
		%	18.7%	66.6%	3.4%	2.9%	4.0%	2.2%	2.2%	100.0%

examinations, and reduce complication rates. In an article published by the American College of Gastroenterology Association on the treatment of diminutive polyps, it was reported that most of the gastroenterologists (78%) tend not to resect diminutive polyps in the middle- and high-risk groups of patients, the elderly, and patients under anticoagulant treatment (9).

A guideline developed by the American College of Gastroenterology Association provides the histopathological evaluation of diminutive polyps and the appropriate optical diagnosis. In this way, unnecessary polypectomies are avoided, complications are reduced, and great economic savings are achieved (8,9).

One of the technologies enabling simultaneous histological diagnosis during colonoscopy is the high-resolution white light colonoscopy technique. The sensitivity rate is low and was reported to be 59%-84% (10,11). Blue light used in narrow band resolution endoscopy, also known as virtual staining endoscopy or blue light endoscopy, reveals the mucosal details and vascular structures in adenomatous polyps, which are characterized by the excessive formation of new vessels and provides simultaneous histopathological information for diminutive polyps at an accuracy rate of 91%-93% during colonoscopy (12,13).

Another important colonoscopy technique is the staining endoscopy. This technique was first used by the Japanese and recently gained popularity. When staining endoscopy is used with high-resolution endoscopy systems, concurrent histological diagnoses with an accuracy rate of 85%-96% have been reported (14,15). This technique requires additional training and experience and slightly extends the colonoscopy time.

In their study, Lieberman et al. (3) detected polyps in 6,360 patients (45%) in the screening colonoscopy of 13,992 asymptomatic patients. 28.5% of the patients had diminutive polyps. 1.7% of the diminutive polyps were found to have advanced precancerous histological characteristics (high-grade dysplasia, villous/tubulovillous, and serrated adenoma), while adenocancer was detected in only one case in a total of 3,744 patients (3). Because of this study, it was reported that there was no need to remove all of the diminutive polyps, and these patients could be followed up periodically.

In our study, polyps were detected in 501 (22.5%) of 2,222 patients. The most frequent indications of colonoscopy were meteorism, constipation, abdominal pain, hematochezia, and anemia.

The polyp detection rate was significantly increased in men over 60 years of age and women over 75 years of age ($p < 0.001$). Polypectomy was performed for all polyps with a diameter greater than 5 mm. However, patients with three or more diminutive polyps underwent excision of only three polyps. We recommended that all patients with polyps detected and excised should undergo a control colonoscopy within one year, following the American Gastroenterological Association postpolypectomy colonoscopy screening guideline (16). Three hundred fifty-two (48.4%) patients had diminutive polyps. Regarding the gender, the rate of diminutive polyp detection was statistically higher in women ($p = 0.003$).

No adenocarcinoma was detected in the histopathological evaluation of the polypectomies. Sixteen (4.6%) patients had an advanced-stage histopathology (tubulovillous and serrated adenoma). Although we have not detected adenocarcinoma in patients with diminutive polyps, the number of high-risk polyps was considerable.

Our result suggests that, at first glance, all polyps encountered in colonoscopy should be excised. However, when patient's characteristics, such as age, gender, and family history or risk factors for CRC, features of the colonoscopy device (high-resolution white light colonoscopy, narrow band resolution colonoscopy, etc.), and experience of the endoscopist are considered, we believe that patients harboring three or more diminutive polyps should be followed up at regular intervals.

The use of anticoagulant drugs and the presence of other comorbidities should also be considered among the patient-related factors. It should be kept in mind that each polypectomy increases both the duration of colonoscopy and the risk of complications.

To avoid unnecessary diminutive polypectomy procedures, it is important to use high-tech endoscopes together with staining endoscopies when possible. Alternatively, simultaneous histopathological evaluation of resected polyps in the colonoscopy unit is necessary. The capabilities of our country and the educational level of the patients and their access to colonoscopy should be considered if a follow-up protocol is to be made. Because of the importance of polypectomy in preventing the development of colon cancer, all polyps should be removed in patients who cannot come for colonoscopic control examinations.

Conclusion

In summary, in our series of 2,222 patients, advanced-stage histopathological results (19.9%) were obtained in polyps larger than 5 mm in diameter. It is concluded that these polyps should be excised. Although the rate of advanced histopathological results in diminutive polyps was relatively low (4.6%), we believe that some of the selected patients who did not undergo excision of all polyps should be included in the follow-up programs. Further multicenter studies with a larger case series are needed in this area.

Ethics Committee Approval: Ethical approval was obtained from Istanbul Esenyurt University (approval number: E-12483425-199-748).

Informed Consent: Written and oral consent were obtained from the patients included in the study, and their data were evaluated within the scope of the study.

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Authorship Contributions: Surgical and Medical Practices - K.T., H.Ö.; Concept - K.T., H.Ö.; Design - K.T., H.Ö.; Data Collection or Processing - K.T., H.Ö.; Analysis or Interpretation - K.T., H.Ö.; Literature Search - K.T., H.Ö.; Writing - K.T., H.Ö.

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Neuromuscular Electrical Stimulation Therapy Effects on the Functional and Motor Recovery of the Upper Extremity in Patients after Stroke: A Randomized Controlled Trial

Nöromusküler Elektriksel Stimülasyon Tedavisinin İnme Sonrası Hastalarda Üst Ekstremitte Fonksiyonel ve Motor İyileşme Üzerindeki Etkileri: Randomize Kontrollü Çalışma

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ABSTRACT

Introduction: This study aimed to investigate the effectiveness of passive neuromuscular electrical stimulation (NMES) combined with conventional rehabilitation program (CRP) in stroke patients in terms of enhancing the motor and functional recovery of the upper extremity (UE), improving spasticity, pain, and ability to engage in daily activities.

Methods: A total of 30 patients with hemiplegia were randomly distributed in two groups. The study group included 15 patients who received a CRP plus passive NMES applied to shoulder girdle muscles and wrist extensors. The control group included 15 patients who received only CRP. Assessments of the UE impairment were made at enrolment, midtreatment, end of treatment, and 2 months thereafter. Follow-up parameters were the Brunnstrom stage, UE parts of the Fugl-Meyer Assessment (FMA), Barthel index, visual analog scale (VAS) score, and Modified Ashworth scale (MAS).

Results: Statistically significant improvements were found in the Brunnstrom stages of the upper extremities and hands, FMA, and VAS score of the study group at the end of therapy and after 2 months. The FMA overall score improved significantly in the control group at the completion of treatment and after 2 months. MAS scores were higher in the control group at the end of therapy and 2 months afterward, but values did not significantly differ between groups.

Conclusion: CRP plus passive NMES treatment applied to shoulder girdle muscles and wrist extensors seems to be no

ÖZ

Amaç: İnmeli hastalarda konvansiyonel rehabilitasyon programı (KRP) ile kombine edilen pasif nöromusküler elektriksel stimülasyonun (NMES); üst ekstremitte (ÜE) motor ve fonksiyonel iyileşme, spastisite, ağrı ve günlük yaşam aktivitelerine katılma becerisini iyileştirme açısından etkinliğini araştırmaktır.

Yöntemler: Otuz hemiplejik hasta randomize olarak 2 eşit gruba ayrıldı. Çalışma grubuna 20 seans KRP'ye ek olarak omuz kuşağı kasları ve el bilek ekstansörlerine pasif NEMS uygulandı. Kontrol grubuna ise sadece 20 seans KRP uygulandı. Değerlendirmeler tedavi başlangıcında, tedavi ortasında, tedavi sonunda ve tedavi bitiminden 2 ay sonra yapıldı. Sonuç ölçütleri olarak; Brunnstrom'un ÜE ve el evrelemesi, Fugl-Meyer Üst Ekstremitte Motor Fonksiyon Skoru (FMA), Modifiye Ashworth skalası (MAS), vizüel analog skala (VAS) ve Barthel indeksi kullanıldı.

Bulgular: Çalışma grubunda tedavi sonrasında ve 2 ay sonraki kontrol değerlendirmesinde üst ekstremitte ve el Brunnstrom evrelemesinde, FMA ve VAS skorunda istatistiksel olarak anlamlı iyileşme görüldü. Kontrol grubunda FMA toplam skorunda tedavi sonu ve 2 ay sonraki kontrolde anlamlı düzeyde iyileşme saptandı. MAS skorları kontrol grubunda tedavi sonunda ve 2 ay sonra daha yüksekti, ancak değerler gruplar arasında anlamlı farklılık göstermedi.

Sonuç: İnmeli hastalarda KRP'sine eklenen omuz kuşağı ve el bilek ekstansörlerine uygulanan pasif NEMS'nin tek



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ABSTRACT

better than CRP alone, but passive NMES therapy is suggested to be used as an adjunct to neurological rehabilitation as it contributes to functional and motor recovery.

Keywords: Motor recovery, neuromuscular electrical stimulation therapy, rehabilitation, stroke, upper extremity

ÖZ

başına konvansiyonel programa üstün olmadığı görülmekle beraber fonksiyonel ve motor iyileşmeye katkıda bulunduğu için nörolojik rehabilitasyona yardımcı olarak kullanılması gerektiği kanaatindeyiz.

Anahtar Kelimeler: Motor iyileşme, nöromusküler elektriksel stimülasyon tedavisi, rehabilitasyon, inme, üst ekstremité

Introduction

The most common cause of disability in the world is stroke and hemiplegia, which is the most severe disorder after stroke, resulting to an upper extremity (UE) dysfunction (1,2). More than 50% of patients with stroke are unable to use their affected hands and arms for daily activities (3). Therefore, the neuromuscular electrical stimulation (NMES) is a potentially beneficial treatment choice for motor enhancement. NMES reveals limb movements by applying an electrical current to weak muscles. Post-stroke rehabilitation combined with NMES effectively prevents muscle atrophy, increases muscle strength, reduces pain and spasticity, and facilitates motor re-learning (2). NMES may also be used to treat various disabilities at home, which is well tolerated by patients (4). Various types of applications are available; however, its use is limited in the field of rehabilitation (5). In practice, mostly non-implanted ones are used for stroke rehabilitation. Repeated muscle contractions occur without the patients' active participation during stimulation (6).

In this study, whether NMES combined with a conventional rehabilitation program (CRP) could improve the UE function to a greater extent than CRP alone in patients with hemiplegia was investigated.

Methods

From November 2015 to April 2016, a total of 30 patients with stroke, who was referred to our center for hospitalization to engage in 4-week therapy programs were recruited. Ethics committee approval was obtained for the research from the University of Health Sciences Turkey, Istanbul Training and Research Hospital Local Commission on Ethics (approval number: 736, date: 20.11.2015). Informed consent was obtained from patients who participated in this study.

Inclusion criteria includes age of 40-80 years old, absence stroke history, unilateral hemorrhagic, or thromboembolic stroke, time elapsed after stroke of 0-18 months, and hand and UE Brunnstrom stages between 1 and 4. Exclusion criteria includes non-fulfillment of the above inclusion criteria, decompensated heart failure, presence of implanted pacemaker, lower motor neuron lesion affecting the upper limbs, clinically active reflex sympathetic dystrophy syndrome, spinal cord injury, traumatic brain injury, severe cognitive deficit, and/or a neurological disorder such as epilepsy, Parkinson's disease, or multiple sclerosis.

The Brunnstrom approach is a technique that classifies patients into six phases based on muscle tone and synergy patterns. Therefore, after the stroke, the neurologic progress of each case was assessed, and the treatment method was planned with regard to the recovery degree

defined via the current procedure. The examination was performed one by one for the UE, hand, and lower extremity. Elevated Brunnstrom degree represents good outcome (7). Motor evaluation was assessed with the UE motor subgroup score of the Fugl-Meyer Motor Assessment (FMA) (8). Turkish reliability and validity study of the FMA was done (9,10), which was developed to test the motor control in patients after stroke hemiplegia. The FMA is used clinically and in research settings to analyze disorder severity and motor enhancement, and prepare and evaluate therapy (8).

The Barthel index (BI) tests the independence level of patients in their daily activities (i.e., eating, taking a bath, dressing up, bowel and bladder control, toileting, transfer in a wheelchair, walking, and climbing the stairs). The index reveals the needed assistance for support. This evaluation method has been designed for patients undergoing stroke rehabilitation (11). The Turkish version of the BI was verified to be accurate and reliable by Küçükdeveci et al. (12). Score varies between 0 and 100, where 0-20 points indicate complete dependence, 21-61 advanced dependence, 62-90 intermediate dependence, 91-99 mild dependence, and 100 signifies complete independence.

The 5-point Ashworth scale is the most common scale used to determine muscle tone. The updated Modified Ashworth Scale (MAS) was developed by adding one grade (+1) to the original Ashworth scale (13). The MAS was used in our rehabilitation clinic.

Pain intensity was measured using a visual analog scale (VAS). VAS is widely used in health outcome research to quantify pain, which is normally described as a single 100 mm horizontal line anchored by 2 verbal descriptors (e.g., absence of pain; most severe pain ever felt). Increased pain is demonstrated by higher ratings (14).

In our prospective, randomized controlled trial, 30 patients who met the inclusion criteria were randomized into two groups by order of hospitalization. The study group included 15 patients who received CRP (range-of-motion, stretching, strengthening, mobilization, Bobath, Brunnstrom exercises, positioning, splinting, and walking training) plus passive NMES, whereas the control group included 15 patients who received CRP only. The wrist extensor muscles (extensor digitorum communis and extensor carpi ulnaris), deltoideus, and supraspinatus were stimulated with superficial electrodes in the study group. A portable two-channel neuromuscular stimulator (Globus-Genesy model 1200, Treviso, Italy) was used. The frequency of the stimulus was set between 20 and 50 Hz. The current amplitude was adjusted to a suitable amount for the patient (0-100 mA). The position of the electrode on

the supraspinatus was 1.5 cm above the midpoint of the spine of the scapula; the site of electrode settlement for the posterior deltoid was two finger widths down to the posterior edge of the acromion. The negative electrode was located just above the wrist crease for the wrist extensors, and the positive electrode was affixed to an area near the lateral epicondyle. Stimulation therapies were performed 5 days a week for 20 min for 4 weeks in the study group. Assessments of UE impairment were made at enrolment (week 0), midtreatment (week 2), end of treatment (week 4), and 2 months thereafter.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences software v. 22.00 for Windows (SPSS Inc., Chicago, IL, USA). Categorical data are expressed as numbers with percentages for descriptive analyses, whereas continuous data are expressed as means with standard deviations (SDs). The normality of distributions was verified using the Kolmogorov-Smirnov test.

Within- and between-group differences were investigated. Wilcoxon's signed rank test was used to compare non-normally distributed variables, and the Paired Sample t-test was used to compare normally distributed variables both pre- and post-treatment between two groups. Between-group comparisons were made using the Mann-Whitney U

test, the unpaired t-test was used for continuous variables, and the chi-square test or Fisher's exact test (as appropriate) was used for categorical variables. The cut-off for statistical significance in all analyses was 0.05.

Results

Demographic characteristics and clinical parameters are presented in Table 1. No statistically significant finding was found in any demographic feature between groups ($p>0.05$). In the study group, statistically significant improvements were found in the Brunnstrom stages of the UE and hand; the FMA arm, coordination, and total scores; and the VAS at the completion of treatment and 2 months later ($p<0.05$) (Table 2, 3). The FMA total score improved significantly in the control group at the completion of the treatment and after 2 months (Figure 1). MAS values of the shoulder, elbow, and wrist were higher in the control group at the end of the therapy and two months thereafter (Table 4). However, no statistically significant differences were found between two groups in terms of follow-up parameters ($p>0.05$). In addition, no significant difference was found between groups in the mid- and post-treatment and 2-month control in Brunstrom UE stage, Brunstrom hand stage, BI, and VAS parameters, which were assessed by repeated measures analysis ($p>0.05$). MAS shoulder values gradually decreased in the study group while it increased gradually in the control group (Figure 2-4).

Table 1. Demographic and clinical characteristics of patients

		Study group (n)	Control group (n)
Sex (male/female), (n)		8/7	7/8
Age (years) (mean \pm SD)		67.5 \pm 8.5	70.0 \pm 6.8
Marital status, n (%)	Married	10 (66.7)	9 (60)
	Divorced	5 (33.3)	6 (40)
Job, n (%)	Self-employed	3 (20.0)	2 (13.3)
	Housewife	7 (46.7)	7 (46.7)
	Retired	4 (26.7)	4 (26.7)
	Worker	1 (6.7)	2 (13.3)
Education, n (%)	Illiterate	5 (33.3)	3 (20.0)
	Primary school	8 (53.3)	6 (40.0)
	Secondary school	1 (6.7)	4 (26.7)
	High school	1 (6.7)	2 (13.3)
Plegic side, n (%)	Right	8 (53.3)	7 (46.7)
	Left	7 (46.7)	8 (53.3)
Dominant side, n (%)	Right	14 (93.3)	14 (93.3)
	Left	1 (6.7)	1 (6.7)
Comorbid diseases, n (%)	Diabetes	4 (26.7)	6 (40.0)
	Hypertension	13 (86.7)	13 (86.7)
	Ischemic heart disease	3 (20.0)	7 (46.7)
	Hyperlipidemia	0 (0.0)	2 (13.3)
Smoking, n (%)		2 (13.3)	2 (13.3)
Stroke type, n (%)	Thromboembolic	13 (86.7)	12 (80.0)
	Hemorrhagic	2 (13.3)	3 (20.0)
Transient ischemic attack		2 (13.3)	5 (33.3)
Time to commencement of rehabilitation		4.2 \pm 4.5	3.5 \pm 2.2
Data are presented as n (%) for categorical variables and means \pm SDs for continuous variables. n: Number of patients, SD: standard deviation			

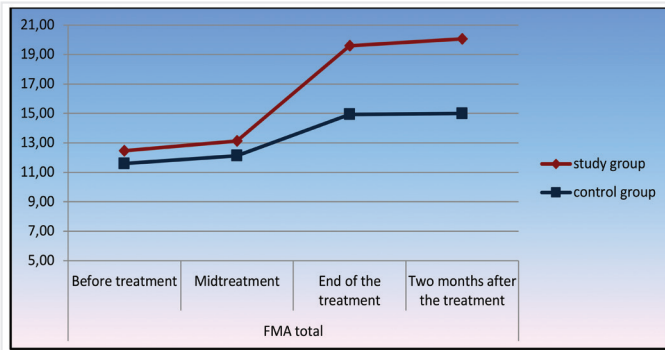


Figure 1. Fugl-Meyer Motor Assessment total score

FMA: Fugl-Meyer Motor Assessment score

Discussion

In this trial, all stroke patients had stable baseline values of all scores prior to treatment. After 20 sessions of UE rehabilitation combined with NMES, improved clinical values were observed in the study group and were sustained to the 2-month follow-up. Spasticity worsened in the control group. However, no statistically significant differences were found between groups.

NMES is widely used in the recovery of patients who had sustained neurological injuries such as stroke, spinal cord injuries, or other neurological disorders including paralysis and paresis. NMES has been used for joint mobility, joint contracture reduction, edema reduction, circulation improvement, atrophy prevention, muscle strength and

Table 2. Motor function assessment

(Mean ± SD)	Fugl-Meyer					
		Upper extremity	Wrist	Hand	Coordination	Total
Before treatment	Study group	9.0±6.8	0.9±1.9	1.6±2.8	0.7±1.5	12.5±13.1
	Control group	8.9±8.5	0.4±1.3	1.8±3.4	0.5±1.2	11.6±13.1
2. week (midtreatment)	Study group	9.6±7.0	1.0±1.9	1.6±2.8	0.7±1.5	13.1±13.3
	Control group	9.2±9.1	0.6±1.5	1.8±3.3	0.5±1.2	12.1±14.1
4. week(end of the treatment)	Study group	13.0±8.7*	1.8±2.8	1.7±2.7	1.5±2.0*	19.6±17.3*
	Control group	10.1±9.0	1.3±2.0	1.3±2.1	0.5±1.2	14.9±15.4*
2 months after the treatment	Study group	13.3±9.4*	2.0±3.2	1.7±2.6	1.5±2.1*	20.1±18.1*
	Control group	10.56±9.0	1.3±1.9	0.9±2.0	0.5±1.1	15.0±15.2

*p<0.05, SD: standard deviation

Table 3. Assessment of motor recovery, functional status, and pain

(Mean ± SD)		Brunnstrom stage		Barthel index	VAS shoulder	VAS wrist
		Upper extremity	Hand			
Before treatment	Study group	1.8±0.9	1.5±1.1	47.7±30.7	4.0±2.2	1.7±2.6
	Control group	1.7±1.2	1.8±1.2	29.7±32.1	5.6±2.8	3.7±2.9
2. week (midtreatment)	Study group	2.1±1.1	1.7±1.1	49.3±31.8	4.1±2.1	1.5±2.1*
	Control group	1.8±1.1	1.9±1.2	31.3±31.9	5.6±2.1	3.9±2.8
4. week (end of treatment)	Study group	2.1±1.3*	2.4±1.8*	56.0±32.8*	3.2±1.9*	1.5±1.7*
	Control group	1.9±1.3	2.2±1.5	36.0±32.5	5.3±1.8	3.9±2.8
2 months after the treatment	Study group	2.5±1.4*	2.5±1.9*	58.0±30.3*	3.8±2.0*	1.1±1.4*
	Control group	1.9±1.3	2.0±1.4	33.7±32.2	6.2±2.0	4.5±3.3

*P<0.05, SD: standard deviation, VAS: visual analog scale

Table 4. Spasticity assessment using the MAS

(Mean ± SD)	Modified Ashworth scale			
		Shoulder	Elbow	Wrist
Before treatment	Study group	1.2±1.1	0.9±0.7	1.0±2.7
	Control group	0.7±0.7	0.7±0.7	0.8±0.7
2. week (midtreatment)	Study group	1.1±0.7	0.9±0.7	0.9±0.7
	Control group	0.9±0.8	0.9±0.7	0.9±0.9
4. week (end of the treatment)	Study group	1.1±0.6	1.0±0.7	0.8±0.6
	Control group	1.2±0.8	1.2±0.7*	1.1±0.6*
2 months after the treatment	Study group	0.9±0.7	1.0±0.7	0.7±0.6
	Control group	1.5±1.0*	1.3±0.7*	1.3±1.0*

*P<0.05, SD: standard deviation, MAS: modified Ashworth scale

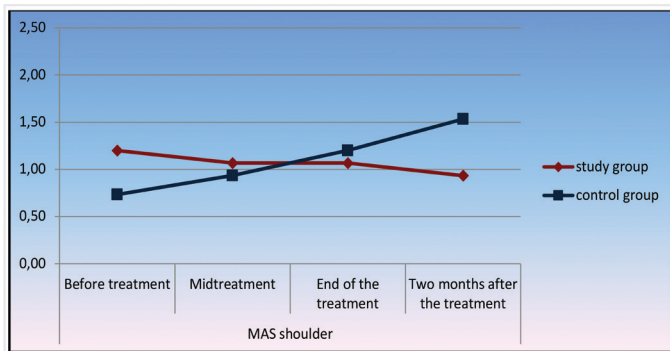


Figure 2. Modified Ashworth Scale shoulder

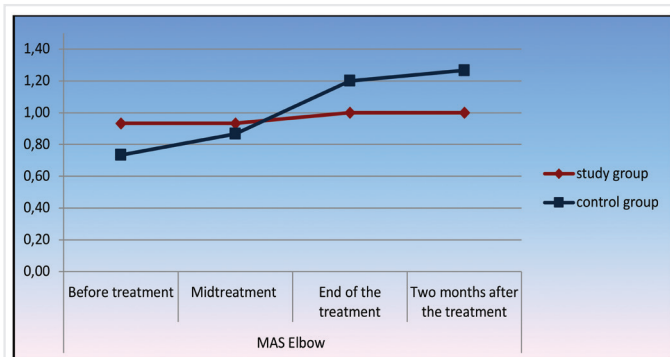


Figure 3. Modified Ashworth scale elbow

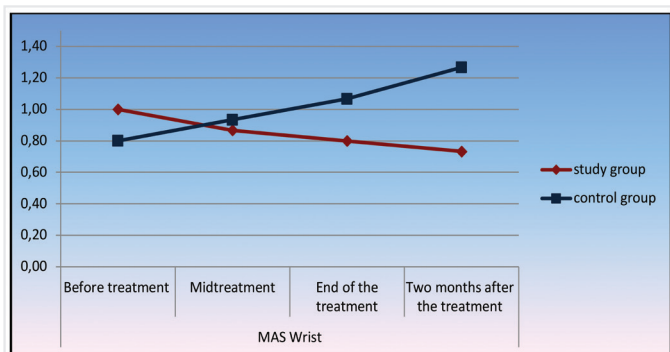


Figure 4. Modified Ashworth scale wrist

sensory perception improvement, spasticity reduction, discomfort reduction, and gait disorders correction (15). Peripheral impacts of NMES include increased strength of contraction, increased muscle mass, transformation from glycolytic type 2 muscle fibers to oxidative type 1 muscle fibers, and vasodilatation by arterial response regulation (16,17).

In previous studies, NMES was usually applied to the wrist extensors (18-20). Chuang et al. (21) found that therapeutic electrical stimulation of the supraspinatus and posterior deltoid muscles showed to effectively reduce shoulder subluxation and pain, increase muscle force, and promote shoulder stabilization in patients who are hemiplegic. Therefore, in the present study, application of both distal and proximal regions is preferred since the shoulder and hand are functional units in UE rehabilitation (2,21).

In literature, NMES application was seen used more often in the first year after stroke (6). In our study, the time to start rehabilitation was 4.2 ± 4.5 months in the study group and 3.5 ± 2.2 months in the control group, in accordance with the literature. The number of sessions and application time were also compatible with that of the literature.

NMES improves the motor and functional status of patients who had stroke. Hsu et al. (22) reported that NMES enhances UE function. Authors compared three groups over 4 weeks: 30 min of stimulation per day, 60 min per day combined with a regular rehabilitation program, and a control group (the regular rehabilitation program alone). They concluded that at least 10 h of NMES combined with regular rehabilitation may enhance the recovery of UE function in patients who had stroke during the early period (22). Rosewilliam et al. (23) recruited patients who had stroke with no UE function, and demonstrated that repetitive NMES for 30 min (on- and off-periods: 15 s) applied twice each working day for 6 weeks can trigger repeated wrist extension and improved wrist function. Boyaci et al. (18) investigated the effects of active and passive NMES; a sham control group was included. No statistically significant differences were found between the active and passive NMES groups in any parameter evaluated at the end of the treatment (18). In our study, after 20 sessions of UE rehabilitation coupled with NMES, enhanced follow-up parameters (Brunnstrom, FMA, BI) showing motor function were observed in the study group and were sustained for 2 months, but this result was not found statistically significant.

A higher MAS scores cause disruption of synergistic muscle activity. Patients who had stroke usually develop compensatory movements when using their paretic UE. Decreased MAS values of the elbow, wrist, and finger joints strengthen the coordination of muscles. In addition, the flexibility of the proximal and distal joints aids proper hand-grip and release (3). However, effect of NMES on spasticity is still controversial. Passive stretching of the extensor muscles of the forearm in addition to NMES significantly reduces spasticity (20). Santos et al. (24) showed that NMES applied to the flexor and extensor muscles of the wrist decreases spasticity in patients who are hemiplegic. Sahin et al. (20) evaluated the effectiveness of superficial electrical stimulation on spasticity of the wrist flexor muscles following stroke and reported that NMES along with wrist extensor muscles stretching was more efficient than stretching alone in terms of reducing spasticity. In the present study, MAS values of the shoulder, elbow, and wrist were significantly higher in the control group at the completion of therapy and after 2 months.

In a study investigating the effectiveness of NMES treatment on shoulder pain in patients with chronic hemiplegia, NMES was applied for 6 hours a day for 6 weeks. At the conclusion of the report, a substantial reduction in pain was found (25). In a randomized controlled trial consisting of 90 patients, NMES was applied to the wrist and finger extensors for 30 min a day for 6 weeks. As a result, important advancement in the level of pain was reported (26). In our study, substantial improvement was observed in the VAS score in the study group at completion of therapy and after 2 months.

Conclusion

CRP plus passive NMES treatment of the shoulder girdle and elbow extensor muscles seems to be no better than CRP alone, but we

suggest that NMES should be used as an adjunct during neurological rehabilitation programs because NMES contributes to functional and motor recovery and decrease spasticity and pain. The type of treatment (active or passive) and duration of stimulation maximizing the effects of NMES remain to be further investigated.

Ethics Committee Approval: Ethics committee approval was obtained for the research from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Commission on Ethics (approval number: 736, date: 20.11.2015).

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Evaluation of the Risk Factors Associated with Dislocation Following Cementless Bipolar Hemiarthroplasty of the Hip in Elderly Patients: A Nested Case-Control Study

Yaşlı Hastalarda Çimentosuz Bipolar Kalça Hemiartroplastisi Sonrası Çıkık Gelişimi ile İlişkili Risk Faktörlerinin Değerlendirilmesi: Yuvalandırılmış Olgu Kontrol Çalışması

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ABSTRACT

Introduction: Although a well-known advantage of the cementless fixation technique is that it prevents bone cement implantation syndrome, with lower perioperative mortality, the risk factors associated with dislocation after cementless bipolar hemiarthroplasty (BHA) have not yet been sufficiently investigated. This study aimed to investigate the incidence of dislocation following cementless BHA of the hip in elderly patients with displaced femoral neck fractures. The related risk factors are also examined.

Methods: In this nested case-control study, patients who had undergone BHA for femoral neck fracture at a single tertiary referral center were retrospectively reviewed. Three control patients from the cohort who had not experienced dislocation were selected for each patient who developed dislocation following BHA. Clinical and radiographic outcome measures were then assessed to determine the risk factors for dislocation following BHA.

Results: Of the 103 patients available for the analyses in the current study, 23 patients (12 females, 11 males) with dislocation were selected as the study group and 70 patients (33 females, 37 males) without dislocation were included in the control group. Univariate analyses revealed significant differences between the two groups in terms of number of postoperative surgical site infections, dementia, center-edge angle, and femoral offset. Two independent risk factors associated with dislocation, namely, infection and dementia, were identified during multivariate model analysis.

Conclusion: Patients with postoperative surgical site infection or dementia are at greater risk for developing dislocation after cementless BHA.

Keywords: Cementless bipolar hemiarthroplasty, dislocation, risk factors, femoral neck fracture

ÖZ

Amaç: Çimentosuz fiksasyon tekniğinin iyi bilinen avantajları, düşük perioperatif mortalite ile kemik çimentosu implantasyon sendromunu önlemesi olmasına rağmen, çimentosuz bipolar hemiarthroplasti (BHA) sonrası dislokasyona bağlı risk faktörleri henüz literatürde yeterince araştırılmamıştır. Bu çalışma, yer değiştirmiş femur boynu kırığı olan yaşlı hastalarda kalçanın çimentosuz BHA'sını takiben çıkık insidansını ve ilişkili risk faktörlerini araştırmayı amaçladı.

Yöntemler: Bu yuvalanmış olgu kontrol çalışmasında, tek bir üçüncü basamak merkezde femur boyun kırığı nedeniyle BHA uygulanmış hastalar geriye dönük olarak incelendi. BHA'yı takiben çıkık gelişen her hasta için kohortlardan çıkık yaşamamış üç kontrol hastası seçildi. BHA sonrası dislokasyon gelişimi ile ilgili risk faktörlerini belirlemek adına çeşitli klinik ve radyografik sonuç ölçütleri değerlendirildi.

Bulgular: Analiz için uygun olduğu belirlenen toplam 103 hasta arasından dislokasyon geliştirmiş olan 23 hasta (12 kadın, 11 erkek) çalışma grubu olarak seçildi. Kontrol grubuna çıkık geliştirmemiş toplam 70 hasta (33 kadın, 37 erkek) dahil edildi. Tek değişkenli analizler, postoperatif cerrahi alan enfeksiyonlarının sayısı, demans, merkez kenar açısı ve femoral off-set açısından iki grup arasında önemli farklılıklar ortaya koydu. Çok değişkenli model analizinde, dislokasyonla ilişkili iki bağımsız risk faktörleri olarak: Enfeksiyon ve demans tespit edildi.

Sonuç: Ameliyat sonrası cerrahi alan enfeksiyonu veya demansı olan hastalar çimentosuz BHA'dan sonra dislokasyon gelişme riski altındadır.

Anahtar Kelimeler: Çimentosuz bipolar hemiarthroplasti, çıkık, risk faktörleri, femur boyun kırığı



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Introduction

The incidence of femoral neck fractures has steadily increased along with the improvement of the average life expectancy and social activities of elderly patients (1,2). The most common treatment options for patients with displaced femoral neck fractures include bipolar hemiarthroplasty (BHA) or total hip arthroplasty (THA); of these, BHA is cited as the most widely performed procedure in the treatment of these patients in the USA (1).

Compared with THA, BHA is a less invasive surgery characterized by lower blood loss, shorter operation times, and lower initial costs (3). One of the major causes of treatment failure following BHA is hip dislocation. The literature reports an incidence of dislocation ranging from 1% to 11%, which indicates that this complication may be secondary to patient-related factors, such as a history of neurological disease or weakness of the abductor muscles, or surgery-related factors, such as the choice of surgical approach and prosthesis type (4-8).

BHA prostheses can be implanted via the cemented or cementless techniques, and both approaches have comparable clinical results (9,10). Although a well-known advantage of the cementless fixation technique is that it prevents bone cement implantation syndrome, with lower perioperative mortality (11,12), to the best of our knowledge, the risk factors associated with dislocation after cementless BHA have not yet been sufficiently investigated. The aim of the present study, therefore, is to investigate the incidence of dislocation following cementless BHA of the hip in elderly patients with displaced femoral neck fractures. The related risk factors are also examined.

Methods

A retrospective chart review of patients who had undergone BHA for femoral neck fracture between 2012 and 2019 at a single tertiary referral center was conducted in this work. Written informed consent was obtained from all participants prior to their participation in this study. The inclusion criteria for the study were a diagnosis of unilateral femoral neck fracture due to low-energy trauma, treatment by cementless BHA, age of 65 years or older, a minimum of 1 year of follow-up, complete medical records and radiographic images, and willingness to participate in the study. The exclusion criteria included a diagnosis of femoral neck fracture due to high-energy trauma, pathological hip fracture, a history of polytrauma, a history of previous hip surgery, loss to follow-up, death during the first year of follow-up, and inadequate radiographic imaging.

Study Population and Design

A total of 241 patients were assessed according to the above eligibility criteria. Exclusion of 138 patients left 103 patients available for analysis in this study. A nested case-control design was used to analyze the risk of experiencing hip dislocation following BHA. Three control patients from the cohort who had not experienced dislocation were selected for each patient with dislocation on the basis of age (± 3 years), gender, and time of surgery (the approximate ratio of 1:3 case-to-control). The approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 2657, date: 08.01.2021).

Surgical Technique

All BHA procedures were performed via a standard posterior approach by four experienced orthopedic surgeons. A cementless bipolar prosthesis was implanted in all of the patients (F40, Biomet, Inc., Warsaw, IN, USA). A standard management protocol, including general or spinal anesthesia, thrombosis prophylaxis, a suitable perioperative antibiotic administration for infection prophylaxis, and physical rehabilitation, was used in all operations. Low-molecular weight heparin was administered as a thrombosis prophylaxis 12 hours prior to surgery and terminated as the patients gained full mobility. Full weight bearing was allowed immediately postoperatively if tolerated by the patients. All patients received a standardized rehabilitation program under the supervision of physiotherapists.

Clinical Outcome Measures

The length of time from hospital admission to operation, the length of hospital stay, the length of hospitalization in the intensive care unit (ICU), the time from operation to dislocation, the presence of postoperative surgical site infection, the type of anesthesia, any medical comorbidities, and the American Society of Anesthesiologists (ASA) score of each patient were obtained from the hospital database.

The type of anesthesia administered was categorized as regional or general. Medical comorbidities involved heart disorders (i.e., congestive heart failure, myocardial infarction), diabetes mellitus, chronic pulmonary disorders, and dementia. ASA scores were documented to assess the physical status of the patients upon admission (13).

Radiographic Outcome Measures

The acetabular abduction angle (AA), femoral offset (FO), center-edge (CE) angle, and limb length discrepancy (LLD) were measured from the first postoperative anteroposterior hip radiographs collected by an experienced orthopedic surgeon. AA ($^{\circ}$) was calculated as the angle between the horizontal line passing through the ischial tuberosities and the line from the acetabular teardrop to the lateral acetabular margin. FO (mm) was calculated as the perpendicular distance between the axis of the femoral shaft and the center of rotation. LLD (mm) was measured by calculating the difference in vertical distance from the inter-teardrop line to the lesser trochanter between both sides (Figure 1).

Statistical Analysis

IBM SPSS Statistics software version 20.0 (IBM Corp., Armonk, New York, NY, USA) was used for statistical analysis, and $p < 0.05$ was regarded as statistically significant. Normality tests were conducted using the Shapiro-Wilk test. Data are presented as "minimum," "maximum," "median," "IQR" "arithmetic mean," "number," and "percentage." The data of the study group were converted to nested case-control data based on a 1:3 ratio of patients to controls. For univariate analyses, parametric data were compared by Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed ones. Non-parametric data were compared using the χ^2 test or Fisher's exact test. For multivariate analyses, conditional logistic regression analyses were performed using a backward elimination technique to identify

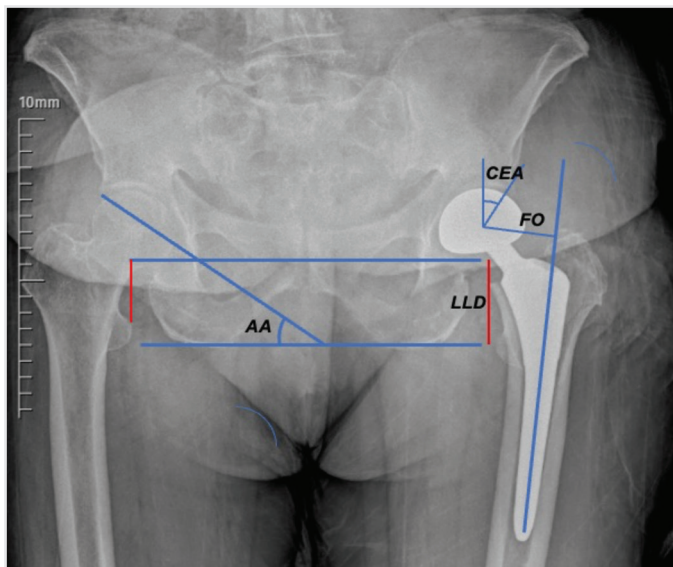


Figure 1. Measurements of center-edge angle, abduction angle, leg length discrepancy, and femoral offset

CEA: Center-edge angle, AA: abduction angle, LLD: leg length discrepancy, FO: femoral offset

independent risk factors for the development of dislocation of hip BHA, with significant variables ($p < 0.25$) as in univariate analyses.

Results

Demographic Characteristics

Of the 103 patients available for the analyses in the current study, 23 patients (12 females, 11 males) were chosen as the study group because they had experienced at least one dislocation following BHA (3 developed recurrent dislocations). A total of 70 patients (33 females, 37 males) who experienced no dislocation were included in the control group. The demographic characteristics of the study population are presented in Table 1. The mechanism of dislocation was atraumatic in 17 patients (74%) and a simple fall in 6 patients (26%).

Univariate Analysis

Table 2 summarizes the clinical and radiographic outcomes of both groups. Univariate analyses showed significant differences between the study and control groups with respect to the following outcome measures: number of postoperative surgical site infections, dementia, CE angle, and FO.

Table 1. Demographic characteristics of the study participants

Characteristic		Study group (23 patients)	Control group (70 patients)	p
Age on admission (year)	Minimum-maximum	68-95	69-96	0.75 ^a
	(Mean ± SD)	81±6.26	82±5.7	
Gender	Female/male	12/11	33/37	0.83 ^b
Side	Right/left	10/13	33/37	0.96 ^b

^aStudent's t-test, ^bPearson's χ^2 test, * $p < 0.05$, SD: standard deviation

Table 2. Comparative analyses of clinical and radiographic outcomes between the case and control groups

		Study group	Control group	p
Clinical outcome measures				
Length of hospital stay	Min-max	5-15	2-27	0.103
	Median-IQR	9-6	8-2	
Length of hospitalization in the ICU	Min-max	0-5	0-6	0.095
	Median-IQR	1-0	0-1	
Number of postoperative surgical site infections	-	9/23 (39%)	5/65 (7%)	0.001**
Type of anesthesia	Regional/general	19/4	54/16	0.32
Dementia		9/23 (39%)	7/70 (10%)	0.003*
ASA	ASA 1-2	8 (34.8%)	32 (45.7%)	0.25
	ASA 3-4	15 (65.2%)	38 (54.3%)	
Radiographic outcome measures				
Acetabular abduction angle	Min-max	29-43	28-44	0.076
	Median-IQR	35-9	33.5-8	
Center-edge angle	Min-max	30-52	32-54	0.037*
	Mean ± SD	40.78±6.01	43.49±5.06	
Femoral offset	Min-max	20-47	20-47	0.047*
	Mean ± SD	32.74±7.2	35.76±5.88	
Limb length discrepancy (mm)	Min-max	0-13	0-15	0.28
	Median-IQR	1.1-1.8	1.9-1.93	

ICU: Intensive care unit, ASA: American Society of Anesthesiologists, IQR: interquartile range, SD: standard deviation, * $p < 0.05$, ** $p < 0.01$
min: minimum, max: maximum

Multivariate Analysis

Variables identified as statistically significant at a p value of 0.05 in the univariate model were included in the multivariate logistic regression to measure their effects on the development of hip BHA dislocation. The multivariate model found the following two significant independent variables that were strongly associated with the risk of developing dislocation: infection and dementia (Table 3).

Discussion

The results of this study indicated an incidence of dislocation of 9.5% after cementless BHA through the posterior approach in elderly patients with displaced femoral neck fractures. Multivariate logistic regression revealed a possibly increased risk for BHA dislocation associated with the development of postoperative site infection and the presence of dementia in these patients.

The dislocation incidence of 9.5% obtained in the current study is comparable with previous reports indicating an incidence of dislocation after BHA ranging from 1% to 11% (6,14,15). However, the literature remains controversial regarding the risk factors that play a role in the development of dislocation after BHA in elderly patients. Several studies have revealed different risk factors ranging from patient-related factors (e.g., history of neurological disease and weakness in the abductor muscles) to surgery-related factors (e.g., choice of surgical approach and prosthesis type) (6-8,16). A prospective cohort study by Enocson et al. (16) on 739 consecutive hips determined that the posterior approach is the only factor associated with a significantly increased risk of dislocation. A study by Kim et al. (6) reported that patients with a CE angle $\leq 44^\circ$ were significantly more prone to develop dislocation than patients with a CE angle $> 44^\circ$. Similarly, Zhang et al. (2) found a significant association between a CE angle $\leq 45.4^\circ$ and dislocation after BHA. In our study, although we found that the CE angle is significantly lower in the group with dislocation after BHA than in the control group after univariate analysis, we did not find a significant relationship between these parameters during multivariate logistic regression analysis. Mukka et al. (14) stated that, in addition to a smaller CE angle, the shortening of the FO and a shorter leg could increase the dislocation rate by decreasing the tension in peripheral soft tissues. In the present case, we

found no significant association between either the FO or LLD and the development of dislocation.

In addition to radiographic parameters, various clinical parameters have been investigated as possible risk factors for the development of dislocation after BHA. For example, Mukka et al. (14) reported that mental status is more likely to be associated with dislocation than age, gender, ASA score, or other factors. Similarly, Madanat et al. (8) determined that dislocation is not associated with age, gender, BMI, dementia, alcohol consumption, living environment, operation time, or operator experience. Similar to Mukka et al. (14) but in contrast to Madanat et al. (8), our logistic regression analysis identified dementia as an independent risk factor for the development of dislocation following BHA. However, in agreement with both studies, we also observed no association between dislocation and other clinical factors, such as age, gender, side of operation, type of anesthesia, ASA score, length of hospital stay, and length of hospitalization in the ICU.

The effect of cement use during hemiarthroplasty on the risk of dislocation remains a controversial issue. Some authors have reported that the use of a cemented stem increases the risk of dislocation (15), while others have determined that stem fixation decreases the dislocation risk (17). In our study, because BHA prostheses were implanted in all patients without the use of cement, we were unable to compare the outcomes of the cementless and cemented techniques. Nonetheless, our reported rate of dislocation is similar to the rates cited in the previous studies discussed above.

Hemiarthroplasty is a popular treatment option for hip fractures in the elderly population; however, many factors that can affect dislocation may occur concomitantly in elderly patients because of the high number of comorbidities that generally accompany aging. For example, muscular dystrophy, cerebrovascular disease, chronic alcoholism, drug use, muscle coordination, and balance disorders may affect the risk of dislocation. Thus, careful examination of the patient's comorbidities during the preoperative period may be helpful in reducing the risk of dislocation following hemiarthroplasty. Surgical technique errors that may cause dislocation, such as component malposition, implant selection, and the surgeon's experience, are other factors that require separate investigations.

Table 3. Results of multivariate logistic regression analysis

		B	S.E.	Wald	df	Sig.	Exp (B)
Step 1	Length of hospital stay	-0.059	0.086	0.480	1	0.489	0.942
	Length of hospitalization in the ICU	-0.276	0.255	1.175	1	0.278	0.759
	Number of postoperative surgical site infections	1.511	0.775	3.801	1	0.051*	4.530
	Dementia	1.634	0.711	5.278	1	0.022*	5.123
	ASA	0.091	0.631	0.021	1	0.885	1.096
	Acetabular abduction angle	-0.112	0.067	2.752	1	0.097	0.894
	Center-edge angle	0.091	0.060	2.309	1	0.129	1.095
	Femoral offset	0.008	0.052	0.025	1	0.875	1.008
	Constant	-0.772	4.060	0.036	1	0.849	0.462

ICU: Intensive care unit, ASA: American Society of Anesthesiologists, *p<0.05

Study Limitation

The present study included several limitations that must be considered when interpreting the results. First, this study has a relatively small sample size, which limits the power of the results. However, the power was strengthened by the use of a nested case-control design, which is often adopted when the outcome is rare or when the feature of interest is difficult to obtain. In the current study, we performed a 1:3 ratio nested case-to-control study. For each dislocation patient, we matched three control patients in terms of age and sex to eliminate several confounding factors and increase the reliability of the study.

Conclusion

Evidence from this study showed that postoperative surgical site infection and dementia are independent risk factors for hip dislocation following BHA in elderly patients with displaced femoral neck fractures. Further controlled, randomized, prospective studies are needed to confirm the feasibility and effectiveness of cementless stem fixation in BHA.

Ethics Committee Approval: The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 2657, date: 08.01.2021).

Informed Consent: Written informed consent was obtained from all participants prior to their participation in this study.

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First Case-Control Study of Intestinal Parasites in Follow-up Schizophrenia Patients: Are We Overlooking the Role of These Agents?

Takip Edilen Şizofreni Hastalarında Barsak Parazitleri Araştırılmasındaki İlk Olgu Kontrol Çalışması: Bu Ajanların Rolünü İnceliyor Muyuz?

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ABSTRACT

Introduction: Disability and decrease in the quality of life owing to the nature of schizophrenia are considered factors that predispose patients to parasitic infections. This study aimed to investigate intestinal parasites in schizophrenia and healthy volunteers with similar age-gender data and to contribute to the literature and/or clinical practice by determining the underlying cause of gastrointestinal complaints (such as side effects of psychiatric drugs or overlooked parasitic infection) in patients with schizophrenia.

Methods: This case-control study included 30 patients with schizophrenia and 30 healthy volunteers. Their stool samples were examined for the presence of intestinal parasites primarily microscopically or serologically in cases requiring differential diagnosis.

Results: The overall positivity rate of intestinal parasites was 25% (15/60). The difference between the intestinal parasite detection rates, which was 36.7% (11/30) in the schizophrenia group and 13.3% (4/30) in the healthy control group, was significant (odds ratio: 3.76; 95% confidence interval: 1.04-13.65; $p < 0.05$). The distribution of parasite species varied: 6 (20%) patients had *Blastocystis* spp., 3 (10%) had *Giardia intestinalis* (*G. intestinalis*), and 2 (6.7%) had *Entamoeba histolytica* in the schizophrenia group, whereas 3 (10%) had *Blastocystis* spp. and 1 (3.3%) had *G. intestinalis* in the healthy control group.

Conclusion: To increase the quality of life of patients with a chronic psychiatric disease such as schizophrenia and to prevent possible transmission, periodic examination of parasitic agents is necessary in addition to psychiatric treatment and further studies are needed.

Keywords: Intestinal parasites, schizophrenia, healthy control

ÖZ

Amaç: Şizofreninin doğası gereği gözlenen yetiyitimi ve yaşam kalitesindeki azalma, sekonder olarak parazitler enfeksiyonlara zemin hazırlayan bir faktör olarak değerlendirilmektedir. Bu olgu-kontrol çalışmasına, şizofreni tanısı ile takip edilen hastalar ve yaş-cinsiyet verileri benzer sağlıklı gönüllüler dahil edilerek bu olgu grubundaki barsak parazitlerinin araştırılması amaçlanmıştır. Ayrıca, şizofreni hastalarındaki gastrointestinal şikayetlerin altta yatan nedeni (psikiyatrik ilaç yan etkisi veya gözden kaçırılan parazitler enfeksiyon varlığı) konusunda bilgi sahibi olunarak literatüre ve/veya klinik pratiğe katkı sağlanması amaçlanmıştır.

Yöntemler: Çalışmaya 30 şizofreni tanılı hasta ve 30 sağlıklı gönüllü dahil edilmiş, toplamda 60 olgudan dışkı örnekleri alınmış ve bu örneklerdeki bağırsak parazitleri öncelikli olarak mikroskopik ayırıcı tanı gereken durumlarda ise serolojik olarak araştırılmıştır.

Bulgular: Çalışmada, barsak parazitlerinin genel pozitiflik oranı %25 (15/60) olarak belirlenmiştir. Şizofreni grubundaki hastalarda %36,7 (11/30), sağlıklı kontrol grubunda %13,3 (4/30) olarak dağılım gösteren barsak paraziti saptanma oranları arasındaki farkın ise istatistiksel olarak anlamlı olduğu belirlenmiştir (olasılık oranı: 3,76; %95 güven aralığı: 1,04-13,65; $p < 0,05$). Şizofreni grubunda 6 olguda (%20) *Blastocystis* spp., 3 olguda (%10) *Giardia intestinalis* (*G. intestinalis*) ve 2 olguda (%6,7) ise *Entamoeba histolytica* saptanmış; sağlıklı kontrol grubunda ise 3 olguda (%10) *Blastocystis* spp. ve 1 olguda (%3,3) ise *G. intestinalis* saptanmıştır.

Sonuç: Şizofreni gibi kronik bir psikiyatrik hastalığı olan hastaların yaşam kalitesinin artırılması ve olası bulaşın engellenmesinde psikiyatrik tedavinin yanı sıra parazitler ajanların da periyodik olarak araştırılması ve bu konuda daha ileri araştırmalara ihtiyaç olduğu düşünülmüştür.

Anahtar Kelimeler: Barsak parazitleri, şizofreni, sağlıklı kontrol



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Introduction

Schizophrenia is a chronic psychiatric disease with an early onset and variable clinical and related disability. The general prevalence of schizophrenia varies between 1% and 1.5%, without significant difference between genders in terms of its incidence, but the age of onset is earlier in men than in women (1). In the etiology of schizophrenia, theories related to genetic factors, obstetric anomalies, intrauterine infections, neurodevelopmental, and neurotransmitters are emphasized (2). Pathogens that can manipulate neurotransmitter levels and are therefore defined as neurotrophic microorganisms have been frequently investigated recently to elucidate the etiology of various psychiatric diseases, especially schizophrenia (3,4).

Slow proliferation, ability to escape from the immune system, potential for latent infection, and affinity to the central nervous system are listed as basic characteristics of neurotrophic microorganisms. Among the neurotrophic microorganisms, viruses in the Herpesviridae family (Herpes Simplex virus 1/2, Epstein-Barr virus, and cytomegalovirus), influenza virus, and *Toxoplasma gondii*, a parasite, are shown as the strongest candidates (5). However, studies investigating the relationship between other medically important parasites and psychiatric diseases have remained quite limited, and the implications of the possible presence of parasitic infection in this patient group have not yet been elucidated.

Parasitic intestinal infections remain an important public health problem in our Turkey, similar to global data. Factors determining the social frequency of parasitic intestinal infections include age, gender, socioeconomic level, education, nutrition, traditions, climatic factors, presence in public areas, and hygienic habits (6). In groups with underlying diseases or need of special care, diagnosis of intestinal parasitic infections gains importance to reduce social transmission and to develop more effective strategies in combating parasitosis (7).

In addition to strengthening this hypothetical approach by investigating the correlation between the pathophysiology of psychiatric disease and microorganisms (8), the investigation of intestinal parasites as comorbid infection agents in patients with psychiatric disorders and disability is underestimated. Increasing the quality of life, preventing possible contamination in hospitalization, which is frequently applied for therapeutic purposes, and providing in-home care in patients who are diagnosed with a chronic psychiatric disease such as schizophrenia due to loss of function (3) are important for both psychiatric clinic and public health.

This study was designed to bridge the research gap in this topic. Patients diagnosed with schizophrenia and healthy volunteers with similar age and gender data were included in this case control study. The presence of intestinal parasites was examined microscopically. ELISA was used in cases where the differential diagnosis was required, and the results obtained were compared with sociodemographic characteristics and disease status.

Methods

A total of 60 patients (30 patients with schizophrenia and 30 healthy volunteers) between January 2020 and September 2020 were included

in this case-control study. The study was approved by the Istanbul Aydın University Non-invasive Clinical Research Ethics Committee (approval number: 2019/128). Written and/or oral informed consent was obtained from all patients.

Thirty patients with schizophrenia living in Istanbul who were followed up in the Department of Psychiatry at Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, were included as the first group. The diagnosis of schizophrenia was made according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. The healthy control group consisted of 30 participants without any psychiatric disease or family history according to semi-structured interviews with the Structured Clinical Interview for DSM-5 and having similar age and gender data with the schizophrenia group. Sociodemographic data of all participants were recorded, and participants using antiparasitic drugs were excluded from the study.

Stool samples were taken from the 60 study participants. Stool samples collected were first examined macroscopically and then microscopically. For microscopic examination, Native-Lugol and formol-ethyl acetate concentration methods were used, and the presence of intestinal parasites in the preparations was evaluated microscopically at 10x and 40x magnifications. If parasite identification was unclear in the microscopic examination, these samples were examined by ELISA (Seramun Diagnostica GmbH, Wolzig, Germany), and the parasitological diagnosis was confirmed.

Statistical Analysis

The number of cases to be included in the study groups was calculated with the G*Power 3.1.9.6 program by taking $\alpha=0.5$ and $\beta=0.20$ so that the power of the test would not be less than 80%. Statistical analysis of the study results was carried out using the IBM SPSS program 26.0 version (IBM Corp., Armonk, NY, USA). Descriptive statistics including tables were used to describe the data. Categorical variables are represented as counts, and frequency distributions were compared with Pearson's chi-square tests. Continuous variables are expressed as median and interquartile range (IQR). Mann-Whitney U test was used to identify differences between groups. To control for confounders that were significant in the univariate analysis, a multiple logistic regression model was employed to investigate the independent association of schizophrenia with intestinal parasites. Odds ratio (OR) along with its 95% confidence interval (CI) was used to assess the relationship between dependent and independent variables. The significance limit was accepted as two-tailed at $p<0.05$.

Results

A total of 60 patients (schizophrenia group, $n=30$; healthy group, $n=30$) were included in this case-control study, and stool samples were examined by microscopic and/or serological methods to detect intestinal parasites.

The median patient age in the schizophrenia group was 37 years (IQR: 47-31) and that in the healthy control group was 40 years (IQR: 46-32), and the two data were comparable (OR: 0.03; 95% CI: -0.10 to 0.13; $p=0.859$). There were 10 (33.3%) female and 20 (66.7%) male patients

in the schizophrenia group and 11 (36.7%) female and 19 (63.3%) male volunteers in the healthy control group, and gender data were evaluated as statistically similar (OR: 1.16; 95% CI: 0.40-3.35; $p=0.787$). In the schizophrenia group, 24 (80%) patients were single and 6 (20%) were married; in the healthy control group, 16 (53.3%) were single and 14 (46.7%) were married, and the difference in the marital status was different (OR: 0.28; 95% CI: 0.09-0.90; $p=0.018$). Similarly, the median total duration of education was 8.5 years (IQR: 14-5) in the schizophrenia group and 12 years (IQR: 16-8) in the healthy control group, and the difference was significant (OR: -0.29; 95% CI: -0.58 to 0.00; $p=0.043$). As regards sociodemographic features, the groups demonstrated significant difference in working status. The number of working/non-working patients in the schizophrenia group was 11 (36.7%)/19 (63.3%) and that in the healthy control was 25 (83.3%)/5 (16.7%), respectively, and the difference was highly significant (OR: 8.64; 95% CI: 2.56-29.07; $p<0.001$). Comparative sociodemographic data of all cases included in the study are shown in Table 1.

The presence of intestinal parasites in stool samples was examined microscopically and/or serologically. Intestinal parasites were detected in 11 (36.7%) patients in the schizophrenia group, while no parasites were found in 19 (63.3%) patients. Intestinal parasite was detected in 4 (13.3%) of the volunteers in the healthy control group, while no parasites were detected in 26 (86.7%). Higher rates of intestinal parasites were detected in the schizophrenia group than in the healthy control group, and the difference was significant (OR: 3.76; 95% CI: 1.04-13.66;

$p=0.021$). In the multivariate logistic regression analysis, only having a schizophrenia diagnosis had a significant influence on the presence of intestinal parasites (OR: 5.16; 95% CI: 1.11-23.97; $p=0.036$), and all results are summarized in Table 2.

The distribution of intestinal parasite species that were microscopically detected and serologically confirmed [for *Entamoeba histolytica* (*E. histolytica*)/*dispar* distinction] between groups was determined. No more than one intestinal parasite was detected in the same stool sample in any study participant. In the schizophrenia group, 6 (20%) participants had *Blastocystis* spp., 3 (10%) had *Giardia intestinalis* (*G. intestinalis*), and 2 (6.7%) had *E. histolytica*. In the healthy control group, *Blastocystis* spp. was detected in 3 (10%) participants and *G. intestinalis* in 1 (3.3%) participant. The distribution of parasite species detected in schizophrenia and healthy control groups is summarized in Table 3.

Discussion

This case-control study investigated intestinal parasites in patients with schizophrenia undergoing follow-up and compared the results with healthy volunteers. Following literature review, to our knowledge, this is the first study that compared the distribution of intestinal parasites between the schizophrenia group and healthy control group. Primarily, this study found that intestinal parasites were detected more frequently in patients with schizophrenia (36.7%) than in healthy volunteers (13.3%), and the difference was significant ($p<0.05$).

Table 1. Sociodemographic characteristics of the participants

		Schizophrenia	Healthy control	Univariate OR (95% CI)	p-value
Age, median, years (IQR)		37 (47-31)	40 (46-32)	0.03 (-0.10 to 0.13)	0.859
Gender, n (%)	Female	10 (33.3%)	11 (36.7%)	1.16 (0.40-3.35)	0.787
	Male	20 (66.7%)	19 (63.3%)		
Marital status, n (%)	Single	24 (80%)	16 (53.3%)	0.28 (0.09-0.90)	0.018
	Married	6 (20%)	14 (46.7%)		
Education median years (IQR)		8.5 (14-5)	12 (16-8)	-0.29 (-0.58 to 0.00)	0.043
Employment, n (%)	Unemployed	11 (36.7%)	25 (83.3%)	8.64 (2.56-29.07)	<0.001
	Employed	19 (63.3%)	5 (16.7%)		

IQR: Interquartile range, OR: odds ratio, CI: confidence interval

Table 2. Distribution of intestinal parasite presence

		Schizophrenia	Healthy control	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Intestinal parasite, n (%)	Negative	19 (63.3%)	26 (86.7%)	3.76 (1.04-13.66)	<0.05	5.16 (1.11-23.97)	0.036
	Positive	11 (36.7%)	4 (13.3%)				

OR: Odds ratio, CI: confidence interval

Table 3. Distribution of intestinal parasite species

Intestinal parasite species	Schizophrenia, n (%)	Healthy control, n (%)
<i>Blastocystis</i> spp.	6 (20%)	3 (10%)
<i>Giardia intestinalis</i>	3 (10%)	1 (3.3%)
<i>Entamoeba histolytica</i>	2 (6.7%)	-
Total	11 (36.7%)	4 (13.3%)

In the study, the most common intestinal parasites in both schizophrenia and healthy control groups were *Blastocystis* spp. (9). The global prevalence of *Blastocystis* spp. varies between 1.5% and 50%, and this proportional difference may be related to bad hygienic habits and development level of patient's geographic location (10). Although its taxonomy, life cycle, and epidemiology are not yet clear, data on the pathogenicity of this parasite, which is widely detected worldwide, are inconsistent. According to current knowledge, if parasite is seen >5 times in a microscope field at 40x magnification and no other parasitic/viral/bacterial agent is detected, it is considered a pathogen, and if the patient experiences clinical signs, parasitism should be treated. Parasitism is still frequently associated with gastrointestinal complaints such as fatigue, anorexia, flatulence, abdominal pain, and diarrhea, which cannot be explained by any other reason (11). *Blastocystis* spp. was found in 6 (20%) of 30 patients with schizophrenia and in 3 (10%) of 30 healthy volunteers. Among the possible reasons for the more frequent detection of the parasites known to be transmitted by the fecal-oral route in the schizophrenia group is poor hygienic habits, which resulted from a lack of self-care.

In this case-control study, the second most common parasite was *G. intestinalis*. *G. intestinalis* is one of the most common anterior intestinal parasites among humans worldwide and is transmitted by contaminated water or food (12). Poor living conditions, living in a crowded house or a dirty environment, and having a low socioeconomic status are among other risk factors associated with transmission (13). *G. intestinalis* infections, which are often asymptomatic in healthy individuals, may lead to varying clinical pictures, ranging from mild diarrhea to severe malabsorption (14). In a study conducted after the water-borne *G. intestinalis* epidemic in Norway in 2004 (15), cases were examined 5 years after the epidemic, and 54.7% (29/53) of the cases were reported to have chronic fatigue syndrome due to giardiasis. In addition, the authors emphasized that pathogens such as *G. intestinalis* should be considered in the differential diagnosis of diseases that may have a psychiatric basis such as chronic fatigue syndrome (15). In our study, *G. intestinalis* was found in 3 (10%) patients in the schizophrenia group and only 1 (3.3%) in the healthy control group.

In our study, *E. histolytica/dispar* was detected microscopically in only two patients in the schizophrenia group, and the species distinction in these cases was made by ELISA. Amebiasis is a common parasitic disease caused by *E. histolytica* (16). Two clinical forms, namely, intestinal and extraintestinal, of clinical amebiasis are caused by *E. histolytica* present in contaminated water and food (17). *E. histolytica* amebiasis has varied prevalence worldwide, which varies between 0.4% and 18.4% in Turkey (18). Serological and molecular-based diagnostic methods should be applied routinely due to the insufficiency of microscopic methods in the differentiation of pathogenic amoeba species (19). Therefore, in our study, the differential diagnosis of two patients with *E. histolytica/dispar* was made by ELISA. In this study, *E. histolytica* was detected in only 2 (6.7%) patients in the schizophrenia group, and this parasite was not found in any participants in the healthy control group. To our knowledge, our study was the first study that comparatively identified intestinal parasites in patients with schizophrenia and healthy volunteers on a case-control basis. Only one study (20) conducted in Ghana in 2015

partially parallels the general concept of our study. That cross-sectional study included 111 patients in a psychiatric hospital, independent of psychiatric diagnosis, and did not include a healthy control group. Intestinal parasites in the included patients were examined only by microscopic methods. The authors reported that intestinal parasites were detected in 13.5% (15/111) of the patients, and the most common parasite was *E. histolytica/dispar* (20). The intestinal parasite detection rate of 13.5% reported in a previous study (20) was lower than that in our study (36.7%), and this difference was thought to be due to the study design and limitations reported by the authors.

Study Limitation

Besides the contribution of our study with preliminary results on the presence of intestinal parasites in patients with schizophrenia, this study has two major limitations that could be addressed in future research. First, this study enrolled a relatively small sample size due to the low compliance of patients with schizophrenia to the nature of this study, which would bias the results toward the null hypothesis. Second, we were unable to evaluate the serological methods for the detection of all intestinal parasites for economic reasons.

Conclusion

In addition to the pathophysiological/etiological basic enlightenment studies in chronic psychiatric diseases such as schizophrenia, further studies are needed to increase public health and the quality of life of the patient. For further research, it will be possible to reduce confusion for the gastrointestinal symptoms associated with parasitic infections or the side effects of antipsychotic drugs used in the treatment. Thus, this study may have clinical contributions to psychiatric treatment compliance.

Ethics Committee Approval: The study was approved by the İstanbul Aydın University Non-Invasive Clinical Research Ethics Committee (approval number: 2019/128).

Informed Consent: Written and/or oral informed consent was obtained from all patients.

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The Relationship of Thyroid Nodules with Total Serum IgE Level and Metabolic Parameters in Patients with Hashimoto Thyroiditis

Hashimato Tiroiditli Hastalarda Tiroid Nodülünün Total Serum IgE Düzeyi ve Metabolik Parametreler ile İlişkisi

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ABSTRACT

Introduction: The literature demonstrates elevated immunoglobulin E (IgE) levels in autoimmune thyroid diseases and their relationship with allergic diseases. The purpose of this study was to describe the relationship between thyroid nodules and total serum IgE levels and metabolic parameters in patients with Hashimoto thyroiditis.

Methods: The study included 627 Hashimoto thyroiditis patients [500 (female: 406, male: 94) with and 127 (female: 101, male: 26) without thyroid nodules] and 292 (female: 224, male: 68) healthy control patients. Total serum IgE levels, metabolic parameters, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol, low-density lipoprotein cholesterol, triglyceride, uric acid, free-T4, free-T3, thyroid stimulating hormone, anti-thyroglobulin, anti-thyroid peroxidase, C-reactive protein (CRP) levels, and sedimentation rate were measured in all groups. Moreover, SPSS was used to analyze the results.

Results: The mean age, serum IgE levels, mean FBG, HbA1c, and CRP levels of the thyroid nodule group were statistically significantly higher than the non-nodule and control groups ($p<0.05$). In all Hashimoto thyroiditis patients, metabolic parameter levels were statistically significantly higher than in control groups ($p<0.05$).

Conclusion: There is a significant relationship between serum total IgE levels and thyroid nodules. Furthermore, thyroid nodule development appears to be influenced by metabolic and inflammatory abnormalities. These findings confirm the presence of multisystem factors in the development of thyroid nodules.

Keywords: Hashimoto thyroiditis, serum total IgE level, thyroid nodules

ÖZ

Amaç: Tiroid nodülü ile alerjik hastalıklar ve yüksek immünoglobulin E (IgE) arasındaki ilişki çeşitli çalışmalarla gösterilmiştir. Burada Hashimato tiroidit tanılı hastalarda tiroid nodülleri ile total serum IgE düzeyi ve metabolik parametreler arasındaki ilişkinin gösterilmesi amaçlanmıştır.

Yöntemler: Çalışmaya 16-78 yaş arası toplam 500 (406 kadın, 94 erkek) tiroid nodülü olan ve 21-73 yaş arası 127 (101 kadın, 26 erkek) tiroid nodülü olmayan toplam 627 hashimato tiroidit tanılı hasta ile 17-76 yaş arası 292 (224 kadın, 68 erkek) kontrol hastası dahil edilmiştir. Tüm hasta ve kontrol gurubunda total serum IgE düzeyi serum metabolik parametreler [açlık kan şekeri (AKŞ), hemogloblin A1c (HbA1c), total kolestrol, düşük yoğunluklu lipoprotein-kolesterol, trigliserit), ürik asit, T4, T3, tiroid stimüle edici hormon, anti-tiroglobulin, C-reaktif protein (CRP) değerleri bakılmıştır.

Bulgular: Tiroid nodüllü hasta grubunun yaş ortalaması ve serum IgE ortalaması, nodülsüz hasta grubu ve kontrol grubuna göre istatistiksel olarak anlamlı şekilde yüksekti ($p<0,05$). Nodüllü hasta grubunda AKŞ, HbA1c ortalaması ve CRP düzeyi kontrol grubu ve nodülsüz hasta grubuna göre anlamlı yüksekti ($p<0,05$). Tüm Hashimato hasta grubunda (grup 1 ve grup 2) metabolik parametreler (total-kol, LDL- Kol, Trigliserit, sedimentasyon, ürik asit) düzeyleri kontrol grubuna göre anlamlı yüksekti ($p<0,05$).

Sonuç: Bu çalışma serum total IgE düzeyi tiroid nodül varlığı arasında güçlü bir ilişki olduğunu aynı zamanda bazı metabolik ve enflamatuvar parametrelerdeki anormalliklerin tiroid nodül oluşumuna katkısı olabileceği gösterilmiştir. Bu durum nodül oluşumunda bazı sistemik nedenlerin varlığını ortaya koyduğunu destekler niteliktedir.

Anahtar Kelimeler: Hashimato tiroidit, serum total IgE düzeyi, tiroid nodül



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Introduction

Hashimoto thyroiditis is an autoimmune disease characterized by the presence of specific autoantibodies against the thyroid gland. Endogenous causes, as well as genetic and environmental factors, contribute to its etiology. Moreover, its prevalence increases with age and female gender. During the course of the disease, nodule development is common. Thyroid nodules are often found during clinical investigations and imaging procedures, and they are significant due to their malignant potential (1). In addition, thyroid nodules are defined by the American Thyroid Association as “thyroid gland lesions which are radiologically distinct from thyroid parenchyma” (2). In the adult population, its prevalence is estimated to be 20-76% by ultrasonography (USG) (1,3,4) and 50-60% in autopsy series (5). Autoimmunity, radiation exposure, genetics, and iodine consumption all play a role in its etiology.

IgE is an antibody that is important in the pathogenesis of allergic diseases. In individuals who are susceptible, antigen-presenting cells (macrophages, B lymphocytes) phagocytose antigens and present them to CD4+ T-lymphocytes in the context of molecules of class II major histocompatibility complex. T-lymphocytes develop a specific sensitivity to these allergens and turn to specific T-lymphocyte subgroup clones. T-helper lymphocytes produce immunoglobulin E (IgE) via interleukin-4 (IL-4) and other cytokines. IgE has been linked to both autoimmune thyroid diseases (AITD) and allergic diseases. Further, IgE levels were found to be elevated, especially in Graves' disease (6-8). The high prevalence of chronic urticaria in AITD patients (9) and the specific IgE development against thyroid peroxidase (TPO), which has been shown to play a role in chronic urticaria pathogenesis (10,11), suggest a strong relationship between thyroid diseases and IgE. However, no studies on the effect of IgE on nodule development have been conducted in AITD.

The purpose of this study was to investigate the effect of IgE on nodule development in Hashimoto thyroiditis patients, as well as the relationship between thyroid nodule presence and inflammatory and metabolic parameters.

Methods

Study Subjects

The study included 500 (female: 406, male: 94, age: 16-78) Hashimoto thyroiditis patients with ultrasonographically proven thyroid nodule presence, 127 (female: 101, male: 26, age: 21-73) Hashimoto thyroiditis patients without thyroid nodules, and 292 (male: 224, female: 68, age: 17-76) healthy subjects as the control group. Moreover, the study was designed to recruit patients from an internal medicine outpatient clinic in a systematic and prospective manner. Smoking, excessive alcohol intake, medication other than for thyroid diseases, and the presence of any other accompanying diseases were all exclusion criteria.

The study protocol was approved by the University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 1950, date: 09.08.2019).

Measurement of Biochemical Parameters

Fasting blood glucose (FBG), triglycerides, C-reactive protein (CRP), uric acid, IgE, total cholesterol, and low-density lipoprotein (LDL) cholesterol

were analyzed using a biochemistry analyzer (Beckman Coulter AU 2700) (Beckman Coulter Inc., Brea, USA). In addition, hemoglobin A1c (HbA1c) parameter was analyzed on the Premier Hb9210 HPLC analyzer (Trinity Biotech, Ireland).

The levels of anti-thyroglobulin, TPO, thyroid stimulating hormone (TSH), free-T4, and free-T3 were analyzed using an immunoassay analyzer [Beckman Coulter DXI 800 (Beckman Coulter Inc., Brea, USA)]. On the other hand, the erythrocyte sedimentation rate was analyzed using the Berkun SDM-100 Auto-instrument (Turkey).

Thyroid Evaluation

Thyroid USG was performed by an experienced radiology specialist using a SSA-770A, Aplio 300 ultrasound machine (Toshiba Medicals, Otawara, Japan) equipped with a 7-15 MHz linear transducer (PLT-1204AT; Toshiba Medical Systems).

Radiological reports of thyroid nodules were reviewed using PACS data of our institution. A thyroid nodule is a discrete lesion that is distinct from the surrounding thyroid parenchyma. The maximum diameter of a thyroid nodule was measured in three planes: longitudinal, transverse, and anteroposterior. Further, these detailed reports included sonographical behavior (hypoechoogenicity vs hyperechoogenicity), cystic or solid components, calcifications, contour properties, and peripheral vascular halo integrity.

Statistical Analysis

For categorical variables, descriptive statistics were reported as a number and percentage, while numerical variables were reported as mean, standard deviation, minimum, maximum, and median. The Kolmogorov-Smirnov test was used to determine the distribution of variables. For the analysis of quantitative independent data, the Kruskal-Wallis H and Mann-Whitney U tests were used. For the analysis of qualitative independent data, the chi-square test was used. The statistical alpha significance level was regarded as $p < 0.05$. Moreover, the statistical analysis was carried out using SPSS 22.0 for Windows program.

Results

The study included a total of 919 patients: 500 Hashimoto thyroiditis patients with thyroid nodules (group 1), 127 Hashimoto thyroiditis patients without thyroid nodules (group 2), and 292 healthy subjects as the control group (group 3).

Table 1 displays laboratory and clinical data from all groups.

The mean age of group 1 was statistically significantly higher than groups 2 and 3 ($p < 0.05$), and the mean age of group 2 was statistically significantly higher than group 3 ($p < 0.05$) (Table 1).

FBG, HbA1c, IgE, and CRP levels in group 1 were statistically significantly higher than in groups 2 and 3 ($p < 0.05$). There was no statistically significant difference in these values between groups 2 and 3 (Table 1).

In groups 1 and 2, uric acid, LDL cholesterol, triglyceride, and sedimentation rates were statistically significantly higher than in group 3 ($p < 0.05$). There was no statistically significant difference in these values between groups 1 and 2 (Table 1).

In groups 1 and 2, the fT3 level was statistically significantly lower than in group 3. However, there was no significant difference in fT3 levels between groups 1 and 2 ($p>0.05$) (Table 1).

In group 2, TSH, anti-TPO, and anti-TG levels were statistically significantly higher than in groups 1 and 3 ($p<0.05$). These values were statistically significantly higher in group 1 than in group 3 ($p<0.05$) (Table 1).

In group 1, there was no correlation between IgE levels and anti-TPO ($p=0.862$) and anti-TG ($p=0.882$) levels. Also, there was no correlation between IgE level and anti-TPO ($p=0.766$) and anti-TG ($p=0.194$) levels in group 2 (Table 2).

Discussion

This study showed that there could be a relationship between thyroid nodules, serum IgE levels, and metabolic and inflammatory parameters in Hashimoto thyroiditis patients. The mean IgE level was found to be 128 UI/mL in most patients and 200 UI/mL or higher in 3% of thyroid nodule patients. In the non-nodule group, the mean IgE level was only 49 UI/mL. This difference was statistically significant, implying that IgE-mediated allergic reaction could be contributing to nodule formation.

IgE is a critical factor in allergic reactions. In studies, the contribution of IgE-mediated inflammation in the AITD development and reactivation

Table 1. Laboratory and clinical data of all groups

	Group 1		Group 2		Group 3		p	
	Mean \pm SD/n, (%)	Med	Mean \pm SD/n, (%)	Med	Mean \pm SD/n, (%)	Med		
Age	53.8 \pm 13.8	55.0	47.9 \pm 14.2	47.0	44.2 \pm 16.1	45.0	0.001 ^K	
Gender	Female	406 (81.2%)	-	101 (79.5%)	-	224 (76.7%)	-	0.320 χ^2
	Male	94 (18.8%)	-	26 (20.5%)	-	68 (23.3%)	-	
FBG	107.5 \pm 34.1	99.0	99.8 \pm 22.3	95.0	102.2 \pm 28.3	95.0	0.001 ^K	
IgE	128.5 \pm 401.7	34.5	49.3 \pm 60.8	28.5	56.9 \pm 80.2	29.0	0.024 ^K	
CRP	0.8 \pm 2.0	0.3	0.5 \pm 0.7	0.2	0.5 \pm 1.0	0.2	0.001 ^K	
Urea	30.2 \pm 10.0	28.0	27.2 \pm 7.7	26.0	27.9 \pm 10.1	26.0	0.001 ^K	
Uric acid	5.2 \pm 1.5	5.1	5.0 \pm 1.3	4.9	4.8 \pm 1.4	4.5	0.001 ^K	
Creatinin	0.7 \pm 0.2	0.7	0.7 \pm 0.2	0.7	0.7 \pm 0.2	0.7	0.570 ^K	
Cholesterol	215.9 \pm 47.3	214.0	215.5 \pm 54.8	220.0	201.7 \pm 46.0	194.0	0.001 ^K	
Triglyceride	149.6 \pm 105.2	121.0	148.7 \pm 93.9	127.0	132.5 \pm 87.0	108.0	0.013 ^K	
HDL	52.2 \pm 12.8	50.0	51.6 \pm 12.3	51.0	51.5 \pm 13.3	49.0	0.596 ^K	
LDL	135.1 \pm 40.6	133.4	139.6 \pm 39.1	137.6	124.4 \pm 39.0	121.2	0.001 ^K	
fT3	3.3 \pm 0.6	3.3	3.4 \pm 0.8	3.3	3.4 \pm 0.6	3.4	0.009 ^K	
fT4	0.9 \pm 0.2	0.9	0.9 \pm 0.3	0.9	0.9 \pm 0.3	0.9	0.195 ^K	
TSH	2.9 \pm 8.7	1.6	7.4 \pm 18.1	2.7	2.6 \pm 6.6	1.8	0.001 ^K	
Anti-TPO	85.6 \pm 232.9	1.2	276.0 \pm 349.2	109.1	1.5 \pm 3.4	0.7	0.001 ^K	
Anti-TG	31.5 \pm 140.6	0.9	105.1 \pm 329.0	9.2	4.1 \pm 51.0	0.9	0.001 ^K	
Sedim	21.5 \pm 15.1	18.0	20.4 \pm 13.1	17.0	18.9 \pm 15.2	14.5	0.007 ^K	
Hb1Ac	6.0 \pm 1.0	5.8	5.8 \pm 0.8	5.6	5.9 \pm 1.0	5.7	0.001 ^K	
WBC	7.2 \pm 2.4	7.0	7.1 \pm 1.6	7.0	7.2 \pm 1.8	7.0	0.676 ^K	
Neutrophil	4.0 \pm 1.6	3.8	3.9 \pm 1.2	3.7	4.0 \pm 1.3	3.7	0.708 ^K	
Lymphocyte	2.4 \pm 1.5	2.3	2.4 \pm 0.7	2.4	2.5 \pm 1.2	2.4	0.051 ^K	
Monocyte	0.5 \pm 0.2	0.5	0.6 \pm 0.2	0.5	0.6 \pm 0.2	0.6	0.303 ^K	
PCT	0.3 \pm 0.1	0.3	0.3 \pm 0.1	0.3	0.4 \pm 1.5	0.3	0.841 ^K	

^K: Kruskal-Wallis (Mann-Whitney U test) / χ^2 : chi-square test. Group 1: thyroid nodule (+), Group 2: thyroid nodule (-), Group 3: control group, SD: standard deviation, FBG: fasting blood glucose, IgE: immunoglobulin E, CRP: C-reactive protein, HDL: high-density lipoprotein, LDL: low-density lipoprotein, fT3: free T3, fT4: free T4, TSH: thyroid stimulating hormone, TPO: thyroid peroxidase, TG: thyroglobulin, Hb1Ac: hemoglobin A1c, WBC: white blood cell, PCT: procalcitonin

Table 2. Relationship between IgE level and thyroid auto-a

	Group 1		Group 2	
	Anti-TPO	Anti-TG	Anti-TPO	Anti-TG
IgE	0.008	0.007	-0.027	0.116
	0.862	0.882	0.766	0.194

Spearman correlation. TPO: Thyroid peroxidase, TG: thyroglobulin, IgE: immunoglobulin E

has been discussed. Elevated IgE levels were found particularly in Graves' disease (30-40%) and Hashimoto thyroiditis (20.8%). However, in other studies, a similar elevation was not found, which was thought to be due to ethnically low rates of allergic diseases (7,12,13).

Several studies involving chronic urticaria and AITD implicated IgE in thyroid autoimmunity (14-16). This data was supported by another study that showed a high prevalence of Hashimoto thyroiditis in chronic urticaria patients and thyroid hormone replacement reduced urticaria symptoms (17). However, no studies have been conducted to demonstrate the effect of IgE on nodule formation in AITD.

Total serum IgE secretion is found on chromosome 5q31, which also contains some cytokines (18,19). IL-13 is an anti-inflammatory cytokine that induces and preserves IgE production and IgE-mediated allergic responses (20). Moreover, 64.7% of patients with high IgE levels also have high IL-13 (7). IL-4 and IL-13 share biologic activity that promotes IgE secretion. Concomitant secretion of IgE and cytokines increases the inflammation and may contribute to thyroid nodule formation.

Impaired fasting glucose, insulin resistance, and lipid abnormalities are all components of metabolic syndrome, which is a major cause of cardiovascular morbidity and mortality. Elevated FBG is associated with type 2 diabetes mellitus (DM), insulin resistance, elevated insulin levels, and a defect of insulin usage at peripheral tissues, and these tissues are susceptible to its proliferative effect. In our study, FBG, HbA1c, and lipid parameters were significantly higher in the nodule group than in the non-nodule group. Other studies have found a link between glucose metabolism disorder and thyroid nodule presence. Wang et al. (21) discovered a relationship between insulin resistance and thyroid nodule size (21). According to other studies, thyroid volume and nodule prevalence increased in type 2 DM and impaired fasting glucose (IFG) (22,23). TSH, insulin-like growth factor-1, and insulin function as mitogenic factors, promoting thyroid nodule formation (24).

IFG and related hyperinsulinemia facilitate cell proliferation. HbA1c levels, metabolic syndrome parameters, and thyroid nodules all showed a positive correlation. It is assumed that hyperinsulinemia, hyperglycemia, and hyperlipidemia cause nodule formation through thyroid proliferation and angiogenesis (25-27).

TSH is directly involved in thyroid cell growth and differentiation, as well as nodule formation (28). Although some studies concluded that TSH could not be used solely as a mitogenic factor (29), others found a strong correlation between thyroid volume and TSH (22,30). Its elevation is important because it increases the risk of malignancy in the presence of thyroid nodules. In our study, TSH levels were normal in the nodule group but elevated in the control group. It was normal in the non-nodule group as well, but it was still higher than in the nodule and control groups when compared (Table 1).

Other studies showed that elevated TSH in normal range was associated with an increased risk of thyroid nodule and malignancy (31,32), implying that TSH could affect thyroid gland and nodule formation even in the normal range. Normal TSH levels in this case could be due to suppression of hyperfunctioning nodules or outsourced hormonal therapy.

Conclusion

Metabolic and inflammatory factors as well as many others contribute to thyroid nodule formation. This study showed a possible relationship between serum IgE levels and thyroid nodules. We contend that the prevalence of thyroid nodules may increase in the presence of IgE-mediated allergic diseases and atopy. Thus, patients with allergies and atopy should be screened for thyroid pathologies using imaging studies as well as blood tests.

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Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 1950, date: 09.08.2019).

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Machine Learning-Based Computed Tomography Texture Analysis of Lytic Bone Lesions Needing Biopsy: A Preliminary Study

Biyopsi Gerektiren Litik Kemik Lezyonlarının Makine Öğrenme-Tabanlı Bilgisayarlı Tomografi Yapısal Analizi: Bir Ön Çalışma

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ABSTRACT

Introduction: Currently, medical imaging has a limited capacity to achieve a final histopathological diagnosis of bone lesions. This study aimed to evaluate the use of machine learning (ML)-based computed tomography (CT) texture analysis to determine benign and malignant behaviors of lytic bone lesions needing a biopsy.

Methods: This retrospective study included 58 patients with lytic bone lesions. Lesion segmentation was independently performed by two observers. After evaluating unenhanced CT images, a total of 744 texture features were obtained. Reproducibility analysis and feature selection were used for dimension reduction. A training data set with a nested cross-validation approach was used for feature selection, optimization, and validation. Testing was executed on the remaining unseen data set. Classifications were done using five base ML classifiers and three voting strategies.

Results: The best predictive performance was achieved using the k-nearest neighbors algorithm with six features. The area under the curve, accuracy, sensitivity, and specificity of the best algorithm were, respectively, 0.774%, 78.1%, 78%, and 78.1% for the validation data set; and 0.861, 82.4%, 82.4%, and 81.5% for the unseen test data set.

Conclusion: The ML-based CT texture analysis may be a promising non-invasive technique for determining benign and malignant behaviors of lytic bone lesions that need a biopsy.

Keywords: Bone, texture analysis, radiomics, machine learning, artificial intelligence

ÖZ

Amaç: Günümüzde, sadece tıbbi görüntüleme ile kemik lezyonlarının kesin histopatolojik tanısını koymak mümkün olmamaktadır. Bu çalışmada, biyopsi gerektiren litik kemik lezyonlarının benign veya malign olduklarını belirleyebilmek için makine öğrenme (MÖ) tabanlı bilgisayarlı tomografi (BT) yapısal analizinin değerini ölçmeyi amaçladık.

Yöntemler: Bu retrospektif çalışmaya litik kemik lezyonu olan 58 hasta dahil edilmiştir. Lezyon segmentasyonu bağımsız iki gözlemci tarafından gerçekleştirilmiştir. Toplamda, kontrastsız BT görüntülerinden 744 yapısal özellik çıkartılmıştır. Boyut küçültme, tekrarlanabilirlik analizi ve özellik seçimi ile yapılmıştır. Özellik seçimi, optimizasyon ve doğrulama, iç içe geçmiş çapraz doğrulama yaklaşımına sahip bir eğitim veri kümesi kullanılarak yapılmıştır. Geriye kalan görünmeyen veri seti üzerinde test yapılmıştır. Sınıflandırmalar, beş temel MÖ sınıflandırıcısı ve üç farklı oylama stratejisi kullanılarak yapılmıştır.

Bulgular: En iyi tahmin performansı, altı özelliğe sahip k-nearest neighbors algoritması ile elde edilmiştir. En iyi algoritma değerinin eğri altındaki alan, doğruluk, duyarlılık ve özgüllük değerleri doğrulama veri seti için sırasıyla; %0,774, %78,1, %78 ve %78,1; görünmeyen test veri seti için ise sırasıyla; %0,861, %82,4, %82,4 ve %81,5 idi.

Sonuç: MÖ tabanlı BT yapısal analizi, biyopsi gerektiren litik kemik lezyonlarının benign ve malign davranışlarını tahmin etmek için ümit verici, invazif olmayan bir teknik olabilir.

Anahtar Kelimeler: Kemik, yapısal analiz, radyomik, makine öğrenme, yapay zeka



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Introduction

Texture analysis, which is a vital part of radiomics, is used to change standard medical images into high-dimensional quantitative data by calculating distribution and patterns of voxels or pixels (1,2). The literature has widely suggested that texture analysis might have a potential value in predicting certain underlying pathology or outcomes in different organs or systems (2). Contrary to standard qualitative evaluation, texture analysis may provide an objective, non-invasive assessment of the medical images, possibly leading to better decision-making in patient management (2,3). Moreover, artificial intelligence offers robust and reliable tools that learn data patterns and then make predictions on unseen instances for better decision support to manage such high-dimensional quantitative data that the texture analysis supplies (2,4).

Imaging of bone lesions has heavily relied on radiographs for a long time (5). Nowadays, it comprises technologically more advanced armamentarium, including positron emission tomography (PET), ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) (5,6). From a diagnostic point of view, all of these imaging methods can contribute to tissue characterization by narrowing the range of differential diagnoses and then indicating the most appropriate course of action afterward (7). In other words, these approaches have a limited capacity to achieve a final histopathological diagnosis (6). In particular, CT can help determine the calcification pattern in the bone lesion matrix, identify occult destruction, or even localize the nidus of an osteoid osteoma (5,6). However, if we consider all possible lesion types that can be encountered in clinical practice, it has a limited capability in tissue characterization. Interestingly, unenhanced CT texture analysis is being used to evaluate many different pathologies located in various organs or systems with a promising predictive performance (8-11).

In our work, we assessed the future value of unenhanced CT texture analysis for foreseeing benign and malignant behaviors of lytic bone lesions that need biopsy in clinical practice using various state-of-the-art machine learning (ML) algorithms and strategies.

Methods

Ethics

All study procedures, including waiver of informed consent for medical records review, were approved by our institutional review board. The approval form the University of Health Sciences Turkey, Istanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 1965, date: 29.08.2019).

Patients

Biopsy-proven bone lesions examined between January 2016 and May 2019 were obtained from our picture archiving and communication system. The exclusion criteria of patients were as follows: 1) mixed or sclerotic bone lesions, 2) unavailability of unenhanced CT in our archive, 3) quality problems in CT study, and 4) indefinite border or small (≤ 5 mm) lesions. No other criterion regarding the malignancy status of

the patients was applied. A simplified flowchart for patient selection is presented in Figure 1.

Computed Tomography Protocol

CT scans were performed using different scanners as follows: a 128-slice multidetector CT (Ingenuity, Philips Healthcare, Cleveland, OH, USA), a 64-slice multidetector CT (Aquilion, Canon Medical Systems, Otawara, Japan), and a 2-slice helical CT (HiSpeed, General Electric Company, Fairfield, CT, USA). Overall, the CT parameters were as follows: 1) tube voltage of 100-140 kV, 2) tube current of 97-500 mAs, 3) slice thickness of 0.5-5 mm, 4) pixel size of 0.162-0.976 mm, and 5) no contrast medium administration.

Technical Workflow

To provide a basic understanding and a larger view to the reviewers, we summarized our technical workflow in a flowchart in Figure 2.

Preprocessing

To reduce inter-scanner differences, all CT images were normalized using the ± 3 sigma technique that centers voxel gray-level values at the mean with the standard deviation (SD) (12). Normalization was established on the following expression:

$$f(x) = \frac{s[x - \mu(x)]}{\sigma(x)}$$

where $f(x)$ is the normalized image gray-level value, x is the original gray-level value, $\mu(x)$ is the mean gray-level value, $\sigma(x)$ is the SD of the image gray-level value, and s is the scaling factor, which was 100 in this study.

Resampling and rescaling of pixel spaces to an in-plane resolution of 1×1 mm² were performed because comparing texture characteristics necessitates identical spatial resolution (13).

We used a fixed bin-width to obtain an ideal bin count between 16 and 128 for gray-level discretization (14,15). To obtain this, a preliminary extraction of first-order parameters was performed in all patients included in this work to calculate the gray-level range and optimal bin

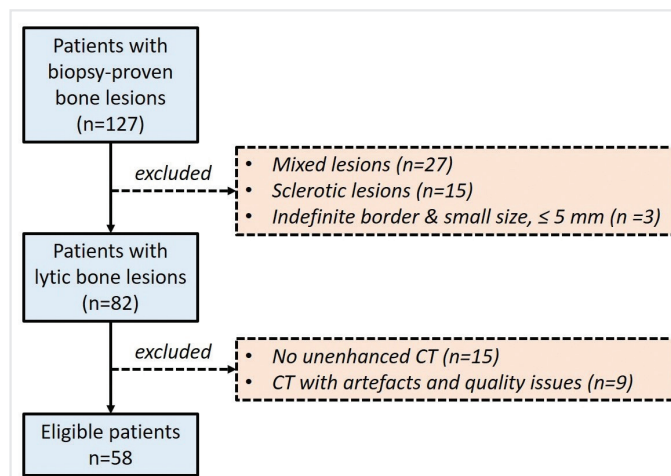


Figure 1. Patient selection flowchart

CT: Computed tomography

width. The discretization was established on the following mathematical expression:

$$X_{b,i} = \left\lfloor \frac{X_{gl,i}}{W} \right\rfloor - \left\lfloor \frac{\min(X_{gl,i})}{W} \right\rfloor + 1$$

where $X_{b,i}$ is the gray-level value after discretization, $X_{gl,i}$ is the gray-level value before discretization, and W is the bin-width value, which was 2 in this study.

Padding was applied with a distance value of 5 using original gray-level intensity.

Texture Analysis

By depicting a polygonal region of interest (ROI), the lytic bone lesions were segmented using the largest representative axial image slice of unenhanced CT. To minimize the partial volume effect from visually healthy structures, the ROI was carefully depicted, considering the clear lesion margin. The segmentation style is presented in Figure 3. Two observers segmented the lesions for a feature reproducibility analysis. The possible influence of the slice selection bias was considered since this might be a major concern of texture analysis, which is based on a single slice (16,17). Therefore, each observer was blind to the selected slices by the other observer.

PyRadiomics software program (PyRadiomics 2.0.1; Python 2.7.13; Numpy 1.13.1; SimpleITK 1.1.0; PyWavelet 0.5.2) was used for extracting texture features (18). Original, filtered, and wavelet-transformed images were used for extracting the features. Laplacian of Gaussian (LoG) filter was used for image filtrations with values of 2, 4, and 6 mm presenting with fine, medium, and coarse patterns, respectively. The following are the extracted texture features: 1) 18 first-order features, 2) 14 gray-level dependence matrix features, 3) 24 gray-level co-occurrence matrix features, 4) 16 gray-level run-length matrix features, 5) 16 gray-level size zone matrix features, and 6) 5 neighboring gray-tone difference matrix features. These six groups of features were derived from one original,

three LoG-filtered, and four wavelet-transformed images, which add up to 744 features per lesion in total. Detailed feature names and classes are presented in the Online Supplement. Comprehensive descriptions and mathematical expressions for these features can be found on the software program website and in the references (19-23).

Data Handling

The radiomic data underwent randomization, standardization, and stratified sampling.

The standardization of radiomic feature values was performed by centering and scaling the values by the mean and SD, respectively. Then, before data sampling, the order of data sets related to patient identifiers was randomized.

The whole data set was sampled to create training and unseen test data set splits, with proportions of 70% and 30%, respectively. The data split was created to prevent possible information leakage. Class balance in the training and unseen test data sets was ensured using stratified sampling, which sets the same class balance in the whole data set to the training and testing data sets. Training data set was used in classifier-specific feature selection, model development, optimization, and validation. The remaining data set, which is unseen by the feature selection and ML algorithms, was used for the unbiased testing of the model.

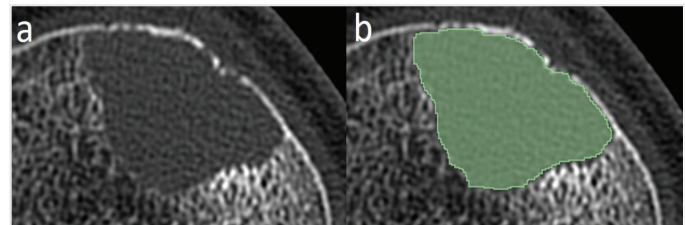
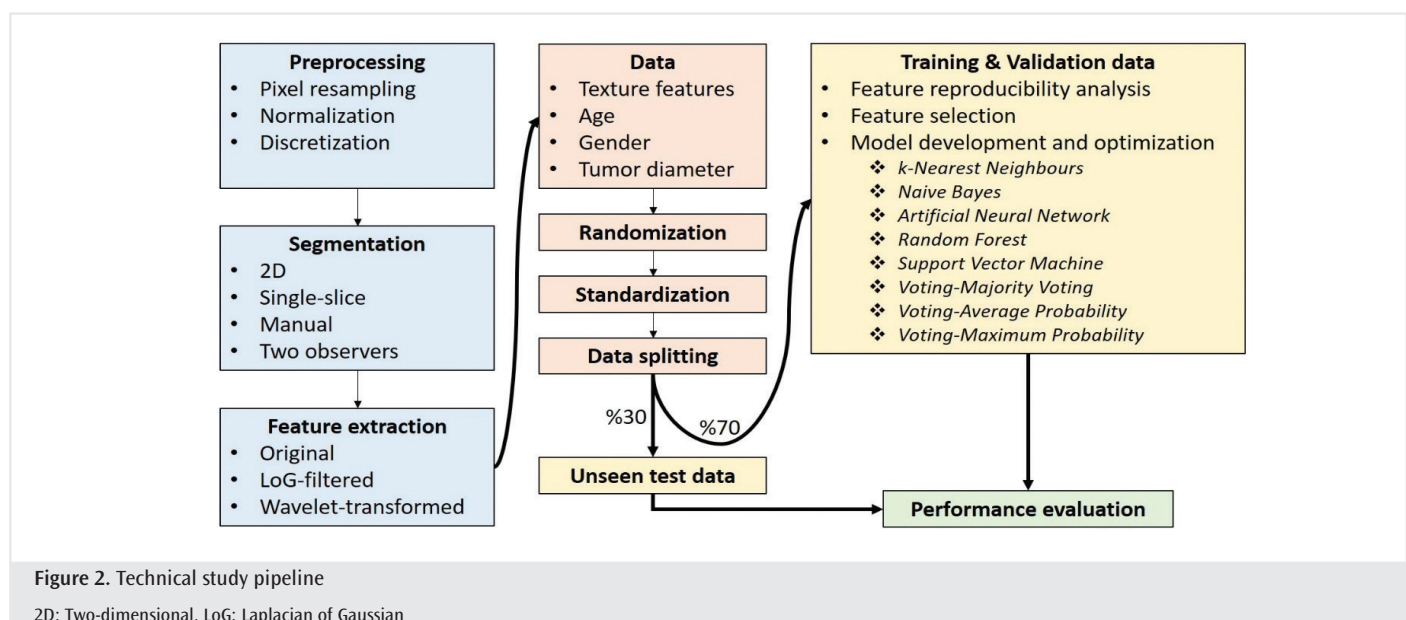


Figure 3. Lesion segmentation. (a) Unenhanced computed tomography image of a 51-year-old man with a giant cell tumor in the proximal tibia. (b) Lesion is segmented using the largest representative axial image slice with a particular focus on the contour



Dimension Reduction

A feature reproducibility analysis was initially used, followed by a classifier-specific feature selection algorithm to reduce the dimension of the training data.

For the reproducibility analysis, the intra-class correlation coefficient (ICC) was calculated for each texture feature and a clinical variable (maximum tumor diameter) using a two-way model, single rating, and absolute agreement. In the following dimension reduction step, which is also called feature selection, only features with ICC ≥ 0.75 that indicated good and excellent inter-observer reproducibility were included.

Waikato Environment for Knowledge Analysis (WEKA) toolkit version 3.8.2 was used for the feature selection (24). In the feature selection and model validation process, a nested cross-validation method with 5-fold inner and 10-fold outer loops was used. An incremental wrapper-based subset search method along with a wrapper attribute evaluator was used (25,26). The features were graded by their probabilistic significance, which was computed as a two-way function in the search method. The attributes undergoing more than one inner cross-validations were classified in the outer loop. Of note, age, gender, and maximal lesion diameter were also included in the feature selection as clinical variables besides the texture features.

Machine Learning-based Classifications

WEKA toolkit was used for ML-based classifications (24). The five base ML algorithms used were as follows: k-nearest neighbors, naive Bayes, random forest, support vector machine, and artificial neural network (27). In addition, these algorithms were also used in an ensemble learning technique called voting with three strategies (majority voting, average probability, and maximum probability) (28).

Considering the potential bias of the internal validation techniques, the performance evaluation was performed both in the training data as validation and in the unseen data as testing (29). The performance of the algorithms was mainly evaluated using the area under the receiver operating characteristic curve (AUC). Moreover, the accuracy, sensitivity, specificity, precision, F-measure, and Matthews correlation coefficient were also determined for further evaluation. For sensitivity and specificity, the weighted averages were also calculated.

Reference Standards for Classifications

The reference standards for the classifications were based on the official histopathological reports. Primary malignancies, secondary malignancies, and systemic malignancies were grouped as malignant lesions (30). Other lesions were grouped as benign lesions (30).

Conventional Statistical Analysis of Baseline Characteristics

Based on the value distribution, the parametric or non-parametric statistical tests were used to compare age and maximum lesion diameter between training and testing data sets. The chi-square test was used to compare the proportions of the gender. A p-value of less than 0.05 indicated statistical significance.

Results

Baseline Characteristics

A total of 58 patients met our eligibility criteria. Of them, 41 and 17 patients were randomly assigned to the training and test datasets, respectively. The following class distributions were in almost perfect balance using stratified sampling: 28 benign vs 30 malignant for the whole data, 20 benign vs 21 malignant for the training data, and 8 benign vs 9 malignant for the test data. There was no statistically significant difference in age ($p=0.191$), gender ($p=0.488$), and maximum lesion diameter ($p=0.447$) between the training and unseen test data sets. The baseline characteristics of the patients and their lesions are presented in Table 1.

Dimension Reduction

Inter-observer reproducibility was good or excellent in 464 of 744 texture features (ICC: ≥ 0.75). Additionally, the inter-observer agreement for the maximum lesion diameter was excellent (ICC: 0.905). All the reproducible texture features (ICC: ≥ 0.75) and clinical variables (age, gender, and maximum lesion diameter) were contained in the following feature selection process based on an algorithm.

In total, 15 texture features and 1 clinical variable were selected (Figure 4). Using the classifier-specific feature selection algorithm for each ML classifier to perform optimization, selected feature subsets were substantially different across the models created. Selected feature subsets are presented in Table 2. The selected feature numbers for each classifier ranged from 2 to 6. Considering all selected features, there was a predominance of the features extracted from the wavelet-transformed images. Based on feature classes, first-order and gray-level co-occurrence matrix features outnumbered the others. The only clinical variable selected by the algorithms was the maximum lesion diameter, which was included in the feature subset of k-nearest neighbors (Figure 5).

Machine Learning-based Training and Nested Cross-validation

Considering the five base ML classifiers, the AUC and accuracy metrics ranged from 0.724 to 0.774 and from 73.2% to 78.1%, respectively. The best performance was achieved by the k-nearest neighbors, with a weighted average sensitivity and specificity of 78% and 78.1%, respectively. Regarding the three voting strategies, the AUC and accuracy metrics ranged from 0.712 to 0.757 and from 75.6% to 82.9%, respectively. The majority voting achieved the best performance, with a weighted average sensitivity and specificity of 75.6% and 75.8%, respectively. Nested cross-validation performance metrics of the ML algorithms on the training data set are presented in Table 3.

Machine Learning-based Unseen Testing

Considering the five base ML classifiers, the AUC and accuracy metrics ranged from 0.715 to 0.861 and from 70.6% to 82.4%, respectively. The k-nearest neighbors achieved the best performance, with a weighted average sensitivity and specificity of 82.4% and 81.5%, respectively. Regarding the three voting strategies, the AUC and accuracy ranges were

Table 1. Baseline characteristics of 58 study patients

Characteristics	Whole data (n=58)	Training and validation data (n=41)	Unseen test data (n=17)
Age (years)	56.6	54.9	60.8
Gender, n (%)			
Female	21 (36.2)	16 (39)	5 (29.4)
Male	37 (63.8)	25 (61)	12 (70.6)
Mean lesion diameter (mm)*	31.1	28.9	36.6
Benign lesions, n (%)			
Neoplastic	3 (5.2)	3 (7.3)	0 (0.0)
Non-neoplastic	25 (43.1)	17 (41.5)	8 (47.1)
Malign lesions, n (%)			
Metastasis	17 (29.3)	12 (23.3)	5 (29.4)
Plasma cell malignancy	8 (13.8)	5 (12.2)	3 (17.6)
Other malignant lesions	5 (8.6)	4 (9.7)	1 (5.9)
Lesion location, n (%)			
Acetabulum	2 (3.4)	2 (4.9)	0 (0.0)
Femur	6 (10.3)	3 (7.3)	3 (17.6)
Fibula	1 (1.7)	1 (2.4)	0 (0.0)
Humerus	4 (6.9)	3 (7.3)	1 (5.9)
Iliac	8 (13.8)	6 (14.6)	2 (11.8)
Ischium	2 (3.4)	1 (2.4)	1 (5.9)
Calcaneus	1 (1.7)	1 (2.4)	0 (0.0)
Rib	2 (3.4)	1 (2.4)	1 (5.9)
Mandibula	1 (1.7)	1 (2.4)	0 (0.0)
Pubis	1 (1.7)	0 (0.0)	1 (5.9)
Radius	1 (1.7)	1 (2.4)	0 (0.0)
Sacrum	7 (12.1)	5 (12.2)	2 (11.8)
Scapula	2 (3.4)	2 (4.9)	0 (0.0)
Sternum	1 (1.7)	1 (2.4)	0 (0.0)
Tibia	4 (6.9)	1 (2.4)	3 (17.6)
Vertebra	15 (25.9)	12 (29.3)	3 (17.6)

*Based on the three-dimensional maximum lesion diameter. Unless otherwise stated, data represent number of patients or lesions

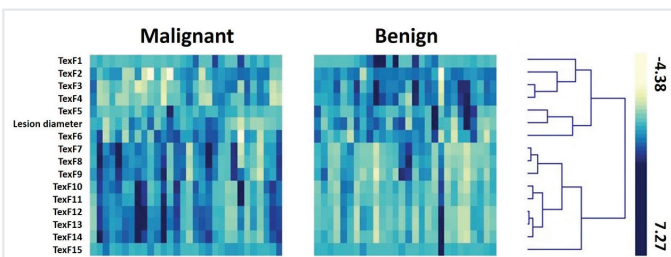


Figure 4. Heatmap and unsupervised clustering of the texture features selected for all machine learning algorithms

TexF1: Strength in wavelet image (high-low), TexF2: informational measure of correlation-2 in wavelet image (low-low), TexF3: entropy in wavelet image (low-low), TexF4: difference entropy in wavelet image (low-low), TexF5: size zone nonuniformity in original image, TexF6: inverse difference normalized in wavelet image (low-low), TexF7: dependence variance in original image, TexF8: large dependence emphasis in original image, TexF9: inverse variance in wavelet image (low-high), TexF10: maximum probability in wavelet image (low-low), TexF11: joint energy in wavelet image (low-low), TexF12: uniformity in wavelet image (low-low), TexF13: gray-level nonuniformity normalized in wavelet image (low-low), TexF14: gray-level nonuniformity normalized in original image, TexF15: large dependence low gray-level emphasis in Laplacian of Gaussian-filtered image with 4 mm lesion diameter, maximum lesion diameter

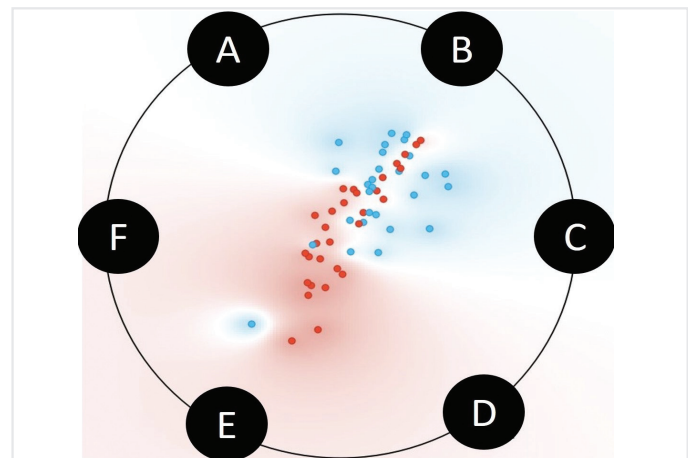


Figure 5. Two-dimensional projection of the selected features for the best machine learning algorithm (k-nearest neighbors)

A: Strength in wavelet image (high-low), B: informational measure of correlation-2 in wavelet image (low-low), C: joint energy in wavelet image (low-low), D: maximum lesion diameter, E: gray-level nonuniformity normalized in wavelet image (low-low), F: uniformity in wavelet image (low-low)

Table 2. Selected feature subsets for each machine learning algorithm

Algorithm	Selected features (feature class and image type)	ICC
k-Nearest neighbors	Uniformity (first-order, wavelet-LL)	0.835
	Gray-level nonuniformity normalized (GLRLM, wavelet-LL)	0.819
	Joint energy (GLCM, wavelet-LL)	0.897
	Maximum tumor diameter	0.905
	Informational measure of correlation 2 (GLCM, wavelet-LL)	0.808
	Strength (NGTDM, wavelet-HL)	0.908
Naive Bayes	Uniformity (first-order, wavelet-LL)	0.835
	Large dependence low gray-level emphasis (GLDM, LoG-4 mm)	0.887
Support vector machine	Uniformity (first-order, wavelet-LL)	0.835
	Maximum probability (GLCM, wavelet-LL)	0.849
Random forest	Uniformity (first-order, wavelet-LL)	0.835
	Difference entropy (GLCM, wavelet-LL)	0.849
	Joint energy (GLCM, wavelet-LL)	0.897
	Inverse difference normalized (GLCM, wavelet-LL)	0.760
Artificial neural network	Uniformity (first-order, wavelet-LL)	0.835
	Gray-level non-uniformity normalized (GLRLM, wavelet-LL)	0.819
	Entropy (first-order, wavelet-LL)	0.796
	Dependence variance (GLDM, original)	0.819
	Large dependence emphasis (GLDM, original)	0.826
	Inverse variance (GLCM, wavelet-LH)	0.772
Voting-majority voting	Uniformity (first-order, wavelet-LL)	0.835
	Gray-level non-uniformity normalized (GLRLM, wavelet-LL)	0.819
	Size zone non-uniformity (GLSZM, original)	0.908
Voting-average probability	Uniformity (first-order, wavelet-LL)	0.835
	Joint energy (GLCM, wavelet-LL)	0.897
Voting-maximum probability	Uniformity (first-order, wavelet-LL)	0.835
	Gray-level non-uniformity normalized (GLRLM, original)	0.861

ICC: Intra-class correlation coefficient, GLRLM: gray-level run-length matrix, GLCM: gray-level co-occurrence matrix, NGTDM: neighboring gray-tone difference matrix, GLDM: gray-level dependence matrix, GLSZM: gray-level size zone matrix, LoG: Laplacian of Gaussian, LL: low-low, HL: high-low, LH: low-high

0.708 to 0.806 and 70.6% to 76.5%, respectively. Voting strategy based on maximum probability achieved the best performance, with a weighted average sensitivity and specificity of 75.6% and 75.8%, respectively. Performance metrics of the ML algorithms on the testing data set are presented in Table 4.

Discussion

Study Overview

We assessed the future predictive value of the ML-based CT texture analysis to distinguish benign and malignant behaviors of lytic bone lesions that need a biopsy procedure in clinical practice. We created models using five base ML classifiers and three different voting strategies. The predictive performance of the models was evaluated using two approaches: 1) training along with a nested cross-validation approach and 2) testing on an unseen data set (or a random holdout). For each base classifier and voting strategy, a different feature subset was selected. The k-nearest neighbors achieved the best predictive

performance. Using this base ML algorithm, more than 80% of the patients were sorted rightly. The voting strategy yielded no improvement in the predictive performance.

Practical Implications

Differential diagnosis of benign lytic bone lesions usually includes fibrous dysplasia, eosinophilic granuloma, enchondroma, giant cell tumor, non-ossifying fibroma, osteoblastoma, aneurysmal bone cyst, solitary bone cyst, chondroblastoma, brown tumor, and infection-related pathologies (30). On the other hand, the differential diagnosis for the malignant lytic lesion category is a little shorter and mainly includes metastasis, myeloma, rare osteosarcoma, and chondrosarcoma (30). Also, Ewing’s sarcoma and leukemia should be considered in the pediatric age group. Conventionally, differentiation of these lesions is made by age, lesion localization, and qualitative imaging features such as periosteal reaction, cortical destruction, lesion margins, matrix pattern, and transition zone (30). However, these features may overlap between benign and malignant lesions, leading to diagnostic confusion

Table 3. Nested cross-validation in training data

Algorithm	Accuracy (%)	Sensitivity (%)	Specificity (%)	Precision (%)	F-Measure	MCC	AUC	Confusion matrix*		
								B	M	R
k-Nearest neighbors	78.1	80.0	76.2	76.2	0.780	0.562	0.774	16	4	Benign
		76.2	80.0	80.0	0.780			5	16	Malign
Naive Bayes	75.6	90.0	61.9	69.2	0.783	0.539	0.757	18	2	Benign
		61.9	90.0	86.7	0.722			8	13	Malign
Support vector machine	75.6	95.0	57.1	67.9	0.792	0.560	0.761	19	1	Benign
		57.1	95.0	92.3	0.706			9	12	Malign
Random forest	75.6	75.0	76.2	75.0	0.750	0.512	0.742	15	5	Benign
		76.2	75.0	76.2	0.762			5	16	Malign
Artificial neural network	73.2	80.0	66.7	69.6	0.744	0.470	0.724	16	4	Benign
		66.7	80.0	77.8	0.718			7	14	Malign
Voting-majority voting	75.6	80.0	71.4	72.7	0.762	0.516	0.757	16	4	Benign
		71.4	80.0	78.9	0.750			6	15	Malign
Voting-average probability	82.9	95.0	71.4	76.0	0.844	0.681	0.719	19	1	Benign
		71.4	95.0	93.8	0.811			6	15	Malign
Voting-maximum probability	78.0	90.0	66.7	72.0	0.800	0.581	0.712	18	2	Benign
		66.7	90.0	87.5	0.757			7	14	Malign

*B and M indicate classification results. Benign and malign indicate reference standards.
MCC: Matthews correlation coefficient, AUC: area under the curve, B: benign, M: malign

Table 4. Testing on the remaining unseen data

Algorithm	Accuracy (%)	Sensitivity (%)	Specificity (%)	Precision (%)	F-Measure	MCC	AUC	Confusion matrix*		
								B	M	R
k-Nearest neighbors	82.4	75.0	88.9	85.7	0.800	0.648	0.861	6	2	Benign
		88.9	75.0	80.0	0.842			1	8	Malign
Naive Bayes	82.4	87.5	77.8	77.8	0.824	0.653	0.806	7	1	Benign
		77.8	87.5	87.5	0.824			2	7	Malign
Support vector machine	70.6	87.5	55.6	63.6	0.737	0.450	0.715	7	1	Benign
		55.6	87.5	83.3	0.667			4	5	Malign
Random forest	76.5	75.0	77.8	75.0	0.750	0.528	0.792	6	2	Benign
		77.8	75.0	77.8	0.778			2	7	Malign
Artificial neural network	82.4	87.5	77.8	77.8	0.824	0.653	0.792	7	1	Benign
		77.8	87.5	87.5	0.824			2	7	Malign
Voting-majority voting	70.6	75.0	66.7	66.7	0.706	0.417	0.708	6	2	Benign
		66.7	75.0	75.0	0.706			3	6	Malign
Voting-average probability	70.6	87.5	55.6	63.6	0.737	0.450	0.778	7	1	Benign
		55.6	87.5	83.3	0.667			4	5	Malign
Voting-maximum probability	76.5	87.5	66.7	70.0	0.778	0.549	0.806	7	1	Benign
		66.7	87.5	85.7	0.750			3	6	Malign

*B and M indicate classification results. Benign and Malign indicate reference standard.
MCC: Matthews correlation coefficient, AUC: area under the curve, B: benign, M: malign

(30). Some conditions called tumor mimickers may even make the diagnosis much more challenging (31). While evaluating such conditions, unnecessary diagnostic work-up, including invasive procedures, might

be related to patient morbidity, discomfort, and high economic cost. Therefore, differentiating benign lesions from malignant ones by non-invasive methods is necessary.

It may seem that the technique proposed might have low clinical applicability since the biopsy would be performed on all such lesions. In other words, even if the clinicians were about 80% sure that a lesion was benign; one would still likely perform a biopsy. However, this investigation should be considered a preliminary work, with its many obvious limitations. We think there is more room for improvement of this technique to make it more useful in clinical practice.

Previous Works

Most of the radiomic studies about lytic bone lesions evaluated the performance of computer-aided or automatic lesion detection systems, with a particular focus on spinal bone lesions (32-36). Meanwhile, other papers worked on lesion classification problems using texture analysis. Larhmam et al. (37) worked on spinal metastasis classification using conventional MRI images and achieved an accuracy of 90.1%. Reischauer et al. (38) published a prospective study in patients with prostate cancer along with bone metastasis by investigating the potential value of texture features extracted from apparent diffusion coefficient maps in treatment response assessment (38). Acar et al. (39) worked on ML-based CT texture analysis to distinguish metastatic and completely responded sclerotic bone lesions in patients with prostate cancer (39). In our study, rather than lesion detection, we focused on the lesion classification with a different perspective, i.e., distinguishing benign and malignant lesions that need a biopsy in clinical practice. Furthermore, we included spinal lesions and ones from different locations.

Study Limitations

There are a few limitations to the generalizability of our results. First, the main limitations were the retrospective nature of the study and the relatively small number of patients. Second, lesions from different locations were included in this work. It would be worth looking at specific locations such as the spine or pelvic bones. Nonetheless, the major constraint for this was the limited number of patients considering major locations. Third, we only used unenhanced CT with a rather heterogeneous protocol in this preliminary work. The imaging protocol heterogeneity was due to the usage of different scanners, which may represent the clinical practice and improve the generalizability of the findings. The patients' other imaging studies, such as PET-CT and MRI, were also heterogeneous, and some had been performed in different centers. Because of these, we were unable to use other techniques for texture analysis. On the other hand, other imaging methods including MRI and PET-CT/MRI should be evaluated in future works. Fourth, we used a single-slice two-dimensional manual segmentation. Although a few slice-based or three-dimensional volumetric segmentation would be much more illustrative for the lesion texture, it is too difficult to use in clinical practice unless it is performed with automated methods. The major problem of the two-dimensional texture analysis in such large lesions is the slice selection bias, which was considered in this work (16,17). Fifth, although we performed separate testing on the unseen data set or a holdout data set, there was no external data set. On the other hand, we plan to perform independent external validation when appropriate data are available. Sixth, we only conducted quantitative analysis on the lesions that we performed a biopsy procedure. Because some of the patients were referred to our hospital for the biopsy

procedure, not all the imaging data were available to conduct a proper qualitative analysis for comparison.

Conclusion

This preliminary work suggests that the ML-based CT texture analysis may be a promising non-invasive technique to distinguish benign and malignant behaviors of lytic bone lesions that need a biopsy. By improving the above mentioned limitations of this work, future research may have the potential to increase the predictive performance of this method. We hope this comprehensive work will provide a base for future research.

Ethics Committee Approval: The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 1965, date: 29.08.2019).

Informed Consent: All study procedures, including waiver of informed consent for medical records review, were approved by our institutional review board.

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Paradoxical Embolism After a Traffic Accident: A Rare Case of Thrombus Entrapped in a Patent Foramen Ovale

Trafik Kazası Sonrası Gelişen Paradoks Emboli: Nadir Görülen Bir Olgu, Patent Foramen Ovalede Trombüs Tuzaklanması

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ABSTRACT

Paradoxical embolism is the passage of a thrombus formed in the venous system through shunts in the lung or heart into the systemic circulation. The most common intracardiac shunt is a patent foramen ovale (PFO). Since the transition of a thrombus formed in the right heart to the left heart and systemic circulation through the PFO is a temporary situation, the entrapped thrombus in the PFO is extremely rare. Herein, we present a case, including the diagnosis and treatment, of a paradoxical embolism in a 53-year-old female with a non-vehicle traffic accident who developed a pulmonary embolism and acute cerebral infarction.

Keywords: Paradoxical embolism, entrapped thrombus in PFO, surgical treatment in paradoxical embolism

ÖZ

Paradoks emboli akciğer veya kalpteki şantlar aracılığıyla venöz sistemde oluşan bir trombüsün sistemik dolaşıma geçmesi olarak bilinir. En sık görülen intrakardiyak şant patent foramen ovaledir (PFO). Sağ kalpte oluşan bir trombüsün PFO aracılığıyla sol kalbe ve sistemik dolaşıma geçişi geçici bir durum olduğundan PFO'daki trombüs tuzaklanması son derece nadir görülür. Burada araç-dışı trafik kazası sonrası pulmoner emboli ve akut serebral infarktüs gelişen 53 yaşındaki bir kadın hastadaki paradoksal embolinin tanı ve tedavisiyle ilgili bir olgu sunuyoruz.

Anahtar Kelimeler: Paradoks emboli, PFO'da trombüs tuzaklanması, paradoks embolide cerrahi tedavi

Introduction

Paradoxical embolism is a clinical situation in which a thrombus originating from the venous system passes into the systemic circulation through an intracardiac or pulmonary shunt (1). The two most common causes of paradoxical embolism are a patent foramen ovale (PFO) and arteriovenous malformation (2). The clinical diagnosis is based on detecting an arterial embolism due to an intracardiac defect or pulmonary arteriovenous shunt with the source of the venous embolism (3). Depending on the location of the embolism, neurological deficits due to ischemic stroke, chest pain, and electrocardiographic changes due to myocardial infarction, acute abdominal pain due to gastrointestinal ischemia, back pain and hematuria due to renal infarction, and pain and coldness in the extremities due to peripheral arterial occlusion may occur.

A PFO is a cardiac anomaly that can be detected in approximately 25% of the general population. It occurs due to septum primum and septum secundum not fusing after birth and is a strong risk factor for paradoxical

embolism. On the other hand, an atrial septal aneurysm (ASA) is an anomaly in the fossa ovalis region. The atrial septum protrudes into the right or left atrium by 1 cm or more. It is rarely seen in the general population, with a frequency of 2% compared with that of a PFO (3,4). The coexistence of PFO and ASA is associated with a significantly increased risk of cerebrovascular events compared with the risk of either seen alone (5). Since the transition of the thrombus from the right heart to the left heart through a PFO is a temporary situation, the image recording of a thrombus trapped in a PFO is extremely rare.

A PFO is closed passively under normal physiological conditions due to the pressure difference between the left and right atria. In Valsalva maneuvers (coughing, sneezing, straining, urination, others), the right atrial pressure can surpass that of the left atrial pressure, temporarily creating a shunt from right to left and creating a paradoxical embolism through the PFO. A pulmonary embolism and other causes of pulmonary hypertension may create a paradoxical embolism by making a shunt temporarily and permanently in the presence of a PFO.



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Herein, we present a case, including diagnosing and treating a paradoxical embolism in a 53-year-old female patient with a non-vehicle traffic accident who developed a pulmonary embolism and acute cerebral infarction.

Case Report

The consent of the patient and her relatives was obtained provided that their medical data would be used only for scientific purposes, and their identity information was kept confidential.

A 53-year-old female patient with diabetes was brought to the emergency room by the emergency team due to a non-vehicle traffic accident. Her first evaluation revealed a large hematoma in her right occipital region, a non-displaced pelvic fracture, and a left humerus fracture. Her physical examination showed that her blood pressure was 130/80 mmHg, pulse was 85/min, her consciousness was clear, central imaging was normal, and her respiratory system examination was normal. The patient had stable vital signs and was directed to orthopedic surgery for the humerus fracture.

We were consulted after the patient was operated on for the left humerus fracture because she experienced sudden shortness of breath, tachypnea, and hypotension during the orthopedic service follow-ups. The patient had previously consulted neurology due to short-term loss of consciousness and speech disorder, and a transient ischemic attack was considered according to her brain imaging. The patient's ECG was taken at 120/min sinus tachycardia, blood pressure was 100/50 mmHg, and her bedside echocardiography showed that the ejection fraction was normal. However, the right heart cavities were enlarged, and the right ventricular functions regressed. Pulmonary computed tomographic pulmonary angiography (CTA) was requested, with a preliminary diagnosis of a massive pulmonary embolism. Her CTA showed that a filling defect compatible with an acute embolism in the right main pulmonary artery, pulmonary branches leading to the right upper lobe, branches leading to the bilateral lower lobe, and segmental-subsegmental branches. The patient was taken to the cardiology intensive care unit. Thrombolytic therapy was not considered because the patient had a recent history of surgery and cerebrovascular events. Percutaneous mechanical intervention was not considered because of her elevated blood pressure after intravenous fluid administration, and the patient was hemodynamically stable. So, low molecular weight heparin was administered to the patient.

In the control echocardiography of the patient, the ejection fraction was normal, and the right heart spaces were wide, the right ventricle apical akinetic, and the trapped thrombus appearance was observed in the PFO extending from the right atrium to the left atrium. In transesophageal echocardiography (TEE), which was later performed to detect the thrombus, the thrombus was seen in both atria trapped in the PFO. The fragment in the right atrium was in two parts, and the longest length was 1.7 cm, and the one in the left atrium extended into the left ventricle was 9 cm (Figure 1, 2; Video 1, 2).

Whether to have the surgery was left to the patient, who was considered high risk for thrombolytic therapy. Although the patient and her relatives were told about the embolic risks that the patient might experience,

they did not accept the surgical procedure. Afterward, low molecular weight heparin treatment was stopped, and a heparin infusion was started. The surgical option was re-explained upon recurrent consciousness and speech impairment in the patient's follow-up and general diffusion restrictions in both brain parenchyma suggesting an embolic infarction in central imaging. When the patient and her relatives accepted the surgical procedure, the patient was transferred to cardiovascular surgery. Surgery was performed to close the PFO, remove the intracardiac thrombus, and install an inferior vena cava.

After surgery, the patient's hemodynamics improved rapidly, and no complications developed. The patient was evaluated one month after discharge. Her control echocardiography showed no intracardiac thrombus image, her right heart cavities regressed, and her RV contraction had improved.

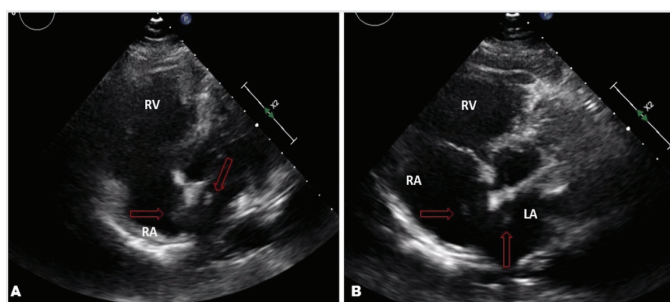


Figure 1. Transthoracic echocardiography demonstrating hyperechogenic density images of a trapped thrombus image in the interatrial septum with enlargement of the right ventricle and the right atrium (A, B)

RV: Right ventricle, RA: right atrium, LA: left atrium

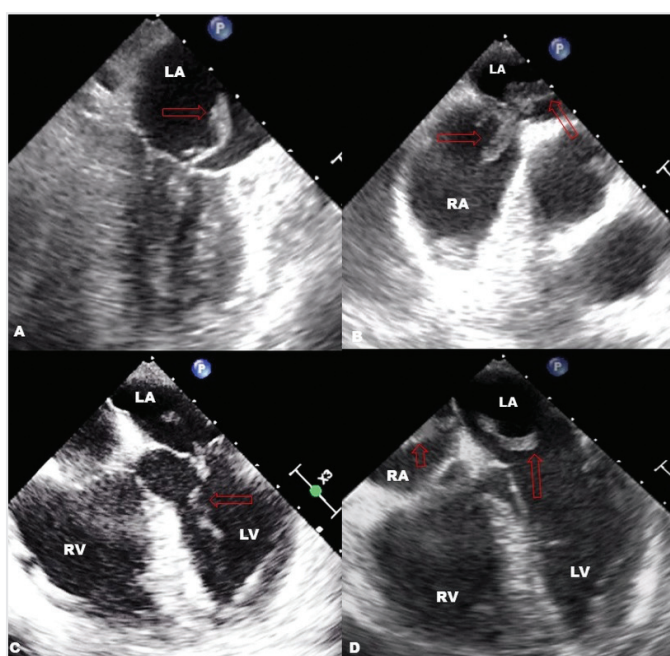


Figure 2. Transesophageal echocardiography demonstrating a large and long trapped thrombus image in the interatrial septum with an enlargement of the right ventricle and the atrium that extends from the mitral valve to the left ventricle (A-D)

LA: Left atrium, RA: right atrium, RV: right ventricle, LV: left ventricle

Discussion

Interest has increased in diagnosing PFO, which is a common condition found in 25% of the general population, after its association with paradoxical embolism. In particular, advances in TEE have played an essential role in the diagnosis of PFO.

An entrapped thrombus in the PFO is rarely seen. TEE is a highly reliable and excellent imaging method for diagnosing a trapped thrombus. Computed tomography is essential for evaluating the heart and examining other organs that can be reached by an embolism, such as the lungs and the brain.

No clear consensus exists in PFO regarding patient management and treatment planning for a trapped thrombus. Thrombolytic therapy, anticoagulant therapy, surgical treatment, and percutaneous treatments were applied individually or in combination in various clinics in different patient groups. An inferior vena cava filter is generally recommended when a high risk of mortality exists due to a massive pulmonary embolism with contraindications to anticoagulant therapy and inadequate anticoagulant therapy (6).

In a study, 84 patients with a trapped thrombus in a PFO were investigated. Of these, 55 were treated surgically, 21 were treated with heparin, and 11 were treated with thrombolytic therapy. The mortality rates for the treatments were 13%, 14%, and 36%, respectively (7).

Consequently, heparin treatment may be an option in patients with high comorbidity and cerebrovascular events and has mortality rates similar to surgical treatment. Thrombolytic therapy is chosen more frequently in the high-risk group but is associated with higher mortality (7). Also, systemic thrombolytic therapy and systemic anticoagulant therapy may present a high risk by causing rupture of the thrombus and hemorrhagic transformation of large ischemic strokes. Closure of the PFO following surgical thrombectomy for paradoxical embolism and entrapped thrombus has become the favored method in high-risk patients. More extensive studies with randomized clinical trials comparing acute thrombectomy with conservative medical therapy are required.

In this case, we evaluated thrombolytic treatment as a high risk in the patient's recent history of cerebrovascular events and multiple traumas. Therefore, the surgical treatment option was considered in the foreground. Another risk factor for thrombolytic therapy was the breakdown of the intracardiac thrombus and its embolism to the lung and systemic circulation. The inferior vena cava filter was applied because of the high mortality of the pulmonary embolism that the patient would experience due to recurrent venous thromboembolism.

Conclusion

Paradoxical embolism can lead to life-threatening situations by causing a pulmonary and systemic embolism. An elevated pressure gradient

between the right and left atria increases the risk of systemic embolism. Clinical suspicion is the most important step in making a diagnosis. Since it mostly progresses with pulmonary embolism, paradoxical embolism must be included in the differential diagnosis of pulmonary embolism and systemic embolism. Since a missed diagnosis typically leads to a fatal outcome, early diagnosis and treatment are essential to prevent mortality and morbidity.

Ethics

Informed Consent: The consent of the patient and her relatives was obtained provided that their medical data would be used only for scientific purposes.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - Ş.A.K., Y.A., A.S.G., M.A.D.; Design - Ş.A.K., Y.A., A.S.G., M.A.D.; Data Collection or Processing - Ş.A.K.; Analysis or Interpretation - Ş.A.K., Y.A., A.S.G., M.A.D.; Literature Search - Ş.A.K.; Writing - Ş.A.K., Y.A.

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Secukinumab-induced Oral Lichen Planus: A Report of Case and Review of Literature

Sekukinumab İlişkili Oral Liken Planus: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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ABSTRACT

Recent years, we are witnessing a more frequent use of biological agent treatments. Secukinumab (SEC) has been used successfully in the management of psoriasis, psoriatic arthritis, and ankylosing spondylitis. However, the cases of SEC-related lichen planus (LP) are rarely encountered in the literature. Herein, this report presents a case of oral LP induced by SEC in a 33-year-old patient with psoriasis. In addition, this report aims to review the lichen reactions associated with SEC in the literature. In conclusion, LP cases attributable to SEC use are increasingly being observed in new reports. Clinicians who use SEC in their patients should be aware of this side effect and observe patients in terms of cutaneous-mucosal LP. With the introduction of new interleukin-17 (IL-17) inhibitors, the reporting of side effects is crucial for learning whether LP is class side effects or drug-specific side effects for clarifying pathogenesis. Dermatologists and rheumatologists should be aware of the very rare negative effect of IL-17 inhibitors.

Keywords: Secukinumab, IL-17 inhibitors, lichen planus, psoriasis

ÖZ

Biyolojik ajan tedavileri son yıllarda artan sıklıkta kullanılmaktadır. Sekukinumab (SEK) sedef hastalığı, psoriatik artrit ve ankilozan spondilitte başarıyla kullanılmaktadır. Sekukinumab ile ilişkili liken planus (LP) olgularına literatürde nadiren rastlanmaktadır. Burada, sedef hastalığı olan 33 yaşında bir kadında sekukinumab ile indüklenen oral LP olgusunu sunuyoruz. Ek olarak literatürdeki sekukinumab ile ilişkili liken reaksiyonlarını da gözden geçirmeyi amaçladık. Sonuç olarak, SEK kullanımına bağlı LP olguları yeni raporlarla artmaktadır. Hastalarında SEK kullanan klinisyenler bu yan etkinin farkında olmalı ve hastalarını kutanöz ve mukozal LP açısından gözlemlemelidir. Yeni interlökin-17 (IL-17) inhibitörlerinin kullanılmaya başlanmasıyla, LP yan etkisinin sınıf yan etkileri mi yoksa ilaca özgü yan etkiler mi olduğunu ve patogenezi açıklığa kavuşturmak için yan etkilerin raporlanması önemlidir. Dermatologlar ve romatologlar IL-17 inhibitörlerinin çok nadir olumsuz etkilerinin farkında olmalıdır.

Anahtar Kelimeler: Sekukinumab, IL-17 inhibitörleri, liken planus, psoriasis

Introduction

Paradoxical drug reactions are unexpected drug reactions. Paradoxical psoriasis is the most common paradoxical reaction during tumor necrosis factor-alpha treatment, which is one of the biological agent treatments (1). There has been an increasing use of biological agent treatments in recent years. Secukinumab (SEC) has been used successfully in the management of psoriasis, psoriatic arthritis, and ankylosing spondylitis (2). However, the cases of SEC-related lichen planus (LP) are rarely encountered in the literature (3-7).

Herein, this report presents a case of SEC-induced oral LP in a 33-year-old woman with psoriasis. In addition, this report aims to review the lichen reactions associated with SEC in the literature. Dermatologists and rheumatologists should be aware of the very rare negative effect of interleukin-17A (IL-17A) inhibitor SEC.

Case Report

SEC treatment was initiated in a 33-year-old patient who was followed up with psoriasis and previously received methotrexate, cyclosporine, and narrow-band ultraviolet B phototherapy treatments. In this SEC-



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treated case for about three months, psoriasis area severity index 100 was reached. The patient had no other disease than psoriasis. Moreover, there was no other drug use other than SEC.

In the third month of treatment, reticular plaques appeared in the buccal area on the oral mucosa of the patient (Figure 1). Biopsy and direct immunofluorescence were performed from the oral mucosa of the case with the preliminary diagnosis of LP and pemphigus vulgaris. In the laboratory parameters, normal or negative were the remaining peripheral blood count, C-reactive protein, liver enzyme, creatinine, antinuclear antibody, U1RNP, Sm, Ro, La, SCL-70, CENP, Jo- 1, dsDNA, and PmScl. The histopathology revealed band-like lichenoid infiltration and basal vacuolar changes (Figure 2). Direct immunofluorescence examination was negative. Oral LP was diagnosed clinically and histopathologically. The evaluation of Naranjo adverse drug reaction (ADR) probability scale revealed that the case had 6 points (6/10; probable ADR). The final diagnosis was a paradoxical drug reaction with SEC-induced oral LP. SEC was not discontinued because the reaction was not life-threatening. Oral lichen was controlled with topical corticosteroid treatment. In the follow-up of the patient for six months, the lesions have remained stable and the follow-up was continued. Informed consent was obtained from the patient for the publication of this case report and images.

Discussion

IL-17A is a cytokine that is believed to play a key role in the pathogenesis of psoriasis (8). SEC is a fully humanized anti-IL-17A monoclonal



Figure 1. Reticular plaques on the right buccal area

antibody. Many cutaneous side effects of SEC, including LP/lichenoid reactions (LR), have been reported previously (9). In the literature, we have determined five case reports for SEC-related LP (3-7). Our case was the youngest patient among them.

Although Doolan et al.'s (3) case did not have oral mucosal involvement, all others had involvement of oral mucosa (4-7). Maglie et al.'s (7) case had both oral mucosa and trunk involvement. In our case, only oral mucosal involvement was present. LP/LR lesions occurred in patients from 1 week to 8 months after the onset of SEC treatment in the literature. In our case, lichen lesions developed in the third month of treatment. Treatment was discontinued in four patients (4-7) who developed a SEC-related reaction; in one of them, SEC administration was changed to that of Ixekizumab (5). In our case, as in Doolan et al. (3), SEC treatment was not stopped because the lesions were stable. In patients who were discontinued SEC, there was an improvement in lesions between four weeks and eight weeks (4-7). In our case, who SEC treatment was not ceased, the lesions did not recover completely, but remained stable, similar to the case of Doolan et al. (3).

The literature reported two cases of concomitant oral candidiasis cases (5,6). Histopathology was performed in four of five patients, and one case was diagnosed clinically and dermoscopically. Histopathology was compatible with LP in two patients and with LM in two patients. Our case was histopathologically compatible with LP and no simultaneous candida was detected. Table 1 shows detailed information about all the cases reported in the literature along with our case.

Several hypotheses have been proposed to explain the LP side effects of SEC. SEC may trigger oral LP development by causing oral candidiasis (6). Another factor is dendritic cell upregulation and an increase of type I interferon (IFN) after IL-17 neutralization (3). An obvious increase in plasmacytoid dendritic cells and IFN in cutaneous and oral lesions in LP also supports this result (10). However, it is not clear how the reaction was triggered.

Thompson et al. (4) believed that oral LR were the class side effects of IL-17 blockers. However, Capusan et al. (5) believed that this was a drug-specific side effect rather than a class side effect because the same side effects are not observed after switching to Ixekizumab. More case reports and observations are needed to clarify this situation.

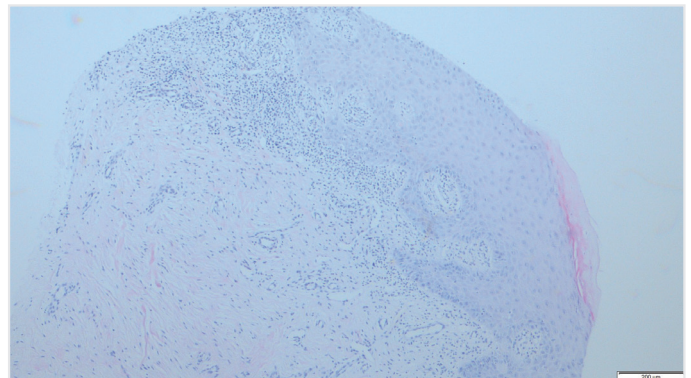


Figure 2. The band-like lichenoid infiltration and basal vacuolar changes in the histopathology (hematoxylin and eosin, x40)

Table 1. Literature data to date about the LP/LM due to secukinumab use

Author-year	A/G	Clinical findings	Histopathology	Time to reaction	Time to resolution	Cessation of IL-17	Outcome	Therapy for reaction
Thompson et al. (4), 2016	62/M	Painful erosions and ulcers on the lower lip	Consistent with LM	1 week	6 weeks	Yes	Recovery	Triamcinolone 0.1%
Komori et al. (6), 2017	74/F	Painful whitish plaques on the left buccal mucosa	Consistent with LP	5 months	2 months	Yes	Recovery	Amphotericin B
Doolan et al. (3), 2017	56/M	Thickened plaques on ankles bilaterally (hypertrophic LP)	Consistent with LP	6 months	NR	No	Stabilized	Betamethasone dipropionate cream (0.05%)
Maglie et al. (7), 2018	50/M	Violaceous papules on the trunk and oral plaques	Clinical and dermoscopic diagnosis	1 months	4 weeks	Yes	Recovery	Cyclosporine
Capusan et al. (5), 2018	45/M	Painful ulcerative lesions on dorsum of the tongue	Consistent with LM	8 months	8 weeks	Switched to Ixekizumab	Recovery	Itraconazole intralesional steroid
Our case	33/F	Reticular plaques on the buccal mucosa	Consistent with LP	3 months	NR	No	Stabilized	Topical steroid

A: Age, G: gender, M: male, F: female, LP: lichen planus, LM: lichenoid mucositis, NR: not reported, IL: interleukin

LP and LR cases attributable to SEC use are increasingly being observed in new reports. Clinicians who use SEC in their patients should be aware of this side effect and observe patients in terms of cutaneous-mucosal LP. With the introduction of new IL-17 blockers, the reporting of side effects is important for learning whether LP and LR are class side effects or drug-specific side effects and clarifying pathogenesis.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case report and images.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.D., S.A.T.; Concept - M.D., S.A.T.; Design - M.D., S.A.T.; Data Collection or Processing - M.D., S.A.T., S.G., F.K.; Analysis or Interpretation - M.D., S.A.T., S.G., F.K.; Literature Search - S.A.T., S.G.; Writing - M.D., S.A.T., S.G.

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Rupture of Urinary Bladder: A Sequelae of Tonic-clonic Seizure Complications

Mesane Rüptürü: Tonik-Klonik Nöbet Komplikasyonlarının Bir Sekeli

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ABSTRACT

Seizures are capable of causing different types of physical injuries ranging from superficial contusions up to severe head injuries or even bone fractures. Herein, we report a case that had a rupture of the urinary bladder after a tonic-clonic seizure. In this report, we will highlight the clinical presentation of this case, laying more emphasis on the diagnostic significance.

Keywords: Urology, neurology, seizure, bladder rupture

ÖZ

Nöbetler yüzeysel kontüzyonlardan şiddetli kafa yaralanmalarına ve hatta kemik kırıklarına kadar farklı tipte fiziksel yaralanmalara neden olabilir. Ancak tonik-klonik nöbet sonrası mesane rüptürü gelişen bir hasta olgusu yaşadık. Teşhisin önemine vurgu yaparak aşağıdaki klinik sunumu vurgulayacağız.

Anahtar Kelimeler: Üroloji, nöroloji, nöbet, mesane rüptürü

Introduction

Patients with seizure attacks often suffer a multitude of collateral injuries to the head, face, and teeth. Tongue biting and bone fractures have been reported in some cases. Majority of these injuries occur during generalized myoclonic seizures or tonic-clonic seizures (1). Rupture of urinary bladder following acute stroke symptoms is a rare complication (2). This report presents a patient who developed urinary bladder rupture following acute stroke symptoms and a generalized tonic-clonic seizure. This complication will be further discussed in this report.

Case Report

A 74-year-old male presented to the emergency department with symptoms of acute stroke. He was found lying on the floor by his family, without speaking or moving for two hours. The patient had a past medical history of dyslipidemia (non-compliant to medication) and cerebrovascular stroke two years ago, with no neurological deficit. The patient was subjected to cerebral angiogram computed tomography (CT) and magnetic resonance imaging for cerebrovascular stroke assessment. During the imaging studies, the patient developed a generalized tonic-clonic seizure whose etiology was unknown. He was admitted as a case of Status Epilepticus, while he complained of moderate, continuous, and

generalized abdominal pain. His general examination revealed a large left inguinal swelling, which was irreducible and non-tender, without underlying skin changes. The patient's urinary bladder was not palpated.

In the following day, the patient was subjected to abdominal CT without contrast to ascertain the content of the left inguinal hernia and exclude complications. The CT scan revealed the presence of free intra- and retroperitoneal contrast material. The contrast material was seen in relation to the left anterior bladder wall. The patient did not receive any oral, rectal, or intravenous contrast. The contrast seen was related to the prior cerebral angiography CT, which was extravasating from the left anterior wall of the bladder (Figure 1). The patient's prostate was enlarged (179 mL) and moderate hydronephrosis was seen. Mild amount of free fluid at the perihepatic, paracolic gutters, and pelvic regions were also recorded. Urinary catheter was not inserted before or during the examination. Urine output and renal function tests were within normal limits. The patient was diagnosed as urinary bladder perforation with inguinal hernia and was subjected to emergency exploratory laparotomy with bilateral inguinal hernioplasty and bladder repair. Postoperatively, the patient experienced hematuria, which resolved with bladder irrigation. He was not on medications for benign prostatic hyperplasia (BPH). Verbal consent was obtained from the patient.



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Discussion

Common injuries that occur in patients with seizures include soft tissue injuries (lacerations), fractures, and tongue injuries. They can be as severe as burns and drowning (3). The probability of complicated trauma is higher in patients who experience generalized tonic-clonic seizures and myoclonic seizure attacks (1,4). According to the type and severity of the seizure, we can predict the severity of the organ injuries. A spontaneous urinary bladder injury following a seizure is a very rare complication (5).

Pal et al. (2) suggested that urinary bladder injury is very rare, given that the bladder sometimes loses control and evacuates during the seizure attack. The combination of urethral obstruction (due to BPH in our case), distended bladder in old male patients, and increased intra-abdominal pressure during a seizure episode could lead to a spontaneously ruptured bladder (4). The distended urinary bladder wall becomes thin, especially in the weak areas, such as the dome (5). These predisposing factors lead to bladder rupture at the weakest point associated with increased intra-abdominal pressure caused by the seizure attack (2). Similar mechanisms of bladder injury have been reported in some patients, which were most likely due to the increased intra-abdominal pressure associated with a full bladder (2).

So far, only five cases of bladder injury following a seizure attack has been described in literature. All cases were incidental following myoclonic and generalized tonic-clonic seizure. Among these, two cases of bladder rupture were reported following unmodified electroconvulsive therapy (5-7). Two patients presented with acute abdomen and hematuria on catheterization after an attack of generalized tonic-clonic seizures; one of them was a psychotic patient on medications (8) and the other patient had a history of fall after seizure attack, developing urine retention for 24h (9). The last patient with the diagnosis of schizophrenia had two generalized tonic-clonic seizure attacks within an hour and, during the second attack, he had fecal incontinence, but not urinary incontinence (5).

In our case, there were no symptoms or signs of a ruptured urinary bladder on initial presentation, as there was no severe abdominal pain



Figure 1. (A-D) Non-contrast enhanced computed tomographic images. There is an extravasated contrast material to both the paracolic gutters and retroperitoneal area (short arrows). (B,D) At the left anterior wall of the bladder, there is a defect and contrast material extravasated through the side (arrowheads). (D) A large inguinal defect with a herniated portion of the urinary bladder (long white arrow)

(acute abdomen). The patient had no complaints of any symptoms pertaining to urinary tract abnormalities; however, the condition was discovered incidentally.

With the advent of high-frequency probes, evaluation of urinary bladder and free fluid in the pelvis at higher sensitivity can be done using advanced ultrasonography techniques. Detection of peritoneal free fluid in the presence of normal viscera or collapsed urinary bladder after the transurethral saline injection is considered to be highly positive for urinary bladder rupture (10). However, CT is the best diagnostic standard for detecting urinary bladder rupture with high sensitivity and specificity. Chan et al. (6) stated that CT cystography is a proper method for detecting bladder rupture. CT reconstructed images could be useful in identifying the exact site of bladder injury (6).

Spontaneous urinary bladder rupture following a seizure is rare and is associated with significant morbidities, which may be detrimental if undetected. A careful physical and radiologic examination should be done to rule out unexpected traumatic events.

Ethics

Informed Consent: Verbal consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Y.A., A.A., E.Y., F.A., W.I.; Concept - Y.A., A.A., E.Y., F.A., W.I.; Design - Y.A., A.A., E.Y., F.A., W.I.; Data Collection or Processing - Y.A., A.A., E.Y., F.A., W.I.; Analysis or Interpretation - Y.A., A.A., E.Y., F.A., W.I.; Literature Search - Y.A., A.A., E.Y., F.A., W.I.; Writing - Y.A., A.A., E.Y., F.A., W.I.

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

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Ischemic Stroke in Patient Diagnosed with Ulcerative Colitis in the Active Phase: A Case Report

Aktif Dönemde ve Yeni Tanı Konmuş Ülseratif Kolitli Hastada Gelişen İnme: Olgu Sunumu

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ABSTRACT

Ulcerative colitis (UC) and Crohn's disease are the two major types of inflammatory bowel disease (IBD). The close relationship between inflammation and thrombosis also affects the clinical course and severity of IBD. While venous thrombus is common in IBD, as in many other inflammatory diseases, arterial thrombus, and stroke are rare. Herein, we present a case of a newly diagnosed UC in the active phase of stroke despite being followed up with prophylactic anticoagulant therapy.

Keywords: Ulcerative colitis, inflammation, arterial thrombus, stroke

ÖZ

Ülseratif kolit (ÜK) ve Crohn hastalığı inflamatuvar barsak hastalığının (İBH) iki ana türüdür. Enflamasyon ve trombüs arasındaki yakın ilişki aynı zamanda İBH'nin klinik seyrini ve ciddiyetini de etkiler. Diğer birçok inflamatuvar hastalıkta olduğu gibi İBH'inde venöz trombüs yaygın iken, arteriyel trombüs ve inme çok nadir görülür. Sunulmuş olan olgu, profilaktik antikoagülan tedavi altında izlenmesine rağmen inme geçiren aktif dönemde ve yeni tanı almış bir ÜK hastasıdır.

Anahtar Kelimeler: Ülseratif kolit, enflamasyon, arteriyel tromboz, inme

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) of the large bowel and is characterized by symptoms, including bloody diarrhea, fecal urgency, and abdominal cramps. Crohn's disease and UC are the two major types of IBD (1,2). Since it has been reported for the first time by Bagen and Barker (3) in 1936, it is known that the risk for arterial and venous thrombosis is increased in IBD. The close relationship between inflammation and thrombosis also affects the clinical course and severity of IBD as seen in many other inflammatory diseases (2-4). Acquired (smoking, use of steroid therapy, immobilization, inflammation, endothelial dysfunction, dehydration, and surgery) and inherited risk factors (factor V leiden mutation and prothrombin gene mutation) were defined for thrombosis (5). In IBD, thrombosis can commonly develop in deep leg veins and the pulmonary system and less frequently in the cerebrovascular system, portal, mesenteric, hepatic, and retinal veins (6-8). While it is less common in the arterial system compared to the venous system, thrombosis can occur in the aorta, retinal, renal, coronary, carotid, and iliac arteries (9,10). Arterial thrombus, particularly stroke, is rare in IBD (11). Until now, observational studies have provided

conflicting findings on whether IBD is associated with an increased risk of stroke (11-13).

Case Report

A 46-year-old female patient with known diagnoses of hypertension (HT) and diabetes mellitus (DM), using amlodipine and intensive insulin treatments, neither consuming alcohol nor smoking, without a known allergy, and with family histories of ischemic heart disease in her father and cerebrovascular disease in her brother presented to our gastroenterology outpatient clinic due to complaints of gradually increasing bloody diarrhea, severe fatigue, and high fever for approximately one month. She complained that her bloody diarrhea gradually increased in the last two weeks, occurring more than 30 times in a day, and that almost all of them were bloody and mucous stool. She also complained of high fever and abdominal pain occurring in the last few days. On physical examination, blood pressure was 130/80 mmHg, temperature was 38.6 °C, and pulse was 98/min. On abdominal examination, there was no rebound tenderness or defense to palpation. With a prediagnosis of UC, rectosigmoidoscopy was performed in



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the patient under emergency conditions. The mucosa was in the appearance of erosion and ulceration continuously from the transverse colon to the anal canal. The mucosa was fragile with spontaneous bleeding (Mayo Endoscopic score: 3). Many biopsies were taken and the tissue sample was sent for cytomegalovirus (CMV) polymerase chain reaction (PCR) (Figure 1). The patient was admitted to our clinic with prediagnoses of fulminant colitis, active UC, and infectious colitis. There were no toxic megacolon findings in the upright abdominal X-ray. Abdominal ultrasound showed no specific findings. Blood test results were as follows: white blood cell: 13,560/mm³ (normal range: 4,000-10,000 mm³), hemoglobin: 8.2 g/dL (NR: 12-16 g/dL), C-reactive protein (CRP): 423 mg/L (NR: 0-5 mg/L), ESR: 78/h (NR: 0-20 mm/h), fasting glucose: 220 mg/dL (NR: 70-110 mg/dL), albumin: 3.4 g/dL (NR: 3.5-5.5 g/dL), and hepatitis B surface antigen: negative. Abundant leukocytes and erythrocytes were observed on microscopic examination of fecal specimens. The presence of amebic antigen was negative in the fecal specimens. Clostridium Difficile Toxin A and B were negative in the fecal specimens after three tests were performed. Oral intake of the patient was discontinued due to prediagnoses of activation/fulminant UC (severe active colitis according to Truelove-Witts clinical activity index) based on clinical, laboratory, imaging, and endoscopic findings. Based on these findings, the following treatments were started: mesalazine (4,000 mg/day), methylprednisolone (40 mg/day), ciprofloxacin, metronidazole, intensive insulin treatments, and subcutaneous low molecular weight heparin (LMWH) in prophylactic dose as an anticoagulant agent. During the follow-up of the patient, the fever was ceased on the third day, vital signs were stable, the number of daily defecation increased to about 5-6 times per day, and CRP regressed to 32 mg/dL. We achieved colonoscopic biopsy results while the treatments of the patient were continued and findings consistent with the active phase of UC were reported and CMV-PCR was found to be negative. Meanwhile, the treatments of the patient were continued and her general condition began to improve. However, a sudden onset throbbing headache localized in the frontal region and aphasia developed on the seventh day of hospitalization. The patient's vitals and blood glucose level were normal. On neurological examination, pupils were isochoric, pupillary light reflexes were normal, meningeal irritative sign was absent, muscle strength was full, sensory examination was normal, orientation and cooperation were normal, but there was a slurred speech and repetition disorder. A neurological consultation was performed. No pathological finding was determined on cranial computed tomography (CT) scan. A cranial diffusion magnetic resonance

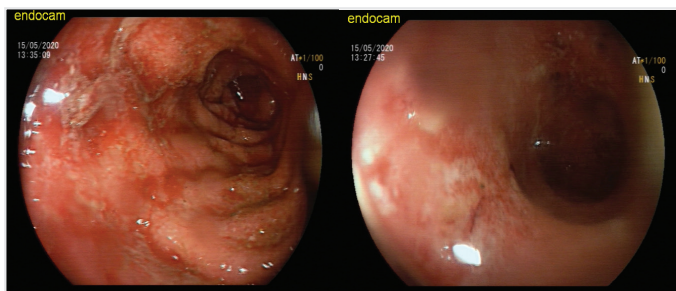


Figure 1. Active ulcerative colitis condition in sigmoid colon and ascending colon (Mayo Endoscopic score: 3)

imaging (MRI) was performed at the end of the first hour. An infarct area consistent with thromboembolism related to the posterior branch of the left middle cerebral artery (MCA) and showing restricted diffusion in the insular region of the left parietal lobe was observed (Figure 2). Based on these findings, with the diagnosis of left parietal lobe ischemic infarct, acetylsalicylic acid (ASA) (300 mg) was started as anti-aggregant therapy and the prophylactic LMWH dose was increased. Hypodense areas revealing that ischemia was settled in the left parietal lobe were observed in control cranial CT scan performed at the end of the second day and the ischemic area in the insular region of the left parietal lobe in a cranial diffusion MRI performed at the end of the second day became apparent (Figure 3). No significant narrowing was observed in the cranial and cervical MRI angiographic examinations performed for etiological reasons. Echocardiography was within normal limits. Her elder brother has a history of cerebrovascular accident. Therefore, a hematological consultation was done for thrombophilic etiology. Her tests performed for antinuclear antibody, lupus anticoagulant, anticardiolipin immunoglobulin M (IgM)/IgG, anti-beta 2 glycoprotein IgM/IgG, factor V leiden mutation, and prothrombin gene mutation yielded negative results and her homocysteine level was within normal limits. Levels of her protein C, protein S, and anti-thrombin III activity was planned to be determined after discontinuation of the antiaggregant therapy. With these findings, no thrombophilic condition was determined. During the long-term follow-up of the patient, aphasia gradually decreased with the LMWH and ASA therapies. The patient experienced a new UC attack accompanied with widespread peripheral bilateral arthritis five months after the first diagnosis. She was hospitalized, steroid therapy was restarted, and azathioprine therapy was added. Since she experienced

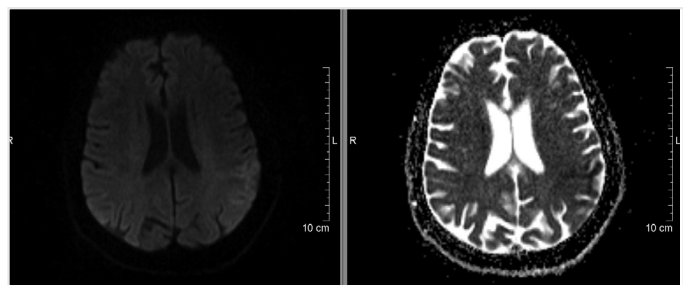


Figure 2. Left MCA infarct in cranial diffusion MRI (performed in the first hour)

MCA: Middle cerebral artery, MRI: magnetic resonance imaging

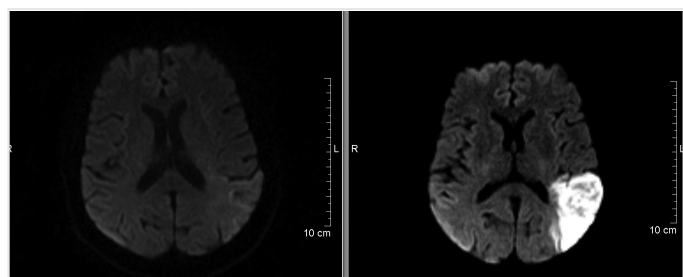


Figure 3. Left MCA infarct in cranial diffusion MRI (performed at the end of the second day)

MCA: Middle cerebral artery, MRI: magnetic resonance imaging

pancreatitis with azathioprine therapy, anti-tumour necrosis factor (TNF) therapy (infliximab) was started. Informed consent was obtained.

Discussion

Herein, we describe a case of ischemic stroke. She was a female newly diagnosed of UC in the active phase. While the activity of the disease was reduced under the treatments with prophylactic LMWH, anti-biotherapy, steroid, and mesalazine, a sudden onset headache and aphasia developed on the seventh day of treatment. A left MCA infarct was determined on the cranial imaging performed. A neurological consultation was done and antiaggregant therapy was started immediately. The dosage was raised to the optimal level. A reduction was determined in the aphasia within few days. During the long-term follow-up of the patient, the aphasia gradually decreased with LMWH and ASA therapies. In our investigations, no inherited thrombophilic risk factor was determined for the stroke etiology. To be in the active phase of UC, use of steroid therapy, HT, and DM can be accepted as risk factors for thrombosis. Our patient experienced a new UC and arthritis attack five months after the first diagnosis during the follow-up. Treatment of our patient was switched to infliximab therapy. This condition was suggestive of an initial thrombotic event that was associated with poor prognosis. In the report presented in 2008 by Joshi et al. (11) a 24-year-old female patient had been diagnosed with UC six months earlier. A severe headache and global aphasia developed while she was taking mesalazine and steroid treatments and an infarct of the left MCA was reported. This patient and our patient were almost identical. The adequate response for steroid treatment was not observed in this case and total colectomy was performed shortly afterward. In our patient, treatment was switched to infliximab therapy (11). Thrombotic events involving the central nervous system are unusual. Cases of cerebral venous sinus thrombosis in IBD are well described (14,15). Arterial thromboembolic complications occur less frequently and majority of these cases seem to occur after surgery (16,17). In the study performed in 2016 by Akpınar et al. (5) in which a total of 3,128 patients with IBD, were retrospectively screened, it was reported that thromboembolic event was observed in 20 patients and thrombosis was seen most commonly in deep leg veins and the pulmonary veins and that cerebral vein thrombosis developed only in 1 patient. Cerebral arterial thrombosis was not reported (5). Pancolonic and active UC have also been suggested as a risk factor for stroke and significant morbidity has been found to be associated with arterial complications (18). Our patient was a case of UC with pancolonic involvement. Her Mayo Endoscopic score was 3, CRP was 423 mg/L, and ESR was 78 mm/hour. She was a serious/severe patient according to Truelove-Witts clinical activity index. Although prophylactic LMWH treatment was started at the beginning from her hospitalization and the disease activity decreased at the end of the third day, a cerebral infarct developed on the seventh day of her hospitalization. Treatment of thrombosis in IBD comprises preventive prophylactic therapy and anti-coagulation therapy. Prophylactic anti-coagulation treatment is recommended in patients with IBD, especially in the active phase of the disease and during hospitalization (19). The agent recommended for prophylactic anti-coagulation treatment is LMWH. In IBD diagnosed with thrombosis, LMWH, warfarin, or rivaroxaban can be used as the

treatment options. Durations of the use of the agents in treatment are controversial. While the therapy should be maintained until remission in thrombosis diagnosed during the active phase of the disease, life-long therapy is recommended in thrombosis occurring in the absence of active disease and underlying inherited thrombophilic states (20).

Reports are available on the risk of recurrence and complication of IBD in patients experiencing thrombosis and it will be better to switch the therapy to an upper level (azathioprine and anti-TNF) to establish long-term remission (5). In our patient, a new attack of UC and arthritis developed few months after cerebral infarct. Steroid therapy was administered again and infliximab therapy was initiated as an upper-level therapy. IBD is a prothrombotic condition. Although venous thromboembolic events are more commonly observed, arterial thrombosis can also be seen. Prophylactic anti-coagulation treatment should be necessarily started during hospitalizations, especially in the active phase of the disease. A cerebral infarct developed in our patient despite the prophylactic anti-coagulation treatment during the active phase of the disease. Early diagnosis and treatment are important for the reduction of the morbidity and mortality of patients developing a cerebral infarct. We followed up our patient very closely, performed immediate cranial imaging and neurological consultation, and started the therapy without delay. As a result, aphasia recovered gradually with time.

Unfortunately, we observed that awareness of the high risk for thromboembolic complications in IBD was low. In particular, stroke is not a well-known complication despite being a serious clinical picture with mortality and morbidity. Therefore, we think that it is necessary to potentially inhibit the disease activation and inflammation in patients with IBD during the active phase of the disease or during hospitalization. It is also important to start prophylactic anti-coagulation treatment and follow-up the thromboembolic events.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

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