

# The Effect of a Single Session of Eccentric Exercise on Proprioception and Oxidative Stress in Knee Osteoarthritis: A Preliminary Study

## Tek Seans Egzantrik Egzersizin Propriyosepsiyon ve Oksidatif Stres Üzerine Etkisi: Ön Çalışma

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**ABSTRACT Objective:** Isokinetic strengthening exercises are widely used in the rehabilitation of knee osteoarthritis. The main aim of the present study was to examine the effects of eccentric exercise on proprioception in knee osteoarthritis. In addition, the oxidative damage and fatigue were also investigated. **Material and Methods:** Twelve patients with knee osteoarthritis, and eleven healthy women underwent an eccentric exercise session of the dominant leg. Delayed-onset muscle soreness (DOMS), isometric peak torque (IPT), joint position angle (JPA) and joint reaction angles (JRA) with and without visual feed-back, serum creatine kinase (CK), potassium (K), lactate dehydrogenase (LDH), malondialdehyde (MDA), nitric oxide (NO) and glutathione were evaluated before, immediately after, 24<sup>th</sup> and 72<sup>nd</sup> h after the exercise. **Results:** No significant difference was found between the groups in terms of age, baseline laboratory variables, IPT, DOMS, JPA, JRA, CK, K, LDH, MDA, NO, and glutathione levels ( $p>0.05$ ). Muscle damage (DOMS, CK), increased oxidative stress (MDA) and impaired proprioception (JPA, JRA) were occurred in response to high intensity eccentric exercise in both groups ( $p<0.05$ ). The angles deviating from the reference angle (JPA) and JRA values independent of time and group was significantly higher in without visual feedback measurements ( $p\leq 0.001$ ). **Conclusion:** In early onset knee osteoarthritis rehabilitation, we recommend individual eccentric exercise protocols combined with proprioceptive exercise to improve muscle strength and to ensure proper motor response by increasing the proprioceptive perception. Exercise induced oxidative stress is an important consideration for optimal performance, and recovery process.

**ÖZET Amaç:** Diz osteoartriti tedavisinde izometrik güçlendirme egzersizleri yaygın olarak uygulanmaktadır. Bu çalışmanın temel amacı, diz osteoartritiinde eksantrik egzersizin propriyosepsiyon üzerine etkilerini incelemektir. Ayrıca, oksidatif hasar ve yorgunluk da araştırılmıştır. **Gereç ve Yöntemler:** Diz osteoartriti olan 12 hasta ve 11 sağlıklı kadının dominant bacağına eksantrik egzersiz seansı uygulandı. Gecikmiş başlangıçlı kas ağrı (DOMS), izometrik pik tork (IPT), görsel geri bildirimli ve bildirimli eklemler pozisyon açısı (JPA) ve eklemler reaksiyonu açıları (JRA), serum keratin kinaz (CK), potasyum (K), laktat dehidrojenaz (LDH), malondialdehid (MDA), nitrikoksit (NO) ve glutatyon egzersizden hemen önce, hemen sonra, 24 ve 72. saatlerde değerlendirildi. **Bulgular:** Gruplar arasında yaş, ilk laboratuvar değerleri, DOMS, IPT, JPA, JRA, CK, K, LDH, MDA, NO ve glutatyon düzeyleri benzerdi ( $p>0,05$ ). Yüksek yoğunluklu eksantrik egzersize yanıt olarak, her iki grupta da kas hasarı (DOMS, CK), oksidatif strese artış (MDA) ve propriyosepsiyonda bozulma (JPA, JRA) saptandı ( $p<0,05$ ). Görsel geri bildirim olmadığında, zaman ve gruptan bağımsız olarak JPA ve JRA değerleri belirgin yüksekti ( $p\leq 0,001$ ). **Sonuç:** Erken başlangıçlı diz osteoartrit rehabilitasyonunda, kas gücünü artırmak ve propriyoseptif algıyı arttırarak uygun motor yanıtını sağlamak için propriyoseptif egzersiz ile kombine bireysel eksantrik egzersiz protokollerinin uygulanmasını tavsiye ediyoruz. Egzersize bağlı oksidatif stres, optimum performans ve iyileşme sürecinde göz önünde bulundurulması gereken bir unsurdur.

**Keywords:** Eccentric exercise; fatigue; knee osteoarthritis; muscle strength; oxidative stress; proprioception

**Anahtar Kelimeler:** Eksantrik egzersiz; yorgunluk; diz osteoartriti; kas gücü; oksidatif stress; propriyosepsiyon

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The knee is the most frequently involved joint in osteoarthritis (OA).<sup>1</sup> Conservative treatment is advocated in patients with mild to moderate OA of the knee and isokinetic strengthening exercises are widely used in the rehabilitation of knee OA.<sup>2,3</sup> However, eccentric exercises can cause micro-injury to the muscle and connective tissue with muscle lengthening under tension.<sup>4,5</sup> Muscle pain and tenderness generally develops 24 hours after exercise and is termed as, delayed onset muscle soreness (DOMS).<sup>6</sup> An acute inflammatory response, resulting from metabolic, mechanical, oxidative stress may explain the DOMS.<sup>7</sup>

Generation of free radicals, which are increased in the muscles and plasma during exercise, leads to muscle injury, which were found to begin the antioxidant mechanisms, organizing the regeneration and adaptation of the muscle to exercise.<sup>7</sup> Malondialdehyde (MDA) is a free radical, which levels out during exercise and is correlated with creatine kinase, which is sign of muscle damage. During and after exercise, nitric oxide (NO) production increases due to inducement of the activity of NO synthase in ischemia-reperfusion.<sup>8</sup> Glutathione (GSH) is an anti-oxidant which prevents the rise of lipid peroxidation, the indicator of oxidative stress.<sup>9</sup>

Efficient position sense and muscle reaction time, which are both affected by visual and auditory stimuli, are essential for confident human movement in daily activities.<sup>10</sup> Muscle reaction time is defined as a certain period between presentation of external stimulus and appropriate motor response to the stimulus. It reflects the persons' neurophysiological, cognitive and information processes.<sup>11</sup> Eccentric exercise of the upper or lower limbs disturbs the position sense and muscle reaction time.<sup>10</sup>

Numerous studies have investigated the relationship between strength exercises and fatigue or muscle damage, proprioception and knee osteoarthritis, in separate studies.<sup>7-10</sup> To our knowledge, this is the first study to evaluate together the effects of eccentric exercise on proprioception, oxidative stress, muscle fatigue and strength in knee OA. The main purpose of this study is to compare patients diagnosed with knee OA to healthy people with respect

to knee proprioception and muscle reaction angle after eccentric exercise. Furthermore, fatigue, muscle strength and oxidative damage were also investigated.

## MATERIAL AND METHODS

### SUBJECTS

Twelve female patients with knee OA who met the American College of Rheumatology (ACR) criteria with grade II or III knees according to the Kellegren-Lawrence Grading, together with eleven healthy postmenopausal women were recruited.<sup>12</sup> Approval was obtained from the Ethics Committee of the Turkish National University Hospital (May 2009/240). The study was conducted between January and September 2010 at the same National University Hospital.

We followed the ethical guidance which recommends adherence to the 2008 version of the Declaration of Helsinki. All subjects were informed verbally and written consent was obtained prior to participation. All were non-smokers and postmenopausal. Exclusion criteria included known anemia, experience with musculoskeletal-neurological limitations, known inflammatory conditions, alcohol use greater than one drink per week, use of anti-inflammatory medications, lipid lowering medications and significant major systemic diseases. During the experimental period, subjects were requested not to take any medication, change their diet or perform any resistance exercise.

### EXPERIMENTAL DESIGN

The exercise protocols were undertaken by all participants using their dominant leg and were measured by an isokinetic dynamometer (Cybex Norm, Ronkonkoma, New York). Age, body mass index (BMI), initial laboratory data and Lequesne index of the all participants were recorded. DOMS, isometric peak torque (IPR), joint position angle (JPA) and knee joint reaction angle (JRA) to release were evaluated before, immediately after as well as 24 and 72 hours after the exercise. Creatine kinase (CK), potassium (K), lactate dehydrogenase (LDH), MDA, NO and GSH were determined at the same time-points. Differences in measures over time were

compared between the patients with knee osteoarthritis and controls. The Lequesne index is a 10-question survey given to patients with knee OA. It has five questions pertaining to pain or discomfort, one question dealing with maximum distance walked, and four questions about activities of daily living. The total questionnaire was scored on a 0 to 24 scale. Lower scores indicated less functional impairment.<sup>13</sup>

## EXERCISE

Participants were seated (100° hip angle) with the lateral femoral condyle aligned with the axis of rotation of the dynamometer and the ankle cuff attached proximal to the lateral malleolus.

Each participant's functional range of motion was set electronically between full extension (0°) and 90° of knee flexion. Before the exercise, participants made a warm-up consisting of 5 min. of cycling, followed by 5 min. of stretching exercises of the lower limbs.

The exercise protocol consisted of six sets of ten eccentric maximal voluntary contractions of knee extensors, flexors at an angular velocity of 60°s<sup>-1</sup> with a 1 min. rest between sets.

## BLOOD ANALYSIS

Blood samples were drawn by antecubital venipuncture, immediately centrifuged at 2.000×g for 10 min at 4°C. Serum samples were stored in Eppendorf tubes at -70°C until the analyses were carried out. Determination of serum K, LDH and CK were performed using a ROCHOP800 auto-analyzer.

Plasma lipid peroxide levels were estimated by the method as per Kurtel et al.<sup>14</sup> Lipid peroxidation was quantified by measuring the formation of the thiobarbituric acid reactive substances. The lipid peroxide level was expressed in terms of an MDA equivalent using an extinction coefficient of 1.56 x 10<sup>5</sup> M-1cm<sup>-1</sup>.<sup>15</sup>

The GSH levels were determined by the method as per Kurtel et al., calculated assuming a molar extinction coefficient of 13.000 at 412 nm.<sup>14</sup> Measurements of GSH and MDA were carried out using a spectrophotometer (UV 1208, Japan).

NO levels were estimated by the method as per Miranda et al.<sup>16</sup> Samples were measured at 540 nm using an ELISA reader.

## MUSCLE SORENESS

Participants determined soreness of the distal region of the quadriceps by self palpation using a visual analog scale from 0=no soreness to 10=extremely sore.<sup>17</sup>

## MUSCULAR STRENGTH

Isometric maximal muscle strength of dominant knee extensor and flexor muscles were evaluated. For isometric contractions, subjects were asked to sustain maximal effort for 10 seconds at fixed knee joint angles of 90°. The highest three peak torque (N.m) values were recorded.

## POSITION SENSE AT THE KNEE

Participants sat upright on the isokinetic dynamometer, all evaluations were applied to dominant legs with visual or without visual feedback in random order. The angles were measured by isokinetic dynamometer as Pachalis et al. had applied.<sup>10</sup> The leg moved from 0°(full extension) to 90°(knee flexion). The investigator positioned the lower limb at 45° (reference angle) knee flexion, maintained it for 10 s, returned the leg to the initial position (90°) then the subjects were asked to recall the reference position, they then actively moved their limb to the target angle (45°) and would hold it for about 2s. The angles deviating from the reference angle (JPA), as measured through degrees (in absolute values), were recorded. Four trials were performed, the two best were recorded. The test-retest reliability in the position sense, with or without visual feedback (measured in five individuals on four consecutive days) was 0.74 and 0.76, respectively.

## KNEE JOINT REACTION ANGLE TO RELEASE

The isokinetic dynamometer was used for the evaluation of JRA, with or without visual feedback, as Pachalis et al. had applied.<sup>10</sup> The lower dominant limb was passively positioned by the investigator at one of the four different angles (0°, 15°, 30°, 45°) in random order.

When the muscles of the lower limb relaxed at the predetermined angle, the investigator let the limb fall without warning. The instruction given to participants was to stop the fall of the limb as soon as it was perceived as being released. The angle through which the limb moved before the participants managed to stop the motion was recorded and sustained the JRA.

Four trials were performed, the two best were recorded. The test-retest reliability in the joint reaction angle to release with or without visual feedback (measured in five individuals on four consecutive days) was 0.75 in both cases.

### STATISTICAL ANALYSIS:

The Shapiro-Wilk test was used to test the normality of the variables. After controlling the distribution of variables, they were summarized as mean± standard deviation and median (minimum; maximum). The independent sample t-test or Mann Whitney U test was used to examine the differences between control and patient groups with respect to demographic variables. To investigate the main and the interaction effects of factors, the two-way mixed ANOVA and the non-parametric analysis of longitudinal data in factorial experiments were performed after determining whether the variables met the necessary assumptions

(Homogeneity of variance-covariance, sphericity, normality of residuals). When the assumptions did not meet, the ANOVA-type statistic ( $n < 200$ ) were calculated for the experiments with LD designs (the F1\_LD\_F1 for group\*time factors, F1\_LD\_F2 for group\*visual\*time factors, LD\_F1 for main effects of time). The changing of variables according to time was shown with the relative treatment effect (RTE) in graphs. IBM SPSS Statistics for Windows 21.0 (IBM Corp. Released 2012, Armonk, NY: IBM Corp.) software was used in statistical analyses. The “nparLD” package was used for factorial design in R program.<sup>18,19</sup> The statistical significance level was accepted as  $p < 0.05$ .

### RESULTS

There was no statistically significant difference between the groups in terms of age and laboratory variables ( $p > 0.05$ ) (Table 1). However, BMI and Lequesne index scores were significantly higher in the patients ( $p = 0.017$  and  $p = 0.008$ , respectively).

At least one measurement time was different from others with respect to DOMS ( $p < 0.001$ ). DOMS significantly increased post-exercise measurements ( $p < 0.001$ ) (Table 2). No significant difference was found between the groups concerning DOMS ( $F = 0.229$ ;  $p = 0.584$ ).

**TABLE 1:** Demographic and laboratory variables in groups.

Variables	Control	Patient	t/Z	p
	Mean±SD	Mean±SD		
	Median (min; max)	Median (min; max)		
Age (year)	53.0 (49.0; 66.0)	54.0 (49.0; 62.0)	Z=-0.186	0.880
BMI (kg/cm <sup>2</sup> )	29.0±4.3	34.0±4.8	t=-2.602	0.017
Hb (g/dl)	13.3±0.6	13.2±1.0	t=0.384	0.705
Htc (%)	39.4±1.9	39.2±2.7	t=0.180	0.859
ESR (mm/sa)	22.6±10.8	22.3±7.7	t=0.076	0.940
CRP (mg/L)	3.8 (1.9; 13.0)	2.5 (2.1; 6.7)	Z=-0.648	0.525
TSH (Um/ml)	1.6 (0.5; 3.2)	1.6 (0.6; 4.1)	Z=-0.031	0.976
Vit D (µg/L)	6.2 (2.0; 24.4)	7.4 (3.0; 30.6)	Z=-0.894	0.379
Albumin (g/dl)	4.1 (3.8; 5.2)	4.1 (3.8; 5.2)	Z=-0.681	0.525
ALP (U/L)	79.0 (44.0; 103.0)	88.0 (4.0; 107.0)	Z=-0.585	0.566
Lequesne score	4.2±3.2	9.5±5.1	t=-2.906	0.008

ALP: Alkaline phosphatase, BMI: Body Mass Index, CRP: C reactive protein, Hb: Hemoglobin, Htc: Hematocrit, ESR: Erythrocyte Sedimentation Rate, TSH: Thyroid stimulating hormone, Vit D: Vitamine D; SD: Standard deviation, min: Minimum, Max: Maximum, t / Z: test statistics obtained from Independent sample t test and Mann Whitney U test, respectively.

**TABLE 2: DOMS (Delayed onset muscle soreness) with respect to time in groups.**

DOMS Group	Time				
	Pre Median (min; max)	Immed Median (min; max)	Median (min; max)	72 Median (min; max)	Total Median (min; max)
Control	0 (0; 0)	3.5 (1; 8)	4.5 (0; 9)	3.5 (0; 10)	3 (0; 10)
Patient	0 (0; 0)	3 (0; 5)	4 (0; 6)	3 (0; 8)	3 (0; 8)
Total	0 (0; 0) <sup>a</sup>	3 (0; 8) <sup>b</sup>	4 (0; 9) <sup>b</sup>	3 (0; 10) <sup>b</sup>	

The ANOVA-type statistics from F1\_LD\_F1 design: Group F=0.299; p= 0.584, Time F=37.542; p<0.001, Group\*Time F=0.160; p=0.910.

Pairwise comparisons of times: p<0.001 for Pre-Immed, 24, 72 comparisons; p=0.113 and p=0.977 for Immed-24, 72; p=0.235 for 24-72.

min: Minimum, Max: Maximum, a, b are showing the differences.

There was no significant difference between the groups in terms of IPT regardless of time (p=0.451 and p=0.353 for extensor and flexor, respectively). Extensor peak torque steadily increased in the post-exercise measurements in both groups (Table 3).

The interaction effects (group\*visual\*time; group\*visual/visual\*time/group\*time) in terms of JPA and JRA values were not significant (p>0.05) (Table 4). When the main effects were evaluated, it was determined that the JPA and JRA values was significantly higher in without visual feedback measurements except the JPA (real) (p≤0.001; for JPA (real) p=0.163).

The JRA value was compared according to different angles in the groups. While the interaction (groups\*angle) and the group's main effect were not

significant (F=0.968; 0=0.404 and F=2.139; p=0.144, respectively), a statistically significant difference was determined at least one angle case in terms of JRA (F=424.710; p<0.001). All pairwise comparisons of different angles were found significant (all p values <0.001). The JRA values were 0.81-0.52-0.39-0.28 for 0°, 15°, 30°45°, respectively. The disturbances of JRA were highest at 0°angle, lowest at 45° angle.

There was no significant interaction (group\*time) and group main effects in terms of CK, K, LDH, MDA, NO, and glutathione levels (p>0.05) (Table 5). The main effect of time was found to be statistically significant level different only in CK and MDA variables (p<0.001). The levels of CK were significantly increased at 24 h and 72 h (p<0.05) (Figure 1c). Levels of MDA significantly increased just

**TABLE 3: IPT (isometric peak torque) values with respect to time and groups.**

Group	Time				
	Pre	Immed	24	72	Total
	Mean±SD Median (min; max)	Mean±SD Median (min; max)	Mean±SD Median (min; max)	Mean±SD Median (min; max)	Mean±SD Median (min; max)
<b>Isometric extensor peak torque (N m)</b>					
Control	84.7±18,4	91.4±24.2	97.6±28.3	94.2±22.8	92.3±22.9
Patient	79.6±12.9	86.3±22.4	87.6±25.1	86.1±21.7	84.3±20.0
Total	82.0±15.6 <sup>a</sup>	88.7±22.8 <sup>a,b</sup>	92.3±26.5 <sup>b</sup>	89.9±22.0 <sup>a,b</sup>	
<b>Isometric flexor peak torque N m)</b>					
Control	21.5 (13.5; 32.0)	15.3 (11.5; 36.0)	19.8 (13.0; 35.5)	25.3 (15.5; 96.5)	21.0 (11.5; 96.5)
Patient	17.0 (10.0; 24.5)	15.5 (8.0; 38.0)	17.0 (8.5; 50.5)	17.0 (15.0; 55.0)	17.0 (8.0; 55.0)
Total	19.0 (10.0; 32.0) <sup>a</sup>	15.5 (8.0; 38.0) <sup>a</sup>	17.5 (8.5; 50.5) <sup>a</sup>	20.0(15.0; 96.5) <sup>b</sup>	

The ANOVA-type statistics from F1\_LD\_F1 design: Group F= 0.862; p= 0.353, Time F= 5.749; p=0.001, Group\*Time F= 0.777; p= 0.488

Pairwise comparisons of times:p=0.114 and p=0.788 for Pre-Immed, 24; p=0.002 for Pre-72; p=0.063 for Immed-24; p<0.001 for Immed-72; p=0.050 for 24-72.

SD: Standard deviation, min: Minimum, Max: Maximum, a, b are showing the differences

**TABLE 4:** The results of the ANOVA- type statistics from F1\_LD\_F2 design for JPA (joint position angle) and JRA (joint reaction angle) variables.

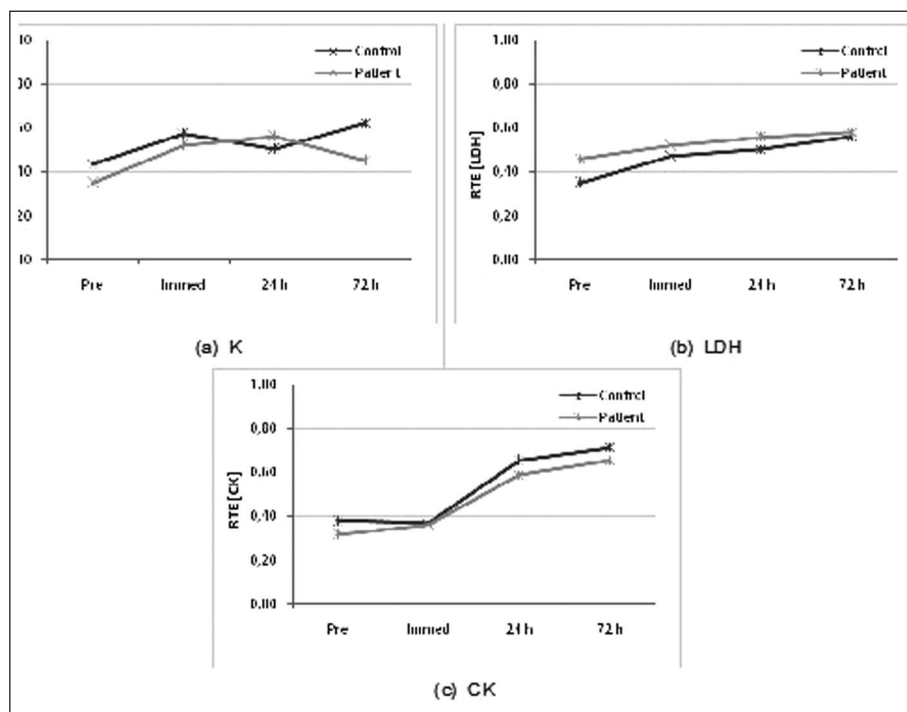
Factors	Variable					
	JPA (absolute) F; p	JPA (real) F; p	JRA 0° F; p	JRA 15° F; p	JRA 30° F; p	JRA 45° F; p
Group	2.012; 0.156	1.405; 0.236	0.806; 0.369	0.057; 0.811	0.568; 0.451	0.154; 0.695
Visual	12.060; 0.001	1.950; 0.163	24.040; <0.001	53.490; <0.001	15.052; <0.001	37.461; <0.001
Time	2.041; 0.120	2.000; 0.135	2.261; 0.092	1.189; 0.308	2.559; 0.063	0.767; 0.492
Group*Visual	1.169; 0.280	0.292; 0.589	0.168; 0.681	2.207; 0.137	0.001; 0.997	0.897; 0.344
Visual*Time	1.080; 0.343	0.649; 0.549	0.612; 0.570	0.436; 0.695	0.575; 0.567	0.765; 0.475
Group*Time	0.287; 0.789	0.110; 0.898	0.603; 0.580	1.333; 0.264	0.221; 0.851	0.250; 0.829
Group*Visual*Time	1.402; 0.246	2.155; 0.106	1.463; 0.229	2.220; 0.094	0.782; 0.460	0.059; 0.953

**TABLE 5:** The results of the ANOVA- type statistics from F1\_LD\_F1 design for K (potassium), LDH (lactate dehydrogenase), CK (serum creatine kinase), MDA (malondialdehyde), Glutathion, NO (nitric oxide) variables.

Factors	Variable					
	K F; p	LDH F; p	CK F; p	MDA F; p	Glutathion F; p	NO F; p
Group	0.504; 0.478	0.380; 0.538	0.264; 0.607	0.035; 0.852	0.915; 0.339	3.739; 0.053
Time	2.246; 0.084	2.335; 0.084	30.335; <0.001	12.158; <0.001	0.710; 0.536	0.221; 0.828
Group*Time	0.910; 0.431	0.158; 0.895	0.215; 0.757	1.542; 0.214	0.984; 0.394	0.078; 0.942

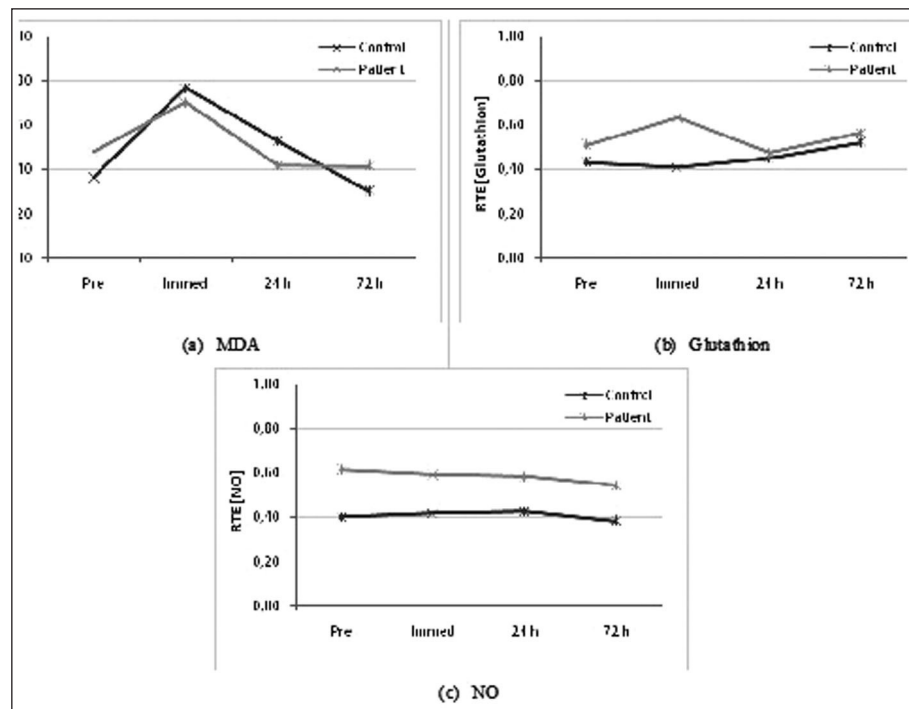
Pairwise comparisons of times for CK: p=0.423 for Pre-Immed; p<0.001 for Pre-24, 72, Immed-24,72; 24-72.

Pairwise comparisons of times for MDA: p<0.001 for Pre-Immed; p=0.181for Pre-24; p=0.143 for Pre-72; p<0.001 for Immed-24, 72; p=0.05 for 24-72.



**FIGURE 1:** The changes of relative treatment effects (RTE) of K (potassium), LDH (lactate dehydrogenase) and CK (creatinine kinase) variables according to group visual time (Values are given in U/L for CK and LDH, mmol/L for K).





**FIGURE 2:** The changes of relative treatment effects (RTE) of MDA (malondialdehyde), Glutathione and NO (nitric oxide) variables according to group\*visual\*time (nmol/ml, nmol/ml,  $\mu\text{mol/l}$ , respectively).

after exercise ( $p < 0.001$ ) and there was a decrease at 24 h and 72 h MDA values according to Immed ( $p < 0.001$ ) while the MDA values obtained from 24 h and 72 h were not a statistically significant difference from pre values ( $p > 0.05$ ) (Figure 2a).

## DISCUSSION

To our knowledge, this is the first study that evaluated the effects of eccentric exercise on muscle fatigue, muscle strength, proprioception and oxidative stress in knee OA together in one study. All markers used to determine cellular damage showed an expected increase after the exercises but there were no significant differences between the groups. Therefore, eccentric exercise can be suggested to strengthen the muscles in an OA knee. Immediately after the exercise, DOMS, JPA, JRA, MDA, NO, glutathione levels, serum K and LDH levels increased.

JPA, JRA, MDA, NO, glutathione levels decreased to the pre-exercise levels in 72 hours. While DOMS, isometric peak torque, K and LDH levels steadily increased in the post-exercise measurements, CK was significantly increased in 24 to 72 hours.

Childs et al. assessed CK, LDH and they indicated that both CK and LDH were significantly elevated from baseline levels on post-exercise measurements and returned to pre-exercise values by day 7.<sup>20</sup> We did not evaluate them on the 7<sup>th</sup> day. Other studies demonstrated that CK levels increase significantly immediately after the exercise, then returning to pre-exercise CK levels on the 72<sup>nd</sup> hour.<sup>8,21</sup>

Exercise-induced oxidative stress is involved in muscular damage and soreness which results from strenuous exercise. In our study, as well as other studies, found increased oxidative stress markers reported in blood as a result of the increased levels of lipid peroxidation products and enzymatic markers of muscle damage after eccentric exercise.<sup>20,22</sup> In our study, NO and glutathione levels, especially MDA levels immediately increased after the exercise, similarly to the studies of Atalay and Stagos.<sup>8,23</sup> However, other studies indicated glutathione levels decreased after the exercise.<sup>24,25</sup> This variation has been shown in the response of different individuals to eccentric exercise induced that oxidative stress. Therefore, oxidant stimuli can be affected by many

different factors including, genetic, biochemical and physiological factors.<sup>26</sup> Dietary factors (alcohol, caffeine, cigarette, protein consumption etc) were considered throughout our study.

As is commonly known, muscle weakness, especially quadriceps, was shown as the stronger predictor of functional limitations in patients with knee OA.<sup>26,27</sup> Stagos and Weerakkody reported that muscle damage induced by eccentric exercise results in an immediate and prolonged reduction in muscle function, together with a significant decline of isometric torque.<sup>23,28</sup> Although muscle damage was induced by eccentric exercise in our study, we saw the increase in muscle strength in both groups, even with a single session of an eccentric exercise protocol. The changes in muscle strength were not significantly different between groups. The increase of muscle strength from the flexor group was less pronounced. Perhaps this can be overcome by neural adaptation in the long-term isokinetic strengthening exercise protocol.

DOMS is a symptom of eccentric exercise-induced muscle damage. Although the underlying mechanism of DOMS remains uncertain, it is usually accepted that DOMS is caused by inflammation of the damaged muscle and the efflux of substances from the damaged tissue to the extracellular region that sensitize the nerve endings.<sup>5</sup> Subjects were instructed to quantify the magnitude of muscle soreness for a palpation they experienced based on a subjective rating scale. Although it varies widely among individuals, it has been reported to be the most commonly used tool for assessing pain sensation.<sup>29</sup> In many studies, muscle soreness decreased on day 7 after eccentric exercise.<sup>20,30</sup> In our study, on the first day after exercise, it showed a significant increase and then it tended to decrease.

Together with visual input, vestibular input, the input from mechanoreceptors in the skin, muscles, tendons, ligaments and joint capsules provide the central nervous system has information about the limb position and enables postural control. Adequate position sense and muscle reaction angle are required for safe human movement. In agreement with our findings, several studies have reported that

position sense and muscle reaction angle of the limb were impaired after eccentric exercise.<sup>10,31-33</sup> In contrast, Pachalis et al's study demonstrated that position sense and muscle reaction angle to a release of the lower limbs may adapt in response to a repeated bout of eccentric exercise, leading to lesser disturbances.<sup>34</sup> Another study showed that changes in all measures of DOMS, plasma CK activity, myoglobin concentration) did not increase significantly after the second exercise bout.<sup>35</sup> In our study, we could not prove that the disturbance of the position sense and muscle reaction angle was progressively less because of the single session eccentric exercise protocol. On the other hand, our study values of JPA were higher in patients but this difference was not only in post-exercise measurements but also in pre-exercise measurements between groups. This result may be the consequence of the deterioration of alignment mechanoreceptors localized in the knee joint capsule, meniscal cartilage, lateral collateral ligament, anterior cruciate ligament in knee osteoarthritis or articular deafferentation defined by Irrang et al.<sup>1,36</sup>

The disturbances of JRA were higher where the limbs were at a more extended position, similar to Pachalis's study.<sup>10</sup> It is a possible reason for preferentially greater damage of type 2 muscle fibers during eccentric exercise. Type 2 muscle fibers are primarily responsible for high-speed contractions. Because of the need for requiring high response after a more extended position (0 and 15 degrees) as compared to angles in more flexed position (30 and 45 degrees), the reaction angle of the limb is higher at 0 degree. Alternatively, this can be explained by the effect of gravity, forces and vectors when the extremity is at different angles.

In this study, since all the subjects were female, we could not generalize our findings. This is the first limitation to our study. Controversies arise regarding the effect of sex on the magnitude of muscle damage and inflammatory response.<sup>37</sup> Oestrogen is a strong antioxidant and membrane stabiliser. The influence of oestrogen is a potential difference in susceptibility to exercise induced muscle damage.<sup>38</sup> Therefore, postmenopausal women were recruited in our study.



Another limitation was that only twelve subjects were examined but many parameters were evaluated together with repeated measurements. Although most previous studies mentioned the relationship between resistive exercises and oxidative stress in healthy subjects or eccentric exercise in knee osteoarthritis or proprioception and knee osteoarthritis; to the best of our knowledge, the effect of eccentric exercise on fatigue, proprioception and oxidative damage have not been researched together in knee osteoarthritis.<sup>3,10,23,39</sup>

Ethical approval for this study was obtained in May 2009 and the study was conducted between January and September 2010. Then some researchers in the study left the university where the study was conducted and could not continue to study where they worked, and finally we decided to write as a preliminary study, but of course there was a delay in preparing the article notification.

Our results suggest that increased oxidative stress and impaired proprioception occur in response to high intensity eccentric exercise in healthy and knee osteoarthritis groups especially immediately after the exercise. Exercise-induced oxidative stress is

an important consideration for optimal performance, and recovery process. In early onset of knee OA rehabilitation, we recommended individual eccentric exercise protocols within long term regimes combined with proprioceptive exercise to improve muscle strength and to ensure proper motor response by increasing the proprioceptive perception.

Further studies are necessary to include prolonged resistive exercise programmes combined with proprioceptive exercises with larger samples to confirm our findings.

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#### Conflict of Interest

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

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