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Effectiveness of exercises performed after platelet-rich plasma in patients with knee osteoarthritis: randomized controlled study

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Abstract. The aim of this study was to investigate the effects of exercises performed after *Platelet-Rich Plasma (PRP)* on pain, function, quality of life and muscle strength in individuals with knee osteoarthritis (OA). *Material and Method*. Forty patients with grade 2 and 3 knee OA according to the Kellgren-Lawrence radiological classification were randomly assigned to the study (Group 1; PRP+Exercise) and control groups (Group 2; PRP). Group 1 was assigned a 5-day-a-week exercise program for 4 weeks after PRP application, while Group 2 did not receive any treatment after PRP. Pre- and post-treatment pain severity of the patients was evaluated with Visual Analog Scale (VAS), muscle strength with hand dynamometer, quality of life with Short Form (SF-12) and functional status with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Evaluations were performed 2 days and 4 weeks after the PRP application. *Findings*. The study was completed with 19 cases in Group 1 and 17 cases in Group 2. In the intragroup evaluations of both groups, a significant difference was observed in the VAS-Rest and VAS-Activity scores ($p=0.001$), SF-12 physical and mental scores ($p<0.05$), WOMAC pain, stiffness, function and total scores ($p=0.001$), and in the quadriceps and hamstring muscle strengths ($p=0.001$). When the change values between the groups were compared, the decrease in VAS-Rest-Activity ($p=0.001$), the change in SF-12 physical ($p=0.001$) and mental scores ($p=0.005$), and the increase in quadriceps and hamstring muscle strength ($p=0.001$) showed a statistically significant difference in favor of Group 1. There was no significant difference in the scores of the WOMAC subscales and the total score. *Conclusion*. Doing exercise after PRP is more effective in reducing pain, increasing quality of life and muscle strength than applying PRP alone.
Keywords: *Platelet-Rich Plasma, exercise, pain, function, quality of life.*

Introduction

Osteoarthritis (OA) is a chronic, degenerative joint pathology that threatens healthy aging (1). It is known that approximately 250 million people worldwide suffer from OA. Between the ages of 50 and 75, the knee is the most affected joint with an incidence of 16%-17% (2). Chronic pain, decrease in lower extremity muscle strength and physical function are the main problems affecting quality of life in patients with knee OA (3).

The general aim of the treatment in patients with knee OA is to reduce pain, increase lower extremity muscle strength, improve functionality and quality of life. In conservative treatment, non-pharmacological therapy such as exercise, education, and lifestyle changes, non-steroidal anti-inflammatory drugs, opioids, hyaluronic acid (HA), and pharmacological methods such as platelet-rich plasma (PRP) are frequently preferred.

PRP is a concentrated extract of platelets from autologous blood. It is known that intra-articular PRP application in patients with OA reduces inflammation and supports chondrogenesis. Thanks to its antinociceptive and cell-proliferative characteristics, PRP is thought to inhibit the OA process (5, 6). The purpose of PRP treatment is to trigger the repair mechanisms of the body. Platelets play an important role in the healing process through the growth factors and bioactive molecules they secrete (7). These bioactive molecules work in harmony and trigger occurrences such as proliferation, migration, synthesis of collagen and other extracellular matrix proteins on local cells, and even changes in cell phenotype and arrangement (8). These molecules play a major role in enabling PRP to increase inflammation, coagulation, cell differentiation, proliferation, angiogenesis and remodeling.

The positive effect of PRP on pain treatment and knee functions has been shown in many studies in which it is compared with hyaluronic acid and placebo groups, and this positive effect has been reported for knee OA at all grades (normal, minor, mild moderate, severe) (9). In addition, studies comparing placebo treatment and HA and PRP have shown that the use of PRP generally leads to better clinical results in moderate and severe knee OA (10). Exercise has been proven to be effective in reducing pain, increasing muscle strength and improving functions in patients with knee OA (4, 11).
Although the effects of PRP and exercise on pain and functional status in knee OA have been revealed in the literature, there is a lack of studies examining the effects of exercise after PRP on pain, muscle strength, quality of life and functionality. Therefore, we aimed to examine the effects of exercise after PRP on pain, functionality, quality of life and muscle strength in patients with knee OA.

Material and Method

Study Design. The study was designed as a prospective, randomized controlled study. It was carried out in accordance with the principles of the "Helsinki Declaration" and ethics committee approval was obtained from the Clinical Research Ethics Committee.
Participants. The study was carried out with patients diagnosed with knee OA who applied to the Physiotherapy and Rehabilitation Polyclinic of XXX Hospital between 20.12.2018 and 03.02.2020.
Patients aged between 45-65 years, diagnosed with Grade 2 or 3 knee OA according to Kellgren-Lawrence radiological criteria (12), and who had not received physiotherapy in the last 6 months were included in the study. The cases with a chronic neurological or rheumatological disease, previous lower extremity surgery, and cognitive problems were excluded from the study. Informed consent and written permission were obtained from all individuals participating in the study.
Interventions. PRP treated cases were randomly divided into two groups. Two days after PRP was applied to the patients in Group 1, an exercise program was started under the supervision of a physiotherapist. In Group 2, PRP was applied alone and no additional application was performed. The cases in both groups were asked not to receive any additional medical treatment during the intervention.
A total of 20 sessions of therapeutic exercise program were assigned to Group 1, 5 days a week for 4 weeks.
The exercise program was started with isometric exercises targeting hip and knee muscles, terminal knee extension (at 0-15˚), hamstring/quadriceps stretching in the first week. Knee ROM exercises were added to the program in the second week. Isometric exercises were performed with contractions lasting 10 seconds, with 20 repetitions including 10 seconds of relaxation; terminal knee extensions were performed with 20 repetitions with 5 seconds of contractions; and stretching exercises with 10 repetitions x 10 seconds. The number of the repetitions of the isometric and terminal knee extension exercises was increased to 30 in the third and fourth weeks. In the third week, resistance hamstring and quadriceps exercises were added to the program. The resistance level was determined through the De Lorme technique. First, the patient's 1 Maximum Repetition (MR) was found. Then, 10MR was determined by taking 1/3 of 1MR and adding 1-2 kg to this value. Initially, 50% of 10MR was performed with 10 repetitions, then 75% of 10MR with 10 repetitions, and in the last set, all of 10MR was performed with 10 repetitions (13). The patients trained with resistance that had been determined for 5 days, and the amount of resistance was redetermined by performing 1MR assessment again at the beginning of the next week. In the fourth week, mini squats and stationary bikes, which are closed kinetic chain exercises, were added to the exercise program. Mini squats were performed at 0-30° knee flexion range of motion, holding still at 30° flexion for 5 seconds with 20 repetitions, and stationary cycling was performed for 10 minutes. The treatment was finalized by assigning home exercises.
Evaluation Methods. The personal information, disease-related information and sociodemographic data of the patients participating in the study were collected with the "Patient Evaluation Form" before the PRP application. In this form, the patient's personal information such as name, surname, age, gender, height, body weight, body mass index, occupation, marital status, education level, as well as information such as concomitant diseases and medications were questioned.
Pain, functional status, quality of life and muscle strength of all patients were evaluated. All evaluations were performed twice each patient in both groups, before and after the treatment (week 4). The patients' pain at rest and during activity were evaluated with the Visual Analog Scale (VAS), their functionality with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and their physical and mental

health-related quality of life with the Short Form-12 (SF-12), and their quadriceps and hamstring muscle strength measurement with a hand dynamometer MF2 (Microfet 2 Manual Muscle Tester).
VAS is a scale used in subjective pain assessment and provides numerical representation of the intensity of pain felt. The number "0" on a ten-centimeter horizontal line represents "no pain" and the number "10" represents "unbearable pain". Participants were asked to mark the place they thought represented the severity of the pain they felt at rest and during activity, and the place they marked was determined as the pain intensity in centimeters (14).
WOMAC is a multidimensional, self-administered scale. The scale consists of 3 sub-headings titled pain, stiffness and physical function and a total of 24 questions. The maximum score is 20 for pain, 8 for stiffness, and 68 for physical function. A higher score is associated with worse symptoms, limitations, and physical health (15).
Physical and mental health related quality of life was evaluated with SF-12. The lowest total score is 0, the highest is 100, and a higher score is positively correlated with better quality of life (16).
For the quadriceps and hamstring muscle strength measurement, the patient was seated on the side of the bed with the arms crossed over the chest with the hands on the shoulders, and the hip and knee flexed at 90 degrees. For the quadriceps strength measurement, the patient was asked to extend his/her knee, and after the extension was completed, he/she was asked to place the dynamometer 1-2 cm above the malleolus level and perpendicular to the leg, to perform a maximum voluntary isometric contraction (MVIC), and to maintain this contraction for 5 seconds. The measurement was repeated 3 times in succession with 30-second intervals, and the average of the 3 measurements was taken (17). For the measurement of hamstring strength, the patient was asked to perform MVIC and to maintain it for 5 seconds by placing the dynamometer 1-2 cm above the lateral malleolus on the back of his/her leg while he/she was sitting on the side of the bed with his/her knees at 90° flexion. The measurement was repeated 3 times in succession with 30-second intervals, and the average of the 3 measurements was taken (18). A 2-minute rest interval was given between the quadriceps and hamstring strength measurements. The measurements were recorded in kg.
Number of Samples. Sample count was calculated using the “Instant sample count calculation” program. Calculation was also made according to VAS. Based on a minimal clinical significance difference of 11.1 points for VAS, 9.1 points for standard deviation, and a significance α level of 0.05, β level of 5 percent, desired power of 95 percent, the number of samples was calculated as 18 for each group (19). Considering the possible dropouts during the follow-up period, the sample number was determined as 40.
Randomization and blindness. Forty participants were randomly divided into 2 groups as PRP+exercise (Group 1; n=20) or PRP (Group 2; n=20). An online randomization web service “ResearchRandomiser” (https://www.randomizer.org/) was used to group the participants. Random numbers from 1 to 40 produced by the program for both groups were prepared by a researcher who did not have clinical participation in the study, and he/she wrote them sequentially on indexed cards. Prepared cards were folded by the same researcher and placed in opaque envelopes sealed with some adhesive. Then, an envelope was opened for each participant and he/she was assigned to a group according to the selected index card. The subjects were blinded to the applied methods. All evaluations were performed by a researcher who did not know which group the cases belonged to.
Statistical Analysis. Mean, standard deviation, median, lowest and highest frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables is measured with the Kolmogorov-Smirnov test. In the analysis of normally distributed independent quantitative data, independent samples t-test was used, and paired t-test was used in the analysis of quantitatively dependent data. Mann-Whitney U test was used in the analysis of independent quantitative data, Wilcoxon test in the analysis of dependent quantitative data, and Chi-square test in the analysis of independent qualitative data. Analyzes were performed with the SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA). Statistical significance level was accepted as $p<0.05$.

Results

The study started with 40 participants who fulfilled the inclusion criteria. A total of 4 participants were excluded from the study since two of them went out of the city, and the other two delayed their follow-up due to the fear of COVID-19 contamination. A total of 36 participants, i.e. 19 in Group 1 (mean age: 60.74±2.66 years) and 17 (mean age: 60.53±3.65 years) in Group 2, completed the study. No statistically significant difference was found in the demographic data of the groups ($p>0.05$) (Table I).

Table I. Demographic characteristics of groups

	PRP+Exercise Group Mean±SD / n (%)	**PRP group** Mean±SD / n (%)	*P*
Age (years)	60.74 ± 2.66	60.53 ± 3.65	0.846*
Gender (female - male)	13 (68.4%) – 6 (31.6%)	12 (70.6%) – 5 (29.4%)	0.888*
Height (cm)	158.42 ± 8.13	158.71 ± 9.57	0.924$^{\neq}$
Weight (kg)	76.16 ± 7.79	77.18± 9.84	0.732*
BMI (kg/cm²)	30.29 ± 1.29	30.55 ± 1.41	0.594*

BMI: body mass index; n: the number of individuals; PRP: platelet rich plasma; SD: standard deviation
**p value was found using Independent sample t-test, $^{\neq}$p value was found using Chi-square test.*

At the end of four weeks, it was observed that resting and activity pain decreased statistically in both groups (p=0.001). Although VAS-Rest was lower in Group 1 than Group 2 before the treatment (p=0.018), when the pain variation between the groups was examined, the decrease in both VAS-Rest and VAS-Activity showed a statistically significant improvement in favor of Group 1 (VAS-Rest p=0.001; VAS-Activity p=0.001) (Table II).

Table II. Changes in VAS-Rest and Activity, SF-12 Physical - Mental and WOMAC scores within and between groups

		PRP+Exercise Group Mean ±SD	**PRP group** Mean ±SD	*p***
VAS-Rest	B.T	4.48 ± 0.96	5.22 ± 0.81	**0.018**
	A.T	1.08 ± 0.75	3.26 ± 0.74	
	B.T-A.T Difference	-3.39± 0.58	-1.96 ± 0.53	**0.001**
	p*	**0.001**	**0.001**	
VAS-Activity	B.T	6.36 ± 1.08	6.98 ± 0.88	0.073
	A.T	1.86 ± 0.78	4.38 ± 0.82	
	B.T-A.T Difference	-4.50 ± 0.70	-2,60± 0.49	**0.001**
	p*	**0.001**	**0.001**	
SF-12 Physical	B.T	38.36 ± 1.49	36.66 ± 2.41	**0.015**
	A.T	49.75 ± 2.50	41.39 ± 3.24	
	B.T-A.T Difference	11.39 ± 2.35	4.73 ± 2.02	**0.001**
	p*	**0.001**	**0.001**	
SF-12 Mental	B.T	49.75 ± 2.50	46.56 ± 2.65	0.073
	A.T	55.98 ± 5.11	49.31 ± 3.17	
	B.T-A.T Difference	6.87 ± 4.83	2.74 ± 3.00	**0.005**
	p*	**0.001**	**0.014**	
WOMAC-Pain	B.T	4.63± 1.86	5.38 ± 1.30	0.175
	A.T	1.78 ± 0.75	2.82 ± 0.72	
	B.T-A.T Difference	-2.84± 1.20	-2.55 ± 0.65	0.395
	p*	**0.001**	**0.001**	
WOMAC-Stiffness	B.T	5.39 ± 1.81	5.77 ± 1.06	0.451
	A.T	2.07 ± 1.02	2.86 ± 0.73	
	B.T-A.T Difference	-3.31 ± 1.05	-2.91 ± 0.75	0.422
	p*	**0.001**	**0.001**	
WOMAC-Function	B.T	4.37 ± 1.16	4.87 ± 1.52	0.276
	A.T	1.81 ± 0.50	2.39 ± 0.81	
	B.T-A.T Difference	2.56 ± 0.79	2.48 ± 0.75	0.757
	p*	**0.001**	**0.001**	
WOMAC-Total	B.T	14.40 ± 3.87	16.03 ± 3.28	0.185
	A.T	5.80 ± 1.91	8.08 ± 1.74	
	B.T-A.T Difference	8.59 ± 2.02	7.95 ± 1.79	0.320
	p*	**0.001**	**0.001**	

A.T: After treatment; B.T: Before treatment; n: the number of individuals; PRP: Platelet rich plasma; SD: standard deviation p: Paired sample t-test; p**: Independent sample t-test.*

It was observed that the SF-12 quality of life scores increased both mentally and physically in both groups (p<0.05). The SF-12 physical subscore was statistically higher in Group 1 before the treatment (p=0.015), and a statistically significant difference was found in favor of Group 1 when the change in both the SF-12

physical and mental scores between the groups was analyzed following the treatment (SF-12 physical: p=0.001, SF-12 mental: p=0.005) (Table II).
Statistically significant improvement was observed in WOMAC pain, stiffness, physical function, and in total scores in both groups at the end of 4 weeks (p=0.001). There had been no difference in WOMAC subscores and total scores of the groups before the treatment. When the changes in the post-treatment WOMAC subscores and total scores of the groups were compared, no statistically significant difference was found between the two groups (pain: p=0.395; stiffness: p=0.42; physical function: p=0.757; total: p= 0.320) (Table II).
The muscle strength of the quadriceps and hamstring muscles, which had not been different between the two groups prior to the treatment, increased in both groups after the treatment (Group 1 quadriceps: p=0.001; hamstring: p=0.001; Group 2 quadriceps: p=0.001; hamstring: p=0.002). When the change in muscle strength for both muscles between the groups was examined after the treatment, it was found that the muscle strength increased significantly in favor of the PRP + exercise group (quadriceps: p=0.001; hamstring: p=0.001) (Table III).

Table III. Means of changes in muscle strength measurements within and between groups

		PRP+Exercise Group (Group 1; n=19)		**PRP Group** (Group 2; n=17)		*p value**
		Mean±SD	Median	Mean±SD	Median	
Quadriceps muscle strength (kg)	**B.T**	9.70± 0.86	9.40	10.87 ± 0.80	9.10	0.221
	A.T	12.48 ± 0.94	12.40	11.23 ± 0.83	9.40	
	B.T-A.T Difference	2.77 ± 0.28		0.43 ± 0.14		**0.001**
	p value*	**0.001**		**0.001**		
Hamstring muscle strength (kg)	**B.T**	10.96 ± 0.64	10.80	10.87 ± 0.80	10.60	0.373
	A.T	11.78 ± 0.72	11.60	11, 23 ± 0.83	11.00	
	B.T-A.T Difference	0.80 ± 0.21		0.36 ± 0.32		**0.001**
	p value**	**0.001**		**0.002**		

A.T: After treatment; B.T: Before treatment; n: the number of individuals; PRP: Platelet rich plasma; SD: standard deviation; The p value was found using the Mann-Whitney U test. P** value was found using the Wilcoxon test.*

Discussion and conclusion

In our study, in which we investigated the effects of exercise after PRP in individuals with knee OA, it was found that exercise after PRP was more effective in reducing pain, increasing quality of life and muscle strength compared to PRP alone.
Among the injection applications aimed at symptom relief and functional improvement in patients with knee OA, PRP has gained popularity in recent years (20). In individuals with knee OA, it is aimed to stimulate cartilage repair with PRP injections, to alleviate the symptoms of OA and to delay the need for joint replacement surgery (21). Although there are studies in the literature showing the effects of PRP in the treatment of knee OA, there is no study to our knowledge examining the effect of exercise on pain, quality of life, function and muscle strength after PRP.
It has been reported in the literature that PRP may cause an inflammatory response and cause pain and discomfort in patients that can last for several days after injection (11). Therefore, the first session started 2 days after the PRP application for all patients in the exercise group.
In the study by Huang et al., when the group treated with quadriceps isometric exercises was compared with that treated with nonsteroidal anti-inflammatory drugs, pain reduction was significant in both groups one month after the treatment, and the decrease in the exercise group was higher, and the decrease in the exercise group was found to be more significant in the evaluation made after three months (22).

In our study, there was a change of -3.39±0.58 and -1.96±0.53 units in the VAS-Rest scores, and a change of -4.50±0.70 and -2.60±0.49 units in the VAS-Activity scores in Group 1 and Group 2 respectively after the treatment. Consistent with the literature, there was a statistically significant improvement in VAS Rest and Activity scores in both groups as a result of the treatment (p=0.001). We attribute the greater decrease in both Rest and Activity pain in Group 1 to the positive effect observed with exercise.

In patients with knee OA, pain, limitations in joint range of motion and loss of muscle strength lead to limitations in the functional activities of the patients and negatively affect their quality of life. Quality of life is an important outcome measure for evaluating health status and treatments. Acosta-Olivo C.A. et al. (23) compared PRP treatment applied once and three times in patients with knee OA in their study, in which quality of life was evaluated with SF-12 as in our study. Evaluation was repeated at the 6th, 12th, 24th, and 48th weeks following the treatment. In the study in question, a significant increase was observed in both groups in the physical score at the end of the 48th week, but no significant increase was observed in the mental score in either group (23).

In our study, after a single session of PRP application, the SF-12 physical score improved 11.39±2.35 units in the PRP+exercise group and 4.73±2.02 units in the PRP group, while the SF-12 mental score improved 6.87±4.83, 2.74±3.00 units, respectively. As a result of the treatment, unlike the literature, statistically significant improvement was observed in SF-12 physical and mental sub-scores in both groups, but it was more in the exercise group. The improvement observed in quality of life in both groups in our study shows that PRP is effective on quality of life. In addition, the statistically significant improvement in both physical and mental quality of life in the group in which exercise treatment was applied, compared to the other group, indicates that exercise treatment positively affects the quality of life.

Among the various disease-specific tools used to assess functional impairment in OA, the WOMAC function scale is the most widely used one in clinical trials. In the study Spakova et al. conducted, 120 patients with knee OA were divided into two groups and PRP treatment was applied to one group and hyaluronic acid treatment to the other. Their functionality was evaluated with the WOMAC index at the 3rd and 6th months following the treatment (24). As a result of the evaluations, the improvement in the WOMAC index in the PRP group was found to be more significant than that in the group received hyaluronic acid treatment (24). In their study investigating the effects of PRP and prolotherapy on pain and function in patients with knee OA, Rahimzadeh et al. found a statistically significant decrease in WOMAC function, pain, stiffness and total scores in the PRP group at the end of the first month following the treatment (25). In their study comparing PRP, hyaluronic acid and saline treatment, Lin et al. evaluated patients with knee OA through the WOMAC score at the 1st, 2nd, 6th, and 12th months after the treatment. Although there was a significant change in the WOMAC scores in all groups, the significant change in the PRP group continued for 12 months (26). Exercises were not incorporated into any treatment in these studies in the literature. However, our study differs from them in that exercises were incorporated. In our study, the WOMAC scale was used to evaluate the functional status of the patients, which is in line with the literature. After the treatment, statistically significant improvement was observed in all subscales of the WOMAC scale in both groups. When the intra-group improvements of the WOMAC total score were examined after the treatment, an improvement of 8.59±2.02 units was observed in Group 1 and of 7.95±1.79 units in Group 2, but no statistically significant difference was observed between the groups in terms of functionality. Our study shows that adding exercise treatment to PRP is not effective in increasing function at the end of the 4th week. In our opinion, that our results are similar to the literature may be not because of the ineffectiveness of the exercise, but of the short duration of the treatment and follow-up and the limited number of patients.

It is known that there is a 20-45% decrease in muscle strength in the quadriceps muscle in patients with knee OA compared to healthy individuals (27). In the study Anwer et al. conducted with knee OA patients, isometric exercise treatment was applied to one group and no treatment was applied to the other group. It was reported that muscle strength increased significantly in the exercise group at the end of the 5th week (28). In the study Lin et al. carried out, one group of patients with knee OA was assigned strengthening exercises, another group proprioception exercises, and no exercise was assigned to the control group. In the evaluation performed after the treatment that was applied 3 times a week for 8 weeks, the muscle strength increased statistically significantly more in the strengthening exercise group (29). In the study Wu et al. conducted, patients with bilateral knee OA were treated with PRP injection and saline treatment, and the change in knee extension and flexion strengths after the treatment was evaluated. At the end of the 6-month follow-up, although the extensor knee strength increased significantly in the PRP group compared to the

flexor, there was no significant difference between the two groups (30). We found in our study that both quadriceps and hamstring muscle strength increased statistically significantly in both groups after the treatment, but this difference was greater in the PRP+exercise group. Consistent with the literature, exercise treatment has been shown to be more effective in increasing muscle strength than PRP alone. The strengthening effect of strengthening exercises is associated with both hypertrophy and neural adaptation. Moritani et al. (31) indicated that neural adaptation was effective in strength increases in the beginning, and both neural adaptation and hypertrophy played a role in subsequent gains, and hypertrophy began to be effective especially after the first 3-5 weeks. We believe that the effect achieved in the increase in strength thanks to the exercise program, which was planned to last 4 weeks due to clinical conditions, is the result of neural adaptation. We think that this change in muscle strength obtained in our study may also be associated with pain reduction.

Our study strengths. We think that we have contributed to the related literature by conducting the first study in the literature investigating the effects of exercises performed after PRP on pain, quality of life, physical function and muscle strength in patients with knee OA.

Limitations. Among the limitations of our study are that we applied only 4 weeks of exercise and we did not evaluate the long-term results following the exercise treatment. We believe that the effects of exercise will be revealed more clearly in future studies in which the treatment period will be extended and longer follow-ups will be performed.

Although the exercise program following PRP was applied for only 4 weeks in individuals with knee OA, it was found to be more effective in reducing pain, increasing quality of life and muscle strength compared to PRP alone.

Conflict of interest. None declared.

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