



Early improvement in physical activity and function after total hip arthroplasty: Predictors of outcomes

Tuba Güler¹, Filiz Sivas¹, Fatma Gül Yurdakul¹, Ersin Çelen², Ali Utkan², Bedriye Başkan¹, Hatice Bodur¹, Bülent Özkurt²

¹Department of Physical Medicine and Rehabilitation, Health Sciences University, Ankara Numune Training and Research Hospital, Ankara, Turkey

²Department of Orthopedics and Traumatology, Health Sciences University, Ankara Numune Training and Research Hospital, Ankara, Turkey

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ABSTRACT

Objectives: This study aims to assess early changes in physical activity and function after total hip arthroplasty (THA) using both subjective and objective methods, and to identify predictors of outcomes of THA.

Patients and methods: Between October 2014 and October 2015, a total of 50 patients (14 males, 36 females; mean age 57.1±13.0 years; range, 31 to 75 years) with end-stage primary hip osteoarthritis who were scheduled for THA and 50 age- and sex-matched controls (10 males, 40 females; mean age 52.9±9.3 years; range, 36 to 75 years) were included in the study. Pain was evaluated using the Numeric Rating Scale (NRS), physical function using the Lequesne Index, physical capacity using the Six-Minute Walking Test (6MWT), and physical activity using both International Physical Activity Impact Questionnaire Short Form (IPAQ-SF) and step count monitor. Data at baseline and six weeks and six months were recorded.

Results: Pain severity was significantly lower after THA at six weeks and six months (NRS scores: 2.83 and 0.82, respectively; $p < 0.001$), compared to baseline. Physical function, capacity, and activity significantly improved after THA at six weeks and six months with a mean Lequesne Index score of 2.62 and 1.02, respectively. The mean 6MWT distance was 272.62 at six weeks and 326.16 at six months. The mean IPAQ and 6MWT results were similar between the patient and control groups at six weeks and six months. Age, presence of comorbidities, and baseline Lequesne Index score were found to be effective on functional outcomes of THA. Age and baseline 6MWT scores were correlated with physical capacity after THA.

Conclusion: Our study showed a significant early improvement in pain severity and physical activity and function at six weeks and six months after THA, compared to baseline values. Baseline values and age were the positive predictors of improved postoperative function and physical capacity.

Keywords: Osteoarthritis, pain, physical activity, physical function, total hip arthroplasty, total hip replacement.

Osteoarthritis (OA) is the most common cause of arthritis. The 2016 Global Burden of Disease study ranked it as the second most rapidly rising cause of years lived with disability after diabetes mellitus and reported an OA incidence of 199/100,000 individuals.^[1]

Single-joint OA may affect the lumbar spine and hand, hip, or knee joints. Hip OA is less common than knee OA and presents equally in men and women.^[2] The main goals of OA management are to minimize pain, improve function, and modify the process of joint damage by targeting modifiable

risk factors.^[3] Conservative OA management requires non-pharmacological interventions such as exercise, weight loss, and walking aids. Pharmacological interventions include topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine, capsaicin, or intra-articular glucocorticoid injection.

Total hip arthroplasty (THA) is the gold-standard intervention in OA patients unresponsive to conservative treatment. It has been proven to be effective in reducing pain and improving joint function significantly.^[4] However, 9% of patients undergoing THA still experience residual joint

Corresponding author: Tuba Güler, MD. SBÜ Ankara Numune Eğitim ve Araştırma Hastanesi Fiziksel Tıp ve Rehabilitasyon Kliniği, 06800 Çankaya, Ankara, Türkiye.

e-mail: tubakulu@yahoo.com

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pain postoperatively.^[5] The high rate of unfavorable outcomes after surgery may be associated with the presence of individual problems, such as pain at other joints and comorbidities.^[6]

Evaluation of postoperative outcomes requires a quantitative assessment of several parameters. Self-reporting questionnaires are the most common method of physical function and activity assessment.^[7] Also, devices such as accelerometers and pedometers have gained popularity in recent years owing to their easy-to-use design and the lack of recall bias associated with questionnaires.^[8]

In the present study, we hypothesized that (i) patients with THA would benefit from surgery with similar physical activity and capacity with the age- and sex-matched controls at the postoperative sixth weeks, which is an earlier endpoint, compared to previous studies; (ii) preoperative physical function and capacity values and several socio-demographic factors such as age, sex, occupation, body mass index (BMI), comorbidities, and marriage would affect the outcomes of THA. Therefore, in this study, we aimed to assess early changes in physical activity and function after

THA using both subjective and objective methods, and to identify predictors of outcomes of THA.

PATIENTS AND METHODS

This single-center, prospective study was conducted at Ankara Numune Training and Research Hospital between October 2014 and October 2015. A total of 50 patients (14 males, 36 females; mean age 57.1 ± 13.0 years; range, 31 to 75 years) with Grade 4 end-stage primary hip OA according to the Kellgren-Lawrence^[9] classification who were unresponsive to conservative treatment and scheduled for THA and 50 age- and sex-matched controls (10 males, 40 females; mean age 52.9 ± 9.3 years; range, 36 to 75 years) who had no arthroplasty and no pain in the lower extremity among the family members or attendants of hospitalized patients were included in the study. Patients aged above 75 years with accompanying joint diseases or advanced pulmonary and cardiovascular diseases which can affect mobilization, patients having prior contralateral hip surgery within the last 12 months, patients with mental problems that can affect participation in the study, and those inconvenient for follow-up due to far

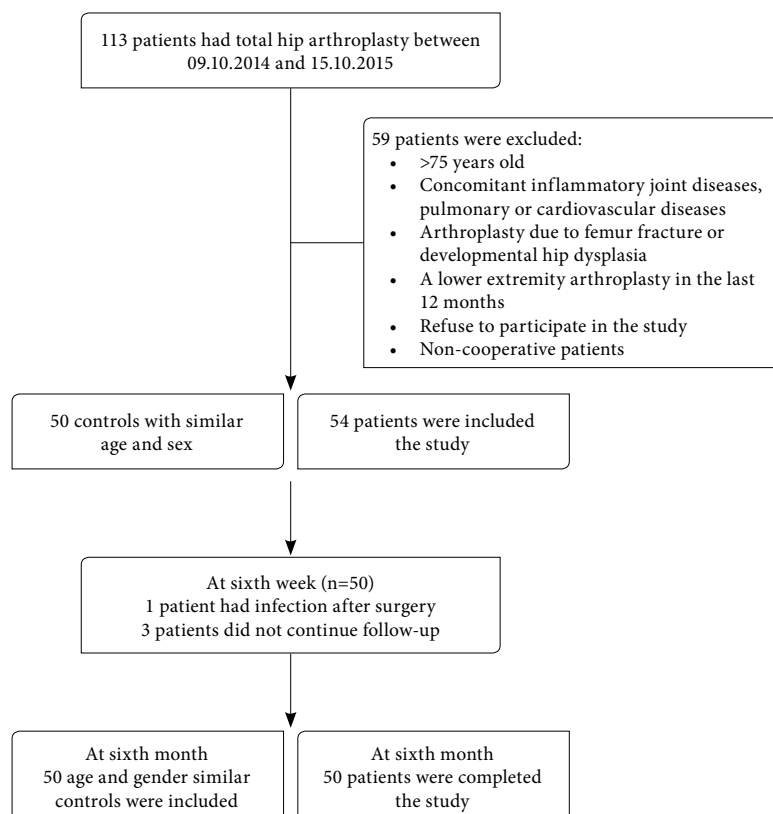


Figure 1. Study flow chart.

distance from the hospital were excluded. A written informed consent was obtained from each participant. The study protocol was approved by the Ankara Numune Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data including baseline demographic and clinical characteristics of the patients and controls were recorded. Pain (Numeric Rating Scale [NRS]), physical function (Lequesne Index), physical capacity (Six-Minute Walking Test [6MWT]), and physical activity (International Physical Activity Questionnaire-Short Form [IPAQ-SF] and step count monitor) were recorded at baseline and at six weeks and six months in the patients with THA. Controls were evaluated with the 6MWT for physical capacity and IPAQ-SF for physical activity. The study flow chart is shown in Figure 1.

Interventions and follow-up measures

All THA surgeries were carried out by two orthopedic surgeons at a single center. All operations were performed via the anterolateral approach, and all patients received the uncemented prosthesis. All patients were evaluated for pain, physical function, capacity, and activity at one week before surgery and at six weeks and six months after surgery.

Postoperative treatment protocol

Postoperative pain was managed by tramadol and paracetamol as analgesics. However, in the late period following wound healing (after three weeks), the patients were allowed to take diclofenac 150 mg/day or its equivalent dose of NSAIDs. A postoperative rehabilitation program of weight-bearing exercises was performed by all patients.

Pain severity

Pain severity was evaluated using the NRS, a numeric scale on which 0 indicates no pain and 10 indicates the most severe pain the patient has ever experienced. Reliability and validation studies of the scale have been conducted in patients with chronic pain.^[10]

Physical function

Lequesne Index is a valid and reliable index in the Turkish population and is a subjective 10-question survey to assess physical function in OA patients. It consists of five questions about pain or discomfort, one question about maximum distance walked, and four questions about activities of daily living. It is

scored on a 0 to 24 scale. Lower scores indicate less functional impairment with values ≤ 7 considered as mild to moderate, 8 to 13 as severe, ≥ 14 as extremely severe impairment.^[11,12]

Physical capacity

Physical capacity was assessed by the 6MWT, it is an objective method to evaluate exercise tolerance. It was performed on an unobstructed bare 30 meters (m) floor where every 3 meters were marked. The patients were allowed to complete the test by reducing their walking speed or stopping and getting some rest, if needed.^[13] Maximum walking distance (meters) within six min was measured. An advantage of the 6MWT is that it allows the patients to exercise in the test model that they are familiar with. The 6MWT was previously used in studies evaluating patients with THA.^[13,14] Previous studies showed that 6MWT distance in patients with lower extremity arthroplasty was found to be about 300 to 400 meters.^[15,16]

Physical activity

Physical activity was assessed using the International IPAQ-SF and step count monitor. The IPAQ-SF which has been shown to be reliable and valid in the Turkish population is a subjective method of seven questions used to evaluate time spent in sitting, walking, and moderate-to-severe activities in the past seven days.^[17] We used the metabolic equivalent of task (MET)-min score to calculate the energy required for the physical activities. Standard MET values are as follows: sitting= 1.5 MET, walking= 3.3 MET, moderate physical activity= 4.0 MET, and severe physical activity= 8.0 MET. Using these values, daily and weekly levels of physical activity were calculated. Values less than 600 MET-min/week were assessed as low, 600 to 3,000 MET-min/week as moderate physical activity, more than 3,000 MET-min/week as high physical activity. Step count monitor is a device used to count how many steps patients walk daily. Patients wore the step activity monitor (TKS1257/ BTM life) on the right wrist and were told to wear it from the time they woke up, until they went to bed. The mean steps per day were calculated for all patients. Basset et al.^[18] indicated that step counts could be measured easily and definitely and this parameter has relations with physical health variables. Takenaga et al.^[14] used the step activity monitor as a valid parameter for the patients after THA.

Statistical analysis

A power analysis was performed using the G* power version 3.0.10 program (Heinrich-Heine-Universität

Düsseldorf, Düsseldorf, Germany) to ensure the adequate sample size. To obtain a power of 0.90 [α (Type I error) was 0.05 and β (Type II error) was 0.10, and analysis of variance test with three repetitions], an appropriate total sample size was calculated as 50 for this study.

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean \pm standard deviation (SD), median (min-max), or number and frequency. The Shapiro-Wilk test was used to test for the normality of the distribution of data. The Mann-Whitney U, Student's t-, and chi-square or Fisher's exact tests were used to compare continuous and nominal variables between groups. Analysis of pain, physical functioning, and physical capacity were conducted by repeated measured analysis of variance (ANOVA). The factors which would be effective on the physical function levels with the Lequesne Index scores and physical capacity with the 6MWT at six months after surgery were evaluated with the multivariate logistic regression analysis. The Lequesne Index

scores and 6MWT results were evaluated in both groups. Using the Lequesne Index, the first group consisted of 0-point score which indicates no pain and no disability and the second group consisted of 1 to 7 points which indicate mild-to-moderate functional impairment. The 6MWT results were assessed in both groups according to a walking distance of <300 meters and \geq 300 meters. Univariate analysis included variables and at least moderately significant variables (i.e., age, sex, comorbidities, and marriage) were selected for the multivariate logistic regression analysis. A *p* value of <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the patients and controls are shown in Table 1. The mean NRS score at baseline was 7.7 ± 0.3 . The mean score at six weeks and six months postoperatively were 2.8 ± 0.3 and 0.8 ± 0.2 , respectively. There was a statistically significant difference between the scores at baseline and at six weeks and six months ($p < 0.001$).

Table 1. Demographic and clinical characteristics of study population

	Patients with THA (n=50)			Controls (n=50)			<i>p</i>
	n	%	Mean \pm SD	n	%	Mean \pm SD	
Age (year)			57.1 \pm 13.0			52.9 \pm 9.3	0.077
Body mass index (kg/m ²)			29.2 \pm 5.2			28.1 \pm 5.0	0.497
Sex							0.349
Female	36	72		40	20		
Male	14	28		10	20		
Body mass index							0.112
Normal weight	11	22		12	24		
Overweight	22	44		13	26		
Obese	14	28		24	48		
Morbid obese	3	6		1	2		
Marital status							0.554
Living with a partner	39	78		36	72		
Living alone	11	22		14	28		
Working status							0.334
No	41	82		37	74		
Yes	9	18		13	26		
Comorbidities							0.313
No comorbidities	19	38		24	48		
Diabetes mellitus	4	8		8	16		
Hypertension	8	16		10	20		
Asthma-chronic bronchitis	3	6		1	2		
Gastritis	9	18		10	20		
Depression	2	4		1	2		
Hypothyroidism	3	6		2	4		
Urolithiasis		1		-	-		

THA: Total hip arthroplasty; SD: Standard deviation.

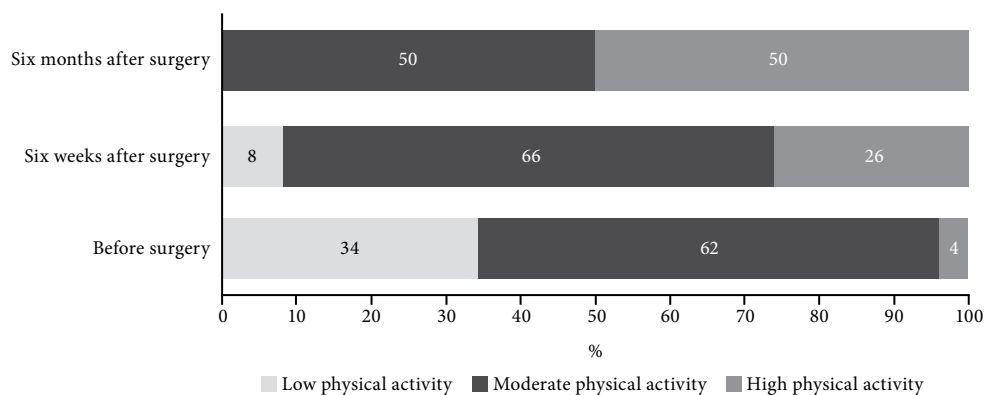


Figure 2. The rate of patients in the physical activity categories according to the International Physical Activity Questionnaire-Short Form.

The mean Lequesne Index scores at baseline and at six weeks and six months were 14.6 ± 0.6 , 2.6 ± 0.2 , and 1.0 ± 0.2 , respectively. There was a statistically significant difference between the mean scores at baseline and at six weeks and six months ($p < 0.001$). At six months, data 25 patients showed no functional disability with 0 Lequesne Index score.

The mean walking distance at baseline and at six weeks and six months was 189.9 ± 16.1 m, 272.6 ± 11.2 m, and 326.2 ± 12.4 m, respectively, indicating a statistically significant difference

between the mean scores at baseline and at six weeks and six months ($p < 0.001$).

The mean IPAQ-SF scores at baseline and at six weeks and at six months were 953.2 ± 139.0 MET-min/week, $2,125.6 \pm 165.6$ MET-min/week, and $2,870.8 \pm 229.7$ MET-min/week, respectively. There was a statistically significant difference between mean scores at baseline and at six weeks and six months ($p < 0.001$). The patients were further classified according to the level of physical activity as low, moderate, and high. The rate of patients in

Table 2. Clinical assessments before and after total hip arthroplasty

	Mean±SD	Mean±SE	95% CI	p
Numeric Rating Scale				
Baseline	7.7±0.3			
Six weeks after surgery	2.8±0.3	4.9±0.2	3.89 - 5.04	<0.001
Six months after surgery	0.8±0.2	2.0±0.1	1.86 - 2.17	<0.001
Lequesne Index				
Baseline	14.6±0.6			
Six weeks after surgery	2.6±0.2	11.9±0.4	11.15 - 12.56	<0.001
Six months after surgery	1.0±0.2	1.6±0.1	1.17 - 2.02	<0.001
6MWT (meter)				
Baseline	189.9±16.1			
Six weeks after surgery	272.6±11.2	-82.7±9.2	-101.15 - -64.24	<0.001
Six months after surgery	326.2±12.4	-53.5±4.8	-63.15 - -43.92	<0.001
IPAQ-SF (MET-min/week)				
Baseline	953.2±139.0			
Six weeks after surgery	2,125.6±165.6	-1,172.4±146.0	-1,465.87 - -879.01	<0.001
Six months after surgery	2,870.8±229.7	-695.170±164.7	-1,020.10 - -364.23	<0.001
Step counts				
Baseline	4,091.5±235.9		-2,600.02 - -1,045.65	
Six weeks after surgery	5,914.4±400.9	-1,822.8±386.7	-1,579.14 - -778.73	<0.001
Six months after surgery	7,093.3±488.9	-1,178.9±199.2		<0.001

SD: Standard deviation; SE: Standard error; CI: Confidence interval; 6MWT: Six-minute walking test; IPAQ-SF: International Physical Activity Questionnaire-Short Form; * p value for baseline and at six weeks after surgery; ** p value at six weeks and six months after surgery.

Table 3. Physical activity and capacity difference between patients and controls

	Patients with THA (n=50)	Controls (n=50)	<i>p</i>
	Mean±SD	Mean±SD	
IPAQ-SF (MET-min/week)			
Baseline	953.2±139.0	2,507.2±142.9	<0.001
Sixth week	2,125.6±165.6		0.115
Sixth month	2,870.8±229.7		0.481
6MWT (meter)			
Baseline	189.9±16.1	335.5±14.3	<0.001
Sixth week	272.6±11.2		0.112
Sixth month	326.2±12.4		0.589

THA: Total hip arthroplasty; SD: Standard deviation; IPAQ-SF: International Physical Activity Questionnaire-Short Form; MET: Metabolic equivalent of task; 6MWT: Six-minute walking test.

Table 4. Multiple logistic regression analysis showing the association between Lequesne Index scores and 6MWT and risk factors

	B	SE	<i>p</i>	95% CI
Lequesne Index score				
2* (Patients with mild to moderate functional impairment)				
Constant	-5.088	1.950	0.009	1.024-1.197
Age	0.102	0.040	0.011	1.151-1.936
Baseline Lequesne	0.401	0.133	0.003	0.831-1.082
Body mass index	0.053	0.067	0.428	1.094-19.522
Presence of co-morbidity	1.531	0.735	0.037	
6MWT				
2** (walking distance was ≥300 meters)				
Constant	-0.183	2.872	0.039	
Age	-0.066	0.033	0.048	0.877-0.999
Baseline 6MWT	0.018	0.005	0.001	1.007-1.029
Body mass index	0.133	0.081	0.100	0.975-1.339

6MWT: Six-minute walking test; SE: Standard error; CI: Confidence interval; * The reference category is: 1.00 (no pain and no disability, Lequesne Index score was 0); ** The reference category is: 1.00 (6MWT results <300 meters).

each category at baseline and at six weeks and at six months are shown in Figure 2.

The mean step count at baseline and at six weeks and six months were 4,091.5±235.9, 5,914.4±400.9, and 7,093.3±488.9, respectively. There was a statistically significant difference between the step counts at baseline and at six weeks and six months, respectively ($p<0.001$). Pain, physical function, capacity, and activity scores before, at six weeks and six months of surgery are summarized in Table 2.

The physical activity using the IPAQ-SF and physical capacity using the 6MWT at three endpoint times were compared between the patient and control groups. Both baseline scores (IPAQ-SF and 6MWT) were lower in the patients compared to the controls, although there was no significant difference at six weeks and six months (Table 3).

In patients with THA, socio-demographic characteristics and baseline functional status which

may affect the physical function and physical capacity at six months after surgery were evaluated using the multivariate logistic regression analysis. Physical function was assessed in two groups: (i) patients with no pain and no disability (Lequesne Index score was 0) and (ii) patients with mild-to-moderate functional impairment (Lequesne Index score was 1-7). Physical capacity was assessed in two groups according to the walking distance was <300 meters and ≥300 meters (6MWT results). Variables including age, sex, BMI, comorbidities, working status, living with a partner, baseline Lequesne Index scores, and walking distance were assessed using the univariate analysis and at least moderately significant variables were included in the multivariate analysis. A significant correlation was found between the Lequesne Index scores, and age, comorbidity, and baseline Lequesne scores, while age and baseline walking distance were found to be correlated with the 6MWT (Table 4).

DISCUSSION

The aim of the current study was to assess the improvement of physical activity and capacity with objective measurements and self-reported questionnaires after THA at an earlier endpoint, compared to previous studies. The results confirmed our first hypothesis that patients benefited from surgery and they had similar physical activity and capacity with the age- and sex-matched controls at the postoperative sixth week and month. In addition, our second hypothesis regarding that preoperative physical function/capacity values and several socio-demographic factors would be effective on the outcomes of THA was also supported. Multivariate logistic regression analysis revealed that baseline physical function/capacity values and age were effective on both physical function and capacity along with the presence of comorbid disease which increased the functional impairment.

Total hip arthroplasty is a frequently performed procedure in orthopedic surgery. Outcomes of THA have been assessed with pain, function, physical capacity, and health-related quality of life parameters.^[19-21] Measurement of pain after THA is a challenging task, as all data about pain after surgery is dependent on the definition of the pain and when to measure it. Failure or complications of surgery is not necessarily the cause of postoperative pain experienced by THA patients. Many factors come into play and, thus, standardization of postoperative pain measurements regarding duration, frequency, character, and time of measurement is a necessary step in evaluating etiologies of pain and its management course. Most studies reporting pain after THA have demonstrated a significant reduction in pain levels. Fletcher et al.^[22] reported moderate-to-severe chronic residual pain levels in less than 12% of patients. Wylde et al.^[23] also reported severe persistent pain in only 6% of patients. This is consistent with our study showing a 63% reduction in the NRS after six weeks and this ratio was improved to 89.6% at six months.

Total hip arthroplasty provides older patients with the chance to be treated cost-effectively and improving physical function for the rest of their life. In a review by Jones et al.^[20] reported that functional independence was a key factor in the postoperative recovery and added that functional gains appeared after than pain reduction. Similarly, Ritter et al.^[24] reported the same conclusion regarding physical function at six months, one year, and two years. In contrast, some authors reported that physical function in THA patients did not

improve after surgery, but even became worse. These authors who reached the same conclusion interpreted it as an effect of the other musculoskeletal comorbidities in these patients.^[6,25-27] Another comment regarding the functional benefit of the patient after joint surgery is that functional improvement is associated with the patient's expectations. It was reported that expectations were not correlated with preoperative functional health status and expectation of complete pain relief after surgery was an independent predictor of improved physical function at six months after surgery.^[28] In our study, all patients were assessed by the Lequesne Index as severely impaired before surgery; however, at six weeks, which is early compared to other studies, we found that all patients regressed to the mild impairment category. A total of 25 (50%) of the patients had no disability according to the Lequesne Index scores at six months, supporting more functional recovery over time. On the other hand, rapid improvement of functional status may depend on the fact that patients with more functional impairment refuse to participate in the study.

Physical activity after THA must be designed according to the patient's need and lifestyle. Avoiding contact sports and high joint loading activities are necessary also in preventing postoperative complications.^[29] In the present study, we assessed physical activity levels after surgery using the 6MWT, IPAQ-SF, and step count monitor. Our patients showed a significant increase in the distance walked, activity score, and steps per day as early as six weeks.

Expected daily step count in a healthy adult is 6,000 to 8,500.^[30] Our patients' preoperative daily step count was 4,090 which is less than expected. At six weeks, after THA step count increased to almost 5,900, but still below expected. At six months, the patients reached nearly 7,000 steps which are in the range of healthy older adults and above expected values for the disabled. This is consistent with previous studies by Fujita et al.^[31] and Kinkel et al.^[32] where they found an increase in the walking cycles at six months and one year.

The 6MWT measures the walking capacity objectively and gives information about walking speed endurance and ability to routinely walk. Previous studies indicated a significant improvement in the 6MWT after THA at three/six months and one year.^[33-37] In accordance with the previous data, we found that 6MWT results had significant improvement at six months; however, we found that there was a significant increase in the results of the sixth week as

an early measurement. Moreover, the 6MWT results were compared with age- and sex-matched controls and we found that the patients with THA were able to reach scores of controls even at six weeks. Pain, the main symptom of OA and the main indication of the operation, had also an effect on physical capacity and function. Therefore, pain relief after surgery was thought to be effective in early physical capacity increase.

Self-reported physical activity as well as objectively calculated step count or walking distance has presented considerable changes before and after the orthopedic surgery. In a similar way, Alvarez et al.^[38] showed that the IPAQ score had a moderate positive correlation with accelerometers. A study from Japan also revealed that patients had improved light and moderate physical activities after THA at six and 12 months.^[31] Their results supported that 12-month physical activity scores of patients which were similar with age-matched controls, while controls had higher physical activity levels at six months and before surgery. In our study, the patients' total MET-min/week scores increased after surgery at six weeks and six months based on the results of objective physical activity parameters. Compared to the controls, we found no significant difference at six weeks and six months, although the patients' values were worse at the beginning. Improvement in pain levels and increased walking capacity may have changed the patients' perception and assured them to be more confident about performing different activities. The fact that patients who volunteered to participate in the study and relieved for pain would be motivated to increase the physical activity. As a consequence, this motivation may have affected the early increase in physical activity.

Despite improved technical procedures in THA surgery, some patients still complain of pain and functional deficits regarding the outcomes after THA. Therefore, predicting the indicators of good outcomes after the operation has come into prominence and has attracted the attention.^[39] In this way, the appropriate patient selection for surgery may be facilitated. In a study investigating the type of surgery as a factor affecting postoperative outcomes, the results were similar between the direct anterior approach and the other surgical approaches.^[36] In a study by Tilbury et al.,^[40] which examined the factors affecting functional outcomes after THA, socio-demographic data, preoperative function, and preoperative patients' expectancy were evaluated. The authors found that

improved preoperative function and expectancy were associated with better outcomes, while BMI negatively affected the functional outcomes. However, Weber et al.^[39] found no significant relationship between age, sex, BMI, and good response to THA, while they reported that preoperative patient-reported functional outcomes seemed to be a predictor for postoperative responses. In a similar study, preoperative functional status referred as an effective factor for postoperative outcomes.^[27] In the present study, we assessed the predictors for postoperative function and physical capacity. Consistent with the literature, our results supported that preoperative measurements were associated with postoperative Lequesne Index scores and 6MWT results. Age, one of socio-demographic characteristics, was found to be effective on both function and physical capacity, while the presence of comorbid disease was associated with the Lequesne Index scores. Although it is expected that age and systemic comorbid diseases would decrease walking distance and increase functional disability, it would be useful to analyze our preliminary results in studies with a larger patient size.

To the best of our knowledge, this is the first study to evaluate changes in pain, physical function, capacity, and activity using both subjective and objective measures as early as six weeks after THA. However, our study has some limitations that need to be reported. The small sample size is main limitation. We excluded patients with advanced pulmonary and cardiovascular diseases which could have decreased the patients' walking capacity. Short period use of the step count monitor was another limitation of this study. Some patients spent an extra-effort to walk more than their actual capacity, as they were motivated to meet their physicians' expectations. Therefore, selection bias may have occurred in the present study.

In conclusion, patients with OA showed significantly decreased pain levels and improved physical function and activity as early as six weeks and up to six months after THA surgery and they had similar physical activity and capacity with the age- and sex-matched controls at the postoperative sixth month. Preoperative values and age were the positive predictors of improved postoperative function and physical capacity. However, further large-scale, prospective studies are needed to confirm these findings.

Declaration of conflicting interests

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