

## Original Article

# Acupuncture around the greater tuberosity of the femur combined with acupuncture at Xuehai acupoint alleviates the postoperative pain of elderly patients with intertrochanteric fracture

Hanjing Li<sup>1</sup>, Biao Wang<sup>2</sup>, Chuanyuan Chen<sup>2</sup>

Departments of <sup>1</sup>Traditional Chinese Medicine, <sup>2</sup>Orthopedics, Fuzhou Second Hospital Affiliated to Xiamen University, Fuzhou, Fujian Province, China

Received February 27, 2021; Accepted March 28, 2021; Epub July 15, 2021; Published July 30, 2021

**Abstract:** Objective: To determine the efficacy of acupuncture around the greater tuberosity of the femur (AGTF) combined with acupuncture at Xuehai acupoint for postoperative pain in elderly patients with intertrochanteric fracture. Methods: A total of 97 elderly patients with intertrochanteric fracture treated by proximal femoral nail antirotation (PFNA) were enrolled and randomly assigned into an observation group (Obs group, n=48) and a control group (Con group, n=49). The Obs group was treated by aspirin and AGTF combined with acupuncture at Xuehai acupoint for analgesia, while the Con group was treated by aspirin alone for analgesia. Both groups were treated for 7 consecutive days. The two groups were compared in pain degree (visual analog scale (VAS) score) after operation and hip joint function (Harris score), daily living ability (modified Barthel index (MBI) score), bone metabolism-related indexes, and inflammatory factors before and after treatment. Results: At 1-7 d after operation, both groups had gradually lower VAS scores, and at 5 and 7 d after operation, the Obs group had a lower VAS score than the Con group (both  $P<0.05$ ). Additionally, at 2 months after operation, both groups had higher Harris scores and MBI scores, and the scores of the Obs group were both higher than those of the Con group (both  $P<0.05$ ). At 7 d after operation, both groups showed a decrease in serum beta collagen degradation products ( $\beta$ -CTX) and an increase in procollagen type I amino-terminal propeptide (PINP) (both  $P<0.05$ ), but the differences between the two groups in  $\beta$ -CTX and PINP were insignificant ( $P>0.05$ ). Moreover, at 7 d after operation, both groups showed a decrease in C-reactive protein (CRP) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and the two levels in the Obs group were lower than those in the Con group (both  $P<0.05$ ). Conclusion: For elderly patients with intertrochanteric fracture, AGTF combined with acupuncture at the Xuehai acupoint can more effectively relieve their postoperative pain and postoperative inflammation and more strongly promote their postoperative recovery of hip joint function.

**Keywords:** Greater tuberosity of the femur, Xuehai acupoint, intertrochanteric fracture, pain

## Introduction

Intertrochanteric fracture is a common fracture, accounting for approximate 4.0% of all fractures in the body, and among cases with hip fracture, more than half are diagnosed as intertrochanteric fracture [1]. Intertrochanteric fracture is often accompanied by osteoporosis, so it is common among middle aged and elderly people [2]. Artificial hip replacement and closed reduction-based proximal femoral nail antirotation (PFNA) are both frequently adopted surgical methods for the treatment of intertrochanteric fractures. They can contribute to patients'

early postoperative ambulation and joint function recovery, but corresponding postoperative pain has always been challenging for orthopedic surgeons [3, 4]. Therefore, orthopaedists focus on finding an effective way to relieve the pain of patients after fracture surgery and promote their early ambulation.

One study has revealed that acupuncture at the Xuehai acupoint can alleviate dysmenorrhea to a certain extent, and one other study by Jia et al. has pointed out that acupuncture around a designated site can relieve the pain of patients with severe pressure sores [5, 6]. However,

there is no study on the analgesic effect of acupuncture around a designated site combined with acupuncture at the Xuehai acupoint on elderly patients with intertrochanteric fracture after operation. Therefore, this study mainly discussed the effect of the combined therapy on postoperative pain of elderly patients with intertrochanteric fracture and analyzed its effect on their bone metabolism.

### Materials and methods

#### *General materials*

A total of 97 elderly patients with intertrochanteric fracture who were admitted to our hospital from December 2018 to January 2020 were enrolled and prospectively studied. They were randomly assigned to an observation group (Obs group, n=48) and a control group (Con group, n=49). Both groups were given PFNA. After operation, the Con group was given Aspirin Enteric-coated Tablets for analgesia, while the Obs group was additionally given acupuncture around the greater tuberosity of the femur (AGTF) combined with acupuncture at Xuehai acupoint for analgesia based on the analgesia treatment for the Con group.

Inclusion criteria of the study: Patients between 65 and 85 years old, patients clinically confirmed with intertrochanteric fracture by related imaging examination, patients who would receive PFNA, patients whose fracture was type A1, A2, or A3 in AO classification, patients with closed unilateral fracture, and initially treated patients [7]. Exclusion criteria of the study: Patients with blood coagulation dysfunction, patients unable to tolerate surgical therapy, patients with multiple fractures or pathological fractures, patients extremely intolerant of pain, patients with severe comorbid heart, brain, liver or kidney diseases, patients with a history of fainting during acupuncture treatment, patients with malignant tumors, patients involved in other projects at the same time, and those unable to cooperate with the study due to mental disorders. All participants enrolled in this study signed the informed consent forms, and an approval was obtained for the study from the Ethics Committee of our hospital.

#### *Methods*

Both groups were treated by PFNA under continuous epidural anesthesia. After operation,

the Con group was required to orally take Aspirin Enteric-coated Tablets (50 mg; Shanghai Pharmaceuticals Sine, China) at 100 mg/time and 2 times/d for 7 consecutive days.

The Obs group was additionally given AGTF combined with acupuncture at the Xuehai acupoint for analgesia based on analgesia therapy for the Con group [8, 9]. The acupoint around the greater trochanter for acupuncture on the patient was disinfected routinely, and a disposable Hao needle, one specific needle for acupuncture (0.3 mm × 75 mm, Beijing ZhongyanTaihe Medical Equipment Co., Ltd., China) was selected, and inserted along the longitudinal axis of the femoral neck of the patient until there was a sense of hard object contact. At this time, the inserted depth of the needle was approximate 50 mm. Then, the Xuehai acupoint of the patient was disinfected routinely, and a disposable Hao needle (0.3 mm × 50 mm) was also selected, and inserted into the acupoint at about 30 mm. Moreover, electroacupuncture was applied to the anterior and posterior edges of femoral trochanter with intensity tolerable to the patient at 1 time/d for 7 consecutive days.

#### *Outcome measures*

*Primary outcome measures:* (1) The visual analog scale (VAS) was used to evaluate the pain degree of patients on the 1<sup>st</sup>, 3<sup>rd</sup>, 5<sup>th</sup> and 7<sup>th</sup> day after operation [10]. A 10 cm-long vernier gauge with 10 scales from 0 points to 10 points was adopted. 0 points means painless and 10 points means the most severe unbearable pain.

(2) The Harris score was used to evaluate the hip joint function of each patient from pain, function, deformity and joint mobility before operation and at 2 months after operation [11]. Each item was given 25 points, and a higher score indicates better recovery of the hip joint function.

*Secondary outcome measures:* (1) The modified Barthel index (MBI) was adopted to evaluate daily living ability of patients before operation and at 2 months after operation [12]. MBI has a total score of 100 points, and a higher score suggests better daily living ability.

(2) Venous blood (5 mL) was sampled from each patient before operation and at 7 d after

**Table 1.** Comparison of baseline data between the two groups (n,  $\bar{x} \pm sd$ )

Indicators	Observation group (n=48)	Control group (n=49)	$\chi^2/t$	P
Gender (n)			0.842	0.359
Male	27	23		
Female	21	26		
Age (years)	70.2 $\pm$ 5.4	71.4 $\pm$ 4.9	1.145	0.255
BMI (kg/m <sup>2</sup> )	22.29 $\pm$ 2.18	22.44 $\pm$ 1.63	0.383	0.702
Fracture AO classification (n)			2.650	0.266
A1	15	12		
A2	20	16		
A3	13	21		
One side (n)			0.497	0.481
On the left side of the	24	28		
On the right side	24	21		
Fracture cause (N)			2.506	0.286
Fall	25	33		
The external force	13	8		
Other	10	8		

operation, followed by centrifugation to separate its serum. Then electrochemiluminescence immunoassay was adopted to determine the levels of bone metabolism-related indexes including beta collagen degradation products ( $\beta$ -CTX) and procollagen type I amino-terminal propeptide (PINP) in the serum, and enzyme-linked immuno-sorbent assay (ELISA) to quantify C-reactive protein (CRP) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in the serum. The adopted reagent kits were all purchased from Shanghai Wanjiang Biotechnology Co., Ltd. (China).

#### Statistical analyses

This study adopted SPSS 20.0 for data statistics. Enumeration data, expressed as (n/%), were analyzed by the  $\chi^2$ , and measurement data, expressed as ( $\bar{x} \pm sd$ ), were compared within groups before and after therapy via the paired t test and between groups via independent sample t test.  $P < 0.05$  indicates a significant difference.

## Results

#### Baseline data

There was no significant difference between the two groups in baseline data (all  $P > 0.05$ ), so they were comparable (**Table 1**).

#### Postoperative pain

Before operation, there was no significant difference between the two groups in VAS score ( $P > 0.05$ ), while at 1-7 days after operation, both groups gradually had lower VAS scores, and at 5 and 7 d after operation, the Obs group had a lower VAS score than the Con group (both  $P < 0.05$ ) (**Table 2**).

#### Hip joint function (Harris score)

Before surgery, there was no significant difference between the two groups in Harris scores (all  $P > 0.05$ ), while at 2 months after operation, both groups had higher Harris scores, and the Harris score of the Obs group was higher than that of the Con group (both  $P < 0.05$ ) (**Table 3**).

#### Daily living ability (MBI score)

Before surgery, MBI scores of the Obs group and Con group were (57.77 $\pm$ 10.03) and (56.94 $\pm$ 8.84) points, respectively, while at 2 months after surgery, MBI scores were (72.07 $\pm$ 7.94) and (65.59 $\pm$ 8.66) points, respectively. Therefore, before operation, there was no significant difference in MBI score between the two groups ( $P > 0.05$ ), while at 2 months after surgery, MBI score of the Obs group was higher than that of the Con group ( $P < 0.05$ ) (**Figure 1**).

**Table 2.** Comparison of postoperative VAS scores between the two groups (score,  $\bar{x} \pm sd$ )

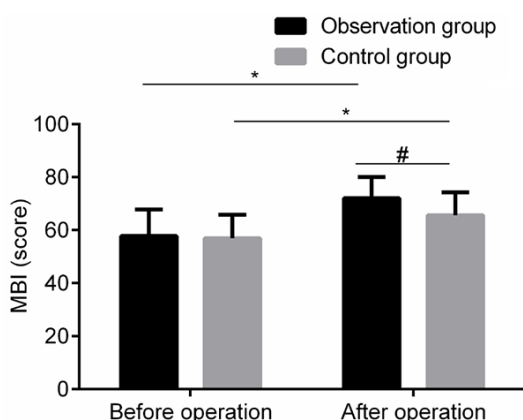
Group	Preoperative	One days after operation	Three days after operation	Five days after operation	Seven days after operation
Observation group (n=48)	7.49 $\pm$ 1.11	6.55 $\pm$ 1.24*	5.03 $\pm$ 1.08*	3.64 $\pm$ 0.83*. <sup>#</sup>	2.10 $\pm$ 0.68*. <sup>#</sup>
Control group (n=49)	7.33 $\pm$ 1.29	6.74 $\pm$ 1.42*	5.22 $\pm$ 1.20*	4.47 $\pm$ 0.95*	3.32 $\pm$ 0.72*

Note: Compared with Preoperative at the same group, \*P<0.05; Compared with the control group, <sup>#</sup>P<0.05.

**Table 3.** Harris scores before and after surgery in the two groups (score,  $\bar{x} \pm sd$ )

Indicators	Time	Observation group (n=48)	Control group (n=49)
The pain	Preoperative	13.39 $\pm$ 3.33	13.74 $\pm$ 3.75
	Two months after operation	20.84 $\pm$ 2.88*. <sup>#</sup>	17.77 $\pm$ 3.08*
Function	Preoperative	12.20 $\pm$ 3.27	12.63 $\pm$ 3.02
	Two months after operation	19.97 $\pm$ 2.64*. <sup>#</sup>	16.69 $\pm$ 2.77*
Deformity	Preoperative	14.76 $\pm$ 3.08	14.94 $\pm$ 3.86
	Two months after operation	21.16 $\pm$ 3.02*. <sup>#</sup>	18.89 $\pm$ 3.63*
Range of motion indicators	Preoperative	14.44 $\pm$ 3.02	13.98 $\pm$ 3.77
	Two months after operation	20.11 $\pm$ 2.11*. <sup>#</sup>	18.18 $\pm$ 3.20*

Note: Compared with Preoperative at the same group, \*P<0.05; Compared with the Two months after operation at control group, <sup>#</sup>P<0.05.



**Figure 1.** Comparison of daily living ability. Compared with Preoperative at the same group, \*P<0.05; Compared with the after operation at control group, <sup>#</sup>P<0.05. MBI: modified Barthel index.

#### Bone metabolism-related indexes

Before surgery, the two groups were not greatly different in the levels of serum  $\beta$ -CTx and PINP (both  $P>0.05$ ), while at 7 d after surgery, both groups showed a decrease in serum  $\beta$ -CTx and an increase in PINP ( $P<0.05$ ), but the differences between the two groups in  $\beta$ -CTx and PINP were insignificant (both  $P>0.05$ ) (Table 4).

#### Inflammatory factors

Before surgery, the two groups were not greatly different in serum CRP and TNF- $\alpha$  (both  $P>0.05$ ), while at 7 d after surgery, both groups showed a decrease in CRP and TNF- $\alpha$ , and the two in the Obs group were lower than those in the Con group (both  $P<0.05$ ) (Table 5).

#### Discussion

Intertrochanteric fracture is a common and intractable osteoporotic fracture among the middle-aged and elderly. Artificial hip replacement and PFNA are frequently adopted operative methods for it, but after such treatment, patients will suffer enormous pain [13, 14]. Effective postoperative analgesia can help patients take out of bed activity as early as possible, and thus contribute their postoperative recovery of joint function [15]. Non-steroidal anti-inflammatory analgesics such as aspirin and celecoxib are conventional postoperative analgesics, but their analgesic effect is limited, and some patients cannot get obvious relief for postoperative pain after taking them [16].

Acupuncture is a common treatment against pain in traditional Chinese medicine. One study has revealed that acupuncture at the Xuehai

**Table 4.** Levels of bone metabolism indexes before and after operation in the two groups ( $\bar{x} \pm sd$ )

Group	Time	$\beta$ -CTx (pg/mL)	PINP (ng/mL)
Observation group (n=48)	Preoperative	545.59 $\pm$ 29.93	40.04 $\pm$ 6.55
	Seven days after operation	444.08 $\pm$ 30.03*	59.96 $\pm$ 5.86*
Control group (n=49)	Preoperative	543.98 $\pm$ 34.47	39.75 $\pm$ 5.95
	Seven days after operation	445.59 $\pm$ 27.58*	59.04 $\pm$ 6.43*

Note: Compared with Preoperative at the same group, \*P<0.05.  $\beta$ -CTx: beta collagen degradation products; PINP: procollagen type I amino-terminal propeptide.

**Table 5.** Levels of inflammatory factors before and after surgery in the two groups ( $\bar{x} \pm sd$ )

Group	Time	CRP (mg/L)	TNF- $\alpha$ (ng/mL)
Observation group (n=48)	Preoperative	76.69 $\pm$ 10.04	104.49 $\pm$ 12.22
	Seven days after operation	9.33 $\pm$ 2.88*. <sup>#</sup>	15.55 $\pm$ 3.20*. <sup>#</sup>
Control group (n=49)	Preoperative	77.73 $\pm$ 9.62	103.78 $\pm$ 10.84
	Seven days after operation	14.30 $\pm$ 3.02*	22.23 $\pm$ 4.06*

Note: Compared with Preoperative at the same group, \*P<0.05; Compared with the Seven days after operation at control group, <sup>#</sup>P<0.05. CRP: C-reactive protein; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ .

acupoint can help relieve the pain of patients with advanced liver cancer [17]. In our study, at 1-7 days after operation, both groups gradually had lower VAS scores, and at 5 and 7 d after operation, the Obs group had a lower VAS score than the Con group. The results imply that additional AGTF combined with acupuncture at Xuehai acupoint based on aspirin can more strongly alleviate the postoperative pain of patients with intertrochanteric fracture, and the alleviation takes effect gradually as time goes by. The results of this study are similar to those of a study by Medda et al., which also holds that the combined therapy is superior to conventional non-steroidal anti-inflammatory analgesics in analgesia [18].

For patients with intertrochanteric fracture, taking out of bed activity as soon as possible is helpful to promote the postoperative recovery of their hip joint function, and is one of the main indexes to evaluate efficacy, as well as being beneficial to their life quality after operation [19, 20]. In this study, at 2 months after operation, both groups got higher Harris scores and MBI scores, and the scores of the Obs group were both higher than those of the Con group. The obtained data denote that in addition to aspirin, additional AGTF combined with acupuncture at the Xuehai acupoint can more effectively promote the recovery of hip joint function of elderly patients with intertrochanteric fracture and improve their daily living abil-

ity. The reason may lie in the fact that the combined therapy can deliver better analgesic effects, and patient's whose pain was relieved by it can take out of bed activity earlier, and the patients can thus have better recovery of hip joint function and higher daily living ability [21].

For the body, surgery is a stressor. Intraoperative operations can bring the body to a state of stress, and then stimulate a variety of cells to release inflammatory factors. As patients recover after an operation, the levels of inflammatory factors decrease gradually [22]. In this study, at 7 d after operation, the Obs group showed lower serum CRP and TNF- $\alpha$  than the Con group, suggesting that in addition to aspirin, additional AGTF combined with acupuncture at the Xuehai acupoint can better alleviate the postoperative inflammatory state of elderly patients with intertrochanteric fracture. It may be explained by the fact that the combined therapy can provide more meaningful analgesic effects, and can thus reduce the stress response of the body to a certain extent [23]. Bone metabolism-related indexes can be used to evaluate fracture healing process. PINP, strongly related with osteoblastic activity, can be adopted for evaluation of bone formation.  $\beta$ -CTx is an index to evaluate bone resorption rate and reflect osteoclast activity. During pathological process, serum  $\beta$ -CTx increases sharply [24, 25]. Our study revealed that at 7 d after operation, both groups showed a decrease in



$\beta$ -CTx and an increase in PINP, but the differences between the two groups in  $\beta$ -CTx and PINP were insignificant. The data imply that bone metabolism of the two groups was improved significantly after PFNA treatment, but the two different postoperative analgesia modes had no obvious effect on bone metabolism. The results are consistent with those of a study by Lisowska et al., which also holds that different analgesic drugs will not affect bone metabolism and bone absorption after operation [26].

However, this study is a single-center study with a limited sample size and short follow-up time after treatment. Therefore, the positive effect of AGTF combined with acupuncture at Xuehai acupoint on pain degree and hip joint function of elderly patients with intertrochanteric fracture after PFNA still needs to be explored by further study with a larger sample size.

To sum up, for elderly patients with intertrochanteric fracture, AGTF combined with acupuncture at Xuehai acupoint can more effectively relieve their postoperative pain and postoperative inflammation and can more strongly promote their postoperative recovery of hip joint function, so it is worthy of clinical promotion.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Chuanyuan Chen, Department of Orthopedics, Fuzhou Second Hospital Affiliated to Xiamen University, No. 47 Shangteng Road, Cangshan District, Fuzhou 350007, Fujian Province, China. Tel: +86-15395913589; E-mail: chenchuanyuan118@163.com

## References

- [1] Horwitz DS, Tawari A and Suk M. Nail length in the management of intertrochanteric fracture of the femur. *J Am Acad Orthop Surg* 2016; 24: e50-e58.
- [2] Orchard T, Yildiz V, Steck SE, Hébert JR, Ma Y, Cauley JA, Li W, Mossavar-Rahmani Y, Johnson KC, Sattari M, LeBoff M, Wactawski-Wende J and Jackson RD. Dietary inflammatory index, bone mineral density, and risk of fracture in postmenopausal women: results from the women's health initiative. *J Bone Miner Res* 2017; 32: 1136-1146.
- [3] Socci AR, Casemyr NE, Leslie MP and Baumgaertner MR. Implant options for the treatment of intertrochanteric fractures of the hip: rationale, evidence, and recommendations. *Bone Joint J* 2017; 99: 128-133.
- [4] Xiao Q and Zhou Z. Perioperative pain management of total hip arthroplasty. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2019; 33: 1190-1195.
- [5] Zhang M and Liu Z. Effects of acupuncture on muscle tension of lower limb in children with spastic cerebral palsy. *Zhongguo Zhen Jiu* 2018; 38: 591-595.
- [6] Jia C, Su B, Gong L, Wang W and Zhang X. Encircling needling combined with physical factor therapy for severe pressure sore. *Zhongguo Zhen Jiu* 2015; 35: 1131-1134.
- [7] Audigé L, Slongo T, Lutz N, Blumenthal A and Joeris A. The AO pediatric comprehensive classification of long bone fractures (PCCF). *Acta Orthop* 2017; 88: 133-139.
- [8] Seval Y, Emre K, Erhan Y, Ahmet K, Suleyman G and Mustafa O. Effect of acupuncture therapy on fracture healing in rats with femur fractures. *J Tradit Chin Med* 2020; 40: 275-283.
- [9] Yao M, Wang Q, Pan HL, Xu ZM and Song AQ. Effect of acupuncture on the expressions of TNF- $\alpha$  and IFN- $\gamma$  in patients with premature ovarian failure. *Zhongguo Zhen Jiu* 2019; 39: 1181-1184.
- [10] Mimouni M, Shamir RR, Cohen AD, El-Yaniv R, Cohen MJ, Joskowicz L and Blumenthal EZ. A Comparison of different scoring terminations rules for visual acuity testing: from a computer simulation to a clinical study. *Curr Eye Res* 2019; 44: 790-795.
- [11] Weel H, Lindeboom R, Kuipers SE and Vervest T. Comparison between the Harris- and Oxford Hip Score to evaluate outcomes one-year after total hip arthroplasty. *Acta Orthop Belg* 2017; 83: 98-109.
- [12] Liu F, Tsang RC, Zhou J, Zhou M, Zha F, Long J and Wang Y. Relationship of barthel index and its short form with the modified rankin scale in acute stroke patients. *J Stroke Cerebrovasc Dis* 2020; 29: 105033.
- [13] Liu L, Sun Y, Wang L, Gao Q, Li A, Wang J and Gao Y. Total hip arthroplasty for intertrochanteric fracture fixation failure. *Eur J Med Res* 2019; 24: 39.
- [14] Hoffmann MF, Khoriaty JD, Sietsema DL and Jones CB. Outcome of intramedullary nailing treatment for intertrochanteric femoral fractures. *J Orthop Surg Res* 2019; 14: 360.
- [15] Gaffney CJ, Pelt CE, Gililland JM and Peters CL. Perioperative pain management in hip and knee arthroplasty. *Orthop Clin North Am* 2017; 48: 407-419.

- [16] Kien NT, Geiger P, Van Chuong H, Cuong NM, Van Dinh N, Pho DC, Anh VT and Giang NT. Pre-emptive analgesia after lumbar spine surgery by pregabalin and celecoxib: a prospective study. *Drug Des Devel Ther* 2019; 13: 2145-2152.
- [17] Xu L, Wan Y, Huang J and Xu F. Clinical analysis of electroacupuncture and multiple acupoint stimulation in relieving cancer pain in patients with advanced hepatocellular carcinoma. *J Cancer Res Ther* 2018; 14: 99-102.
- [18] Medda S, Sullivan RJ, Marquez-Lara A, Araiza ET, Pilon HT, Halvorson JJ and Carroll EA. Treatment of peritrochanteric femur fractures with proximal femur locked plating. *J Orthop Trauma* 2019; 33: 341-345.
- [19] Karakus O, Ozdemir G, Karaca S, Cetin M and Saygi B. The relationship between the type of unstable intertrochanteric femur fracture and mobility in the elderly. *J Orthop Surg Res* 2018; 13: 207.
- [20] Wang YC and Yu WZ. Application of accelerated rehabilitation program for the treatment of intertrochanteric fracture of femur in the elderly. *Zhongguo Gu Shang* 2019; 32: 837-841.
- [21] Şahin M, Ayhan FF, Borman P and Atasoy H. The effect of hip and knee exercises on pain, function, and strength in patients with patellofemoral pain syndrome: a randomized controlled trial. *Turk J Med Sci* 2016; 46: 265-277.
- [22] Marsland AL, Walsh C, Lockwood K and John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. *Brain Behav Immun* 2017; 64: 208-219.
- [23] Kalinichenko LS, Kornhuber J and Müller CP. Individual differences in inflammatory and oxidative mechanisms of stress-related mood disorders. *Front Neuroendocrinol* 2019; 55: 100783.
- [24] Cavalier E, Eastell R, Rye Jørgensen N, Makris K, Tournis S, Vasikaran S, Kanis JA, Cooper C, Pottel H and Morris HA. A multicenter study to evaluate harmonization of assays for N-terminal propeptide of type I procollagen (PINP): a report from the IFCC-IOF joint committee for bone metabolism. *Clin Chem Lab Med* 2019; 57: 1546-1555.
- [25] Zulauf N, Brüggmann D, Groneberg D and Oremek GM. Expressiveness of bone markers in breast cancer with bone metastases. *Oncology* 2019; 97: 236-244.
- [26] Lisowska B, Kosson D and Domaracka K. Positives and negatives of nonsteroidal anti-inflammatory drugs in bone healing: the effects of these drugs on bone repair. *Drug Des Devel Ther* 2018; 12: 1809-1814.