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## Research Article

# Comparison of systemic inflammatory responses of proximal femoral nail versus dynamic hip screw after treatment of patients with pertrochanteric fractures: A prospective comparative study

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## ABSTRACT

**Objective:** The aim of this study was to investigate the differences between the induction of early postoperative inflammatory response and muscle tissue injury biomarkers after treatment of pertrochanteric fractures by dynamic hip screw (DHS) or proximal femoral nail (PFN).

**Methods:** In this prospective comparative study, 40 patients with AO-Müller/Orthopaedic Trauma Association (AO/OTA) 31.A1–31.A2 pertrochanteric fractures were enrolled and allocated one of the two groups based on the treatment type: group DHS, (n = 20, mean age = 78.4 ± 6.9 years) and group PFN (n = 20, mean age = 77.75 ± 7.0 years). Operation time was recorded in both groups. In each patient, circulating levels of high sensitivity interleukin-6 (hs-IL-6), C-reactive protein (CRP), and creatine kinase (CK), and erythrocyte sedimentation rate (ESR) were measured from blood samples collected 1 hour preoperatively and 24 hours postoperatively.

**Results:** The operation time was slightly shorter in group PFN than in group DHS (51.9 ± 21.1 and 38 ± 15.2 min, respectively;  $P = 0.02$ ). DHS and PFN both increased hs-IL-6 (143.81 ± 89.12 and 94.13 ± 67.14, respectively), CRP (98.84 ± 31.81 and 104.4 ± 31.80, respectively), and CK (400.8 ± 31.81 and 250.7 ± 31.80, respectively) 24 hours postoperatively. However, PFN compared to DHS resulted in a lesser increase from baseline to 24 hours postoperatively only in hs IL-6 (58.91 ± 59.02 vs 113.30 ± 76.24, respectively;  $P = 0.0016$ ) and CK (163.6 ± 123.3 vs 310.0 ± 198.3, respectively;  $P < 0.0001$ ). Moreover, there was a positive correlation of CK levels' surgery time in DHS ( $r = 0.38$ ,  $P = 0.0065$ ) and PFN ( $r = 0.45$ ,  $P = 0.0013$ ).

**Conclusion:** The results of this study have shown that PFN can induce a lower early postoperative inflammatory response and muscle tissue injury based on the assessment of hs-IL-6 and CK levels, compared to DHS in after the treatment patients pertrochanteric fractures.

**Level of Evidence:** Level II, Therapeutic Study

## Introduction

Proximal femoral fractures are common in older adults and are associated with higher morbidity and mortality,<sup>1</sup> and their incidence is increasing due to the aging population.<sup>2</sup> However, the current approaches to hip fracture management mainly include surgical interventions. Concerning pertrochanteric fractures, AO/OTA 31.A1–31.A2, the two mainly used fixation methods are Dynamic Hip Screw (DHS) and Proximal Femoral Nail (PFN).<sup>3</sup> Meanwhile, nailing is more reliable in covering all types of intertrochanteric fractures.<sup>4</sup>

These techniques have been reported to have successful long-term outcomes. However, different studies have compared them in terms of the postoperative period and failed to prove the superiority of intramedullary fixation over extramedullary fixation in AO/OTA 31.A1–31.A2.<sup>3</sup> Furthermore, intramedullary fixation surpassed extramedullary fixation for unstable intertrochanteric fracture intervention concerning implant failure and postoperative functional recovery.<sup>5</sup>

Recently, interest has shifted to understanding different types of surgeries and predictive markers in patients with systemic inflammatory findings.<sup>6</sup> These studies included mainly the measurement of several cytokine levels during the posttraumatic course.<sup>7</sup> With this, an abrupt increase in IL-6 levels was found, which was a key cytokine finding after hip surgery with different kinds of surgical procedures.<sup>8</sup> This suggested its involvement in the early stages of the postoperative inflammatory reaction, and its levels were related to the invasiveness of surgical techniques.<sup>9</sup>

Several studies, which investigated the differences between these two implants, were focused on surgical methods and implant failure rather than invasiveness from its usage. However, there were only a few studies that compared the invasiveness of PFN and DHS in both postoperative inflammatory response and muscle injury. We hypothesized that PFN will induce less early postoperative inflammatory response and markers of muscle injury than DHS. Therefore, this study

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aims to compare the differences between the induction of early postoperative inflammatory response and muscle tissue injury biomarkers after treatment of pertrochanteric fractures by either DHS or PFN.

## Materials and Methods

This study was designed as a prospective, comparative/cohort study undertaken in the University Clinical Center of Kosovo (UCCK) between January 01, 2019, and December 01, 2019. The following criteria were used for the selection of patients: (i) all patients older than 60 years old; (ii) with trochanteric region fractures AO/OTA 31.A1–31.A2 diagnosed by examination of plain radiograph in anteroposterior projection; and (iii) with surgery within 1 week of trauma. Meanwhile, those with conditions affecting systemic inflammatory response such as polytrauma, open fractures, existing local or systemic infection, pre-existing coagulopathy disorder, existing malignancy, steroid therapy, and systemic inflammatory diseases were excluded. In addition, all other parameters including age, gender, Body Mass Index (BMI), fractures, the time duration from hospitalization to surgical procedures, fracture types, and operation time were recorded. Moreover, the operations were performed by four certified surgeons who have completed AO basic and advanced courses and were divided into two groups where each group had two surgeons who attended PFN and DHS patients, respectively. The eligible patients for the study were given information regarding the two treatments based on the current orthopaedic knowledge and they were free to choose between two options. Based on their selection, they were assigned to be treated by the surgeons performing DHS or PFN. Patients in whom closed reduction under image intensifier was achieved were included. The first and second groups of patients were treated with DHS (Synthes, West Chester, PA, USA) through an incision of fascia lata and vastus lateralis and percutaneously with PFN, respectively (Synthes-Stratec, Oberdorf, Switzerland). Opioid agents were administered to treat pain to avoid the usage of non-steroid inflammatory drugs and rule out the possible confounding effects from inflammatory markers. Twenty-nine patients had spinal anesthesia while 11 had general anesthesia based on patient and anesthesiologist choice. For deep vein thrombosis prophylaxis, low-molecular-weight heparin and nadroparin calcium injection (Fraxiparine; Aspen, Notre Dame de Bondeville, France) was administered in a dose of 3800 I.U. AXA/0.4 mL subcutaneously preoperatively and daily in the postoperative period. Antibiotic prophylaxis consisting of cefazolin in a dose of 1.0 g or 2.0 g if patients weighted more than 80 kg, 30 min before surgery, and three other doses of 1.0 g every 8 h post-operatively, while for patients allergic to cefazolin, vancomycin 1.0 g was administered 2 h preoperatively and two other doses of 1.0 g every 12 h postoperatively.

The study was approved by the Institutional Ethical Committee of UCCK (2018.380). Participation was voluntary and under the Helsinki

Declaration of 1975 for biomedical research involving human subjects as revised in 2000. All patients gave informed consent prior to inclusion. This study was conducted according to the CONSORT statement for randomized trials (<http://www.consort-statement.org/>), and it was registered on ClinicalTrials.gov (NCT03849014).

## Laboratory analysis

Blood samples from the cubital vein were obtained 1 h preoperatively and 24 h postoperatively. Analysis of Creatine Kinase (CK), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR) was done immediately after collection, while samples for IL-6 were centrifuged at 3000 rpm for 5 min, and plasma was stored at  $-80^{\circ}\text{C}$ .

IL-6 was measured using enzyme-linked immunoassay, high sensitivity human IL-6 ELISA kit (ab46042; Abcam, Cambridge, MA, USA) according to the manufacturer's protocol instructions.

We have examined the plasma concentration of standard systemic inflammation and tissue injury markers, such as CK, CRP, and ESR, using standard methods from the Central Laboratory of the First Affiliated University Clinical Center of Kosovo (UCCK). This was done using a biochemistry analyzer with Electrochemiluminescence Immunoassay (ECLIA) Cobas e411 analyzer (Roche/Hitachi, Roche Diagnostics, Switzerland).

## Statistical analysis

The data in our study were reported as mean  $\pm$  Standard Deviation (SD) and 95% Confidence Interval (CI). Before the statistical analysis was performed, the normal distribution and homogeneity of the variances were tested using descriptive statistics. Differences of means at the patient level for continuous outcomes between groups were analyzed using unpaired *t*-tests and represented as mean  $\pm$  standard deviation. The protocols in our study were analyzed as an additional difference between the mean  $\pm$  Standard Error of the Mean (SEM). To assess the relationship of CK on the duration of surgery, we used Pearson's correlation coefficient and linear regression analysis. The results were significant if  $P < 0.05$  (GraphPad Prism 6.0 software, San Diego, CA, USA)

## Results

### Patient characteristics

Out of 102 patients with pertrochanteric fractures, 87 were eligible and treated by two groups of surgeons. Forty four patients were excluded due to conditions that might affect the systemic inflammatory response. Essentially, we analyzed DHS and PFN patients with 20 patients, each as shown in the consort flow trial diagram (Figure 1).

These patients were adjusted based on age, gender, BMI, fractures, and time duration from hospitalization to surgical procedures. However, the operation time had a slight increase in the DHS group. Demographics and clinical features data are shown in Table 1.

### Effects of PFN and DHS in early Post-Inflammation response

**hs-IL-6 Levels:** To study the impact and comparison of PFN and DHS in tissue inflammation and injury, hs-IL-6 and CRP levels were measured 1 h pre-surgical and 24 h post-surgical period in the plasma. As expected, hs-IL-6 levels were increased after surgery for both DHS (1 h pre-op vs 24 h post-op,  $30.55 \pm 26.58$  and  $143.81 \pm 89.12$  pg/mL, respectively;  $P < 0.0001$ ) and PFN (1-h pre-op vs 24 h post-op,  $35.23 \pm 24.72$  and  $94.13 \pm 67.14$  pg/mL, respectively;  $P < 0.001$ ) (Figure 2A and Table 2). Whereas, the level of increase from the baseline to 24 h post-surgical in hs IL-6 levels are statistically less in the PFN group in comparison with DHS ( $58.91 \pm 59.02$  vs  $113.30 \pm 76.24$ ;  $P = 0.0160$ ). The mean difference was  $54.36 \pm 21.56$  (95% CI: 10.70 to 98.02).

## HIGHLIGHTS

- DHS and PFN increased early postoperative inflammatory response and muscle injury based on the assessment of hs-IL-6 and CK levels.
- PFN induced lower early postoperative inflammatory response than DHS.
- Muscle tissue injury was increased with surgery time, favoring PFN which induced lower muscle injury levels than DHS.
- Our data provide additional evidence for the choosing best option for DHS and PFN surgical intervention techniques in the early total care in patients with trochanteric region fractures when considering the early postoperative inflammatory response and muscle injury.

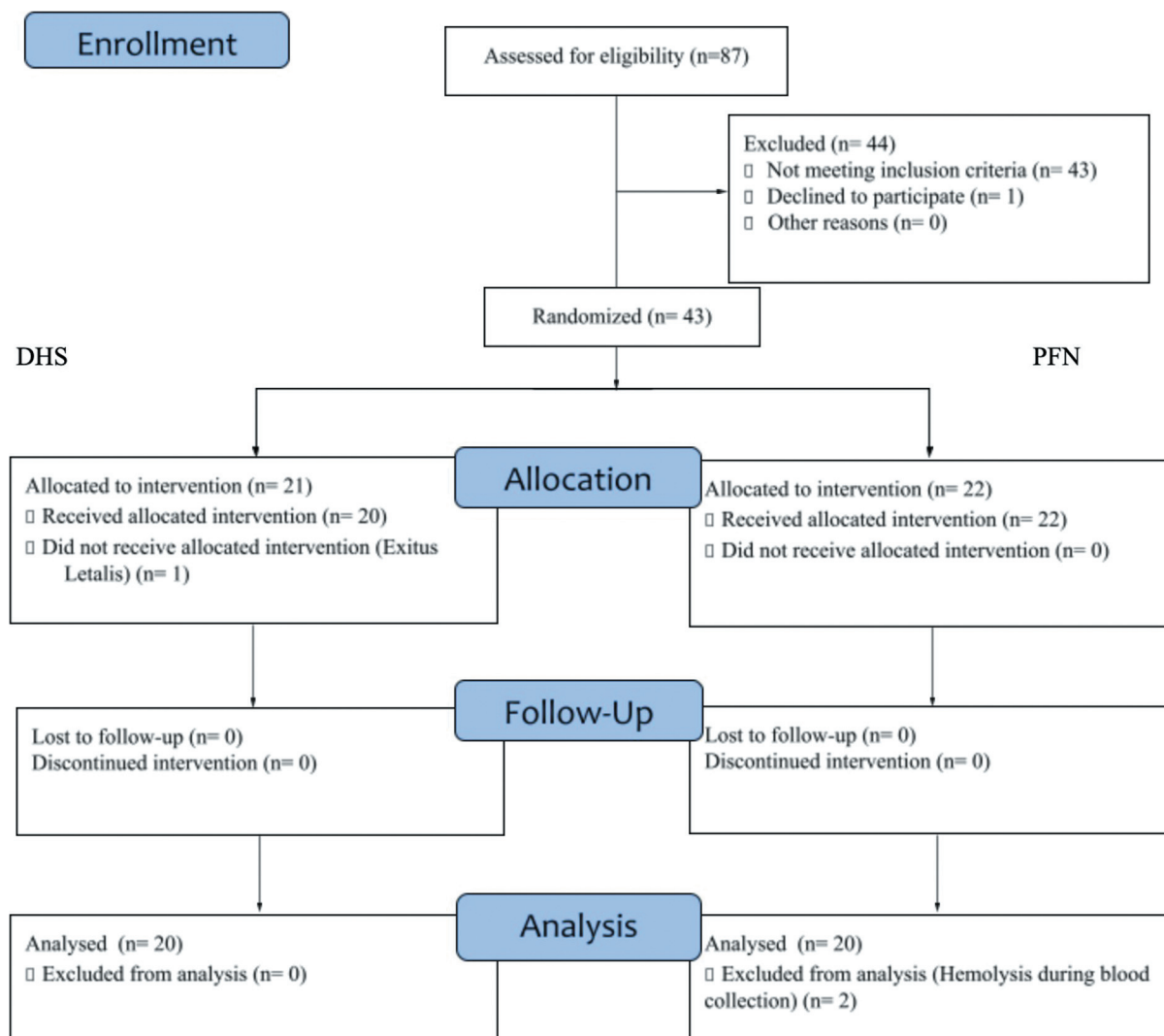


Figure 1. CONSORT trial flow diagram.

Variables	DHS	PFN	P
Number of patients	20	20	
Age (mean ± SD)	78.4 ± 6.9	77.75 ± 7.0	0.76
Gender (M:F) (n)	6:14	5:15	0.79
BMI (mean ± SD)	26.7 ± 4.2	25.3 ± 3.8	0.37
Fracture type (A1:A2)	11:9	13:7	0.79
Time from hospitalization to surgery (mean ± SD)	29.7 ± 20.7	27.7 ± 22.1	0.54
OP time (mean ± SD)	51.9 ± 21.1	38 ± 15.2	<b>0.02</b>

Notes: The Mann–Whitney test was used to find the inter-group significant differences. Significant P are indicated by bold characters.  
DHS, Dynamic Hip Screw; PFN, Proximal Femoral Nail Anti-Rotation; BMI, Body Mass Index; OP, Operation.

**CRP and ESR Levels:** CRP levels were increased after surgery for both DHS (1 h pre-op vs 24 h post-op, 54.14 ± 29.30 and 98.84 ± 31.81 mg/L, respectively;  $P < 0.0001$ ) and PFN (1 h pre-op vs 24 h post-op, 56.98 ± 28.63 and 104.4 ± 31.80 mg/L, respectively;  $P < 0.001$ ) (Figure 2B and Table 2). Meanwhile, non-significant changes were also observed from the baseline to 24 h post-surgical for CRP (44.71 ± 22.28

vs 47.43 ± 20.33,  $P = 0.688$ ) and ESR (5.50 ± 9.34 vs 6.25 ± 7.94,  $P = 0.7859$ ) after comparing PFN with DHS ( $P > 0.05$ ) (Figure 2C and Table 2).

**Effects of PFN and DHS in Muscle Injury CK levels:** Similarly, CK values were increased after the surgery for both DHS (1 h pre-op vs 24 h post-op, 90.80 ± 42.89 and 400.8 ± 31.81, respectively;  $P < 0.0001$ ) and PFN (1-h pre-op vs 24 h post-op, 87.15 ± 28.63 and 250.7 ± 31.80 UI/L, respectively;  $P < 0.001$ ). Whereas, increase in CK values is statistically less in the PFN group in comparison with DHS (163.6 ± 123.3 vs 310.0 ± 198.3,  $P < 0.0001$ ). The mean difference was 146.4 ± 52.21 (95% CI: 40.66 to 252.1) (Figure 2D and Table 2). Furthermore, the operation time was significantly lower in PFN vs DHS (38 ± 15.2 vs 51.9 ± 21 min,  $P < 0.05$ ) (Table 1).

**Surgery time:** There was a positive correlation between CK levels and surgery time in DHS ( $r = 0.38$ ,  $P = 0.0065$ ) and PFN ( $r = 0.45$ ,  $P = 0.0013$ ) (Figure 3 and Table 2). This indicated that timing did not compromise our main findings for outcomes of tissue injuries in PFN.

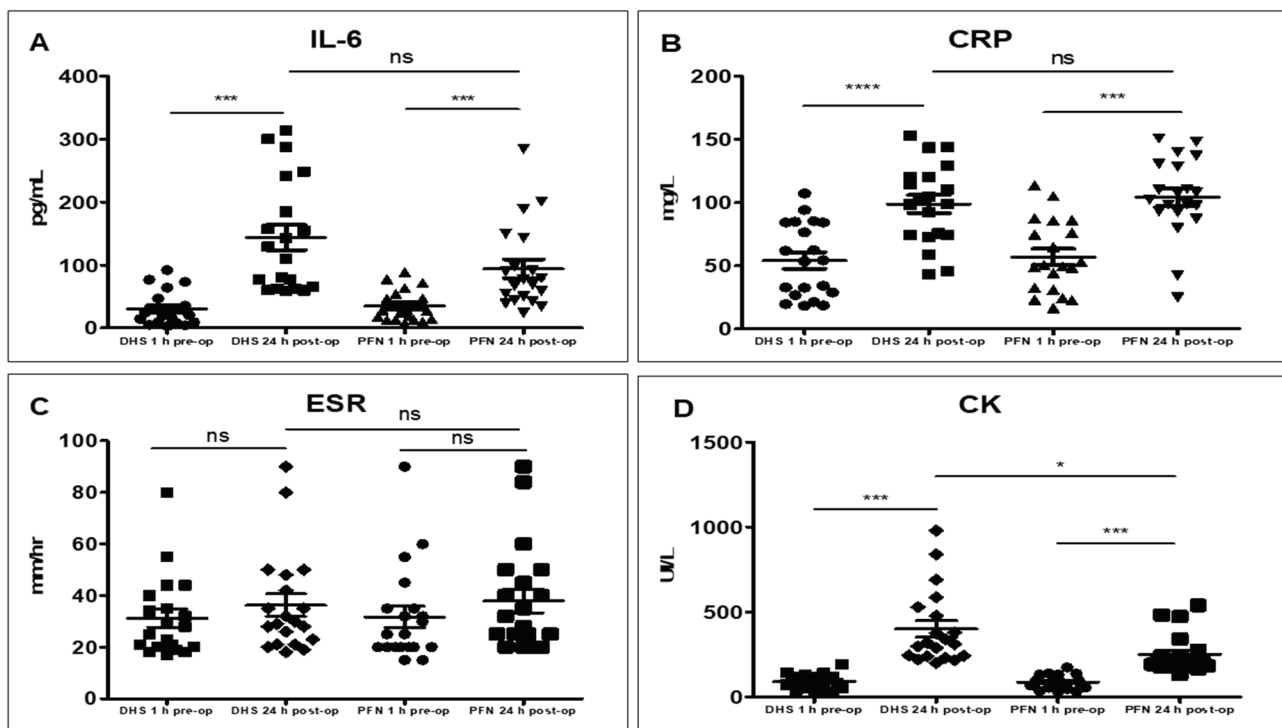


Figure 2. A-D. Effects of PFN and DHS in the systemic release of proinflammatory mediators and muscle injury biomarkers in human plasma. IL-6, pg/mL (A); CRP,mg/L (B); ESR,m/h (C); and CK, UI/L (D) plasma levels from trochanteric region fracture treated patients with PFN or DHS 1 hpre-op and 24 h post-op.0.05, 0.01, and 0.001 (students t-test) vs 1 hand DHS. Values are expressed as mean SD (n=20).

Table 2. Levels of Inflammatory Markers Pre- and Postoperatively

	1h pre-op	24 h post-op	P
DHS (hs-IL-6)	30.55 ± 26.58 (18.11 to 42.99)	143.81 ± 89.12 (102.10 to 185.5)	0.0001
PFN (hs-IL-6)	35.23 ± 24.72 (24.66 to 46.79)	94.13 ± 67.14 (62.71 to 125.6)	0.0007
DHS (CRP)	54.14 ± 29.30 (40.42 to 67.85)	98.84 ± 31.81 (83.95 to 113.7)	0.0001
PFN (CRP)	56.98 ± 28.63 (43.58 to 70.38)	104.4 ± 31.80 (89.53 to 119.3)	0.0001
DHS (CK)	90.80 ± 42.89 (70.73 to 110.9)	400.8 ± 31.81 (297.6 to 503.9)	0.0001
PFN (CK)	87.15 ± 28.63 (68.54 to 105.8)	250.7 ± 31.80 (196.4 to 305.0)	0.0001
DHS (ESR)	31.15 ± 15.65 (23.82 to 38.48)	36.25 ± 19.52 (27.11 to 45.39)	0.3678
PFN (ESR)	31.70 ± 18.57 (23.01 to 40.39)	37.95 ± 20.44 (28.39 to 47.51)	0.3178

Notes: In the table we have shown the levels of IL-6, CRP, CK, and ESR before and after operation. The values are expressed as pg/mL for IL-6, mg/L for CRP, UI/L for CK, and mm/h for ESR. (unpaired t-test). DHS, Dynamic Hip Screw; PFN, Proximal Femoral Nail; IL-6, Interleukin-6; CRP, C-Reactive Protein; CK, Creatine Kinase; ESR, Erythrocyte Sedimentation Rate

### Discussion

This study investigated the changes in postoperative inflammation and muscle damage after two frequently used surgical procedures in pertrochanteric fractures: PFN and DHS. We aimed to compare the preoperative and postoperative levels of inflammatory markers IL-6, CRP, and ESR as well as CK as a muscle marker. To our best

knowledge, this is the first study to compare both devices concerning IL-6 along with other inflammatory and soft tissue markers.

Our key finding in our study was the significant difference between levels of IL-6 after treatment with DHS and PFN. This reflected the superiority of PFN against DHS in terms of systemic inflammatory response. Nowadays, different clinical studies showed the differences between pro-inflammatory biomarkers (IL-1, IL-6, and IL-8) after surgeries.<sup>10</sup> In relation to our study criteria, the general and spinal anesthesia procedures do not affect the systemic inflammatory markers.<sup>11,12</sup> While different studies showed inconsistent IL-6 levels post-operative from different hip fracture surgeries. Meanwhile, few reports investigated the IL-6 levels after DHS and PFN. The initial study was conducted by Del Prete et al.<sup>9</sup> and found that treatment of pertrochanteric fractures with DHS conventional technique resulted in significantly increased IL-6 levels after surgery as compared to minimal invasive ones. However, the measured time point after the surgery was 1 h in this study, which might not represent the peak of inflammation stimuli.<sup>13</sup> Another study from Marino et al.<sup>14</sup> also reported the lower inflammatory profile of IL-6 levels in the PFN 24 h post-surgical period; meanwhile, the general post-operative IL-6 values were even lower than in our study. Interestingly, the high levels of IL-6 can be explained since high sensitivity IL-6 kits were used. This can be supported with the findings of Ebrahimpour et al.,<sup>6</sup> wherein IL-6 values greater than 100 pg/mL were found after treatment of tibial fractures with different surgical techniques (intramedullary nailing, open reduction and internal fixation (ORIF) and percutaneous plating) and high sensitivity IL-6 kits. With this, the key finding in our study was the significantly higher levels of IL-6 after treatment with DHS compared to PFN. This reflected the superiority of PFN against DHS for systemic inflammatory responses.

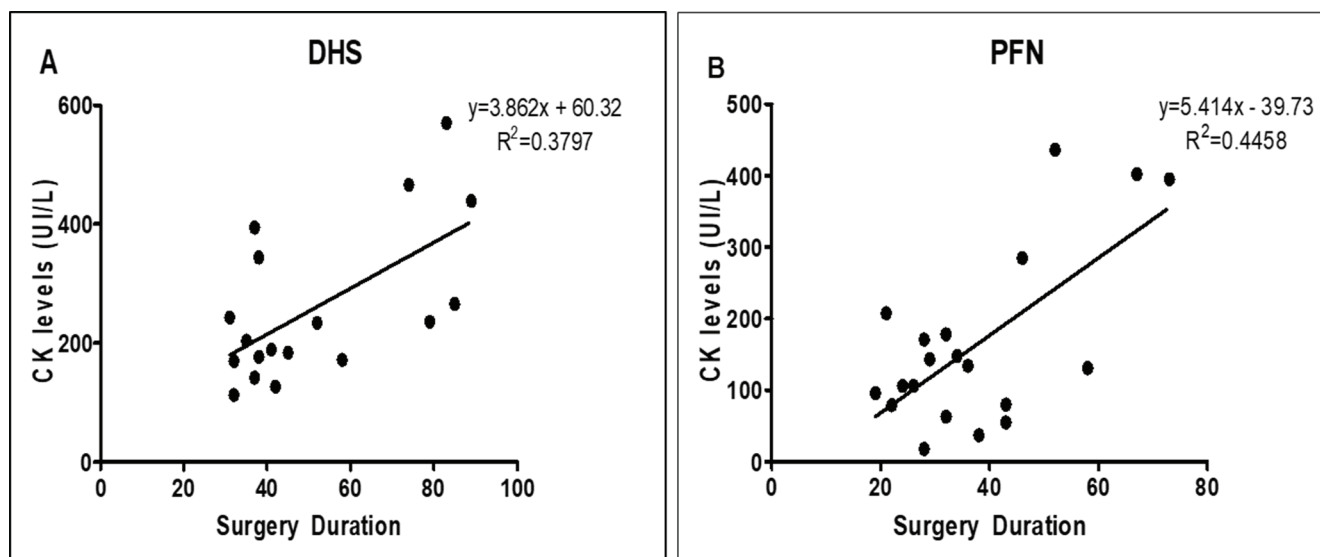


Figure 3. A, B. Correlation between the releases of CK plasma levels throughout the surgery in patients treated with DHS (A) and PFN (B) surgical techniques.

Moreover, the skin incision and muscle dissection are proportional to the BMI values of the patients with the minimally invasive surgery as well,<sup>15</sup> and it is known that the higher BMI affects also the increase in IL-6 values proportionally.<sup>16</sup> However, in our study, the BMI values were normal and did not differ significantly between both groups of the study, thus not showing a significant difference between the IL-6 preoperative values as well. Suggesting so that the levels of IL-6 were solely affected by the type of the surgery.

In addition, we investigated other biomarkers of inflammation (ie, CRP) as an acute-phase protein that was elevated after trauma, during surgery, and related soft tissue injuries.<sup>14,17–22</sup> Moreover, increased levels in the post-operative period were shown to be linked with impaired mental status and other complications in elderly patients.<sup>19</sup> Herein, our results demonstrated these findings without showing any significant difference between the two surgical techniques. These were in line with other related studies<sup>14,23</sup> suggesting that CRP values may not be determinants for differentiating these techniques. Meanwhile, since the CRP values were induced by IL-6,<sup>24</sup> and its peak is normally reached 48 h after hip fracture surgery,<sup>17,19</sup> we failed to catch the peak of CRP values that would have been able to show any possible difference between these surgical procedures.

Moreover, trauma or muscle dissection during surgery has been shown to influence CK levels.<sup>25</sup> This emphasized that surgical procedure invasiveness and time for intervention affected these values.<sup>26</sup> With this, it is worth noting that PFN has a smaller incision compared to DHS.<sup>27</sup> Similarly, this study showed that DHS had higher levels of CK compared with PFN. These findings were also consistent with other studies, wherein greater soft tissue injury was observed for higher CK values for DHS as compared to PFN surgical intervention.<sup>28</sup> However, there were also other studies with contradicting results, as well.<sup>23</sup> In addition, we found a similar study conducted on patients treated with PFN.<sup>14</sup> Their results also suggested that the higher incision in DHS might be an additional potential cause of tissue trauma during DHS surgery. On the other side, we have confirmed the positive correlation of CK levels with both DHS and PFN surgery time, as well. The CK values started to increase also in the short duration of surgery, which might be related to the magnitude of surgery.<sup>26</sup> Therefore, this increase is correlated with the duration of

surgery in the postoperative period.<sup>29</sup> Moreover, increased values were shown to be significantly lower when compared to DHS despite the earlier increase in CK values in the small group of patients in PFN ( $n = 3$ ). This suggested that tissue damage caused by these techniques depends not only on the general cause of the tissue trauma but also due to the duration of procedures. Furthermore, the associated damages that are caused by the time of surgery did not compromise our main findings regarding tissue injury from PFN.

Finally, the hip fractures treated with total hip arthroplasty had elevated ESR in the postoperative period.<sup>20,21</sup> However, these were found to be negligible in both groups. This may be since ESR has a slow rise and reaches its peak after a long period after surgery.<sup>22</sup>

The main limitation of the study was the small sample size. We have only measured some of the leading pro-inflammatory mediators and tissue injury biomarkers in the evaluation of early post-inflammatory response. In addition, the follow-up time was relatively short, and we did not analyze all of the other potential confounding variables.

In conclusion, results showed a lower early postoperative inflammatory response and muscle tissue injury based on the assessment of hs-IL-6 and CK levels upon comparing patients with closed reduction peritrochanteric fractures treated with PFN as compared to DHS. Although future clinical studies are still necessary to further clarify the differences between these surgical procedures, the currently available findings set the stage for larger investigational studies aimed at assessing their differences and priorities for making a reasonable clinical decision for elderly patients with peritrochanteric fractures.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Institutional Ethical Committee of UCCK (2018.380).

**Informed Consent:** Informed consent was obtained from all patients.

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**Conflict of Interest:** The authors have no conflicts of interest to declare.

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