Kocatepe Tıp Dergisi
Kocatepe Medical Journal
27:252-257/Nisan 2026 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

UZUN KEMİK KIRIĞININ ENDOTEL FONKSİYONUNA ERKEN ETKİLERİ; AKIM ARACILI DİLATASYON YÖNTEMİNİ KULLANAN PROSPEKTİF KLİNİK ÇALIŞMA

THE EARLY EFFECTS OF LONG BONE FRACTURES ON ENDOTHELIAL FUNCTION; A PROSPECTIVE CLINICAL STUDY USING THE FLOW-MEDIATED DILATATION METHOD

Mehmet Ali DURSUN[1], Ali AYDIN[2]

[1]Doç. Dr. Mustafa Kalemli Tavşanlı Devlet Hastanesi, Ortopedi ve Travmatoloji Kliniği
[2]Atatürk Üniversitesi Tıp Fakültesi, Ortopedi ve Travmatoloji Ana Bilim Dalı

ÖZET

AMAÇ: Vasküler endotel fonksiyonları inflamatuar süreçlerden etkilenebilir. Uzun kemik kırıklarındaki doku hasarı güçlü bir inflamatuar yanıta neden olabilir. Uzun kemik kırıklarının neden olduğu bu inflamatuar yanıtın erken dönemde endotel fonksiyonları üzerindeki etkisini değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: 2018-2020 yılları arasında uzun kemik kırığı olan ve başka bir hastalığı olmayan 18-60 yaş arası 44 hasta prospektif olarak araştırıldı. Hastaların vasküler endotel fonksiyonlarını akım aracılı dilatasyon yöntemi (FMD) ile değerlendirdik. Akut kırık döneminde inflamatuar sürecin başlangıcında ve inflamasyonun minimal olduğu birinci ayda yapılan ölçümlerin verileri sırasıyla FMD-0 ve FMD-1 olarak kaydedildi.

BULGULAR: Ortalama FMD-0 değerleri 0,082±0,046 (aralığı: 0,005-0,18) olarak ölçüldü. Ortalama FMD-1 değerleri 0,118 ± 0,054 (aralığı: 0,03-0,24) olarak ölçüldü. Hastaların ortalama FMD değerleri birinci ayda anlamlı olarak daha yüksekti (p=0,02). Yaş, cinsiyet, taraf, ekstremite farkı (üst, alt) ile FMD sonuçları gibi diğer parametreler arasında anlamlı bir ilişki yoktu (hepsi için p>0,05).

SONUÇ: Uzun kemik kırıklarının neden olduğu şiddetli inflamasyon, akut dönemde endotel disfonksiyonuna neden olabilir. Uzun kemik kırığı sonrası görülen sistemik komplikasyonların patogenezinde endotel disfonksiyonunun rol oynayabileceği akılda tutulmalıdır.

ANAHTAR KELİMELER: Endotel disfonksiyonu, Akım aracılı dilatasyon, Uzun kemik kırığı.

ABSTRACT

OBJECTIVE: Vascular endothelial function can be affected by inflammatory processes.. Tissue damage in long bone fractures can cause a robust inflammatory response. We aimed to evaluate the effect of this inflammatory response caused by long bone fractures on endothelial functions in the early period.

MATERIAL AND METHODS: We prospectively researched 44 patients aged 18-60 with long bone fractures and no other disease between 2018 and 2020. We evaluated vascular endothelial function using the flow-mediated dilatation (FMD) method. Measurements obtained at the beginning of the acute fracture period and at the first month were recorded as FMD-0 and FMD-1, respectively.

RESULTS: The mean FMD-0 values were measured as 0.082±0.046 (range: 0.005-0.18). Mean FMD-1 values were measured as 0.118 ± 0.054 (range: 0.03-0.24). The mean FMD values of the patients were significantly higher in the first month (p=0.02). No significant relationship was found between other parameters such as age, gender, side, limb difference (upper, lower), and FMD results (p>0.05 for all values).

CONCLUSIONS: Severe inflammation caused by long bone fractures may lead to endothelial dysfunction in the acute period.. It should be kept in mind that endothelial dysfunction may be involved in the pathogenesis of systemic complications in the acute period after long bone fracture.

KEYWORDS: Endothelial dysfunction, Flow-mediated dilatation, Long bone fracture.

Geliş Tarihi / Received: 11.06.2025
Kabul Tarihi / Accepted: 15.10.2025
Yazışma Adresi / Correspondence: Uzm. Dr. Mehmet Ali DURSUN
Doç. Dr. Mustafa Kalemli Tavşanlı Devlet Hastanesi, Ortopedi ve Travmatoloji Kliniği
E-mail: drmehmetalidursun@gmail.com
Orcid No (Sırasıyla): 0000-0003-2679-9351,0000-0001-6964-4363
Etik Kurul / Ethical Committee: Atatürk Üniversitesi Etik Kurulu (09.06.2017/3-28).

INTRODUCTION

The endothelium is a functional barrier between the vessel wall and circulating blood cells. In a healthy endothelium, vasodilator, anti-inflammatory, antithrombotic factors, vasoconstrictor, inflammatory, and prothrombotic factors work in balance. Events that disrupt this balance can cause endothelial dysfunction (1). Clinically, any long bone fracture can have an effect that disrupts this balance. Namely, the natural course of fracture healing begins with activating many inflammatory processes (1). Regional tissue damage in long bone fractures can cause an intense inflammatory response throughout the body. The inflammatory response may be strong enough to cause systemic effects such as fat embolism syndrome (2).

Patients with long bone fractures are among the most frequently treated groups in orthopaedics and traumatology practice. The complication of deep vein thrombosis (DVT), which may develop in the post-fracture period, is still a significant problem. In the etiopathogenesis of thrombosis, coagulopathy, stasis, and endothelial damage appear as the most crucial triad (3). Considering the inflammatory response caused by long bone fractures and the pathogenesis of DVT complications that may develop afterwards, we hypothesize that vascular endothelial dysfunction occurs in the early period after long bone fractures. This study investigates whether the acute inflammatory process that develops after a long bone fracture affects endothelial function.

MATERIALS AND METHODS

Sample size

The sample size was determined by performing a power analysis before the data collection period in order to reduce type 2 errors. The required sample size was calculated using the G-power 3.1 program based on an effect size of 0.8, an error probability of 0.05, and statistical power of 0.80. The required sample size was determined to be at least 42 patients.

The data of 44 patients hospitalized in Atatürk University Faculty of Medicine orthopaedics and traumatology service between 2018-2020 due to long bone diaphyseal fractures were included in the study by prospectively recording. When selecting the sample size, the only study in the literature examining the relationship between fractures and vascular function was the study by Blum et al. FMD measurement was considered the primary outcome (4).

Inclusion criteria

Between 18 and 60 years of age, acute fracture (fracture-time to apply for a maximum of 24 hours), isolated long bone diaphysis fractures (femur, tibia, humerus, radius, ulna, clavicle).The patient's voluntary consent was to be included in the study.

Exclusion criteria

An open fracture, pathological fracture, multiple fractures, multiple system injuries, history of any additional disease or drug use, history of smoking, alcohol or substance use, poor general condition at presentation (unconscious, intubated, blood pressure below 90/60 or need for advanced cardiac support), prolonged waiting time for surgery (fracture-surgery time > two days), prolonged hospitalization (fracture-discharge time > 5 days).

Study design

The age, gender, side, extremity, and long bone fracture information of the patients who met the inclusion criteria were noted. The patients' fractures provided temporary fixation (splint, arm sling, etc.). The patients were evaluated in terms of endothelial functions by ultrasonography (USG) using the flow-mediated dilatation (FMD) technique by a specialist radiologist within the first 24 hours before any treatment was started in the radiology unit of the emergency department. The data obtained in the acute period after the fracture were recorded as FMD-0. Then, the patients were admitted to the ward by starting appropriate treatment protocols, the necessary orthopaedic treatment procedures were completed, and they were discharged. Endothelial functions were re-evaluated by repeating USGs with the FMD technique in the 1st-month post-op of all patients. The obtained data were recorded as FMD-1. This was to repeat the evaluation, waiting for the effect

of the inflammatory response secondary to the fracture healing process and surgical procedures to be minimized. Thus, it was aimed to evaluate the effect of the inflammatory process on endothelial functions. The same radiologist made all USG measurements with the same device and technique. Before starting the study, we applied this technique to healthy volunteers for six months and gained experience.

Flow-mediated dilation technique

Patients were told not to use anything that would affect the measurement, such as cigarettes, coffee, or alcohol, within 8 hours before the measurement. After 30 minutes of rest, the patients were taken to the USG room at room temperature and placed on the radiology bed in the supine position. Measurements were made from the left brachial artery in patients with right upper extremity fractures, while measurements were made from the right brachial artery in all other patients (5). Before measurement, the pre-controlled cuff was placed in the middle of the patient's forearm. Systole and diastole flows were checked with the Doppler feature of the USG device. First, the brachial artery was found from the cubital fossa and viewed proximally.

The basal view of the anteroposterior diameter of the brachial artery was obtained in a longitudinal section approximately 5-7 cm proximal to the cubital fossa **(Figure 1)**.

Figure1: We measured flow-dependent dilatation by connecting the cuff to the middle of the forearm with the patient in the supine position. The most preferred region in the literature is described as the forearm for adults

Basal diameter measurement in images recorded on video; In the longitudinal section, at the end of the diastole, just at the beginning of the P wave, the tunica media was seen, and the distance between the anterior and posterior walls of the vessel was measured and recorded. This process was performed 3-5 times for each patient, and the arithmetic average of the calculated values was taken **(Figure 2)**. After the basal diameter measurement, the cuff was inflated with a pressure of 270-300 mmHg. At this stage, the patient was told about the physiological conditions (numbness in the fingers, loss of sensation, chills, and tingling after the cuff was lowered, and increased fever). Thus, it was aimed that the patient would not move at all. After waiting for 5 minutes, the cuff was abruptly lowered, and dynamic imaging and recording began. The changing brachial artery diameter due to reactive hyperemia was calculated, especially in the 15th, 60th, and 90-second images. After 2 minutes of measurement, the recording was terminated (6). If the change in Fmd value after stress is 10% or more, it is considered normal function, and if it is below 10%, it is considered endothelial dysfunction (7).

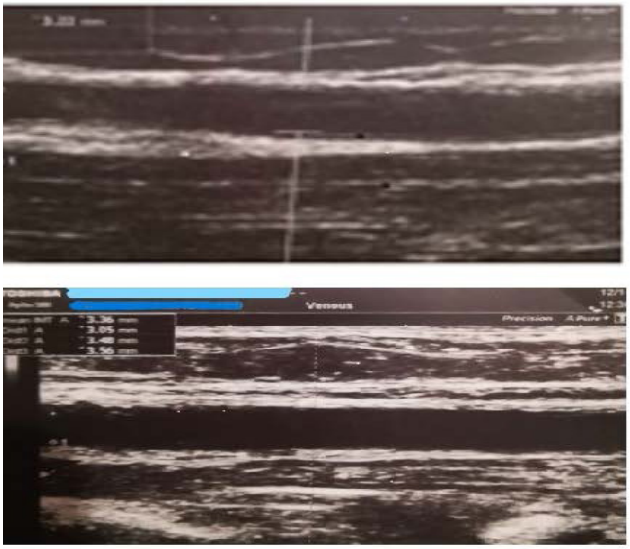

Figure 2: The basal diameter measurement at rest is calculated by taking the arithmetic average after 4-5 consecutive measurements (left picture). In most measurements, it is difficult to see both walls of the vessel wall in a longitudinal section. In the picture on the right, there is a measurement where we can see both walls.

Ethical Committee

Ethics committee approval was obtained for the study with the Atatürk University Ethics Committee Unit meeting number dated 09.06.2017: 3 decision no: 28. This study was supported by Atatürk University The Coordination Unit of Scientific Research Projects. The study design took into account the CONSORT guidelines recommended for prospective studies.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20 statistical analysis program (IBM Corp; Armonk, NY, FMD). Data are presented as mean, standard deviation, median, minimum, maximum, percentage, and count. Because the distribution of the variables did not meet normality, nonparametric tests were used. The Wilcoxon test was used for ordinal measurements. A P-value <0.05 was considered statistically significant.

RESULTS

The mean age of 44 patients was 35(range 19-57). Thirty-four (77%) of the patients were male, and ten (23%) were female. 24 (55%) of the fractures were in the lower extremity (6 femur, 18 tibia), and 20 (45%) were in the upper extremity (10 humerus, 4 radius, 2 ulna, 4 clavicle). Among the upper extremity fractures, 14 were on the left side, and 6 were on the right. Measurements were made on the left arm in 6 patients (13%) and the right arm in 38 patients (87%). The mean FMD-0 values were measured as 0.082±0.046 (range: 0.005-0.18). Mean FMD-1 values were measured as 0.118±0.054 (range: 0.03-0.24). The mean FMD values of the patients were significantly higher in the first month (p=0.02) **(Figure 3)**. 9 out of 24 patients with Fmd below 10% in the first measurement still had FMD values below 10%. There was no significant relationship between other parameters such as age, gender, side, extremity difference (upper, lower), and FMD results (p>0.05 for all). We did not find any difference in fmd values between upper and lower extremity fractures.

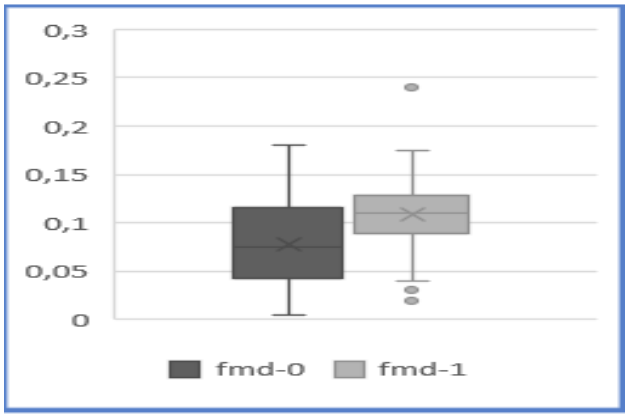

Figure 3: Fmd-1 and Fmd-0 values

DISCUSSION

In this study, we found that early endothelial functions in long bone fractures were lower than the endothelial functions in the first month. We found that this difference was unrelated to other parameters such as age, gender, side, and extremity type (upper, lower).

Endothelial dysfunction has been implicated in the pathogenesis of many diseases. Diabetes, chronic renal failure, hypertension, erectile dysfunction, preeclampsia, polycystic ovary syndrome, coronary artery diseases, and deep vein thrombosis are associated with endothelial dysfunction (8,9). In particular, inflammatory processes are closely related to endothelial dysfunction (10). Therefore, considering inflammatory processes, one of the causes of vascular endothelial dysfunction, we predicted that inflammation secondary to bone fracture may also impair vascular endothelial functions. Because local tissue damage that starts as soon as a long bone fracture occurs can create a systemic inflammatory response, this inflammation may be severe enough to cause systemic complications such as pulmonary embolism, renal failure, or fat embolism syndrome (11).

The only study on fracture and endothelial dysfunction was performed on patients with only one long bone and completely healthy volunteers without any additional disease. The author showed that long bone fractures cause severe inflammation, especially in the first week, with vascular measurements showing both the FMD method and the ankle-brachial index (12). Comparing vascular measurements within three days after fracture presentation and comparing with the control group, the author suggested that inflammation during the fracture caused endothelial dysfunction. In our opinion, the most critical shortcoming of this study is that vascular measurements are not repeated after the inflammation phase is over in patients presenting with fractures. If vascular measurements were repeated after the inflammatory phase or the severe period of inflammation had passed, some patients thought to be due to long bone fractures would have continued to have endothelial dysfunction. As it is known, endothelial

dysfunction can occur without an underlying problem, so we applied the FMD method again to all patients at the 1st-month follow-up. The fact that 9 out of 24 patients with Fmd below 10% in the first measurement still had FMD values below 10% at one month supports this view.

Although the etiology of deep vein thrombosis is still unclear, the most accepted is mechanical or biochemical damage to the vascular endothelium (13). The increase of antioxidants, inflammatory mediators, and coagulation imbalance can damage the vessel wall (14). Long bone fractures cause severe inflammation and damage to the vascular endothelium and pose a risk for deep vein thrombosis by causing stasis due to immobilization in lower extremity fractures (15). Our study did not find any difference in fmd values between upper and lower extremity fractures, but this may be the subject of another study with sufficient and homogeneous patients.

Endothelial dysfunction may begin before symptoms appear at the onset of diseases. This situation has been the subject of many studies in the literature (15-17). The authors emphasized the importance of early diagnosis of endothelial dysfunction. They stated that inexpensive, reproducible reliable tests can be used in large populations, and appropriate screening tests can be used in at-risk individuals (10). A more careful approach may be required regarding systemic complications that may occur in long bone fractures in patients with existing endothelial dysfunction, and this group of patients is waiting to be investigated in terms of this issue.

This study was planned as a clinical study, and standardization could not be established such that all patients had the same age and fracture type. The fractures belonged to different bones of patients of different ages and genders, and the treatment procedures were also different. Standardization of all conditions is only possible with experimental animal studies. All non-standardized conditions among patients may affect the results, which is our study's major limitation. Homogeneous age and gender distribution of the patients, having the same fracture type, and using the same method in the treatment will be a choice that increases the level of evidence. Another study limitation is that the FMD technique was applied with manual probes. Methods using arm holders, automatic probes, and continuous video recording should be preferred for more standardized results. İn addition if there were an another radiolog this study would more stronger because about bias. Another study limitation is that lack of control group.

We found that patients with long bone fractures were exposed to endothelial dysfunction in the acute period. Long bone fractures may cause vascular endothelial dysfunction in the early period. Therefore, fractures in patients with vascular pathology and endothelial dysfunction may trigger or increase the risk of many different complications. The clinical implications of fracture inflammation's ability to affect vascular functions remain to be investigated.

REFERENCES

1. Maruyama M, Rhee C, Utsunomiya T et al. Modulation of the Inflammatory Response and Bone Healing. Front Endocrinol (Lausanne). 2020;11:386.

2. Blokhuis TJ, Pape HC, Frölke JP. Timing of definitive fixation of major long bone fractures: Can fat embolism syndrome be prevented? Injury. 2017;48(1):3-6.

3. Ahmed S, Zimba O, Gasparyan AY. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. Clin Rheumatol. 2020;39(9):2529-43.

4. Blum A, Zarqh O, Peleg A et al. Vascular inflammation and endothelial dysfunction in fracture healing. Am J Orthop (Belle Mead NJ). 2012;41(2):87-91.

5. Padilla J, Johnson BD, Newcomer SC et al. Normalization of flow-mediated dilation to shear stress area under the curve eliminates the impact of variable hyperemic stimulus. Cardiovasc Ultrasound. 2008;4 (6):44.

6. Thijssen DHJ, Bruno RM, van Mil ACCM et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 2019;40(30):2534-47.

7. Riou M, Oulehri W, Momas C et all. Reduced Flow-Mediated Dilatation Is Not Related to COVID-19 Severity Three Months after Hospitalization for SARS-CoV-2 Infection. J Clin Med. 2021;10(6):1318.

8. Bulbul E, Aydin E, Yilmaz E. Evaluation of endothelial dysfunction with cardio-ankle vascular index measurements in patients with erectile dysfunction. Andrology. 2022;10(5):926-30.

9. Dertsiz Kozan B, Karataş Durusoy G, Atkın MS, Utlu B. Diyabetik Retinopatili Hastalarda Cinsel Disfonksiyon Sıklığının Değerlendirilmesi. Kocatepe Tıp Dergisi. 2025;26(3):203-6.

10. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol. 2008;103(5):398-406.

11. Kobbe P, Micansky F, Lichte P et al. TraumaRegister DGU. Increased morbidity and mortality after bilateral femoral shaft fractures: myth or reality in the era of damage control? Injury. 2013;44(2):221-5.

12. Stone J, Hangge P, Albadawi H et al. Deep vein thrombosis: pathogenesis, diagnosis, and medical management. Cardiovasc Diagn Ther. 2017;7(3):276-84.

13. van den Oever IA, Raterman HG, Nurmohamed MT, Simsek S. Endothelial dysfunction, inflammation, and apoptosis in diabetes mellitus. Mediators Inflamm. 2010;2010:792393.

14. Bahloul M, Dlela M, Bouchaala K Post-traumatic pulmonary embolism: incidence, physiopathology, risk factors of early occurrence, and impact outcome. A narrative review. Am J Cardiovasc Dis. 2020;10(4):432-43.

15. Charfeddine S, Ibn Hadj Amor H, Jdidi J et al. Long COVID 19 Syndrome: Is It Related to Microcirculation and Endothelial Dysfunction? Insights From TUN-EndCOV Study. Front Cardiovasc Med. 2021;30(8):745758.

16. Tomimatsu T, Mimura K, Matsuzaki S, et al. Preeclampsia: Maternal Systemic Vascular Disorder Caused by Generalized Endothelial Dysfunction Due to Placental Antiangiogenic Factors. Int J Mol Sci. 2019;30(17):4246.

17. Perico L, Benigni A, Casiraghi F et all. endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 202;17(1):46-64.