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Fat embolism syndrome in patients with bilateral femur fractures: a systematic review and case comparison

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Abstract

Objectives: Fat embolism and fat embolism syndrome (FES) remain common complications following long bone fractures. Incidence is highest after bilateral femur fractures. We performed a systematic review of FES after bilateral femur fractures and present two cases.

Data sources: Systematic literature search of the Cochrane, EMBASE, MEDLINE, Scopus, and, Web of Science Library databases was performed in August 2021. Terms used including plural and alternate spellings: "fat embolism,""fat embolism syndrome,""fat embolus," and "bilateral femur fracture." Articles in German and English were considered. No time frame was applied.

Study selection: Original studies, case series and case reports on fat embolism after bilateral femur fracture were included. Insufficient documentation or patients with relevant previous heath conditions were excluded.

Data extraction: Abstracts were organized using EndNote X9 by Carivate. Three authors independently screened the abstracts; cross check of the extracted data was performed by the senior author.

Data synthesis: Scarcity of articles only allowed for a qualitative synthesis. Data was compared with our cases and situated within the scientific background.

Results: Ten articles were included for qualitative synthesis ($n = 144$ patients). The symptoms were inhomogeneous with neurological deficits being most prominent. Degree of displacement was high, when reported. Although the modes and timing of surgery varied, this appeared unrelated with outcome.

Conclusions: FES remains a relevant complication after bilateral femur fractures, despite damage control strategies and improved reaming techniques. Fracture displacement and reduction maneuvers might play a more substantial role in the formation than previously accredited.

Level of evidence: 4

Keywords: bilateral femur fracture, fat embolism, fat embolism syndrome, femur fracture, long bone fracture, trauma

1. Introduction

Fat embolism is an ongoing clinical problem in patients with acute trauma and long bone fractures.[1] It is mainly caused by intravasation of bone marrow fat and often occurs during/after intramedullary reaming and nailing in diaphyseal femur fractures.[2]

Symptoms of fat embolism differ in severity and expression depending on the location of embolization, with the lung and the brain being the most vulnerable organs.[3] Before fat embolism was identified as caused by unstabilized fractures, the diagnosis was difficult to make and the direct proof of fat droplets by ophthalmoscopy was required. Along with better understanding of the pathophysiology, it became evident, that fat can affect the function of other organs. This led to a change in terminology and a full-blown systemic manifestation was defined as fat embolism syndrome (FES).[4] Radiographically, FES can be diagnosed through ground glass opacities and thickened interlobular septa in a computed tomography-thorax[5] and in the brain by ischemic microlesions in magnetic resonance imaging.[6]

Meek et al proved in an elegant study as early as 1972 that fat globules can be found in the femoral vein after femur fractures.[7] Further studies then suggested that multiple reaming steps, or a

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difficult reduction are of utmost significance in the development of fat embolism, as all these maneuvers lead to intravasation of intramedullary contents.[8–13] Heat generation and osteonecrosis also occurred with early reamer designs, but have been mitigated by changes in reaming technique and reamer design.[14,15] Further focus was laid on the intramedullary pressure increases during reaming as a factor of acute embolization,[16] and that multiple reaming steps can cause a piston effect.[16] Although similar pressure increases may be achievable by a single pass reaming or unreamed nailing[17], the sum of reaming steps induces a higher volume of fat intravasation, just by repeated piston effects.[18] Intraoperative transesophageal echocardiography proved that solid contents are transported into the lung[19] and the initial fatty thrombus is surrounded by platelet aggregation during the passage through the venous system.[20] These changes are accompanied by pulmonary artery pressure increases during reaming.[21] Further studies also proved the influence of the reamer head architecture.[22]

Our group recently hypothesized that the clinical problem of FES has changed along with techniques of ventilation, resuscitation and the technical aspects of reaming.[23] Interestingly, the incidence of FES has decreased from almost 8% to close to 2% since its initial description, especially after the year 2000.[23] Pathological fractures were associated with a higher incidence of FES when compared with traumatic fractures and bilateral fractures (traumatic and pathological) were associated with a higher incidence of FES than unilateral fractures.[23] It is unclear from the literature however, if the reaming alone, the degree of fracture displacement or fat intravasation during reduction play a role and which factor is most relevant.

We, therefore, performed a systematic literature review of bilateral femur fractures and fat embolism that focuses on these particular issues. In addition, we present 2 almost identical cases that developed postoperative FES despite the absence of particular risk factors and review the possible underlying pathophysiological causes.

2. Methods

2.1. Part I: systematic literature review

2.1.1. Methods. We conducted a systematic literature review, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24] The aim was to identify all publications regarding fat embolism (syndrome) after bilateral femur fractures. A systematic literature search of the Cochrane, EMBASE, MEDLINE, Scopus, and Web of Science Library databases was conducted in August 2021. The terms used were: "fat embolism," "fat embolism syndrome,""fat embolus," and "bilateral femur fracture," as well as plural forms and alternate spellings. Terms were truncated and connected by Boolean operators.

Additionally, we screened the references lists of selected studies and of related systematic reviews, to identify any relevant studies missed by the electronic search.

Search results were extracted and documented using EndNote X9 by Carivate. Articles were then de-duplicated and screened independently by 3 authors (YKA, TS, and YKU). A cross check of the extracted data was performed by the senior author (HP). Any disagreement was resolved by a consensus discussion in personal meetings.

2.1.2. Inclusion/exclusion criteria. Due to the scarcity of reports on the matter, we included original studies as well as case reports on a healthy adult trauma population with bilateral femur fractures, if they included the diagnoses "fat embolism" or "fat embolism syndrome." Studies should be reported in English or German and describe trauma mechanism, means of fracture fixation and describe symptoms, complications, or mortality. Reviews, letters, commentaries, correspondences, conference abstracts, expert opinions, editorials, in vitro, and animal experiments were excluded. Further exclusion criteria were insufficient documentation or patients with relevant previous heath conditions (ie, oncological, neurological, or pulmonary diagnoses).

2.2. Part II: case reports with fat embolism after bilateral femur fracture

We review 2 cases of bilateral femur fractures that—in the absence of cofactors—developed postoperative FES and required prolonged artificial ventilation. Case 1 was treated by bilateral closed reduction and external fixation while Case II was treated by retrograde nailing. Their clinical course is described in the Appendix, http://links.lww.com/OTAI/A35.

3. Results

Our search yielded 36 articles after the removal of duplicates. Following initial screening of title and abstract, 14 full text articles were retrieved and assessed for eligibility. Of these, ten met our criteria and were thus included. A flowchart illustrating the selection process can be seen in Figure 1. Out of the 10 remaining articles, 2 were retrospective cohort studies. Therefore, our review includes 129 patients with bilateral femur fractures that were all treated with reamed antegrade[25]—or retrograde nailing.[26] Out of these, 6 developed FES, yet only little information was provided on concomitant chest injury, degree of fracture displacement, time to surgery, or outcome.

The remaining 8 articles were case reports/series discussing a total of 15 patients. Mean age was 26years. Trauma mechanism was almost exclusively motor vehicle accidents. Two patients had a reported chest injury (unknown degree) and other relevant concomitant injuries were reported in 11 patients. Preoperative X-rays were presented in 5 of the 8 studies and all showed severe displacement—at least unilaterally. Time to surgery ranged from <6 hours to >24 hours. Means of fixation included external fixation, reamed nailing or a combination of the 2. Five of the 8 cases describe neurological worsening as the foremost symptom. Overall, 1 patient suffered complete paraplegia sub thoracic vertebra No 9 due to a spinal embolus and 1 patient died from generalized cerebral edema. All other patients made a full recovery. A synopsis of all data is presented in Table 1.

4. Discussion

Although perioperative fat embolism in current clinical practice can be overcome and appears to be less of a life-threatening complication, it continues to be unexpected and its reasons can be multifactorial.[13,23] In this light, it continues to be unclear if the reaming for preparation of intramedullary nailing, the closed or open reduction, or other cofactors play a role.

On 1 hand, our case reports are similar, as 2 different centers selected healthy patients without chest trauma, as the effects of intravasation are known to be augmented with associated chest injuries.[27] In both cases, the patient was extubated after initial fixation. One center selected external fixation to avoid reaming

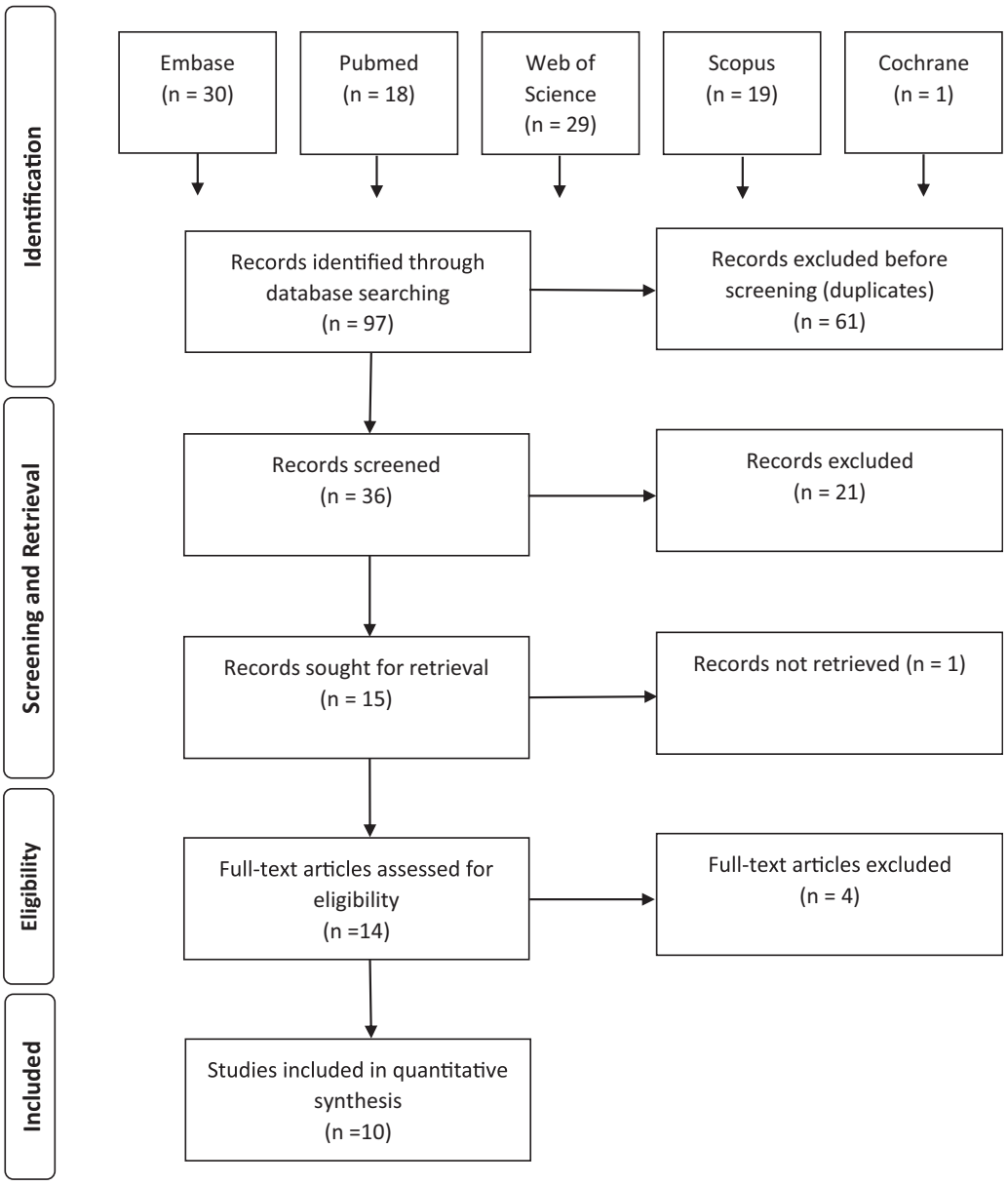

Figure 1. Flowchart illustrating the study selection process.

and 1 center selected retrograde intramedullary nailing to avoid the anterograde piston effect. Both patients appeared to be stable and in good clinical condition preoperatively and demonstrated a delay between extubation and clinical symptoms. In both patients, the neurologic deficit represented the initial cause of concern rather than cardiopulmonary worsening. A synopsis of both cases is presented in Table 2. The case undergoing external fixation was worked up for patent foramen ovale, which was negative. Both patients underwent a work up for coagulopathy and other causes. Both patients presented with severely displaced fractures, while reduction was not particularly difficult. One may, therefore, wonder, if in the patient undergoing external fixation during the evening of admission, hidden hypovolemia may have been the reason for hypercoagulopathy, which was not particularly tested for. Likewise, one may argue that in the patient undergoing bilateral nailing, intraoperative embolization may have played a role. In this retrospective evaluation, it cannot be determined, which aspect is more relevant.

Similar results were revealed by our systematic review. While FES is described as a nonhomogeneous combination of symptoms, neurological deficits are usually the most noticeable. Fractures seem to be mostly severely displaced, as discussed by Ten Duis et al.[13] However, information is too scarce to draw conclusions regarding the role of reduction or the intraoperative course.

In terms of physiological aspects, although the lung can tolerate a certain degree of fat embolization by opening arteriovenous shunts[28] and has a tremendous reserve capacity,[29] secondary mechanisms have been known to occur even after a long time, characterized by additional inflammatory stimuli inside the pulmonary vasculature.[30] Moreover, activation of the coagulation cascade has been described in association with the fat intravasation[31] and, therefore, secondary worsening can occur.[32]

Interestingly, we have failed to find any clinical study that compares these approaches, or discusses clear cut evidence of the relevance of either[23] The only available study that examines both procedures in the absence of chest injury has used an animal

Table 1

Synopsis of the included studies.

Title	Author	Year	Study type	n =	Age	Gender (f/m)	Injury mechanism	Chest injury	Other relevant injuries	Displacement	Time to surgery	Initial operation	Symptoms	Outcome
Fat embolism due to bilateral femoral fracture: a case report	Porpodjs et al	2012	Case report	1	20	0/1	Car accident	no	n.a.	n.a.	9 hours	Reamed nailing	NO R1 P1	Full recovery
Case report-cerebral fat metabolism syndrome after bilateral femoral fracture	Wöhler et al	2013	Case report	1	20	0/1	Car accident	No	Yes	n.a.	<6 hours	External fixation	N1 R1 P1	Full recovery
Bilateral femoral shaft fractures complicated by fat and pulmonary embolism: a case report	Randelli et al	2015	Case report	1	25	0/1	Car accident (pedestrian)	No	No	Yes	>24 hours	External fixation	N1 R1 PO	Full recovery
Fat emboli syndrome and the orthopaedic trauma surgeon: lessons learned and clinical recommendations	Dunn et al	2017	Case report	1	18	1/0	Motorcycle accident	No	Yes	Yes	<6 hours	External fixation (left) reamed nailing (right)	N1 RO PO	Full recovery
The fat embolism syndrome as a cause of paraplegia	Peters et al	2018	Case report	1	19	0/1	Car accident	No	Yes	n.a.	<6 hours	External fixation	N1 R1 P1	Complete paraplegia subT9
Fatal Cerebral Fat Embolism After Pelvic and Multiple Long Bone Fractures without Associated Lung Injury: A Case Report	Hadden et al	2020	Case report	1	29	1/0	Car accident	Yes	Yes	Yes	<6 hours, 48 hours	External fixation - then reamed nailing	N1 RO P1	Death (generalized cerebral edema)
A 21 -year-old Pregnant Trauma Patient with Asymptomatic Fat Embolism; a Case Report	Ayoobi-Yazdj et al	2020	Case report	1	21	1/0	Car accident	Yes	Yes	Yes	2nd day	Reamed nailing	NO R1 PO	Full recovery
Early intervention v/s delayed Intervention? Dilemma In bilateral shaft femur fractures with evolving features of fat embolism - Damage control nailing	Murthy et al	2021	Case serles	8	30 (16–38)	n.a.	Mixed (high energy mechanisms)	n.a.	6/8	Yes	24 to 48 hours	Unreamed nailing	n.a.	Full recovery
Risks and results after simultaneous Intramedullary nailing In bilateral femoral fractures: A retrospective study of 40 cases	Bonnevialle et al	2000	Retrospective cohort	2/40	27.8 (17–50)	(13/27)	Mixed	n.a.	n.a.	n.a.	91.2 hours	Reamed antegrade nailing	n.a.	Mortality 2/40
Retrograde Intramedullary nailing In treatment of bilateral femur fractures	Cannada et al	2008	Retrospective cohort	4/89	30 (16–63)	(43/46)	Almost exclusively motor vehicle accidents	(35/89)	(85/89)	n.a.	n.a.	Reamed retrograde nailing	n.a.	Mortality 5/89

(Symptoms: n = neurological, r = respiratory, p = petechial rash), T9 = Thoracic vertebra No 9.

Table 2

Synopsis of both case reports.

Case	Age	Gender	Injury mechanism	Chest injury	Other relevant injuries	Arrival	Displacement	Time to surgery	Initial operation	Post OP examination	Development of symptoms	Symptoms	Time to discharge	Outcome
Ex-fix (case 1)	19	Male	Motorcycle accident	No	No	Stable	Left> right	Immediately	Bilateral external fixation	Stable	12 to 24 hours	N1 R1 P0	18 days	Full recovery
Reamed nailing (case 2)	18	Male	Motorcycle accident	No	Floating elbow (left)	Stable	Bilateral	Next morning	Bilateral reamed nailing	Stable	12 to 24 hours	N1 R1 P0	13 days	Full recovery

(Symptoms: n=neurological, r = respiratory, p = petechial rash).

model.[33] The authors found that the total embolic load was significantly higher in the intramedullary nailing group, but the type of fracture stabilization used did not significantly affect any of the other outcome measurements: they concluded that a higher pulmonary embolic load can be expected during early intra-medullary femoral fracture stabilization compared with primary external fixation. However, the degree of stimulation to systemic coagulation and pulmonary inflammation by each type of surgery was comparable.

Another experimental study did include a lung contusion in their setup and found that secondary changes (pulmonary permeability, coagulopathy, and neutrophil stimulatory capacity were more sustained at 4 hours after injury in the reamed nailing group.[34]

There are 3 theories attempting to explain the pathogenesis of FES: they are the Mechanical theory, the Biochemical theory and the coagulation theory.

Gauss proposed the mechanical theory, which suggests that fractures result in the extrusion of fat droplets via damaged venules into venous circulation.[35]

This occurs when the intramedullary pressure is greater than the venous pressure at a fracture site. These fat droplets travel to the pulmonary capillary bed of the lungs to cause mechanical obstruction resulting in the pulmonary manifestations of FES. The passage of "echogenic material" passing through the right atrium as detected by Pell et al[36] with transesophageal echocardiography during intramedullary nailing of fractures would seem to support this theory. For fat embolism (FE) to affect other organs, they must cross from the venous to arterial circulation. There are a number of potential routes by which this may occur.

Fat emboli can be small enough to directly pass from venous to arterial circulations in the lungs, moreover even the larger droplets can potentially undergo a significant amount of deformation and are, therefore, able to cross to the arterial circulation.[37] Arteriovenous shunts within the pulmonary circulation have been demonstrated by several studies and may be a potential route for FE to cross into the arterial circulation.[38]

The presence of a Patent Foramen Ovale has been discussed as a potential cause of more sustained cerebral embolisms. Some authors discuss the Patent Foramen Ovale can be present in up to 34% of the adult population, and the rise in right atrial pressure in these patients from the effects of FE on the lungs or indeed mechanical ventilation of the patient.[39]

The mechanical theory does have limitations as it does not explain the development of FES in patients without trauma nor does it explain the typical delay of onset of FES of 24 to 72 hours from the initial trauma.

Lehman and Moore proposed a biochemical theory, focusing on breakdown of neutral fat droplets upon entering the venous circulation undergoing degradation to Free Fatty Acids (FFA), which are considerably more biologically active.[40] FFA's have been shown to cause damage to capillary beds of lungs.[41] The increased levels of catecholamines used in patients with major trauma can induce further lipolysis resulting in increased levels of FFA's. The time taken for the production of these FFA's may explain the time delay seen for the onset of FES after trauma. It has been suggested that raised levels of "C-Reactive Protein," which is elevated in these patients, may cause circulating Chylomicrons, the soluble form of triglycerides, to agglutinate into fat globules. This process may explain the presence of FE in the lungs of patients without trauma.[41]

The coagulation theory suggests that thromboplastin is released along with fat from injured long bones activating the clotting cascade. The resulting fibrin and its degradation products, platelets and fat globules have a direct toxic effect on endothelial lining and increase the permeability of the pulmonary capillaries. The finding of intravascular coagulation is frequently seen in cases of FE. It has been shown that the release of fat into the circulation activates intravascular coagulation with platelet aggregation and clot formation.[42] The procoagulant properties of the released fat is thought to be due to the presence of Tissue Factor, which in turn triggers generation of Thrombin and subsequent formation of fibrin and activation of platelets.[43]

We conclude, that FES continues to represent a relevant complication even in patients without additional risk factors. We also concur that despite extensive research, clinicians appear to be unaware of imminent risks of FES and that despite improvements in reaming techniques, the complication has not been ruled out. Moreover, it continues to occur even when intramedullary instrumentation is avoided completely. Although, in current clinical practice, pulmonary consequences of FES can be managed most often by ventilator support even though prolonged intensive care unit stays may ensue[33,37,44,45] surgeons should continue to be aware of this complication.

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