Title page

Surgical results of atypical femoral fractures in long-term bisphosphonate and glucocorticoid users – relationship between fracture reduction and bone union in 12 cases

Tomofumi Nishino, Kojiro Hyodo, Yukei Matsumoto, Yohei Yanagisawa, Tomohiro Yoshizawa, Masashi Yamazaki

Department of Orthopaedic Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

Please address all correspondence to: Tomofumi Nishino

Department of Orthopaedic Surgery, Faculty of Medicine, University of Tsukuba

1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan

Phone: +81-29-853-3219 Fax: +81-29-853-3162 E-mail: nishino@md.tsukuba.ac.jp

Keywords

Atypical femoral fracture, Bisphosphonate, Glucocorticoid, Surgical results, Fracture reduction

Abstract

Atypical femoral fracture (AFF) associated with bisphosphonate (BP) use is common, and its pathophysiology is considered to involve severely suppressed bone turnover. Surgical results following AFF fixation have not been optimal, with some cases resulting in delayed union or nonunion. Regarding bone healing, glucocorticoid (GC) has similar properties to BP. We investigated the surgical results of AFF fixation in both users of BP and GC, especially with regard to intraoperative fracture reduction.

We included 12 AFFs in 11 patients with a follow-up over one year who all took GC for autoimmune disease and BP for management of GC-induced osteoporosis. Their mean age was 62 years and 10 patients were female. Six fractures were located in the subtrochanteric region of the femur and six were in the diaphysis. Intramedullary nails were used to treat all fractures. Union rate was recorded, and the status of the reduction immediately after the operation was analyzed.

Four of the 12 cases developed nonunion, and three of them required additional surgery. The relationship between alignment, cortical continuity, fracture gap, and bone union was

not significant. In the nonunion cases, cortical continuity on the anteroposterior and lateral views were never confirmed. Even if cortical continuity in either of the views was there, the two limbs resulted in nonunion.

One third of the patients with AFF secondary to long-term BP and GC use developed nonunion despite their fracture reductions being acceptable. We consider it necessary to provide some possible solutions such as biological adjuvant treatments as well as anatomic fracture reductions in these cases.

Text

Introduction

Glucocorticoids are used widely as a treatment for various inflammatory, immune, and allergic diseases. Osteoporosis is one of the important side effects of long-term GC use, and is associated with an impairment in activities of daily living when fragility fractures occur. Furthermore, fragility fractures are considered to be directly associated with mortality [1, 2]. Bisphosphonate (BP) use is recommended in the Japanese guidelines for the management and treatment of glucocorticoid (GC)-induced secondary osteoporosis [3]. BP use can suppress the activity of osteoclasts, but long-term use of BP is associated with a phenomenon called severely suppressed bone turnover (SSBT) [4], which can result in atypical femoral fracture (AFF). Even if BP use is discontinued, a prolonged period is necessary for bone union due to its pathophysiology, and cases of nonunion have been described. In addition, GC use has also been shown to disturb fracture healing. We considered the surgical results and fracture reduction in AFF patients who had long-term both BP and GC use.

Materials and Methods

Subjects

Twelve consecutive limbs in 11 patients who were operated on for AFF in our institution with a minimum follow-up of one year were included this study (Table 1). One patient received a bilateral operation because she injured both sides (cases #7 and #8). The diagnosis of AFF was made in cases that fulfilled the criteria of the second task force of American Society for Bone and Mineral Research (ASBMR) [5]. During this period, all of the AFF patients had received GC treatment for prevention or treatment of GC-induced osteoporosis. The mean follow-up period was 50 months (15-81), including the two patients who died (cases #1 and #2). A fracture lesion of the contralateral side was seen in nine patients, and one of these limbs (case #5) had already fractured and had been treated with an intramedullary nail at another institution. Prodromal symptoms such as thigh pain and dullness occurred in nine limbs. BP was prescribed for all patients and the mean duration of BP use was 75 months (range, 48 -120 months). The type of BP was

changed in three patients over the treatment course. Alendronate was used for all patients except one during the dosage period. No cases of lateral bowing of the femur [6] were observed on X-ray imaging. Table 2 shows the bone-related markers and bone density measured by DEXA (dual-energy X-ray absorptiometry) in this series. However, all of the results could not be provided, and the data are shown for reference.

Study design

As a general rule, a cephalomedullary long nail was used for fractures in the subtrochanteric and proximal portions of the femoral diaphysis and an antegrade intramedullary nail was used for fractures in the central and distal part of the femoral diaphysis. Surgeries were performed on a radiolucent fracture table and anatomic reductions were attempted using various methods. The nails were generally inserted closed after over-reaming at least 2 mm and locked using a lag screw that was placed into the femoral head and neck or from the greater to the lesser trochanter depending on the nail type. Additional operative procedures such as open reduction, bone grafting using reamed bone from the proximal femur, and drilling were added if needed. Postoperatively,

the patients were allowed to be weight-bearing as tolerated and were followed at standard follow-up intervals of 1 month, 3 months, 6 months, and 1 year by the treating surgeons. We retrospectively documented treatment modalities and additional procedures, adjuvant therapies, alignment after reduction, cortical continuity, fracture gap, correction loss, time to healing, and nonunion. Alignment was determined by the evaluation of Egol et al. [7], and malreduction was defined as an alignment greater than 10 degrees in each direction. Cortical continuity was defined as an overlap of each cortical fragment and a fracture gap less than one mm (Fig. 1). If the cortices did not overlap, the direction of translation was documented. A fracture gap was deemed to be present when bone defects more than one mm were present between the two fragments on the anteroposterior (AP) and lateral views. A loss of reduction was defined as greater than two degrees of angulation change between immediate postoperative radiographs and those taken more than 6 months after surgery on the AP and lateral views. Radiographic healing was defined as bridging across three or four cortices and/or a loss of a visible fracture line based on standard AP and lateral views. In cases that resulted in nonunion, the type of nonunion was classified based on

the work of Weber and Cech [8]. A determination of fracture healing was made by the treating surgeons (TN, YM). Informed consent was obtained from all patients, who approved the use and publication of their data. This retrospective study was approved by our institution's ethics review board.

Statistical analysis

We analyzed whether there was a statistically significant difference in bone union with or without malreduction. Fisher's exact test was used to evaluate the significance of the independent variables. The significance level was set at $\alpha = 0.05$. All statistical analyses were performed using Statcel 3 software (OMS, Saitama, Japan).

Results

All of the results are summarized in Table 3. Low-intensity pulsed ultrasonography (LIPUS) and teriparatide were used as adjuvant therapy. Open reduction and bone grafting were used in two cases and drilling for three cases. LIPUS was used for seven cases after case #5 and teriparatide was used in five cases after case #7 excluding a case where a side

effect occurred due to the agent. Regarding malalignment on X-rays, varus was seen in two limbs on the AP view and extension was seen in one limb on the lateral view. Regarding cortical discontinuity on X-rays, the distal fragments in three limbs were translated medially on the AP view and those in eight limbs were translated posteriorly in the lateral view. Complete contact of each fragment on both the AP and lateral views was confirmed in one limb. However, contact of each fragment on both views was never confirmed in two limbs.

Bone union was confirmed in eight limbs at the final follow-up (Fig. 2). The duration to bone union was 6 months at the earliest in three limbs and 2 years at the latest in one limb. Nonunion was confirmed in four limbs and implant failure was observed in two limbs. One limb developed hypertrophic nonunion (#6) with correction loss on both views and underwent dynamization [9] with removal of a distal locking screw at 20 months after the primary surgery, and eventually achieved bone union. In one atrophic nonunion case (#3) where a cephalomedullary long nail had been used to treat a subtrochanteric fracture, implant failure was observed at 18 months after the primary surgery (Fig. 3). The revision

surgery was performed by replacing the inserted failed nail with another type of cephalomedullary long nail. Bone union occurred at 6 months after the revision surgery. One atrophic nonunion case (#10) developed implant failure, even though all of the additional procedures were added (Fig. 4), and the failed implant was replaced by a femoral prosthetic component with a hook plate. Another atrophic nonunion case (#7) was observed conservatively because of only mild symptoms and no implant failure.

The relationships between reduction alignment and bone union were not significant on the AP ($p = 0.58$) or lateral view ($p = 0.67$). The relationships between cortical continuity and bone union were also not significant on the AP ($p = 0.24$) or lateral view ($p = 0.42$). A significant difference was not seen whether or not there was a fracture gap ($p = 0.58$) at the reduction site. A limb where cortical continuity of each fragment was confirmed on both the AP and lateral view resulted in union at 18 months after surgery. There was not a significant relationship between complete reduction and results ($p = 0.67$). All of the two limbs where cortical continuity of each fragment was not confirmed on both views resulted in nonunion. These tended to go on to nonunion ($p = 0.09$). Moreover, there was

no significant relationship between bone union and fracture location ($p = 0.73$) or the kind of implant ($p = 0.73$).

Discussion

Much evidence for the treatment of osteoporosis has accumulated since the development BP, and the usefulness and efficacy of BP is no longer doubted. However, some problems with this treatment remain. In 2005, Odvina et al. reported five femur fractures that suddenly developed during the treatment of nine non-vertebral fractures with alendronate [4]. A concept called SSBT, where the material properties and the strength of the bone were adversely affected by control of bone metabolic turnover, was described for the first time. In 2008, Lenart et al. observed 15 femoral shaft fractures among postmenopausal women treated with alendronate and 10 of them were transverse fractures with beaking of the lateral cortex. They described these fractures as atypical femoral fractures [10]. As a result of these reports, the definition of this was completed at the ASBMR taskforce in 2010 [11], and a second taskforce focusing on pathophysiology was announced in 2013 [5].

As mentioned above, the pathophysiology of AFF was at first thought to be related to BP use. However, BP use was not included as one of the major features of the first ASBMR taskforce in 2010, and only as one of the minor features involving the use of pharmaceutical agents. In the second ASBMR taskforce in 2013, the use of pharmaceutical agents was excluded from even being a minor feature involved with AFF. GC was one of the pharmaceutical agents that was included in the first ASBMR taskforce in addition to BP. GC activates a chronic increase in osteoclasts and a suppression of osteoblasts. It also induces osteocyte apoptosis [12]. It is unknown whether this alone causes AFF, but it is certain that GC is one of the agents that is able to suppress bone metabolism. However, it has been proven that BP decreases fracture risk associated with GC by suppressing the osteoclast activity [13]. Therefore, it is established in the Japanese guidelines to use BP for prevention and treatment of GC-induced osteoporosis [3]. In the guidelines, alendronate and risedronate were given an A recommendation.

In this study, all of the patients had taken GC chronically for autoimmune diseases and they had also taken BP for management of GC-induced osteoporosis. Both GC and BP

are considered to be causes of AFF due to the suppression of bone healing. The results of our treatment were generally considered poor; four limbs developed nonunion and another eight limbs required a long time for bone union to occur. In other words, one third of the cases were considered to have a poor outcome. In typical femur fractures, the nonunion rate has been reported to be 1-5% for fractures of the diaphysis and 3-15% for subtrochanteric fractures [14-19]. However, in cases of AFF, the exact rate has not been identified, but the rate of delayed union and nonunion is thought to be higher [11, 20, 21]. Our results supported these previous findings. Therefore, biological and bone metabolism factors may greatly affect the results.

Considering the surgical methods for AFF, we used intramedullary nails based on the recommendation of the ASBMR taskforce [11]. Intramedullary nails were also recommended for complete fractures in a systematic review by Koh et al. [22]. We performed adequate reaming for all of the cases, with as much as two mm or more of over reaming. More importantly, we attempted to perform anatomic reduction and compression of each fragment intraoperatively when possible. However, reduction is

often difficult because the medullary cavity stiffens and intramedullary canal flaring exists in AFF cases, and a guide pin tends to move eccentrically due to this.

An anatomic reduction is essential in the treatment of many fractures, but has not been advocated for thus far in the treatment of AFF. Although our study only included a few cases, this is the first report to describe the detailed reduction status with respect to the treatment results. Because there were only a few cases in this study, inadequate reduction with cortical discontinuity on both AP and lateral views tended to result in nonunion. Therefore, we must certainly attempt to avoid inadequate reductions. The difference was not statistically significant, but we should nevertheless aim to perform accurate anatomic reductions in surgery.

There were cases that developed nonunion despite acceptable reductions in this study. These cases were considered to have problems associated with reduction status and bone metabolism in the suppression of bone formation. AFF cases associated with both GC and BP treatment should be considered for augmentation with biological treatments. In addition to the adjuvant therapies provided in this study, we should also consider

possibilities of other bioactive adjuvant therapies such as cellular therapy and extracorporeal shock wave therapy [23-25]. Thus, we believe that more accurate anatomic reduction in surgery and some kind of biological adjuvant is needed for ideal treatment of AFF associated with long-term BP and GC use.

In conclusion, a one-third of AFF cases associated with long-term BP and GC use developed nonunion even if their fracture reductions were acceptable. We consider it necessary to provide some possible solutions such as biological adjuvant treatments as well as anatomic fracture reductions in these cases.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical Approval

This retrospective study was approved by our institution's ethics review board.

Acknowledgment

We thank Peter Mittwede, MD, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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Figure legend

Fig. 1. Definition of cortical continuity of each fragment. In the case of cortical discontinuity, the direction of translation of the distal fragment (D) in relation to the proximal fragment (P) was measured.

Fig. 2. Radiographs in case #1, immediately after surgery (a-d) and at latest follow-up (e-h), when bone union had occurred. The alignment was in the normal range on both views (a, c), but the distal fragment was translated posteriorly on the lateral view (d).

Fig. 3. Serial radiographs of case #3 demonstrate atrophic nonunion and implant failure. Preoperative radiographs (a, b) showed a transverse subtrochanteric fracture with lateral cortical thickening and beaking. Immediately after the first surgery (c, d), valgus and cortical discontinuity was evident on both views. After implant failure (e, f), revision surgery was performed (g, h), and this resulted in bone union (I, j).

Fig. 4. Although repositioning was relative good in case #10 with a bone defect only on the medial and lateral aspects on the AP view, it resulted in nonunion and implant failure.

#	Age (yr)	Gender	Follow-up period(mo)	Affected side	Location	Bilateral lesion	Prodrome	Comorbities	Duration of GC use (yrs)	Kind of BP	Duration of BP use (mo)
1	72	Female	60	Right	Subtrochanteric	+	+	Myasthenia gravis, Diabetes mellitus	28	Risedronate	60
2	54	Female	18	Right	Femoral diaphysis	+	+	Dermatomyositis, Interstitial pneumonia	18	Alendronate	48
3	58	Female	81	Right	Subtrochanteric	+	−	Rheumatoid arthritis	12	Alendronate	78
4	54	Female	76	Left	Subtrochanteric	+	−	Rheumatoid arthritis	9	Alendronate	66
5	48	Female	71	Right	Femoral diaphysis	+	+	Systemic lupus erythematosus	21	Alendronate	120
6	67	Female	67	Left	Femoral diaphysis	−	−	Rheumatoid arthritis	30	Alendronate	60
7	78	Female	67	Right	Femoral diaphysis	+	+	Adult Still's disease	11	Alendronate	84
8	78	Female	67	Left	Femoral diaphysis	+	+	Adult Still's disease	11	Alendronate	84
9	50	Female	32	Left	Femoral diaphysis	+	+	Rheumatoid arthritis	20	Alendronate/Minodronate	69
10	79	Female	23	Left	Subtrochanteric	+	+	Adult Still's disease	11	Etidronate/Alendronate	83
11	76	Male	19	Right	Subtrochanteric	−	+	Rheumatoid arthritis	14	Alendronate/Minodronate	83
12	67	Female	15	Left	Subtrochanteric	+	+	Interstitial pneumonia, Diabetes mellitus	9	Alendronate	108
									16.16666667		

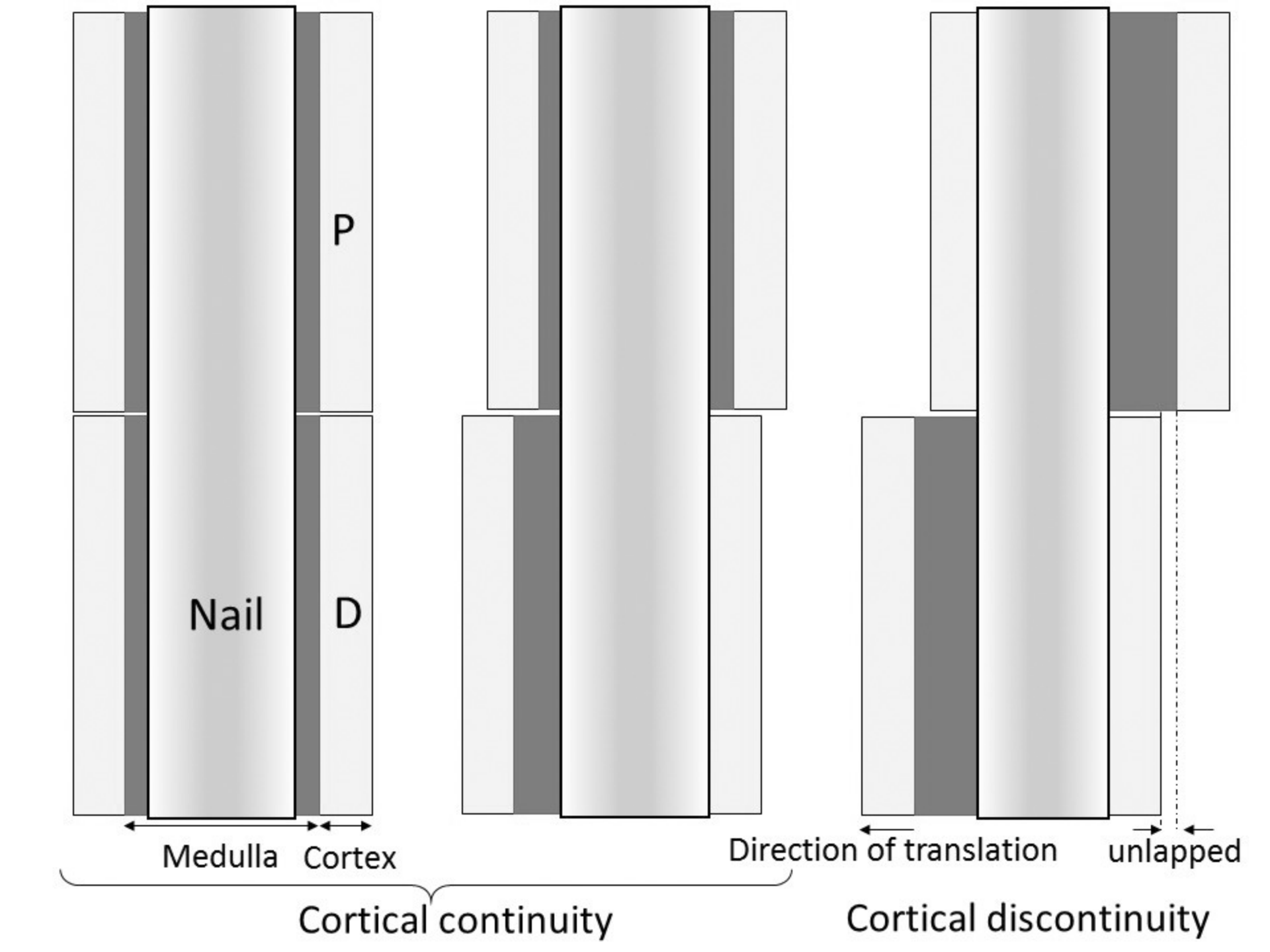
Annotation #1&2: death while f/u #7&8: simultaneous injury #5: operated already

#	Bone-related markers: Unit (normal range)								DEXA (dual-energy X-ray absorptiometry)	
	Ca*	IP	ALP	BAP	intact-P1NP	Total-P1NP	Urinary NTX	TRACP-5b	Lumbar spine	Contralateral femoral neck
	mg/dl (8.5-10.5)	mg/dl (2.7-4.5)	U/l (104-338)	μg/l (3.8-22.6)	μg/l (27-109)	μg/l (18.1-74.1)	/mmol･Cre (14.3-89.0)	mU/dl (120-420)	BMD (g/ cm^2)/ T-score/ YAM (%)	BMD (g/ cm^2)/ T-score/ YAM (%)
1	9.7	2.5	219	N.A.	N.A.	N.A.	30.9	N.A.	1.068/ 2.2/ 106	0.867/ 2.4/ 100
2	9.6	2.5	118	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
3	9.1	3.4	218	10.9	N.A.	N.A.	45	N.A.	0.824/ -1.7/ 81	0.718/ -1.3/ 83
4	9.5	3.1	128	6.2	N.A.	N.A.	31.5	170	0.874/ -1.2/ 86	0.700/ -0.8/ 89
5	9.8	3.3	141	N.A.	35.3	N.A.	N.A.	162	0.987/ -0.2/ 98	0.616/ -1.6/ 78
6	9.3	4.3	335	N.A.	15.1	N.A.	N.A.	295	1.076/ 0.6/ 106	0.570/ -2.0/ 72
7, 8	8.9	2.8	148	N.A.	12.6	N.A.	N.A.	147	1.209/ 1.8/ 120	N.A.
9	9.3	N.A.	248	N.A.	N.A.	11.8	N.A.	110	0.507/ -4.6/ 49	0.476/ -2.9/ 60
10	9.6	3.3	168	N.A.	N.A.	17.4	N.A.	321	0.705/ -2.8/ 70	0.639/ -1.4/ 81
11	9.1	3.2	122	N.A.	N.A.	11	N.A.	N.A.	0.841/ -1.4/ 81	0.551/ -2.5/ 64
12	9	3.6	174	N.A.	N.A.	13.7	N.A.	344	1.106/ 0.9/ 109	0.758/ -0.3/ 96

*Total serum calcium corrected for albumin level

N.A: Not available

#	Location	Implant	Operative procedure			Adjuvant therapy		Malalignment		Cortical discontinuity (-/direction)		Fracture gap	Correction loss		Duration of bone union/nonunion
			Open reduction	Bone graft	Drilling	LIPUS	Teriparatide	AP view	lateral view	AP view	lateral view		AP view	lateral view	
1	Subtrochanteric	Antegrade intramedullary nail	-	-	-	-	-	-	-	-	Posterior	+	-	-	6 months
2	Femoral diaphysis	Antegrade intramedullary nail	-	-	-	-	-	-	-	-	Posterior	+	-	-	10 months
3	Subtrochanteric	Cephalomedullary long nail	-	-	-	-	-	Varus	-	Medial	Posterior	-	-	-	Nonunion (Hypo)
4	Subtrochanteric	Cephalomedullary long nail	-	-	-	-	-	-	-	-	Posterior	-	-	-	16 months
5	Femoral diaphysis	Antegrade intramedullary nail	-	-	-	+	-	-	-	-	-	-	-	-	18 months
6	Femoral diaphysis	Antegrade intramedullary nail	-	-	-	+	-	-	-	-	Posterior	-	+	+	Nonunion (Hyper)
7	Femoral diaphysis	Antegrade intramedullary nail	+	-	+	+	+	-	-	Medial	Posterior	+	-	-	Nonunion (Hypo)
8	Femoral diaphysis	Cephalomedullary long nail	-	-	-	+	+	-	-	-	Posterior	+	-	-	24 months
9	Femoral diaphysis	Antegrade intramedullary nail	-	-	-	+	+	-	-	-	Posterior	+	-	-	6 months
10	Subtrochanteric	Cephalomedullary long nail	+	+	+	+	-	-	-	-	Neutral	+	-	-	Nonunion (Hypo)
11	Subtrochanteric	Cephalomedullary long nail	-	-	-	+	+	-	Extension	-	Posterior	+	-	-	15 months
12	Subtrochanteric	Cephalomedullary long nail	-	+	+	+	+	Varus	-	Medial	-	-	-	-	6 months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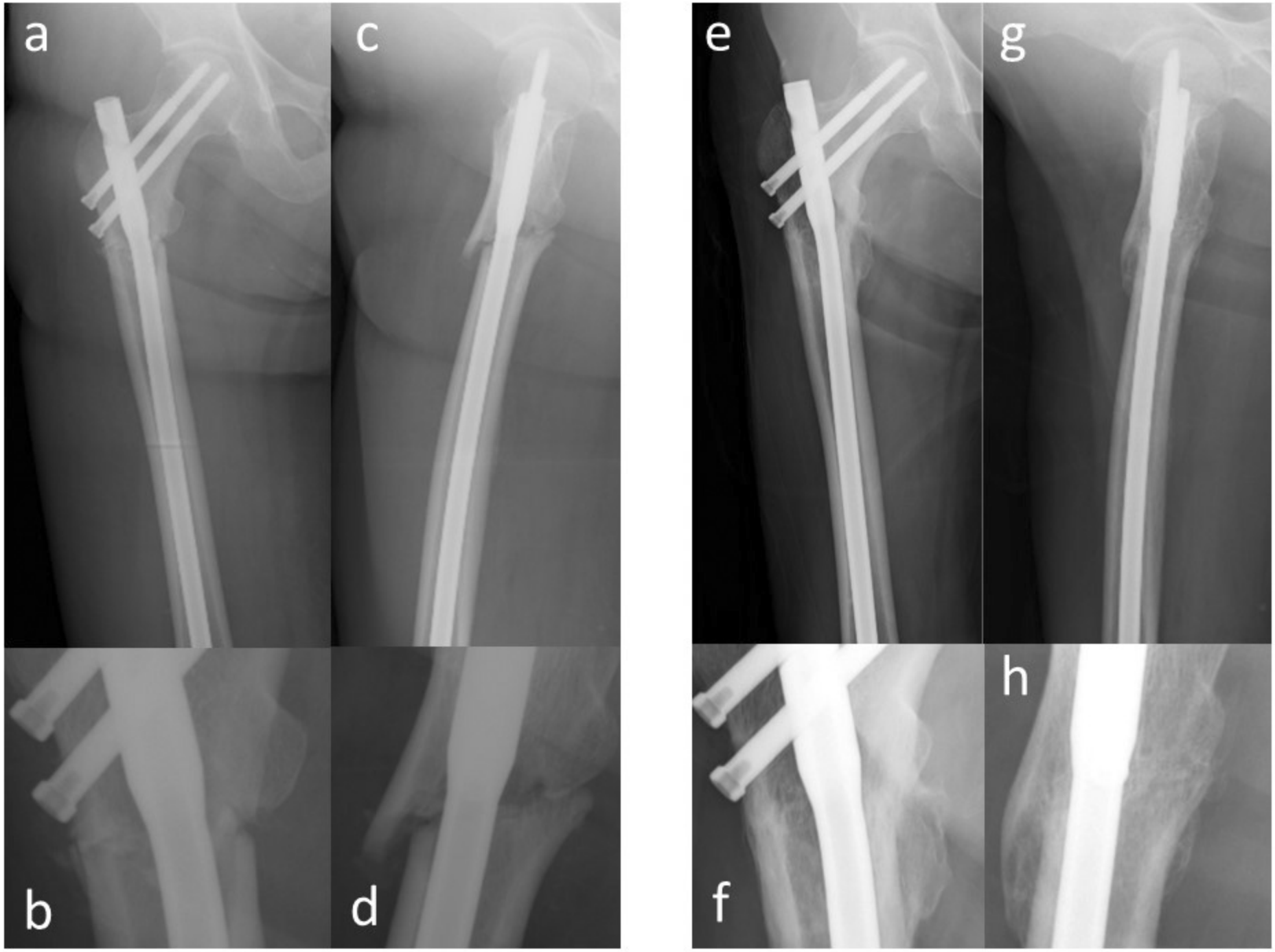
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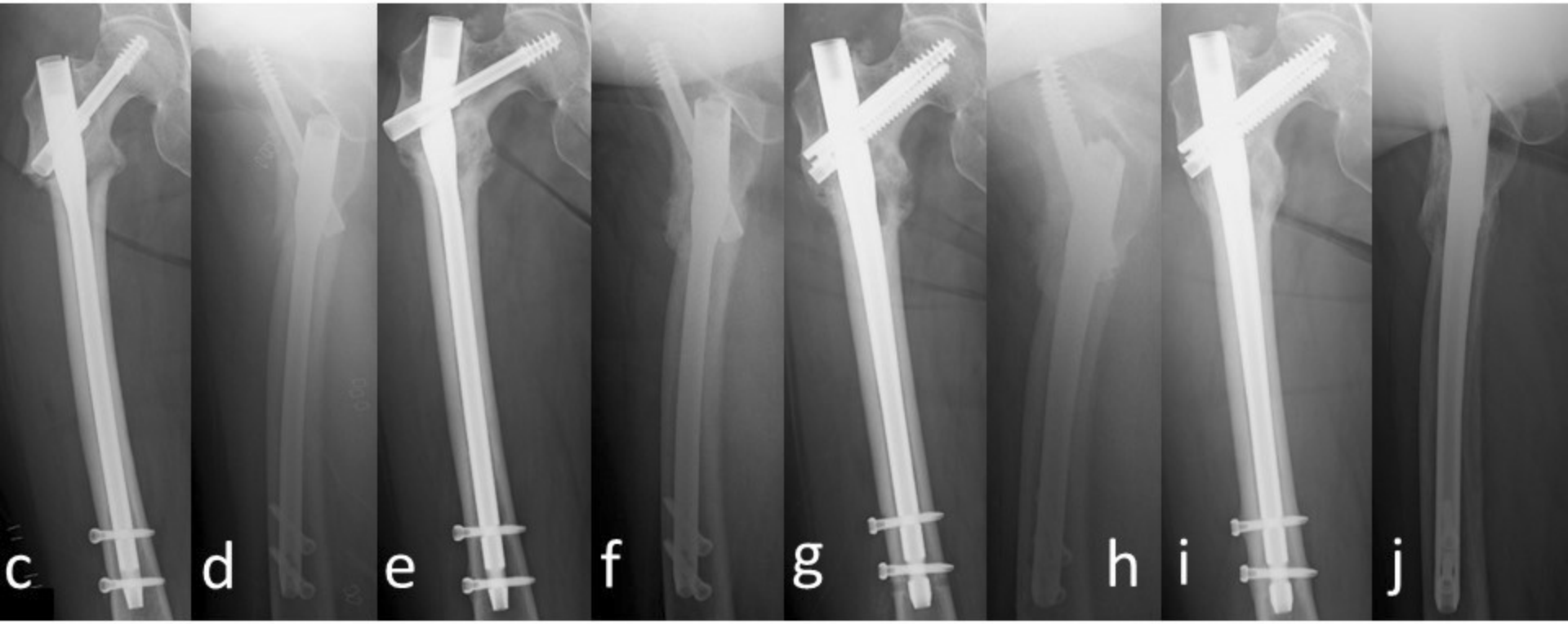
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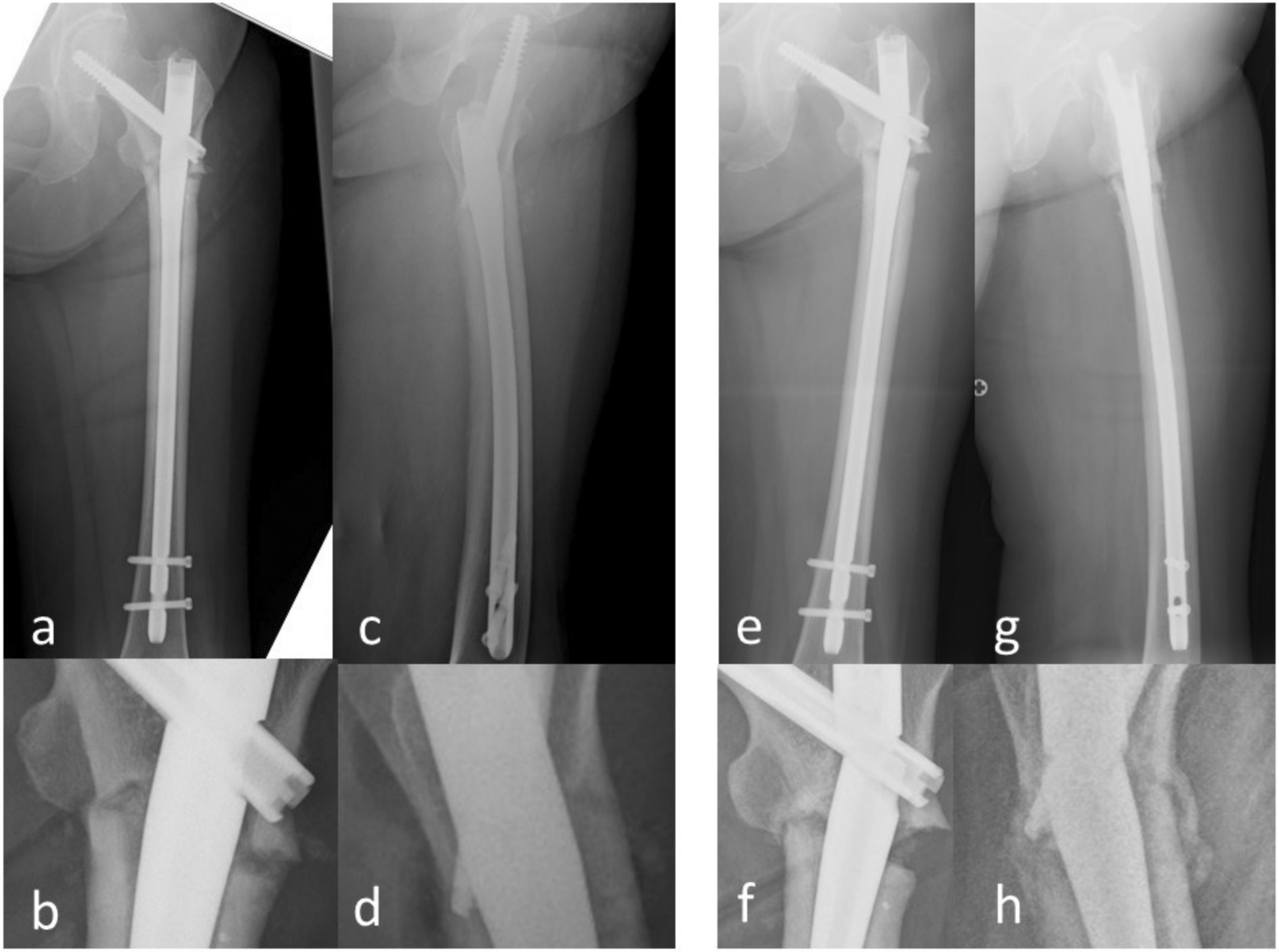
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