ディポカイン（レジスチン，MCP-1）は抑うつ症状の発現に関連している[16,35]．肥満症の改善は脂肪細胞の小型化を促進し，炎症性アディポカインの分泌を抑制し，抗炎症性アディポカイン（アディポネクチン）の分泌を促進し，疼痛治療としての意義が得られるかも知れない．

おわりに

腰痛の慢性化因子としての慢性炎症に着目し，その基盤としての肥満について概説した．運動器疼痛に対しては過度な安静は禁忌であり，適度な運動が治療効果を持つことが明らかにされている．慢性疼痛治療における運動療法の初期の痛みの急激な変化は，それが悪化あるいは改善のいずれかであったとしても，長期的な治療結果を予測するものではないことから，短期的な鎮痛効果と中長期的に継続した結果として得られる鎮痛効果には異なる機序があると考えられる．運動療法は，短期的にはβ-エンドルフィンの増加をもたらし，疼痛下行性抑制系の賦活作用や太径求心性神経線維の活性化による脊髄レベルでのゲートコントロール理論が鎮痛機序に働くとされているが，中・長期的には肥満症の解消から慢性炎症の消退へとつながり，鎮痛効果を持つかも知れない．このような治療機序との関連からも，慢性炎症の基盤としての肥満症と疼痛疾患の関連は解明が期待される．

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文 献

1) Deyo RA, Rainville J, Kent DL: What can the history and physical examination tell us about low back pain? JAMA 268 : 760-765, 1992
2) Main CJ, de C Williams AC: ABC of psychological medicine: Musculoskeletal pain. BMJ 325 : 534-537, 2002
3) Freynhagen R, Baron R, Gockel U, et al: Pain-DETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 22 : 1911-1920, 2006
4) Schmidt CO, Schweikert B, Wening CM, et al: Modeling the prevalence and cost of back pain with neuropathic components in the general population. Eur J Pain 13 : 1030-1035, 2009
5) Behrman M, Linder R, Assadi AH, et al: Classification of patients with pain based on neuropathic pain symptoms: Comparison of an artificial neural network against an establishing scoring system. Eur J Pain 11 : 370-376, 2007
6) Jensen TS, Baron R, Haanpaa M, et al: A new definition of neuropathic pain. Pain 152 : 2204-2205, 2011
7) Imich D, Burgstahler R, Bostock H, et al: ATP affects both axons and schwann cells of unmyelinated C fibers. Pain 92 : 343-350, 2001
8) Baron R, Binder A: How neuropathic is schiatica? The mixed pain concept. Orthopaede 33 : 568-575, 2004
9) Freynhagen R, Baron R: The evaluation of neuropathic components in low back pain. Curr Pain Headache Rep 13 : 185-190, 2009
10) Bastard JP, Maachi M, Lagathu C, et al: Recent advances in the relationship between obesity, inflammation and insulin resistance. Eur Cytokine Network 17 : 4-12, 2006
11) Visser M, Bouter LM, McQuillan GM, et al: Elevated C-reactive protein levels in overweight and obese adults. JAMA 282 : 2131-2135, 1999
12) Guri AJ, Bassaganya-Riera J: Systemic effects of white adipose tissue dysregulation and obesity-related inflammation. Obesity 19 : 689-700, 2011
13) Yoshino T, Kusunoki N, Tanaka N, et al: Elevated serum levels of resistin, leptin and adiponectin are associated with C-reactive protein and also other clinical conditions in rheumatoid arthritis. Intern Med 50 : 269-275, 2011
14) Webb R, Brammah T, Lunt M, et al: Preva-

lence and predictors of intense, chronic and disabling neck and back pain in the UK general population. Spine11：1195-1202, 2003
15) Haba-Rubio J, Tafti M, Heinzer R, et al：Improvement of migraine headaches in severely obese patients after bariatric surgery. Neurology 77：1772-1773, 2011
16) Griffin TM, Fermor B, Huebner J, et al：Diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for osteoarthritis in mice. Arthr Res Ther 12：R130, 2010
17) Gandhi R, Takahashi M, Smith H, et al：The synovial fluid adiponectin-leptin ration predicts pain with knee osteoarthritis. Clin Rheumatol 29：1223-1228, 2010
18) Maves TJ, Pechman PS, Gebhart GF, et al：Possible chemical contribution from chromic gut sutures produces disorders of pain sensation like those seen in man. Pain 54：57-69, 1993
19) Andrade P, Visser-Vandewalle V, Philippens M, et al：Tumor necrosis factor-α levels correlate with postoperative pain severity in lumbar disc hernia patients：Opposite clinical effects between tumor necrosis factor receptor 1 and 2. Pain 152：2645-2652, 2011
20) Karppinen J, Daavittila I, Noponen N, et al：Is the interleukin-6 haplotype a prognostic factor for sciatica? Eur J Pain 12：1018-1025, 2008
21) Kiguchi N, Maeda T, Kobayashi Y, et al：Upregulation of tumor necrosis factor-α in spinal cord contributes to vincristine-induced mechanical allodynia in mice. Neurosci Lett 445：140-143, 2008
22) Myers RR, Campana WM, Shubayev VI：The role of neuroinflammation in neuropathic pain：Mechanisms and therapeutic targets. Drug Discovery Today 11：8-20, 2006
23) Miscio G, Guastamacchia G, Brunani A, et al：Obesity and peripheral neuropathy risk：A dangerous liaison. J Peripheral Nerve System 10：354-358, 2005
24) Kiguchi N, Maeda T, Kobayashi Y, et al：Macrophage inflammatory protein-1α mediates the development of neuropathic pain following peripheral nerve injury through interleukin-1β up-regulation. Pain 149：305-315, 2010
25) Ang DC, Moore MN, Hilligoss J, et al：MCP-1 and IL-8 as pain biomarkers in fibromyalgia：A pilot study. Pain Med 12：1154-1161, 2011
26) Maeda T, Kiguchi N, Kobayashi Y, et al：Leptin derived from adipocytes in injured peripheral nerves facilitates development of neuropathic pain via macrophage stimulation. Proc Natl Acad Soc 31：13076-13081, 2009
27) Tian Y, Wang S, Ma Y, et al：Leptin enhances NMDA-induced spinal excitation in rats：A functional link between adipocytokine and neuropathic pain. Pain 152：1263-1271, 2011
28) Van Damme S, Crombez G, Bijttebier P, et al：A confirmatory factor analysis of the pain catastrophizing scale：Invariant factor structure across clinical and non-clinical populations. Pain 96：319-324, 2002
29) Sullivan MJL, Lynch ME, Clark AJ：Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain conditions. Pain 113：310-315, 2005
30) Leeuw M, Goossens MEJB, Linton SJ, et al：The fear-avoidance model of musculoskeletal pain：Current state of scientific evidence. J Behav Med 30：77-94, 2007
31) Boulanger L, Zhao Y, Foster TS, et al：Impact of comorbid depression or anxiety on patterns of treatment and economic outcomes among patients with diabetic peripheral neuropathic pain. Curr Med Res Opin 25：1763-1773, 2009
32) O'Brien EM, Waxenberg LB, Atchison JW, et al：Negative mood mediates the effect of poor sleep on pain among chronic pain patients. Clin J Pain 26：310-319, 2010
33) Basta M, Chrousos GP, Vela-Bueno A, et al：Chronic insomnia and stress system. Sleep Med Clin 2：279-291, 2007
34) Johnson KG, Ziemba AM, Garb JL：Improvement in headaches with continuous positive airway pressure for obstructive sleep apnea：A restrospective analysis. (Johnson KG, Ziema AM, Grab Jl, ed：Headache.) 2012 (in press)
35) Shelton RC, Miller AH：Eating ourselves to death (and despair)：The contribution of adiposity and inflammation to depression. Prog Neurobiol 91：275-299, 2010

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Perioperative factors affecting the occurrence of acute complex regional pain syndrome following limb bone fracture surgery: data from the Japanese Diagnosis Procedure Combination database

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Abstract

Objective. Complex regional pain syndrome (CRPS) describes a broad spectrum of symptoms that predominantly localize to the extremities. Although limb fracture is one of the most frequently reported triggering events, few large-scale studies have shown the occurrence of and factors associated with CRPS following limb fracture. This study aimed to show the occurrence and identify of those factors.

Methods. Using the Japanese Diagnosis Procedure Combination database, we identified 39 patients diagnosed with CRPS immediately after open reduction and internal fixation (ORIF) for limb fracture from a cohort of 185 378 inpatients treated with ORIF between 1 July and 31 December of each year between 2007 and 2010. Patient and clinical characteristics such as age, gender, fracture site, duration of anaesthesia and use of regional anaesthesia were investigated by logistic regression analyses to examine associations between these factors and the in-hospital occurrence of CRPS after ORIF.

Results. The occurrence of CRPS was relatively high in fractures of the distal forearm, but low in fractures of the lower limb and in patients with multiple fractures. Generally females are considered to be at high risk of CRPS; however, we found a comparable number of male and female patients suffering from CRPS after ORIF for limb fracture. In terms of perioperative factors, a longer duration of anaesthesia, but not regional anaesthesia, was significantly associated with a higher incidence of CRPS.

Conclusion. Although a limited number of CRPS patients were analysed in this study, reduced operative time might help to prevent the development of acute CRPS following limb fracture.

Key words: complex regional pain syndrome, bone fracture, open reduction and internal fixation, factors, regional anaesthesia.

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Introduction

Complex regional pain syndrome (CRPS) is a poorly understood syndrome that describes a broad spectrum of sensory, motor and autonomic-like features that predominantly manifest in the extremities. CRPS is usually encountered in patients recovering from limb trauma and they complain of intense pain that is disproportionate to the inciting event. Furthermore, the activities of daily living are significantly impaired in many CRPS patients because of this intense perceived pain [1]. While the underlying pathophysiological mechanisms of CRPS remain controversial, the autonomic-like, trophic and motor disturbances are key features of CRPS, with the exception of spontaneous pain and allodynia. To elucidate the mechanisms of CRPS onset, some investigations have categorized CRPS into several subgroups based on the key features or somatosensory abnormalities [2, 3]. Since CRPS patients frequently present with different features (e.g. redness or pallor of the skin) and/or somatosensory abnormalities (e.g. hyperalgesia or hypoaesthesia) at various intervals, CRPS is often categorized on the basis of disease duration and the presence of certain features related to these intervals [4, 5]. Given this close temporal clustering of CRPS symptoms and signs, it may be assumed that focusing on a particular time frame for patients with CRPS provides a relatively homogeneous CRPS subgroup for investigations as to its aetiology.

Since the clinical features of CRPS are so diverse, another approach would be to analyse patient demographic data, particularly in terms of a potential triggering event. Limb fracture is one of the most frequently reported triggering events [6]. In attempting to gather a homogeneous CRPS study population, Schurmann *et al.* [7] recruited patients with a limb fracture and demonstrated that the sympathetic nervous system in the affected limb could possibly predict the development of CRPS. Another investigation that included patients with a fracture reported that no psychological factors could predict the development of CRPS, indicating that anxiety and depression are not predisposing factors for CRPS [8]. Furthermore, a prospective evaluation of CRPS patients after fracture revealed that specific bone fractures (i.e. dislocation and intra-articular fracture) are associated with an elevated incidence of CRPS [9]. Therefore, focusing on the triggering events for CRPS, in addition to the time frame, may help to disentangle the underlying mechanisms of its aetiology. However, the precedent study included a mixed-fracture patient cohort, with varied disease duration (within 1 year) and varied treatments for the fracture. As a result, the study identified a diverse array of features for CRPS; for instance, the prevalence of CRPS at 3 months after fracture increased significantly from that at the time of plaster removal (~6 weeks after the fracture), but decreased again by the 1-year mark [9]. Therefore a focus on the triggering events for CRPS proved inadequate as an independent method to elucidate the mechanisms of CRPS onset.

In the present study we sought to find a close-to-homogeneous population and thus sampled data from CRPS patients with at least one common aetiology (i.e. limb bone fracture), one common treatment [i.e. open reduction and internal fixation (ORIF)] and one common phase of disease (i.e. the acute phase of CRPS immediately after bone fracture). We used a nationwide, inpatient database to collect the data because the incidence of CRPS is very low: 5.5 and 26.2 cases per 100 000 person-years in the USA [10] and the Netherlands [6], respectively. Our objectives were to specify the demographic and medical factors that most likely constitute a risk of developing CRPS and to search for potential interventions to reduce the occurrence of CRPS in these limb fracture patients.

Materials and methods

DPC database

We used the nationwide inpatient database, the Japanese Diagnosis Procedure Combination (DPC) database, to collect the data. The details of the DPC inpatient database are described elsewhere [11, 12]. Briefly, the DPC is a Japanese case-mix classification system linked with a lump-sum payment system. All 82 academic hospitals are obliged to adopt the DPC system, while community hospitals can voluntarily adopt it. A survey of DPC hospitals is conducted between July 1 and December 31 each year by the DPC Research Group, funded by the Ministry of Health, Labour, and Welfare, Japan. The survey includes anonymous data of 3.19 million discharged cases from 952 acute care hospitals in 2010, representing ~45% of all admissions to acute care hospitals in Japan. The database includes the following data: the unique identifier of each hospital; patients' age and sex; main diagnoses, co-morbidities at admission and complications after admission that are coded by the International Classification of Diseases 10th Revision (ICD-10) codes; procedures coded by Japanese original codes; duration of anaesthesia (min); length of stay (days) and in-hospital mortality. Co-morbidities present at admission are clearly differentiated from complications after admission. Attending physicians are obliged to record the diagnoses for each patient at discharge with reference to medical charts to optimize the accuracy of the recorded diagnoses. Data compliance is mandatory to obtain reimbursement of medical fees.

The DPC database is a secondary database of administrative claims data. All the data were de-identified in each hospital and the anonymized data were sent to the study group. Informed consent to each patient was therefore waved because of the anonymous nature of the data. Study approval was obtained from the Institutional Review Board at the University of Tokyo.

Data extraction

We identified the records of all patients in the DPC database who underwent surgical repair (i.e. ORIF) for fracture of upper and lower limbs during 2007–10, including fracture of the shoulder and upper arm (ICD-10 code, S42), fracture of the forearm (S52), fracture at the wrist and hand level (S62), fracture of the femur (S72), fracture of the lower leg (S82), fracture of the foot (S92) and fractures involving multiple regions of the upper and lower limbs (T02.2–T02.6). For each patient we extracted the following data: sex, age, main diagnosis, type of surgery, duration of anaesthesia (ranging from the time of induction of anaesthesia to awakening in recovery), type of anaesthesia, length of stay and discharge status.

Fracture sites were categorized into the following three groups: upper limbs (ICD-10 codes, S42, S52 and S62), lower limbs (S72 and S82 and S92) and multiple regions (T02.2–T02.6). The duration of anaesthesia was categorized into three subgroups: $\leqslant$119 min, 120–179 min or $\geqslant$180 min. Regional anaesthesia included spinal

Table 1 Patient characteristics

	All	Upper limb	Lower limb	Both	P-value
Total, *n* (%)	185 378 (100.0)	49 650 (100.0)	133 030 (100.0)	2698 (100.0)	—
Age, *n* (%), years					
⩽59	45 444 (24.5)	24 645 (49.6)	19 758 (14.9)	1041 (38.6)	<0.001
60–79	59 846 (32.3)	17 869 (36.0)	40 961 (30.8)	1016 (37.7)	—
⩾80	80 088 (43.2)	7136 (14.4)	72 311 (54.4)	641 (23.8)	—
Sex, *n* (%)					
Male	63 898 (34.5)	24 283 (48.9)	38 376 (28.8)	1239 (45.9)	<0.001
Female	121 480 (65.5)	25 367 (51.1)	94 654 (71.2)	1459 (54.1)	—
Duration of anaesthesia, *n* (%)					
⩽119 min	101 220 (54.6)	23 806 (48.0)	76 769 (57.7)	645 (23.9)	<0.001
120–179 min	53 413 (28.8)	15 958 (32.1)	36 869 (27.7)	586 (21.7)	—
⩾180 min	30 745 (16.6)	9886 (19.9)	19 392 (14.6)	1467 (54.4)	—
Regional anaesthesia	83 945 (45.9)	7861 (16.4)	75 218 (56.9)	866 (32.4)	—
Length of stay, median (IQR), days	26 (14–44)	8 (4–18)	31 (21–50)	36 (21–60)	<0.001
In-hospital death, *n* (%)	2364 (1.3)	120 (0.2)	2215 (1.7)	29 (1.1)	—

IQR: interquartile range.

anaesthesia, epidural anaesthesia and peripheral nerve blocks.

We identified patients who were postoperatively diagnosed with CRPS during hospitalization with an ICD-10 code-based searching algorithm, including the ICD-10 code M89.0 (algodystrophy, shoulder-hand syndrome, Sudeck's atrophy or reflex sympathetic dystrophy) and G56.4 (causalgia). Japanese physicians have quite strictly diagnosed CRPS since 2005 on the basis of the original Japanese criteria [i.e. (i) continuing pain disproportionate to any inciting event and (ii) the presence of at least two symptoms and at least two signs of sensory, sudomotor, oedema, motor and trophic abnormalities] [13]; this criteria follows that set by Bruehl *et al.* [14] and was first published in 2005. Among these patients, a diagnosis of a peripheral nerve injury was further identified by the ICD-10 code that indicates a specified peripheral nerve injury (G56.1, G56.2, G56.3, G57.0, G57.2, G57.3, G57.4, G57.6, S44$, S54$, S64$, S74$, S84$, and S94$). The ICD-10 code includes symptom diagnosis, which sometimes indicates persistent pain itself but does not always indicate the presence of nerve injury [e.g. other nerve root and plexus disorders (G54.8)]. Therefore we gathered data on patients reliably coded with M89.0 and G56.4 to minimize the risk of including non-CRPS patients in a CRPS research sample.

Statistical analyses

We performed univariate comparisons of proportions using the chi-square test. Univariate and multivariate logistic regression analyses were performed to examine the relationships of each factor with the occurrence of postoperative CRPS. Differences were considered to be statistically significant at $P < 0.01$. All analyses were performed using SPSS software, version 19 (IBM SPSS, Armonk, NY, USA).

Results

Of the 11.6 million inpatients included in the DPC database during 2007–10, we identified 185 378 eligible patients. The background characteristics of the patients are shown in Table 1. The mean age (s.d.) of the patients was 68.6 years (23.2). Females suffered from limb fractures more frequently than males. The average duration of anaesthesia was 137 min (s.d. 116). Overall, 45.9% of patients received regional anaesthesia for ORIF. The number of lower limb fractures ($n = 133\,030$) was larger than that of upper limb fractures ($n = 49\,650$) and combined upper and lower limb fractures ($n = 2698$). The median postoperative length of stay was 8 days [interquartile range (IQR) 4–18] and 31 days (IQR 21–50) following upper and lower limb fracture surgery, respectively. Among these, 39 patients matched the ICD-10 code criteria of CRPS and 4 patients were diagnosed with a co-morbid specified nerve injury in addition to CRPS.

Table 2 shows the relationships between various factors and the occurrence of postoperative CRPS. Patients with upper limb fractures had a significantly higher rate of developing CRPS than patients with lower limb fractures (0.058% *vs* 0.006%, $P < 0.001$). Age and sex were not significantly related to the occurrence of CRPS. A longer duration of anaesthesia was significantly associated with more frequent postoperative CRPS. Regional anaesthesia was also significantly related to the development of CRPS.

The results of the logistic regression analyses are shown in Table 3. In the multivariate model, patients with fractures of the forearm, wrist and hand tended to show a relatively higher rate of CRPS [odds ratio (OR) 2.81, $P = 0.012$] as compared with those patients with fractures of the shoulder or upper arm. In contrast, patients with femoral fractures showed a significantly lower rate of CRPS (OR 0.05, $P < 0.001$). Patients ages

TABLE 2 The occurrence of postoperative CRPS

		n	CRPS	(%)	*P*-value
Total		185 378	39	(0.021)	—
Fracture site	Upper limb	49 650	29	(0.058)	<0.001
	Fracture of shoulder and upper arm (S42)	23 971	9	(0.038)	—
	Fracture of forearm (S52)	20 329	17	(0.084)	—
	Fracture of lower end of radius (S525)	*12 485*	*10*	*(0.080)*	—
	Fracture of lower end of both radius and ulna (S526)	*2058*	*4*	*(0.194)*	—
	Fracture of shafts of both radius and ulna (S524)	*1497*	*3*	*(0.200)*	—
	Fracture of forearm, others	*4289*	*0*	*(0)*	—
	Fracture at wrist and hand level (S62)	5350	3	(0.056)	—
	Lower limb	133 030	8	(0.006)	—
	Fracture of femur (S72)	106 880	2	(0.002)	—
	Fracture of lower leg (S82)	21 801	5	(0.023)	—
	Fracture of foot (S92)	4349	1	(0.023)	—
	Multiple regions of upper and lower limbs (T02.2-T02.6)	2698	2	(0.074)	—
Age, years	⩽9	3398	0	(0)	0.140
	10–19	9365	0	(0)	—
	20–29	6451	4	(0.062)	—
	30–39	6841	2	(0.029)	—
	40–49	7553	3	(0.040)	—
	50–59	11 836	2	(0.017)	—
	60–69	21 800	10	(0.046)	— —
	70–79	38 046	11	(0.029)	—
	80–89	55 347	6	(0.011)	—
	90–99	23 856	1	(0.004)	—
	⩾100	885	0	(0)	—
Sex	Male	63 898	14	(0.022)	0.851
	Female	121 480	25	(0.021)	—
Duration of anaesthesia, min	⩽119	101 220	8	(0.008)	<0.001
	120–179	53 413	14	(0.026)	—
	⩾180	30 745	17	(0.055)	—
Nerve block	No	98 984	30	(0.030)	0.004
	Yes	83 945	9	(0.011)	—

Values in brackets following the fracture descriptions are International Classification of Diseases 10th Revision codes (ICD-10 codes). CRPS: complex regional pain syndrome.

60–79 years showed a higher rate of CRPS, but this result was not significant (OR 2.15, $P = 0.062$). The rates of CRPS were not significantly different between males and females. The group with a long duration of anaesthesia (⩾180 min) showed a higher rate of CRPS as compared with the group with a short duration of anaesthesia (⩽119 min) (OR 5.73, $P < 0.001$); however, the use of regional anaesthesia did not significantly contribute to a decrease in the rate of CRPS.

Discussion

In the present study we found that the demographic data of Japanese CRPS patients were different from those of American and Dutch CRPS patients [6, 10]. While the age distribution of our CRPS patients showed one peak around 60 years of age, which is almost compatible with the American and Dutch CRPS populations, a second peak was observed at ~20 years of age, which is quite disparate. We found that patients with upper limb fractures developed CRPS more frequently than those with lower limb fractures. Some previous reports support this observation; e.g. several studies report that Colles' fracture of the radius has a much higher association with CRPS than other fracture sites [6, 10, 15]. However, the precedent prospective study showed a higher incidence of CRPS in patients with lower limb fracture than those with upper limb fracture [9]. A common characteristic among these previous studies and our present study is that fractures to the distal end of either the upper or lower limbs are at a higher risk of co-morbid CRPS.

It has been generally considered that CRPS occurs more frequently in females than in males [6, 10], but our study showed no significant difference between males and females in the rate of CRPS following limb fracture. Because middle-aged and elderly female patients usually also suffer from osteoporosis, the absolute number of patients with bone fracture is much larger for females than for males. As such, this high incidence of female CRPS patients in older cohorts of previous epidemiological studies would be more noticeable [1, 16]. Furthermore, large populations of female CRPS patients might have other

Table 3 Logistic regression analyses for the occurrence of postoperative CRPS

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Fracture site						
Shoulder or upper arm (S42)	Reference			Reference		
Forearm, wrist or hand (S52 or S56)	2.08	0.94, 4.56	0.069	2.81	1.25, 6.30	0.012
Femur (S72)	0.05	0.01, 0.23	<0.001	0.05	0.01, 0.28	<0.001
Lower leg or foot (S82 or S92)	0.61	0.22, 1.72	0.350	0.66	0.21, 2.05	0.469
Multiple regions (T02.2-T02.6)	1.98	0.43, 9.15	0.384	1.40	0.30, 6.66	0.671
Age, years						
⩽59	Reference			Reference		
60-79	1.45	0.70, 3.01	0.318	2.15	0.96, 4.79	0.062
⩾80	0.36	0.14, 0.93	0.035	1.75	0.61, 5.04	0.300
Sex						
Male	Reference			Reference		
Female	0.94	0.49 ,1.81	0.851	1.21	0.58, 2.52	0.613
Duration of anaesthesia, min						
⩽119	Reference			Reference		
120-179	3.32	1.39, 7.91	0.007	3.15	1.24, 7.97	0.016
⩾180	7.00	3.02, 16.22	<0.001	5.73	2.31, 14.24	<0.001
Regional anaesthesia						
No	Reference			Reference		
Yes	0.35	0.17, 0.75	0.006	1.11	0.46, 2.68	0.817

Values in brackets following the fracture descriptions are International Classification of Diseases 10th Revision codes (ICD-10 codes). CRPS: complex regional pain syndrome.

causative aetiologies aside from bone fracture as compared with male patients. Our present findings show that females with bone fractures do not appear to have a higher risk of developing CRPS as compared with their male counterparts.

The estimated overall incidence of CRPS was 0.026% and 0.0055% per year in the Dutch and American general populations, respectively [6, 10]. Although bone fracture is one of the major causes of CRPS and patients with bone fracture are generally at increased risk for the development of CRPS, the rate of CRPS in patients with ORIF for limb fracture in our study was 0.021%. This is lower than the estimated 22% following the International Association for the Study of Pain (IASP) criteria [17] and ~5% following the criteria of Bruehl *et al.* [14] for the only other study to prospectively evaluate the development of CRPS in ~600 patients with limb bone fracture within 6 weeks after injury [9]. The IASP criteria include a combination of (i) the presence of an initiating noxious event or a cause of immobilization; (ii) continuous pain, allodynia or hyperalgesia with which pain is disproportionate to any inciting event; (iii) evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain and (iv) the absence of a condition that would otherwise account for the degree of pain and dysfunction [17]. Comparatively the criteria by Bruehl *et al.* [14] include (i) continuing pain disproportionate to any inciting event and (ii) the presence of at least one symptom and two signs each of a sensory, vasomotor, sudomotor/oedema and motor/trophic nature. The IASP criteria are highly sensitive but with a low specificity, whereas the criteria by Bruehl *et al.* have a moderate-to-high sensitivity as well as a relatively high specificity. The fact that Japanese physicians have quite strictly diagnosed CRPS since 2005 on the basis of the original Japanese criteria [13] might contribute to the different prevalence rates between our study and the earlier prospective study [9]. In addition, a genetic contribution to pain perception in CRPS patients has been reported [18], and the genetic differences between Japanese and Dutch patients might contribute to the differences in the incidence of CRPS between these two investigations.

We consider that such distinct characteristics of our patients are possibly attributable to our efforts to gather a close-to-homogeneous population and thus recruiting only patients who were diagnosed with CRPS during hospitalization immediately after ORIF for limb bone fracture. Early in the postoperative period, physicians are generally reluctant to assign a diagnosis of CRPS. This may explain why the prevalence of the diagnosis of CRPS increased between 6 weeks to 3 months in the precedent prospective study [9]. We sampled data from CRPS patients within the very acute phase of the postoperative period. Such a limited observation period might result in a possible underestimation of the true prevalence of CRPS. Because of the difference in health care systems between Japan and Western countries, our length of hospital stay was generally longer than those in other reports [19].

There will be a certain number of patients with false-negative diagnoses of CRPS. Approaching this topic from a different angle, in many patients, complaints begin and continue after the inciting event. However, it is clinically uncommon for patient complaints to begin during the period of time elapsed from the inciting event [16]. In addition, there was close temporal clustering of CRPS in ours and other cohorts [4, 5]. Thus it is unlikely that our data would include a considerable number of the false-negative cases. We should consider the likelihood of false-positive cases in the present study. Since the DPC system did not include any records of signs and symptoms of CRPS, we cannot confirm the diagnostic validity of our study retrospectively. However, to enhance specificity in the diagnosis of CRPS, we sampled patients who were reliably coded with CRPS (ICD-10 codes M89.0 and G56.4) and did not include those who were coded with a symptomatic diagnosis of neural disorders. This was because CRPS should be diagnosed in the absence of an alternative condition that would otherwise account for the pain. In addition to these considerations, and because of the reluctance of physicians to assign a diagnosis of CRPS early in the postoperative period, we assume that our data describe a well-selected, albeit small, cohort with few false-positive cases.

To cluster a close-to-homogeneous CRPS subgroup, we gathered only patients who were diagnosed with CRPS during hospitalization immediately after ORIF for limb fracture. Our approach may thus permit better identification of risk factors for the development of CRPS after ORIF for limb fracture early during the postoperative period with distinct characteristics. It should be noted therefore that the results cannot be generalized across all CRPS patients, but is applicable to those patients within a specific CRPS subgroup.

The underlying pathophysiological mechanisms of CRPS remain controversial. One possible explanation is that CRPS stems from neuropathic pain. Limb fractures, including dislocations, can induce peripheral nerve injuries. We found 4 of 39 patients diagnosed as a specified nerve injury; this figure is much larger than the reported 1-2% incidence of nerve injuries induced by limb trauma [20]. In the majority of reported cases, a diagnosis of peripheral nerve injury was made within 4 days of admission [21]. Because our observation period was sufficient, with a median length of stay of at least 8 days, our data would have been satisfactory to detect most of the peripheral nerve injuries occurring subsequent to fracture. Here we found that a longer duration of anaesthesia was associated with a higher incidence of CRPS. This longer requirement for anaesthesia might suggest the occurrence of more severe fractures in our patients and thereby a higher rate of nerve injury. Supporting evidence for this consideration comes from the fact that more severe traumas, such as crushing injuries, can lead to a higher rate of nerve injury [20]. Indeed, in the present study, patients with multiple fractures to the upper and lower limbs were plausibly considered to be the result of high-energy trauma. However, these multiple-fracture patients showed a relatively low association with CRPS. In contrast, we found that patients with fractures to the distal end of either the upper or lower limbs were at a higher risk of co-morbid CRPS. The frequency of nerve injuries to the humerus or femur in response to fracture is reported to be similar to that of the ulna or tibia [20]. These results argue against the hypothesis that more severe traumatic injury is followed by an increased prevalence of nerve injury and suggest that neuropathic pain alone cannot explain the underlying causes of CRPS.

This study aimed to search for any interventions that could contribute to a reduction in the development of CRPS patients in our subgroup of patients. We focused on the relationship between regional anaesthesia and the occurrence of CRPS because regional anaesthesia combined with general anaesthesia may be better than general anaesthesia alone for treating bone fracture patients with ORIF by blocking afferent nociceptive signals from the wound and the bone fracture into the central nervous system and helping to prevent the development of CRPS that can persist long after healing [22]. However, we did not find this to be the case. Instead, in perioperative factors we found that a longer duration of anaesthesia was associated with a higher occurrence of CRPS. In Japan, tourniquet inflation is used to decrease blood loss and improve the operative field visually during standard ORIF for distal end fractures of the upper and lower limbs. We can assume that the longer duration of anaesthesia implies not only a longer operation time, but also a longer inflation period using the tourniquet. Nerve compression and ischaemia by tourniquet inflation induces an increase in spontaneous activity and expansion of the receptive fields of the spinal nociceptive neurons, especially those with receptive fields located proximal to the tourniquet. This results in widely expanded areas of hyperalgesia and allodynia, such as CRPS, in the exposed limb [23]. If we consider that regional anaesthesia could prevent CRPS, one possible underlying cause of the pathological pain associated with CRPS is the central sensitization of the spinal nociceptive neurons induced by continuous nociceptive inputs from wound, bone fracture and ischaemic tissue and neuropathic inputs from nerve compression by tourniquet inflation. However, this mechanism is unlikely, given the present result that regional anaesthesia showed no relationship to the prevalence of CRPS. We propose the ischaemia-reperfusion injury theory as an alternative explanation for the relationship between a higher rate of CRPS and the longer duration of anaesthesia. Reperfusion subsequent to prolonged occlusion of the blood flow to one limb results in hyperalgesia and allodynia, and moreover the exposed limb exhibits an initial phase of CRPS features, such as hyperaemia and oedema [24]. A large body of clinical evidence suggests that, in at least a subset of CRPS patients, the fundamental cause of abnormal pain sensations and CRPS-based symptomatology is ischaemia-reperfusion injury followed by sustained inflammation due to microvascular pathology in deep tissues [25]. Our proposal is supported by the present results that, although there was a longer duration of anaesthesia with ORIF procedures for both upper and lower limb fractures than with a single ORIF procedure for either an upper or lower limb fracture, multiple fractures showed a relatively low association with CRPS. Therefore a longer inflation period with a tourniquet on an exposed limb may be the cause of CRPS.

Several limitations in this study should be acknowledged. First, the recorded diagnoses in the administrative claims database are generally less well validated than those in planned prospective surveys. Second, because the database does not include information on the patients' signs and symptoms or laboratory data, underreporting or biased reporting (withholding sensitive cases) may have potentially led to over- and underestimation of the true occurrence rate of CRPS. Third, although the database represents 45% of acute care in patients in Japan, community hospitals voluntarily participated in the DPC system and patients were not randomly sampled. Fourth, our database lacks the actual duration of the tourniquet time during ORIF. We speculate that ischaemia-reperfusion injury may be a critical event for the initiation of CRPS in a specific subset of patients with limb fracture treated with ORIF. Prospective studies are required to confirm this hypothesis to develop treatment and preventative strategies for CRPS. Our approach of sampling CRPS patients with specified disease duration and aetiology may help to disentangle the underlying pathophysiological mechanisms of our specific subgroups of CRPS patients in a stepwise manner.

Rheumatology key messages

- Forearm fracture is associated with a higher risk of complex regional pain syndrome (CRPS).
- The risk of developing CRPS is equal in male and female limb fracture patients.

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References

1 Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. Pain 1999;80:539-44.

2 Bruehl S, Harden RN, Galer BS *et al*. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain 2002;95:119-24.

3 Gierthumhlen J, Maier C, Baron R *et al*. Sensory signs in complex regional pain syndrome and peripheral nerve injury. Pain 2012;153:765-74.

4 Escobar PL. Reflex sympathetic dystrophy. Orthop Rev 1986;10:646-51.

5 Harden RN, Bruehl S, Galer BS *et al*. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain 1999;83:211-9.

6 de Mos M, de Bruijn AG, Huygen FJ *et al*. The incidence of complex regional pain syndrome: a population-based study. Pain 2007;129:12-20.

7 Schurmann M, Gradl G, Zaspel J *et al*. Peripheral sympathetic function as a predictor of complex regional pain syndrome type 1 (CRPS 1) in patients with radial fracture. Auton Neurosci 2000;86:127-34.

8 Beerthuizen A, Stronks DL, Huygen FJ *et al*. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS 1)—a prospective multicenter study. Eur J Pain 2011;15:971-5.

9 Beerthuizen A, Stronks DL, Van't Spijker A *et al*. Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS 1): prospective study on 596 patients with a fracture. Pain 2012;153:1187-92.

10 Sandroni P, Benrud-Larson LM, McClelland RL *et al*. Complex regional syndrome type 1: incidence and prevalence in Olmsted County, a population-based study. Pain 2003;103:199-207.

11 Sumitani M, Uchida K, Yasunaga H *et al*. Prevalence of malignant hyperthermia and relationship with anesthetics in Japan: data from the diagnosis procedure combination database. Anesthesiology 2011;114:84-90.

12 Uchida K, Yasunaga H, Miyata H *et al*. Impact of remifentanil introduction on practice patterns in general anesthesia. J Anesth 2011;25:864-71.

13 Sumitani M, Shibata M, Sakaue G *et al*. Development of comprehensive diagnostic criteria for complex regional pain syndrome in the Japanese population. Pain 2010; 150:243-9.

14 Bruehl S, Harden RN, Galer BS *et al*. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain 1999; 81:147-54.

15 Atkins RM, Duckworth T, Kanis JA. Features of algodystrophy after Colles' fracture. J Bone Joint Surg 1990;72: 105-10.

16 Veldman PH, Reynen HM, Arntz IE *et al*. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012-6.

17 Merskey H, Bogduk N. Descriptions of chronic pain syndromes and definition. In: Merskey H, Bogduk N, eds. Classification of Chronic Pain, 2nd edn. Seattle: IASP Press, 1994:209-14.

18 Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. Neurology 2005;65:437-43.

19 Yim AP, Arifi AA, Wan S. Coronary artery bypass grafting in the elderly: the challenged and the opportunity. Chest 2000;117:1220–1.

20 Taylor AC, Braza D, Rice JB *et al.* The incidence of peripheral nerve injury in extremity trauma. Am J Phys Med Rehab 2008;87:381–5.

21 Noble J, Munro CA, Prasad VSSV *et al.* Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. J Trauma 1998;45: 116–22.

22 Stojadinovic A, Auton A, Peoples GE *et al.* Responding to challenges in modern combat casualty care: innovative use of advanced regional anesthesia. Pain Med 2006;7: 330–8.

23 Crews JC, Cahall MA. An investigation of the neurophysiologic mechanisms of tourniquet-related pain: changes in spontaneous activity and receptive field size in spinal dorsal horn neurons. Reg Anesth Pain Med 1999;24: 102–9.

24 Coderre TJ, Xanthos DN, Francis L *et al.* Chronic post-ischemia pain (CPIP): a novel animal model of complex regional pain syndrome-type 1 (CRPS-1; reflex sympathetic dystrophy) produced by prolonged hindpaw ischemia and reperfusion in the rat. Pain 2004;112:94–105.

25 Coderre TJ, Bennett GJ. A hypothesis for the complex regional pain syndrome-type 1 (reflex sympathetic dystrophy): pain due to deep-tissue microvascular pathology. Pain Med 2010;11:1224–38.