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Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): Prospective study on 596 patients with a fracture

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ABSTRACT

Limited data are available on the incidence of complex regional pain syndrome type 1 (CRPS1) and on demographic and medical risk factors for the development of CRPS1. The objective of this study was to investigate the incidence of CRPS1 in patients with a fracture using 3 sets of diagnostic criteria and to evaluate the association between demographic/medical factors and the development of CRPS1 diagnosed with the Harden and Bruehl criteria. A prospective multicenter cohort study of 596 patients (ages 18 years and older) with a single fracture of the wrist, scaphoid, ankle, or metatarsal V, recruited patients from the emergency rooms of 3 Dutch hospitals. Of the 596 participants, 42 (7.0%) were diagnosed with CRPS1 according to the Harden and Bruehl criteria, 289 (48.5%) according to the International Association for the Study of Pain criteria, and 127 (21.3%) according to the criteria of Veldman. An analysis of the medical and demographic differences revealed that patients in whom CRPS1 later developed more often had intra-articular fractures, fracture dislocations, rheumatoid arthritis, or musculoskeletal comorbidities. An ankle fracture, dislocation, and an intra-articular fracture contributed significantly to the prediction of the development of CRPS1. No CRPS1 patients were symptom free at 12 months (T3). At baseline, patients with CRPS1 had significantly more pain than patients without CRPS1 ($P < .001$). The incidence of the diagnosis of CRPS1 after a single fracture depends to a large extent on the diagnostic criteria used. After a fracture, 7% of the patients developed CRPS1 and none of the patients were free of symptoms at 1-year follow-up.

1. Introduction

Complex regional pain syndrome (CRPS) is a chronic disabling pain syndrome. Diagnosis is based on signs and symptoms, no gold standard is available. Different sets of criteria exist for diagnosing CRPS type 1 (CRPS1), e.g., the Veldman criteria [39], the International Association for the Study of Pain (IASP) criteria [37], and the Harden and Bruehl criteria [21] (Appendix 1). Pain is the most common symptom; other symptoms include allodynia, hyperalgesia, abnormal skin color, temperature change, abnormal sudomotor activity, edema, tremor, dystonia, and motor/trophic disturbances [31,37,39]. Use of different criteria sets across studies yields variable results that make comparison difficult.

Large prospective studies on the incidence of CRPS1 after a fracture are scarce. The overall limitations of such studies are a small source population [4,13,16,30,34,35], involvement of a single center and the inclusion of only some types of fractures [3,4,6,12–16,23,30,32,34,35], no information available on the used diagnostic criteria or the use of a self-made diagnostic instrument [13,34,36], and no follow-up [4,13,30,32,36]. Therefore, the results of these studies are inconclusive (incidence rates range from 0.9 to 51).

Demographic and medical variables may play a role in the development of CRPS1. Patients with a fracture of the upper extremity are at greater risk of developing the disorder [18,28,29,33,39], and prevalence is higher among women [28,39]. In the literature there is no consensus regarding the influence of fracture type on the chance of developing CRPS1. In addition, the mean age of patients with CRPS at disease onset varies among several studies from 37 to 65 years [2,21,27,33,39,41].

The present study investigates the association between demographic/medical variables and the development of CRPS1, up to 12 months after trauma. The following items are addressed:

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the incidence of CRPS1 in patients after a fracture, using 3 different criteria sets, and
the prevalence of CRPS1 in patients at 3 and 12 months after fracture.

For patients fulfilling the Harden and Bruehl criteria, the following items are addressed:

demographic differences between patients with a fracture who do and do not develop CRPS1;
differences in the following medical variables between patients who do and do not develop CRPS1: occurrence of CRPS1 in the past, number of comorbidities, type/location of fracture, intra-articular fracture, dominant hand, fracture reduction, type of treatment, and duration in plaster; and
the extent to which CRPS1 can be predicted by demographic and medical variables.

2. Patients and methods

2.1. Participants

Patients were recruited from the emergency rooms of 3 hospitals in Rotterdam: 1 university hospital (Erasmus MC) and 2 general hospitals (St. Clara Hospital and Zuider Hospital). Patients who were 18 years or older with a single fracture of the wrist, scaphoid, ankle, or metatarsal V were eligible for the study. Patients were treated conservatively with plaster cast (88.1%), with tape (0.7%), or with both plaster and surgery (10.9%); of 0.3% of the participants the type of treatment is unknown. Exclusion criteria were being unable to complete a questionnaire, living more than 50 km away from the hospital, having nerve damage that could result in a CRPS type 2, or having fractures in more than 1 extremity.

2.2. Design

This was a prospective, multicenter cohort study.

2.3. Procedure

This study was approved by the local medical ethics committee of the Erasmus MC (MEC 223.922/2003/18). After providing written informed consent, participants completed a questionnaire by telephone within 2 weeks after trauma (T0; Fig. 1) covering demographic variables and medical functioning. Immediately after removal of the plaster (T1), patients were interviewed using a form describing 23 symptoms related to CRPS1. When a patient fulfilled 4 of the 4 IASP criteria [37], the patient was referred to a pain specialist with considerable experience with CRPS (F.H.) at the Pain Treatment Center of the Erasmus MC to assess the symptoms and signs of CRPS by using the criteria of Harden and Bruehl. Patients fulfilling the Harden and Bruehl criteria received the standard medical treatment according to the guidelines used in the Netherlands, namely dimethyl sulfoxide cream [42] and physical therapy (to improve functionality). Three months after trauma (T2), all patients completed a second questionnaire.

Patients not fulfilling the criteria at T0, but reporting symptoms suspected for CRPS1 at T1, were at that time referred to the Pain Treatment Center. When the patients fulfilled the criteria of Harden and Bruehl, the earlier-mentioned standard therapy was also started in these patients. All patients diagnosed at T2 with CRPS1 according to the IASP criteria and/or the criteria of Harden and Bruehl were asked to fill in a short questionnaire 1 year after trauma (T3) to evaluate symptoms related to CRPS1. Patients not fulfilling the criteria at plaster removal or at T2, but reporting symptoms suspected for CRPS1 at T3, were at that time referred to the Pain Treatment Center (and treated if necessary).

2.4. Measurements

2.4.1. Demographic and medical

Age, gender, and education level were established. Medical variables concerned the type and location of fracture, intra-articular fracture, fracture reduction, and type of treatment. Medical questions covered occurrence of CRPS1 in the past, dominant hand, type of treatment, pain severity (Numeric Rating Scale), and comorbidities. At T1, the number of weeks in the plaster cast was determined.

2.4.2. Diagnosis of CRPS1

Three sets of criteria for diagnosing CRPS1 were used: the criteria of Veldman [39], the IASP criteria [37], and the criteria of Harden and Bruehl [21] (Appendix 1). In addition, a experienced pain specialist (F.H.) performed a physical examination to establish signs of CRPS. A diagnosis of CRPS1 was made when a patient fulfilled the symptoms and at least 2 signs of the criteria of Harden and Bruehl.

2.4.3. Health-related quality of life

Health-related quality of life was measured at T0 and T2 using the SF-36 scale, which includes 8 subscales (physical functioning, role limitations because of physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations because of emotional problems, and general mental health). The SF-36 has good validity and reliability [1]. A physical and a mental composite score can be computed.

2.4.4. Statistical analysis

Descriptive statistics were used to determine (multiple response) frequencies. Differences in continuous variables between CRPS1 patients and non-CRPS1 were analyzed with the Mann-Whitney *U* test because of the skewed distribution of these variables. Differences in nominal variables between CRPS1 patients and non-CRPS1 patients were analyzed using the Pearson χ^2 test. In case of a 2×2 table, the Fisher exact test (2-sided) was used.

Binary logistic regression analysis (the backward Wald method) was used to evaluate the value of medical variables to predict the development of CRPS1. The hand as fracture location was not entered into the model because none of the patients who developed

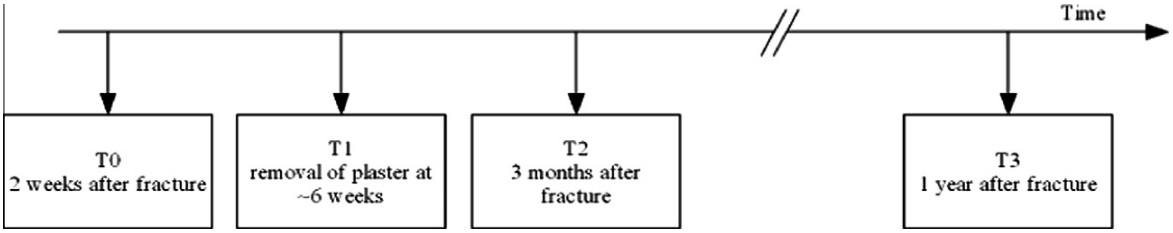

Fig. 1. Time points of measurements in the present study. T0 = baseline, T1 = plaster removal, T2 = 3 months after trauma, T3 = 1 year after trauma. IASP = criteria of the International Association for the study of Pain.

CRPS had a fracture of the hand. A significance level of P-out $\leqslant$.10 was used for the final step of the logistic regression analysis.

To prevent overfitting of the model, before performing this multivariate logistic regression analysis, univariate binary logistic analyses performed using 1 demographic or medical variable were entered into the analyses. Only those of these variables with a regression weight with a significance level of $P < .20$ were entered into the final multivariate logistic regression.

The following variables appeared to fulfill this criterion and were therefore entered into the model: age, sex, education, location of the fracture (wrist, ankle, and foot), fracture reduction, intra-articular fracture [yes/no], dislocation [yes/no]). To prevent multicollinearity, the correlations between the variables that were selected based on the univariate analyses were calculated. As an outcome variable, the diagnosis of CRPS1 according to the Harden and Bruehl criteria was used. Levels of sensitivity and specificity were considered to be of equal value.

To evaluate the power of the logistic regression model's predicted values to discriminate between positive and negative cases, a receiver-operator characteristic curve analysis was performed using the predicted probabilities. To analyze differences between the scores of patients with CRPS1 for both composite scores of the SF-36 (i.e., physical and mental), a Student t-test was performed for independent samples in cases of normal distribution. When the distribution was not normal, a Mann-Whitney U test was applied. Analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 14.0.

3. Results

3.1. Patients

A total of 748 consecutive patients fulfilling the inclusion criteria were asked to participate, and 596 (79.7%) agreed: 217 (36.4%) male and 379 (63.6%) female patients (Fig. 2). The median age was 52.8 (interquartile range [IQR] 33.4 to 63.9) years. The most common education levels were junior (23.8%) or senior vocational education (19.3%). Patients who declined participation did not differ significantly from the participants in gender or preceding trauma, but were older (median age 61.8, range 18 to 89, IQR 37.9 to 74.1 years, $P < .001$).

In 311 patients (52.2%) the upper extremity was affected, and in 285 patients (47.8%) the lower extremity was affected. Median time in plaster was 42 (SD 14.5) days. At T2, 550 patients participated and 46 (7.7%) were lost to follow-up. Patients lost to follow-up at T2 did not differ significantly from those completing follow-up at T2 with regard to age, gender, or pain at T0. At T3, the 246 patients (44.7%) who met the IASP criteria at T2 were asked to fill in a third questionnaire on symptoms of CRPS1; of these, 205 (83.3%) responded. Patients who participated at T3 were significantly older ($P = .01$, median age 55.1, IQR 37.8 to 66.3 years) than patients who did not participate at T3 (median age 52.1, IQR 31.3 to 60.7 years). Patients who participated at T3 were more often female (72.7%) than patients who did not participate at T3 (58.6%) ($P = .001$).

3.2. Symptoms of the criteria sets at the measurement time points

Fig. 3 shows the number of patients at the measurement time points per criteria set. In this figure, only the symptoms of the Harden and Bruehl criteria are shown. The peak of CRPS1 symptoms is seen at 3 months after trauma. In addition, we analyzed the number of patients diagnosed with CRPS1 at any of the time points of measurement. When the IASP criteria are used, 289 (48.5%) patients are diagnosed with CRPS1, compared with 127 (21.3%) using the criteria of Veldman and 76 (12.8%) using the symptom score of the Harden and Bruehl criteria. In total, 42 (14.3%) participants met both the symptoms and signs of the Harden and Bruehl criteria for CRPS1, which is 7.0% of all participants at baseline. Of the 293 patients who fulfilled the criteria of IASP, 53 (18.1%) refused or were unable to attend their referral to the Pain Treatment Center.

3.3. Demographic and medical variables

Table 1 presents the differences in demographic and medical variables between the patients with and without diagnosed CRPS1. An analysis of the medical and demographic differences revealed that patients who developed CRPS1 at a later time more often had intra-articular fractures (50.0% CRPS1 vs 29.4% non-CRPS1), fracture dislocations (64.3% vs 39.4% non-CRPS1), rheumatoid arthritis (14.3% vs 5.3% non-CRPS1), or musculoskeletal comorbidities (54.8% vs 27.6% non-CRPS1).

3.4. Binary logistic regression analysis

Table 2 presents the results of the binary logistic regression analysis. Dislocation, an intra-articular fracture, and the location of fracture (ankle) contributed significantly to the prediction of CRPS1. Using a cutoff value of 0.10, sensitivity was 61.9, specificity was 70.4, and the overall percentage was 69.6. In this analysis, 319 patients without and 42 patients with CRPS were included. The model discriminates quite well between positive and negative cases (receiver-operator characteristic–area under the curve: .75).

The median number of comorbidities in patients with CRPS1 was 2 (IQR 1 to 3.25) compared with 1 (IQR 0 to 2) in those without CRPS1; this difference is significant ($P = .027$). Patients with CRPS1 suffered significantly more often from rheumatoid arthritis compared with those without CRPS1 ($P = .020$). Also, there were significantly more musculoskeletal comorbidities (back pain and arthrosis) in patients with CRPS1 compared with those without CRPS1 ($P < .001$). At T2, the mean number of symptoms of patients with CRPS1 was 14.0 (SD = 4·23); the median number of symptoms at T3 was 9 (range 1 to 21). Patients who developed CRPS1 reported significantly more pain at T0 (within 1 week after trauma) than patients who did not develop CRPS1 ($P < .001$; CRPS1 median 5.6, IQR 4 to 7 vs non-CRPS1 median 3.2, IQR 1 to 5).

Concerning quality of life, at both T0 and T2 the patients with CRPS1 had a similar score to patients without CRPS1 on the mental composite score of the SF-36. For the physical component score at T0, patients with CRPS1 reported a significantly lower quality of life than patients without CRPS1 (CRPS1 mean 27.3, SD 7.42; without CRPS1 mean 34.6, SD 8.56; $t_{(490)} = 5.29$; $P < .001$). At T2, patients with CRPS1 also had a significantly lower physical composite score than patients without CRPS1 (CRPS1 mean 30.8, SD 8.34; without CRPS1 mean 44.9, SD 10.0; $P < .001$).

4. Discussion

This is one of the first prospective studies to describe the incidence of CRPS1 in a large number of patients (n = 596) after a fracture. In this study, the incidence rate of the diagnosis CRPS1 based on the Harden and Bruehl criteria was 7.0%. In the literature, incidence rates of CRPS1 after a fracture vary between 0.9% and 51% [3,4,6,11–16,23,30,32,34–36,41]. The lower incidence in the present study might be explained by the use of diagnostic criteria with a higher specificity (0.94) [8]. The lack of a gold standard for diagnosing CRPS1 leads to varying results across studies; our results indicate that the method used to diagnose CRPS1 to a large extent determines the incidence of CRPS1. After the onset of our study, the

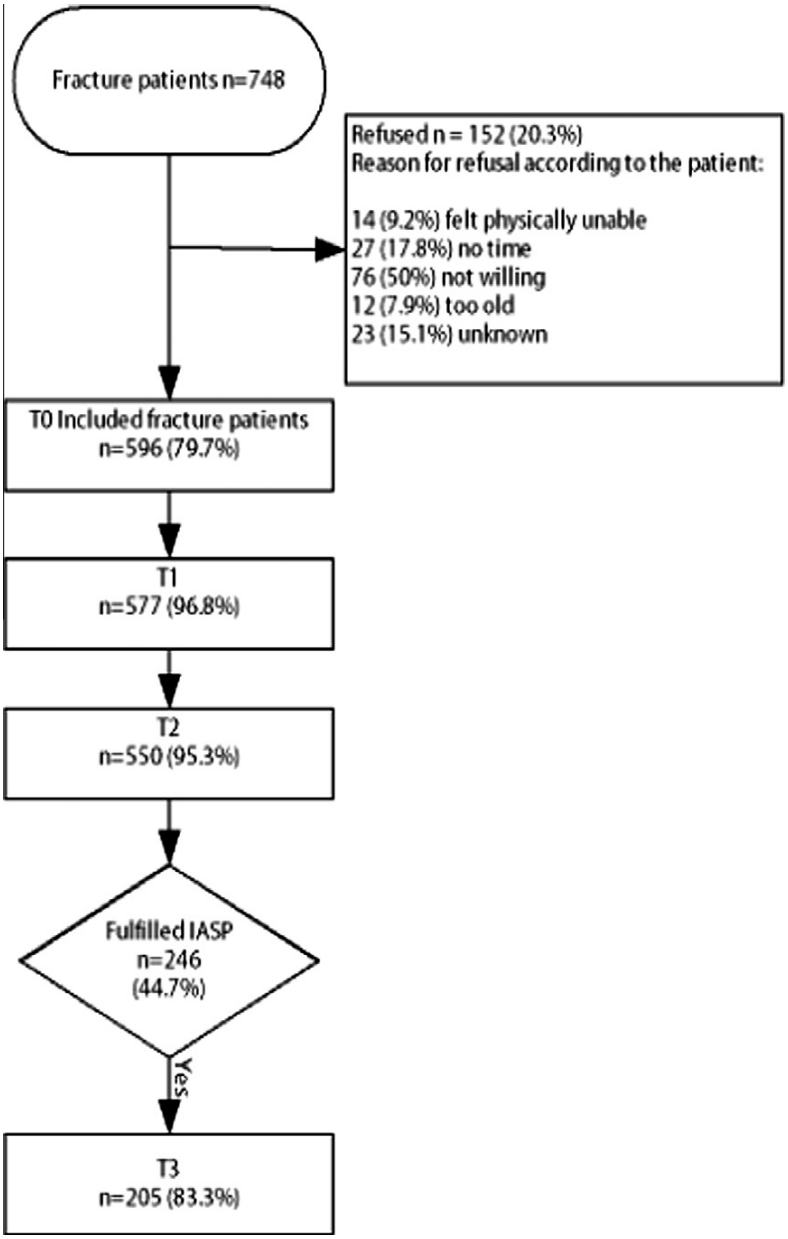

Fig. 2. Flowchart for patient inclusion in the present study. IASP = International Association for the Study of Pain.

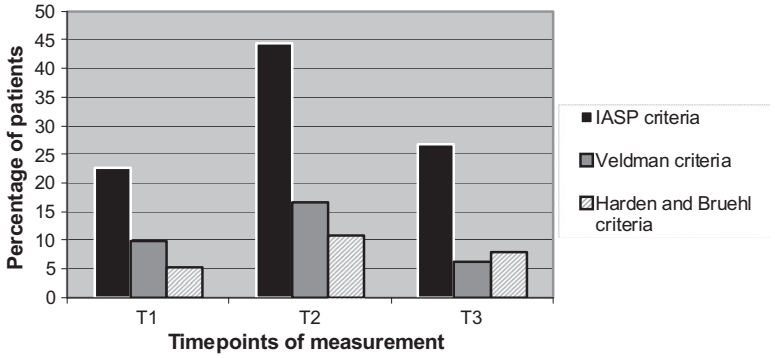

Fig. 3. Percentage of patients fulfilling the different sets of criteria by time points of measurement.

Table 1
Relative frequencies of demographic and medical factors in patients with CRPS1 compared with patients without CRPS1 (non-CRPS1).

Factor	CRPS1 (n = 42)	Non-CRPS1 (n = 453)	*P* value
Sex, n (%)			
Male	11 (26.2)	162 (35.8)	.24
Female	31 (73.8)	290 (64.2)	
Age in years	Mean: 54.0 Range: 22–82 IQR: 40.2–67.4	Mean: 49.8 Range: 18–90 IQR: 33.0–63.6	.18
Education level, n (%)			
No education	1 (2.4)	2 (0.44)	.19
Primary school	6 (14.3)	41 (9.1)	
Junior vocational education	10 (23.8)	105 (23.2)	
Lower general secondary education	8 (19.0)	75 (16.6)	
Senior vocational education	5 (11.9)	87 (19.2)	
Higher general secondary education/ pre-university education	6 (14.3)	59 (13.1)	
Bachelor's degree	6 (14.3)	62 (13.7)	
Master's degree	0 (0.0)	21 (4.6)	
Fracture location, n (%)			
Ankle	21 (50.0)	117 (25.8)	.002
Foot	3 (7.1)	100 (22.1)	
Wrist	18 (42.9)	209 (46.1)	
Hand	0 (0.0)	27 (6.0)	
Dominant hand, n (%)	11 (61.1)	108 (45.4)	.23
CRPS1 in the past, n (%)	2 (5.1)	8 (1.8)	.20
Intra-articular fracture, n (%)	21 (50.0)	131 (29.4)	.006
Fracture reduction, n (%)	17 (40.5)	122 (27.1)	.07
Dislocation, n (%)	27 (64.3)	177 (39.4)	.003
Days in plaster	Mean: 47.8 SD: 17.50	Mean: 42.0 SD: 13.64	.36
Type of fracture treatment n (%)			
Plaster	35 (83.3)	400 (88.9)	.41
Surgery and plaster	7 (16.7)	47 (10.4)	
Tape	0 (0.0)	3 (0.7)	

CRPS1 = complex regional pain syndrome type 1; IQR = interquartile range.

Table 2
Prediction of CRPS1 in the study population.

Covariate	B	Exp (B)	*P* value
Age	.017	1.017	.093
Dislocation	−1.019	.361	.004
Intra-articular	−.890	.411	.009
Foot*	−.604	.547	.354
Ankle*	1.129	3.094	.004
Constant	−2.525	.080	<.001

R2 = .064 (Cox and Schnell), .140 (Nagelkerke). Model $\chi^2_{(8)} = 7{,}104$, $P = .53$.
CRPS1 = complex regional pain syndrome type 1.
* The wrist was used as the reference category.

Budapest criteria [22] were first published. These criteria are those of Harden and Bruehl extended with allodynia to deep somatic pressure and to joint movement. We recommend the use of the Budapest criteria [22] in future studies on CRPS1.

Another explanation for the lower incidence is the exclusion of comminuted fractures in the present study; others have shown that patients with a comminuted fracture have a higher chance of developing CRPS1 [9,41,43]. Also, the different relative frequencies in the distribution of the various types of fractures in our participants might explain the difference in CRPS1 rates compared with the literature.

In the present study, the majority of patients with CRPS1 were female (73.8%), which is similar to other reports [28,29]. However, no significant difference was found in the proportion of women who developed CRPS1 compared with the proportion of men who developed CRPS1. This finding is in accordance with the proposed explanation that the prevalence of wrist fractures in women is the main cause of their relatively higher representation among CRPS1 patients; however, this remains a matter of dispute [26,41].

A relationship between specific fractures and the occurrence of CRPS1 has also been proposed. Sarangi et al. reported that 30% of patients with a tibial fracture develop CRPS1; in our study a similar number was identified (27.3%). The occurrence of CRPS1 after a (displaced) distal radius fracture ranges from 0.9% to 18% [12,13,19,23,30,35,36]. A problem with comparing hazard ratios for developing CRPS1 after a distal radius fracture is the fact that different definitions for this type of fracture are used (e.g., a Colles fracture included or not). In our study, 8.3% of patients with a distal radius fracture (including a Colles fracture) developed CRPS1. The percentage of patients developing CRPS1 after a Colles fracture ranges from 1% to 37% [3,4,6,10,14–16,32]. In the present study, 14% of the patients with a Colles fracture developed CRPS1, thus falling in the middle of the reported range. In our study, there was a significant difference in the fracture location between patients with and without CRPS1. Patients with an ankle fracture had a higher chance of developing CRPS1 compared with patients with other fracture locations. However, there was no significant difference in the chance to develop CRPS1 between the upper and lower extremity. This finding is in contrast with those of others who reported that the upper extremity was affected more often than the lower extremity [28,29,33,39].

There is no consensus on the association between type of fracture and onset of CRPS1. Although several studies found no association between fracture type and the probability of developing CRPS1 [4,14,34], others concluded that CRPS1 occurs more often after more severe fractures [6,41]. Also, there is no consensus on the influence of dislocation of the fracture on the onset of CRPS1. Roumen et al. [32] reported that dislocation does have an effect. However, based on their prospective study on CRPS1 after a Colles fracture, Bickerstaff and Kanis [6] disagree with this observation. Our results support those of Roumen et al. Moreover, our patients with CRPS1 had significantly more intra-articular fractures than patients without CRPS1; this finding supports the results of Zollinger et al. [41] but not the results of others [4,19,32,40].

Furthermore, in the current study, patients who developed CRPS1 more often reported musculoskeletal comorbidities and rheumatoid arthritis than those who did not develop this syndrome. In other words, patients with these comorbidities seem to be more susceptible to developing CRPS1. In addition, there are some indications for a genetic susceptibility for CRPS1 [5,24,38]. Also, there is increasing evidence for immunological involvement in this syndrome, but no definite conclusions can be drawn [7,17,20,25]. Some have reported a frequent (spontaneous) resolution of (all) the signs and symptoms of CRPS1 [6,33,44]. In the present study, the mean number of symptoms between T2 and T3 showed a significant decrease, but none of the 37 CRPS1 patients who participated at T3 (1 year after trauma) were reported to be symptom free. Sarangi et al. [34] found that 22% of the CRPS1 patients still reported symptoms at 1 year posttrauma.

At baseline, patients with CRPS1 rated their pain significantly higher than patients without CRPS1. Moreover, because their pain ratings remained higher, pain could be an important predictor of the development of CRPS1.

Concerning quality of life, CRPS1 patients did not score differently on mental health, but their physical functioning was lower than that of patients without CRPS1 at both T0 and T2. This difference might be explained by the fact that these patients suffer from more symptoms than patients without CRPS1.

The number of patients fulfilling the CRPS1 criteria 1 year posttrauma is relatively low. One explanation is the fact that several symptoms of these criteria (e.g., swelling and temperature asym-

metry) are related to inflammation, which is less pronounced in chronic CRPS1.

Of the patients who were referred to the Pain Treatment Center for diagnosis, 18.1% refused or were unable to attend. Nevertheless, we assume that few CRPS cases were missed, because patients with only a few symptoms apparently felt no need to visit a physician and the chance of these patients developing CRPS1 is low.

In conclusion, an intra-articular fracture, an ankle fracture, and dislocation appeared to be risk factors for the development of CRPS1. Furthermore, in the present study none of the CRPS1 patients were free of symptoms at 1 year after trauma, confirming that CRPS1 is a disabling, long-lasting syndrome.

Conflict of interest statement

All authors declare that they have no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2012.01.026.

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