# Complex Regional Pain Syndrome type I
# &
# Amputation

rijksuniversiteit groningen

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# &

# Amputation

**Proefschrift**

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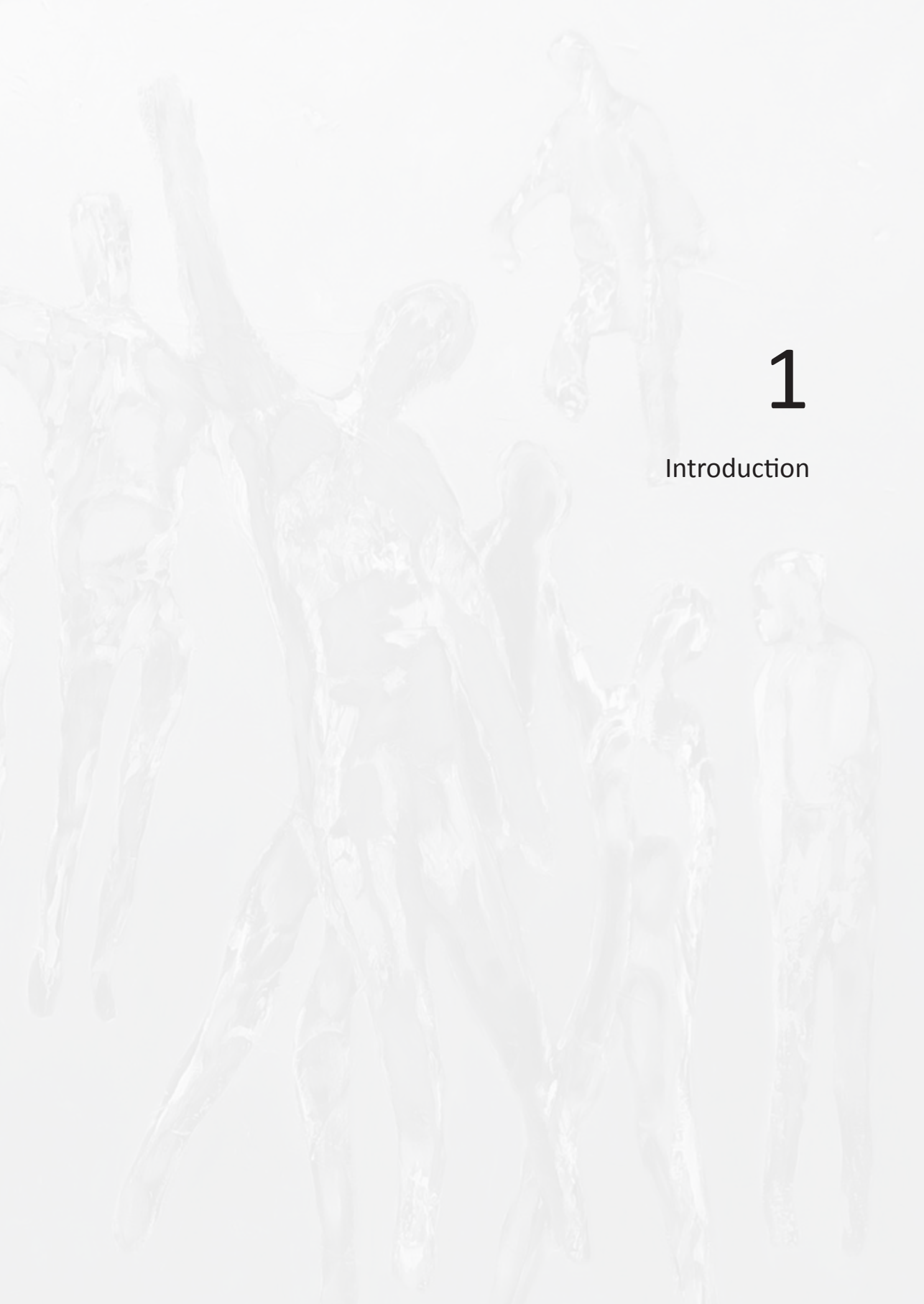
# Contents



# 1

# Introduction

> *"In January 1991 Mrs X, a 46- year old woman, experiences pain in her left foot up to her knee suddenly without a precipitating trauma. The foot and leg are examined by multiple medical specialists and she is diagnosed with Complex Regional Pain Syndrome type I, in those days known as Sudeck's atrophy or reflex sympathetic dystrophy."*

Complex Regional Pain Syndrome type I (CRPS-I) is characterized by severe pain in the distal part of an extremity that may develop spontaneously or after a noxious event (1, 2). The intensity of the pain is disproportionate to the inciting event. The pain is described as burning and continuous, and it may worsen with movement, touch, or stress. Abnormal swelling, changes in skin color and temperature, and changes in sweating in the region of the pain may occur (1). The incidence of CRPS-I is 40.4 and 11.9 per 100,000 person-years at risk for females and males, respectively (3). The average age at onset is 37.5 years (standard deviation [SD], 12 years). The duration of the syndrome ranges from one to 46 years (4). The pathophysiology of CRPS-I is still unknown. Several hypotheses have been suggested e.g. oxidative stress, micro vascular pathology, aberrant inflammatory mechanisms, vasomotor dysfunction, and maladaptive neuroplasticity (5-7).

> *"A period of rehabilitation treatment starts and gives some relieve of symptoms in the beginning, but does not cure the CRPS-I in her foot and leg. In the following years Mrs X tries many other treatments, but without any satisfactory result of complete recovery. In 1999 the foot is swollen but the calf shows atrophy in comparison to her other leg. Both foot and leg have a blue-black appearance and the knee can only partly extend. Mrs X uses a wheelchair outdoors and crutches indoors since she cannot bear touch of or weight on her leg anymore. She is severely disabled since the pain influences her mood, her daily life activities and social life.*

Patients with CRPS-I are treated in accordance with national or international guidelines (8-11). The syndrome usually requires long, intensive treatment. A range of different therapies has been described, including pharmaceutical treatment, injection therapy, surgical sympathectomy, spinal cord stimulation, and paramedical treatment. However, evidence of the effectiveness of most of these treatments is sparse.

Studies among CRPS-I patients showed that a majority of patients (91%) had persistent physical symptoms at 5.5 years after onset of the syndrome and 64% of patients still fulfilled the diagnostic criteria two or more years after onset (12). Other studies have shown that pain intensity was still high 15 years after onset (13) and that 81% of patients stopped working as a result of the pain (4). Sometimes all available or advised treatment options fail. About 16% (95% CI: 9 to 22) of patients in a CRPS-I outcome study reported the syndrome to be severely progressive despite interventions (12). In a minority of

cases treatment does not reduce or resolve pain and the affected limb may become dysfunctional. This painful and dysfunctional limb can prevent participation in daily life activities and work (12).

> *"Mrs X feels stuck with her leg which she by that time addresses as an obstacle. After eight years of struggling she returns to the outpatient rehabilitation clinic, her last resort, and she requests amputation of her leg."*

Requests for amputation from patients with CRPS-I come after long series of failed treatment. Amputation for long-standing, therapy-resistant CRPS-I remains controversial and topic for heated debates among medical specialists.

Looking back in history, amputation for CRPS-I was first mentioned by Klaer in 1948 (14). Several (case) studies on this topic have been published since then. When guidelines mention amputation as a last resort treatment option this is based on only two studies (15, 16). However more studies are available regarding amputation and CRPS-I, therefore the first research question: "What is known in literature on beneficial and adverse affects of amputation in case of CRPS-I" was addressed in a systematic review.

Since early 90s (last century), patients with long-standing, therapy-resistant CRPS-I with a request for amputation from all over the country turn to the outpatient Rehabilitation clinic of the University Medical Center Groningen (UMCG) in The Netherlands. After two publications in Prosthetics and Orthotics International in 1994 and 1997 (17, 18), an increase in requests addressed at Geertzen (physiatrist at UMCG) and his team followed. Guidelines warn against the use of amputation as a last resort treatment option, based on fear of recurrence of the syndrome. The effect of an amputation on quality of life, important to many patients, is not clear from these guidelines and gave rise to the second research question: "How do patients rate their quality of life after amputation of the limb affected by CRPS-I in the UMCG?"

Frequently asked questions by both patients as well as clinicians involve life after amputation including risk of recurrence of the syndrome, occurrence of phantom pain and possibilities for prosthesis fitting. Answers to these questions are mainly based on experiences from patients amputated previously and what has become known from literature since 1948. These questions are also part of the second research question: "What are the rates of recurrence of the syndrome, phantom pain and what are the possibilities for prosthesis fitting in the patients who were amputated in the UMCG because of CRPS-I?"

After several patients, suffering from long-standing, therapy-resistant CRPS-I, had been amputated, the UMCG based team got the overall impression that patients benefitted from the amputation and more patients followed. Since this overall impression was contradictive to what was known from literature and guidelines, a search into characteristics of possible answers lead to believe that resilience of these patients may be a key factor

in the successful amputation of these patients. Resilience is defined as “the process of adapting well in the face of adversity, trauma, tragedy, threats, or even significant sources of stress — such as family and relationship problems, serious health problems, or workplace and financial stressors” (19). The belief that resilience may be a key factor resulted in our third research question: “What are the levels of resilience and post amputation outcomes (CRPS-I symptoms, quality of life, psychological distress and participation in daily life) and what are the associations between resilience and these outcome variables in patients amputated because of CRPS-I.”

In the outpatient clinic, patients meet with the UMCG based team (a team of several specialists) to discuss their wish for amputation. Since outcome after amputation for CRPS-I is negatively addressed in literature, and contradictory to outcome of the population studied in the UMCG, an urge arose to describe the process of informed decision making in the UMCG in order to help other clinicians who face these requests. This process is the main topic of the fourth research question: “What aspects are included in the process of informed decision making in amputations for CRPS-I?”

Sampling of muscle and nerve tissue from the amputated limbs has been part of the procedure since 2000. Analyses of muscle biopsies from CRPS-I affected limbs suggested a process of denervation, re-innervation and denervation again (20). In literature, subtle nerve changes from skin biopsies have been described in CRPS-I (21-24). However, CRPS-I is by definition typically distinguished from CRPS-II by the (clinical) absence versus presence of a nerve lesion (1). Doubts on this differentiation between type I and II have been raised previously (5, 7). Therefore a need for research into nerve biopsies to get more insight in this process seemed logical and was the inspiration for the last research question of this thesis: “What are the characteristics of nerve tissues in limbs amputated because of CRPS-I ?”

> *“After careful examination and discussion with other specialists and Mrs X, the decision for a knee disarticulation amputation follows in 2000.”*

Thus the outline of this thesis is;

*Chapter 2*
Therapy-resistant Complex Regional Pain Syndrome type I: To Amputate or Not?
Research question 1: “What is known in literature on beneficial and adverse affects of amputation in case of CRPS-I?”

*Chapter 3*
Amputation for long-standing, therapy-resistant Complex Regional Pain Syndrome type I
Research question 2:“How do patients with CRPS-I rate their quality of life after amputation in the UMCG?”
“What are the rates of recurrence of the syndrome, phantom pain and what are the possibilities for prosthesis fitting in the patients with CRPS-I who were amputated in the UMCG?”

*Chapter 4*
Resilience in patients with amputation because of Complex Regional Pain Syndrome type I
Research question 3: “What is the association between resilience and post amputation outcome of patients amputated because of CRPS-I?”

*Chapter 5*
Informed decision making in Complex Regional Pain Syndrome type I and amputation
Research question 4: “What aspects are included in the process of informed decision making in amputation for CRPS-I?”

*Chapter 6*
Peripheral nerve pathology in Complex Regional Pain Syndrome type I
Research question 5: “Is nerve pathology present in tissue from CRPS-I affected limbs?”

*Chapter 7*
General Discussion
*Including the sequence of Mrs X’s story.*

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# 2

# Therapy-resistant Complex Regional Pain Syndrome type I: To Amputate or Not?

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# Abstract

## Background

Amputation for the treatment of long-standing, therapy-resistant Complex Regional Pain Syndrome type I (CRPS-I) is controversial. An evidence-based decision regarding whether or not to amputate is not possible on the basis of current guidelines. The aim of the current study was to systematically review the literature and summarize the beneficial and adverse effects of an amputation for the treatment of long-standing, therapy-resistant CRPS-I.

## Methods

A literature search, using MeSH terms and free text words, was performed with use of PubMed and EMBASE. Original studies published prior to January 2010 describing CRPS-I as a reason for amputation were included. The reference lists of the identified studies were also searched for additional relevant studies. Studies were assessed with regard to the criteria used to diagnose CRPS-I, level of amputation, amputation technique, rationale for the level of amputation, reason for amputation, recurrence of CRPS-I after the amputation, phantom pain, prosthesis fitting and use, and patient functional ability, satisfaction, and quality of life.

## Results

One hundred and sixty articles were identified, and 26 studies with Level-IV evidence (involving 111 amputations in 107 patients) were included. Four studies applied CRPS-I diagnostic criteria proposed by the International Association for the Study of Pain, Bruehl et al., or Veldman et al. Thirteen studies described symptoms without noting whether the patient met diagnostic criteria for CRPS-I, and 9 studies stated the diagnosis only. The primary reasons cited for amputation were pain (80%) and a dysfunctional limb (72%). Recurrence of CRPS-I in the stump occurred in 31 of 65 patients, and phantom pain occurred in 15 patients. Thirty-six of 49 patients were fitted with a prosthesis, and 14 of these patients used the prosthesis. Thirteen of 43 patients had paid employment after the amputation. Patient satisfaction was reported in 8 studies, but the nature of the satisfaction was often not clearly indicated. Changes in patient quality of life were reported in 3 studies (15 patients); quality of life improved in 5 patients and the joy of life improved in another 6 patients.

## Conclusions

The previously published studies regarding CRPS-I as a reason for amputation all represent Level-IV evidence, and they do not clearly delineate the beneficial and adverse affects of an amputation performed for this diagnosis. Whether to amputate or not in order to treat long-standing, therapy-resistant CRPS-I remains an unanswered question.

# Introduction

Complex Regional Pain Syndrome type I (CRPS-I), formerly termed reflex sympathetic dystrophy, is characterized by severe pain in the distal part of an extremity that may develop after a noxious event or spontaneously. The intensity of the pain is disproportionate to the inciting event. The pain is described as burning and continuous, and it may worsen with movement, touch, or stress. Abnormal swelling, changes in skin color and temperature, and changes in sweating in the region of the pain vary over time (1).

Various treatments for CRPS-I have been described, including physical therapy, medication, sympathetic nerve block, sympathectomy, and neuromodulation; however, limited evidence is available regarding the effectiveness of these therapies (2,3). To the disappointment of both the patient and the clinician, therapy for long-standing CRPS-I does not result in a cure in many cases and may not even provide any beneficial effects. CRPS-I should therefore be considered a severe condition with a high likelihood of continuing impairment (4). Long-standing, therapy-resistant CRPS-I may culminate in severe pain, infections, and contractures that impede daily activities and participation in society. An amputation may be indicated if a life-threatening infection develops in a patient with therapy-resistant CRPS-I. In other cases, the impairment and/or pain may be severe enough that a patient requests amputation. However, CRPS-I as an indication for amputation remains controversial.

There is ongoing debate regarding the optimal level of amputation for patients with CRPS-I and regarding the prevalence of CRPS-I recurrence and changes in the quality of life after the amputation. Evidence-based guidelines regarding CRPS-I currently state that there is insufficient evidence to demonstrate that amputation contributes positively to the treatment of patients with long-standing, therapy-resistant CRPS-I (3,5). However, those guidelines excluded information published in case reports and are consequently based on only 2 studies (6,7).

Therefore, the primary aim of the current study was to systematically review the available literature, including case reports, regarding CRPS-I as a reason for amputation and to summarize the beneficial and adverse effects of an amputation. A secondary aim was to provide additional information on which clinicians can base their advice to patients with long-standing, therapy-resistant CRPS-I regarding whether to perform an amputation.

# Materials and Methods

### Study Identification and Selection

A literature search was performed with use of PubMed and EMBASE, using MeSH (Medical Subject Headings) terms and free text words associated with Complex Regional Pain Syndrome (including Complex Regional Pain Syndrome, CRPS, dystrophy, algodystrophy, Südeck, and reflex sympathetic dystrophy) combined with amputation. All original studies describing CRPS-I as a reason for amputation and published in Dutch, English, or Danish prior to January 2010 were considered for inclusion. The focus of our review was on the beneficial and adverse effects of amputation as a treatment for patients with CRPS-I, and not on the effects of other treatments. The reference lists of the identified studies were also searched for additional relevant studies that had not been found by the database search.

We excluded studies regarding CRPS-II (causalgia), expert opinions that did not include descriptions of clinical cases, commentaries by editors, commentaries on previous publications or poster abstracts, and studies that described the onset of CRPS-I following an amputation.

### Study Analysis

Each of the included studies was assessed to determine whether it reported on the CRPS-I diagnostic criteria used (table 1), level of amputation, amputation technique, rationale for the level of amputation, reason for amputation, recurrence of CRPS-I after the amputation, phantom pain, prosthesis fitting and use, and patient functional ability, satisfaction, and quality of life. As we were not aware of any formal tool suitable for assessing these case studies, we developed our own assessment tool specific to this patient group and based on assumptions regarding adequacy of reporting. A random sample of 3 studies was assessed by 2 of the authors (MIB, JHBG) to determine the completeness of the assessment tool. These two authors then determined by consensus whether to include or exclude each study. Finally, the same 2 authors used the tool to independently assess each of the included studies. Discrepancies were resolved by discussion until a consensus was reached; a third author (PUD) provided a binding verdict if no consensus could be reached.

### Data Extraction

Data were extracted from the included studies independently by 2 authors (MIB, JHBG). Data for the individual patients were extracted when available; otherwise, summary statistics were extracted. Since the reporting in many of the studies appeared to be incomplete, results are presented as the number of patients with a particular outcome divided by the number of patients for which that outcome was reported, expressed as the percentage and an associated 95% confidence interval.

Table 1

## Diagnostic criteria for CRPS-I as applied in the studies

**Veldman criteria[33]**

(1) 4 or 5 of:
- – Unexplained diffuse pain
- – Difference in skin colour relative to other limb
- – Diffuse edema
- – Difference in skin temperature relative to other limb
- – Limited active range of motion

(2) Occurrence or increase of above signs and symptoms after use

(3) Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury

**IASP criteria[1]**

(1) The presence of an initiating noxious event, or a cause of immobilization.

(2) Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.

(3) Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.

(4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

**Bruehl criteria[32]**

(1) Continuing pain which is disproportionate to any inciting event

(2) Must report at least 1 symptom in each of the 4 following categories
- – Sensory: hyperesthesia
- – Vasomotor: temperature asymmetry and/or skin color changes and/or skin color asymmetry
- – Sudomotor/edema: edema and/or sweating changes and/or sweating asymmetry
- – Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia)and/or trophic changes (hair, nail, skin)

(3) Must display evidence of at least 1 sign in 2 or more of the following categories
- – Sensory: hyperalgesia (to pinprick) and/or allodynia (to light touch)
- – Vasomotor: temperature asymmetry and/or skin color changes and/or asymmetry
- – Sudomotor/edema: edema and/or sweating changes and/or sweating asymmetry
- – Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

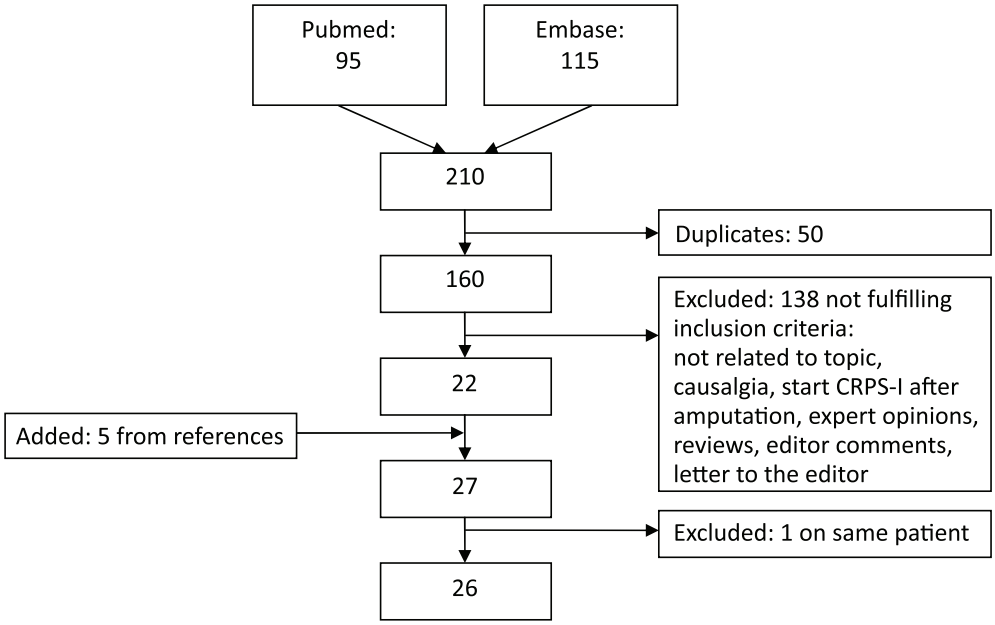
# Results

## Study Inclusion

One hundred and sixty candidate articles were identified by the literature search (after removal of duplicates). One hundred and thirty-eight of these articles were excluded: 110 were not related to the topic, 9 involved causalgia, 8 involved the onset of CRPS-I following amputation, 7 were expert opinions or reviews regarding CRPS-I, 3 were comments by an editor or letters to an editor, and one was not in any of the specified languages. Five additional articles were identified by examining the reference lists of the candidate articles. Two articles very likely involved the same patient (8,9); the less informative of these articles was excluded (9). Thus, 26 studies were available for analysis (figure 1).

Figure 1

Flowchart of the study inclusion




The 26 included articles were published between 1948 and 2009 (table 2). Eleven articles reported on a group of patients who had CRPS-I (case series). Five articles reported on both patients with CRPS-I and patients without CRPS-I, but a subgroup could be identified as having undergone amputation due to CRPS-I. The remaining 10 articles reported on a single patient. No case-control studies were identified, and the studies therefore all represented Level-IV evidence.

Table 2

Overview of studies concerning CRPS-I as a reason for amputation since 1948.

| Author | Term used | Publication date | Type of study | Patients with amputation (n) | Diagnostic criteria |
|---|---|---|---|---|---|
| Klaer | PTD | 1948 | Subgroup | 1 | - |
| Lagier, Van Linthoudt | SA | 1979 | Case series | 2 | - |
| Poplawski et al | PTD | 1983 | Subgroup | 2 | + |
| Churcher | AD | 1984 | Single case | 1 | + |
| Rohrich et al | RSD | 1985 | Single case | 1 | + |
| Eyres et al | RSD | 1990 | Single case | 1 | + |
| Erdmann, Wynn-Jones | RSD | 1992 | Case series | 2 | + |
| Ritt, Jansenb | PTD | 1992 | Case series | 2 | + |
| Chiowanich et al | RSD | 1993 | Single case | 1 | + |
| Szeinberg-Arazi et al | RSD | 1993 | Subgroup | 10 | - |
| Geertzen, Eisma | RSD | 1994 | Single case | 1 | + |
| Stam, Van der Rijst | RSD | 1994 | Case series | 7 | - |
| Dielissen et al | RSD | 1995 | Case series | 28 | Veldman[33] |
| Geertzen et al | RSD | 1997 | Single case | 1 | + |
| Van der Laan et al | RSD | 1998 | Case series | 8 | Veldman[33] |
| Hooshmand, Hashmi | CRPS-I | 1999 | Subgroup | 11 | + |
| Lundborg et al | CRPS-I | 1999 | Case series | 2 | + |
| Emmelot et al | RSD | 2000 | Single case | 1 | - |
| Busfield | RSD | 2004 | Subgroup | 1 | - |
| Lausten-Thomsen, Laursena | CRPS-I | 2005 | Single case | 1 | + |
| Dudzinski | CRPS-I | 2005 | Single case | 1 | - |
| Albrecht et al | CRPS-I | 2006 | Case series | 2 | - |
| De Boer et alb | CRPS-I | 2007 | Case series | 3 | - |
| Enggaard et ala | CRPS-I | 2008 | Single case | 1 | + |
| Groeneweg et al | CRPS-I | 2008 | Case series | 2 | Bruehl[32] |
| Hulsman et al | CRPS-I | 2009 | Case series | 14 | IASP[1] |
| Total | | | | 107 | |

*Language: aIn Danish, bIn Dutch; PTD = posttraumatic dystrophy, SA = Sűdeck's atrophy, AD = algodystrophy, RSD = Reflex Sympathetic Dystrophy, - = No diagnostic criteria applied or only reporting of symptoms, + = symptoms reported, without reporting if patient fulfilled criteria; IASP = International Association for the Study of Pain.*

## Patients

One hundred and seven patients were described. Thirty-eight patients were men and 55 were women; the sex was not reported for the remaining 14 patients in three studies (10-12). The mean age at amputation, calculated on the basis of 21 studies (54 patients), was 40.3 years (7,8,13-31); a median age of 42 years (range, 23 to 73 years) was reported in

one additional study (6). The mean time between CRPS-I onset and amputation, calculated on the basis of 18 studies (48 patients), was 69 months (7,8,13-20,22-25,27,28,30,31); a median time of 30 months (range, 5 months to 18 years) was reported in one additional study (6). The age or the time between onset of the syndrome and amputation could not be derived from the reported information in the remaining studies. The duration of follow-up after amputation was reported in 8 studies (22 patients); the median duration was 16.5 months and the mean was 28 months (15,17-20,23,30,31).

### CRPS-I Diagnostic Criteria

Diagnostic criteria for CRPS-I proposed by the International Association for the Study of Pain (IASP)(1) were applied in one study (14 patients) (15), criteria proposed by Bruehl et al. (32) were applied in one study (2 patients) (22), and criteria proposed by Veldman et al. (33) were applied in 2 studies (36 patients) (6,13). Thirteen studies (27 patients) reported symptoms without noting whether patients fulfilled formal criteria for CRPS-I prior to the amputation (8,10,11,16-19,21,23,24,28,30,31). The symptoms reported in these studies included many different sensory, autonomic, and motor changes (e.g., pain, skin temperature and color changes, swelling, hyperalgesia, allodynia, skin and muscle atrophy, and decreased range of motion). The remaining 9 studies (28 patients) reported the diagnosis without indicating either the diagnostic criteria used or the symptoms (7,12,14,20,25-27,29,34). Radiographic findings were reported in 9 studies (7,8,11,16-18,21,29,30). The first use of the term CRPS-I in the studies included in this review was in 1999 (table 2).

The inciting event was reported for 93 patients in 24 studies (6-8,12-31,34), and included immobilization, soft-tissue injury, and fracture. An unknown cause of the CRPS-I was reported in 4 of the 93 patients (7,15,27). The inciting event was not discussed in the remaining 2 studies (14 patients).

### Treatment Prior to Amputation

Limited information regarding treatment prior to the amputation was reported in the included studies, but treatments employed included physical therapy, medication, sympathetic nerve block, sympathectomy, neuromodulation, occupational therapy, and psychological interventions.

### Amputations: Limb, Level, and Technique

A total of 111 amputations were reported. Four patients each had 2 limbs amputated; these amputations were performed at the same time or within a short time frame. Thirty-seven amputations were reported to involve the upper limb and 63 the lower limb (table 3). The level of amputation was not reported in one study (11 patients) (10). The rationale for the level of amputation was reported in one study (8 patients) (13), in which the location was described as proximal to the level of disturbance of skin sensation. The surgical technique and the duration of the surgery were not reported in any of the studies. Use of epidural pain medication was reported in one study (8 patients) (13). Intra-operative complications were reported to be absent in 5 studies (33 patients) (6,16-18,20) and were not discussed in the remaining studies. Post-operative complications were discussed in 9 studies (44 patients); wound infections, delayed healing, or pressure ulcers were noted in 14 patients

Table 3

Level of amputation in patients with CRPS-I

| Amputation level | Number of amputations | |
|---|---|---|
| Upper limb | 37 | |
| Transhumeral | | 12 |
| Elbow disarticulation | | 0 |
| Transradial | | 10 |
| Fingers or rays | | 2 |
| Level not described | | 13 |
| Lower limb | 63 | |
| Transfemoral | | 16 |
| Knee disarticulation | | 8 |
| Transtibial | | 12 |
| Syme/toes | | 2 |
| Level not described | | 25 |
| Not described | 11 | |
| Total | 111* | |

**Some patients were amputated on more than one limb.*

in 2 of the studies and complications were reported to be absent in the other 7 studies; thus, the rate of post-operative complications was 32% (95% confidence interval [CI], 20% to 47%) (6-8,16-20,22).

## Reasons for Amputation

The reasons for amputation were reported in 20 studies (54 patients) (7,8,13-24,26-31). The predominant reasons for amputation were pain, a dysfunctional limb, and gangrene, infection, or ulcers (table 4). Some studies reported that the amputation was explicitly requested by the patient. A combination of reasons for amputation was reported in most of the 20 studies, with 2, 3, or 4 reasons reported for 45 of the patients (83%) (7,8,13-15,17-21,23,26-31).

## Recurrence of CRPS-I and Occurrence of Phantom Pain

Data regarding CRPS-I recurrence were reported in 14 studies (table 4), although the criteria used for the diagnosis of recurrence were not reported. Thirty-one of 65 patients had a reported recurrence in the stump. A more extensive amputation was performed because of recurrence in 2 patients (21,23). One of these patients also developed CRPS-I in the contra-lateral leg, which was also treated with amputation (23). Two additional patients developed CRPS-I in a different extremity following the initial amputation but did not require an amputation of the second extremity (28,31). Phantom pain was reported in 15 patients in 15 studies (table 4) (7,11,14,16-18,20,21,23,24,27,28,30,31,34).

Table 4

Summary of reasons for amputation and post-amputation outcome in patients with an amputation because of long-standing, therapy resistant CRPS-I

| | Studies# | (n) | (r) | % (95% CI) |
|---|---|---|---|---|
| Reason for amputation | | 54 | | |
| – pain | 7;8;13-15;17-19;21;23;24;26-31 | | 43 | 80% (67 to 88) |
| – dysfunctional limb | 7;8;13-15;17;18;20;23;26-29;31 | | 39 | 72% (59 to 82) |
| – gangrene/infections/ulceration | 7;13;15-18;20;22;23;26;27;29-31 | 65 | 25 | 46% (34 to 59) |
| – explicit wish of the patient | 15;17;18;21-23;26;27;31 | | 24 | 44% (32 to 58) |
| Post-Amputation | | | | |
| Recurrence of CRPS-I | | 37 | | |
| – stump | 6-8;14;15;17-21;23;27;28;31 | 49 | 31 | 48% (36 to 60) |
| – 1 or more other extremities | 23;28;31 | | 3 | 5% (2 to 13) |
| Phantom pain | 7;11;14;16-18;20;21;23;24;27;28;30;31;34 | 19 | 15 | 41% (26 to 57) |
| Prosthesis | | 13 | | |
| *Upper limb* | 6;7;16-18;31;34 | | | |
| – fitted with prosthesis | | 30 | 13 | 68% (46 to 85) |
| – use of prosthesis | | 23 | 3 | 23% (8 to 50) |
| *Lower limb* | 6;20;27;31;34 | | | |
| – fitted with prosthesis | | 11 | 23 | 77% (59 to 88) |
| – use of prosthesis | | 43 | 11 | 48% (29 to 67) |
| Level of functioning | | | | |
| – no limitation in self care or ADL | 6;7;18;20;27;34 | | 9 | 82% (52 to 95) |
| – paid job | 6;7;18;20;27;31;34 | | 13 | 30% (19 to 45) |

*# numbers are reference numbers; (n) total of patients for whom relevant information is available; (r) patients with outcome; ADL = activities of daily living; 95% CI = 95% confidence interval*

## Prostheses, Patient Satisfaction, and Changes in Quality of Life

The fitting of a prosthesis was reported in 9 studies (49 patients) (6,7,16-18,20,27,31,34). Thirty-six patients (73%) were fitted with a prosthesis, and 14 (39%) of the 36 used the prosthesis (table 4). The latter includes one patient who was reported to have been ''successfully fitted,'' (16) which we interpreted to indicate use of the prosthesis after the fitting. Some information regarding the patient's functional ability was reported in 7 studies (52 patients) (6,7,18,20,27,31,34) (table 4). Patient ''satisfaction'' was reported in 8 studies (51 patients) (6,7,18,23,27,30,31,34), but it was often not clear whether this ''satisfaction'' was related to functional ability, pain reduction, or prevention of infection. Changes in quality of life were reported in 3 studies (15 patients) (27,31,34). Quality of life improved in all 3 of the patients described by De Boer et al. (27) and in both of the patients described by Lundborg et al. (31). ''Joy of life'' was reported to improve in 6 of the 10 patients in the remaining study (34).

# Discussion

The literature review revealed 26 studies describing 107 patients who underwent amputation for the treatment of long-standing, therapy-resistant CRPS-I. However, only one study in 2008 and one in 2009 (15,22) used the diagnostic criteria for CRPS-I proposed by the IASP (1) or the criteria proposed by Bruehl et al. (32). This is remarkable since the IASP criteria were published in 1994 and the more stringent criteria of Bruehl et al. were published in 1999. Consequently, we cannot be certain that all of the patients described actually had CRPS-I. The limited use of these internationally accepted criteria has been noted previously, in 2002 (35). Diagnostic criteria for reflex sympathetic dystrophy defined by the American Association for Hand Surgery in 1990 (36) were referred to in some of the other studies, but it was never specifically stated that the patients fulfilled these criteria (7,17). The studies generally also made limited mention of the reasons for amputation, rationale for the level of amputation, amputation technique, complications during or after surgery (including recurrence of CRPS-I), phantom pain, prosthesis use, patient satisfaction, or changes in quality of life.

Recurrence of CRPS-I in the stump following the amputation was reported in 48% of the patients. However, this result was strongly influenced by the outcomes reported in the study by Dielissen et al. in 1995, in which all of the patients were diagnosed with recurrence of CRPS-I (6). The 100% recurrence rate in that study might be related to the application of the criteria proposed by Veldman et al. These criteria permit a diagnosis of CRPS-I even in the absence of pain, which is a curious state of affairs since CRPS-I is a pain syndrome. Alternatively, the high recurrence rate in the study by Dielissen et al. may have stemmed from the specific center at which the study was conducted. We performed a post hoc analysis to assess the impact of the data from Dielissen et al. by reanalyzing the CRPS-I recurrence rate after excluding the 28 patients in that study. Only 3 (8%) of the other 37 patients had a recurrence of CRPS-I in the stump. Thus, the study by Dielissen et al. had a major impact on the estimated recurrence rate. Patients with long-standing, therapy-resistant CRPS-I who are considering amputation should be informed of the variation in published recurrence rates and the consequent difficulty in predicting whether recurrence of the CRPS-I will occur.

The overall prevalence of phantom pain was 41% in the studies that included information on this outcome; the reported prevalence in other published studies has ranged from 9% to 85% (37-40). However, since the frequency of occurrence of phantom pain and the extent of the resulting impairment were not often described in the studies included in the current review, patients with long-standing, therapy-resistant CRPS-I cannot be adequately advised regarding this outcome.

The most commonly reported reasons for amputation were pain and a dysfunctional limb. Gangrene, infection, and ulceration were cited less commonly. Although pain was cited as one of the reasons for amputation in 80% of the patients, none of the studies reported patient satisfaction related to the level of pain following the amputation.

A set of recommendations regarding the amputation procedure used for the treatment of long-standing CRPS-I was published in 1995 (6). One of these recommendations was to amputate proximal to the level of signs and symptoms of CRPS-I in order to reduce the recurrence rate. However, no case studies have been published since 1995 to evaluate the effects of this recommendation.

Only 39% of the patients fitted with a prosthesis actually used it (23% of upper-limb amputees and 48% of lower-limb amputees). A previous report involving amputations for all causes noted a rate of 56% in upper-limb amputees compared with 84% in lower-limb amputees (41). Prosthesis use in our review of patients with an amputation for the treatment of CRPS-I was very low. The included studies did not clearly state the reasons that the prosthesis was not worn, although the residual pain that was commonly reported in the studies may have been one of the reasons. Reports of patient satisfaction and changes in quality of life were so fragmentary that conclusions could not be drawn. Almost one-third of the patients had paid employment after the amputation.

The ratio of men to women who underwent an amputation for the treatment of long-standing, therapy-resistant CRPS-I was 1:1.4. In contrast, the ratio of men to women with CRPS-I has previously been reported to be approximately 1:3 (42), and the ratio of men to women with long-standing CRPS-I (minimum duration, 2 years; mean duration, 5.8 years) has been reported to be 1:4 (4). Thus, men with long-standing CRPS-I appear to undergo amputation at a higher rate than women. This difference could be due to publication bias, if reports regarding men who undergo amputation are more likely to be written and published than reports regarding women. Alternatively, men may choose amputation more often than women do. We do not have evidence regarding these possibilities.

The ratio of upper limbs to lower limbs amputated for the treatment of long-standing CRPS-I was 1:1.7. In comparison, the ratio reported in other studies has ranged from 1:1.5 in a study of the general incidence of CRPS-I (42) to 1:4 in a group of patients with long-standing CRPS-I with a ‘‘poor outcome’’ (4). A ratio of approximately 1:1.6 (similar to the ratio in our review) was found in a group of patients treated for CRPS-I with physical therapy involving exposure to pain (43).

A limitation of case series and case reports, such as those summarized in the current review, is that no controls are present. Consequently, these studies cannot provide strong evidence in favor of or against an intervention. When an outcome occurs in many or all cases, this may reflect a consequence of the intervention. However, a favorable outcome described in a case series or case study may also represent the self-limiting nature of the disease, a placebo effect, regression to the mean, or coincidence. The noted changes in quality of life and functional ability following amputation for the treatment of long-standing, therapy-resistant CRPS-I, for instance, may have resulted from the placebo effect, regression to the mean, or coincidence rather than from the amputation. Thus, conclusions regarding the effects of an amputation cannot be drawn with any certainty from the results of the current review.

Despite these caveats, an amputation can be justified in some cases of long-standing, therapy-resistant CRPS-I (7). In particular, there is little doubt that an amputation is a valid choice for the treatment of therapy-resistant infection after all other CRPS-I treatments have been tried. However, other treatment options should be explored before an amputation is performed for the treatment of severe pain or a dysfunctional limb. For instance, physical therapy involving exposure to pain was recently shown to result in some improvement in function in 95 of 106 patients with long-standing CRPS-I. However, improvement was defined in that study as ''any improvement in walking distance or speed'' if the lower limb was affected or as ''any improvement assessed by means of the Radboud skills test'' if the upper limb was affected. Only 46% of patients would have been considered to have improved if more stringent criteria for functional improvement had been applied. Although the treatment was not specifically aimed at decreasing pain, the average pain score assessed on a visual analog scale decreased from 4.9 to 2.7 (43).

Recently published evidence-based guidelines (3,5) are based primarily on the findings of Stam and van der Rijst (7) and Dielissen et al. (6). The current systematic review also includes data from a number of case reports as well as some larger series. We did not find reason to alter the guidelines regarding amputation for the treatment of long-standing CRPS-I. Evidence regarding the rate of CRPS-I recurrence following amputation remains controversial. Changes in the quality of life following amputation remain poorly reported. The proper level of amputation remains a topic for debate. Further research regarding the level of amputation, recurrence of CRPS-I, patient satisfaction, and changes in quality of life is necessary in order to allow physicians to advise patients considering amputation for the treatment of long-standing, therapy-resistant CRPS-I on the basis of the best evidence. At present, whether to amputate or not in order to treat long-standing, therapy-resistant CRPS-I remains an unanswered question because of weak research design and poor reporting regarding the beneficial and adverse effects of an amputation in this patient population.

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# 3

# Amputation for long-standing, therapy-resistant Complex Regional Pain Syndrome type I

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# Abstract

## Background

Some patients with long-standing, therapy-resistant Complex Regional Pain Syndrome type I (CRPS-I) consider an amputation. There is a lack of evidence regarding the risk of recurrence of the pain syndrome and patient outcomes after amputation. The goal of the present study was to evaluate the impact of an amputation on pain, participation in daily life activities, and quality of life as well as the use of a prosthesis and the risk of recurrence of the pain syndrome in patients with long-standing, therapy-resistant CRPS-I.

## Methods

From May 2000 to October 2008, 22 patients underwent an amputation of a nonfunctional limb at our institution because of long-standing, therapy-resistant CRPS-I. Twenty-one of these patients were included in our study. The median age was 46 years (interquartile range [IQR], 37 to 51 years), the median duration of CRPS-I was 6 years (IQR, 2 to 10 years), and the median interval between the amputation and the study was 5 years (IQR, 3 to 7 years). A semi-structured interview was conducted, physical examination of the residual limb was performed, and the patients completed 2 questionnaires

## Results

Twenty patients (95%) reported an improvement in their lives. Nineteen patients (90%) reported a reduction in pain, 17 patients (81%) reported an improvement in mobility, and 14 (67%) reported an improvement in sleep. Eighteen of the 21 patients stated that they would choose to undergo an amputation again under the same circumstances. Ten of the 15 patients with a lower-limb amputation and one of the 6 with an upper-limb amputation regularly used a prosthesis. CRPS-I recurred in the residual limb of 3 patients (14%) and symptoms recurred in another limb in 2 patients (10%).

## Conclusions

Amputation may positively contribute to the lives of patients with long-standing, therapy-resistant CRPS-I. Patients were likely to use a prosthesis after a lower-limb amputation. The risk of recurrence of CRPS-I was 24%.

# Introduction

Complex Regional Pain Syndrome type I (CRPS-I) may occur after a minor injury, after limb surgery, or spontaneously. Diagnosis is based on patient history and physical examination. Signs and symptoms include pain disproportionate to any inciting event as well as sensory, vasomotor, sudomotor, and motor/trophic changes (1). The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction (1). Complex Regional Pain Syndrome type II is associated with nerve injuries.

The incidence of CRPS-I is 40.4 and 11.9 per 100,000 person-years at risk for females and males, respectively (2). The average age at onset is 37.5 years (standard deviation [SD], 12 years). The duration of the syndrome ranges from one to 46 years (3). One study showed that a majority of patients (91%, n = 65) had persistent physical symptoms at 5.5 years after onset (4,5), and another demonstrated that 64% still fulfilled the diagnostic criteria 2 or more years after onset (6). Other studies showed that pain intensity was still high after 15 years (7) and that 81% of patients stopped working as a result of the pain (3).

The syndrome usually requires long, intensive treatment (7). A range of different therapies has been described, including pharmaceutical treatment, injection therapy, surgical sympathectomy, spinal cord stimulation, and paramedical treatment (3,8). However, evidence of the effectiveness of most of these treatments is sparse (8).

Although rare, wounds or infections can occur as complications of CRPS-I (9-12). Patients can experience the nonfunctional and extremely painful limb as an ‘‘obstacle’’ to living the life to which they aspire, and some want to undergo an amputation to remove that ‘‘obstacle’’. This decision to amputate is not an easy one because of a lack of evidence regarding the risk of recurrence of the pain syndrome and regarding patient outcomes (13). The aim of this retrospective study was to gain insight into the consequences of amputation in patients with long-standing, therapy-resistant CRPS-I regarding pain, participation in activities of daily living, quality of life, use of a prosthesis, and the risk of recurrence of the pain syndrome.

# Materials and Methods

Twenty-two adult patients underwent amputation of a limb affected by CRPS-I at the University Medical Center Groningen from May 2000 to October 2008. CRPS-I was diagnosed according to International Association for the Study of Pain (IASP) criteria (14) and the criteria described by Bruehl et al. (1). All patients had long-standing, therapy-resistant CRPS-I with a nonfunctional limb, unbearable pain, or life-threatening infections. As a result of allodynia, the patients could not tolerate touch of the affected limb. The duration of the pain syndrome was calculated from the first time it was documented in medical records. Treatment received prior to the consultation regarding the amputation was retrieved from the medical records.

Before amputation, all patients had been examined by a physiatrist, one of 3 psychologists or a psychiatrist, a physical therapist, and a vascular surgeon. The psychologist or psychiatrist assessed the patients for major psychopathology, to determine whether the patient had a realistic point of view about the possible beneficial and adverse effects of an amputation, and to determine whether there was a potential for rehabilitation. All of the health-care professionals discussed the indications for amputation and possible beneficial and adverse effects. An amputation was not performed if psychopathology was found. The professionals discussed the indications for, and possible effects of, amputation with the patient and weighed these effects against the patient's expectations. The level of amputation was preferably proximal to the level of the signs of the Complex Regional Pain Syndrome, but it was also influenced by surgical possibilities, prosthetic design, and patient preference. All 22 patients were sent an invitation letter to participate in this qualitative retrospective study. Informed-consent forms were returned with use of a prepaid envelope. Once consent was given, a semi-structured interview was scheduled.

Two questionnaires were sent prior to the interviews: the World Health Organization Quality of Life-Bref (WHOQOL-Bref) (15) and the Groningen Questionnaire Problems after Arm Amputation (GQPAA) (16) or the Groningen Questionnaire Problems after Leg Amputation (GQPLA) (16). Current quality of life was evaluated with the WHOQOL-Bref, a 26-item questionnaire covering 4 domains: physical health, psychological health, social relationships, and environment. The WHOQOL-Bref has good-to-excellent reliability and has performed well in preliminary validity tests (15). WHOQOL-Bref scores were compared with Dutch norm values by calculating the 95% confidence intervals of differences in mean scores. The Groningen questionnaires assess the current use of a prosthesis, and the presence and frequency of impediments due to phantom limb pain and residual limb pain (16).

Interviews were conducted in a hospital near the patient's hometown, or at the patient's residence if the patient preferred that. The interviews were conducted by a psychologist (ES) who had received extensive training in interviewing techniques and were recorded on tape. A physician (HKK-S.) was present. Answers were recorded on a data sheet and compared afterward. Discrepancies between the psychologist's and physician's findings were resolved by discussion and by listening to the recorded interviews. In the invitation

to participate, patients were assured that their responses would be handled with confidentiality and this assurance was repeated verbally prior to the interview. The physician had not been involved in the decision to amputate, and the psychologist had been involved in 8 cases. The physician also had not been involved in the postsurgical rehabilitation, and the psychologist had been involved in one case.

Patients were asked to describe perceived changes in pain, mobility, activities of daily living, household tasks, work, hobbies, sports, relationships, intimacy, mood, physical appearance, worrying, sleep, and body scheme after amputation. Intensity of residual limb pain and phantom limb pain in the last 2 weeks prior to the interview was assessed by using a 100-mmvisual analogue scale (VAS; 0 mm = no pain and 100 mm = unbearable pain). Assessment of recurrence of CRPS-I in the residual limb was performed by the physician using the criteria recommended by Bruehl et al. for research purposes (1).

The research protocol was approved by the local Medical Research Ethics Committee (METc 2009/117). Descriptive data analysis was performed with SPSS for Windows (version 16.0, SPSS, Chicago, Illinois).

# Results

Twenty-one patients agreed to participate in the study: 19 women and 2 men with a median age 46 years (interquartile range [IQR], 37 to 51 years). The median duration of CRPS-I was 6 years (IQR, 2 to 10 years). The median interval between the amputation and the study was 5 years (IQR, 3 to 7 years). The inciting events, reasons for amputation, and level of amputation are summarized in table I.

Table 1

Inciting Events, Reasons for Amputation, and Level of Amputation (n = 21)

| **Characteristics** | **% (n)** | **Characteristics** | **% (n)** |
|---|---|---|---|
| Inciting event | | Level of amputation | |
| Sprained ankle | 33% (7) | Knee disarticulation | 33% (7) |
| Surgery | 19% (4) | Transfemoral | 19% (4) |
| Unknown/spontaneous | 19% (4) | Transtibial | 19% (4) |
| Arthroscopy | 14% (3) | Transhumeral | 19% (4) |
| Overuse | 10% (2) | Transradial | 10% (2) |
| Needle | 5% (1) | | |
| Reason for amputation* | | | |
| Nonfunctional limb | 100% (21) | | |
| Unbearable pain | 100% (21) | | |
| Contracture | 76% (16) | | |
| Wounds | 29% (6) | | |

**Several patients had more than one reason for amputation.*

On average, the patients received 11.1 different types of treatment (range, 3 to 19) prior to the first consultation for amputation. Nineteen patients received differing combinations of exercise therapy, occupational therapy, manipulation, and partial immobilization. Seventeen patients had a sympathetic block or a sympathectomy. Sixteen patients received morphine. Fifteen patients received antidepressants. Twelve patients had electrotherapy, transcutaneous electrical nerve stimulation [TENS], or epidural spinal electrostimulation (ESES). Twelve patients received anti-convulsants, and 9 received anti-anxiety agents.

### Pain

A reduction in pain following amputation was reported by 19 patients (90%; 95% confidence interval [CI], 71% to 97%), and 18 of them reported a major reduction. Eighteen patients (86%; 95% CI, 65% to 95%) experienced residual limb pain, with the median intensity score on the VAS being 46 (IQR, 14 to 63). When the patients rated the impediment due to residual limb pain, the responses were equally divided among much or very much (33%), moderate (33%), and hardly any or none (33%). Seventeen patients (81%; 95% CI, 60% to 92%) experienced phantom limb pain, with a median intensity of 37 (IQR, 18 to 62). Six patients (29%) always experienced the phantom limb pain. Impediment due to phantom limb pain was rated as much or very much by 7 of the 17 patients, moderate by 5, and hardly any or none by 5.

### Changes

Considering all changes, 20 patients (95%; 95% CI, 77% to 99%) reported an improvement in their lives. Seventeen patients (81%; 95%CI, 60%to 92%) reported an improvement immobility and 14 (67%; 95% CI, 45% to 83%), an improvement in sleep (table 2). More than half of the patients reported improvements in mood, physical appearance, washing oneself, clothing, and participation in work. Eight patients (38%; 95% CI, 21% to 59%) did not have any remaining symptoms of CRPS-I. Six patients (29%) felt less understood after the amputation because the people in their environment had expected that all problems would be solved by the amputation.

Prior to the amputation, 16 patients referred to their affected limb as ‘‘that’’ limb, one patient referred to it as ‘‘my’’ limb, and it was not known how 4 patients referred to it. After the amputation, 20 patients (95%) referred to their residual limb as ‘‘mine.’’ One patient stated: ‘‘I have a leg again, instead of a paw.’’

### Level of Activity

Patients differed considerably with regard to their level of activity after the amputation. One patient was completely dependent on the care of others due to CRPS-I in all 4 limbs before the amputation, and the amputation did not change this. Sports participation varied greatly, ranging from participation in Paralympic Games to an inability to participate in any sports activities.

Before amputation, 3 patients (14%) had a paid job, and 3 were part-time students. Afterwards, 8 patients (38%) were working and 6 were students (29%).

Table 2

Perceived Changes After Amputation (n = 21)

| | Improvement | No Change | Deterioration |
|---|---|---|---|
| Pain | 19 | 0 | 2 |
| Mobility | 17 | 2 | 2 |
| Sleep | 14 | 5 | 2 |
| Mood | 12 | 8 | 1 |
| Physical appearance | 12 | 6 | 3 |
| Washing/clothing | 12 | 6 | 3 |
| Work | 11 | 9 | 1 |
| Worrying | 10 | 10 | 1 |
| Housekeeping | 9 | 11 | 1 |
| Hobbies | 8 | 12 | 1 |
| Social contact | 8 | 10 | 3 |
| Sports | 7 | 13 | 1 |
| Intimacy | 6 | 14 | 1 |
| Using a toilet | 6 | 11 | 4 |
| Feeling understood | 5 | 10 | 6 |

**Several patients had more than one reason for amputation.*

## Quality of Life

Fourteen patients (67%; 95% CI, 45% to 83%) reported a good or very good quality of life. Four patients (19%; 95% CI, 8% to 40%) reported a poor or very poor quality of life. The mean scores on the WHOQOL-Bref in our study population were significantly lower than Dutch norm values in all domains except social relationships15 (table 3).

Table 3

WHOQOL-Bref Scores after Amputation Compared with Dutch Norm Values

| | Mean Score* (SD) | | |
|---|---|---|---|
| **Domain** | **Amputation Group** | **Dutch Norm Values** | **Differences in Means* (95% CI)** |
| Physical health | 12.8 (3.3) | 18.3 (3.0) | –5.5 (–7.1 to 23.9)† |
| Psychological health | 14.4 (2.3) | 16.6 (2.8) | –2.2 (–3.6 to –0.8)† |
| Social relationships | 15.1 (3.7) | 15.8 (3.3) | –0.7 (–2.5 to 1.1) |
| Environment | 14.1 (2.9) | 15.9 (2.8) | –1.8 (–3.3 to –0.3)† |

**The score for each domain ranges from 4 to 20. Higher scores denote higher quality of life. †$P \leq 0.05$.*

### Satisfaction with Decision for Amputation

Eighteen patients (86%; 95% CI, 65% to 95%) stated that they would choose to undergo amputation again under similar circumstances. One female patient was not sure. She required the amputation because of a high probability of sepsis but did not want the amputation. Another patient could not pinpoint the exact reasons why she would not choose to have an amputation again, although she had problems with the fitting of her prosthesis and psychosocial problems after moving to another location. The third patient could not get used to the short upper residual limb, and her grandchildren were afraid of it.

### Use of a Prosthesis

Prostheses were fitted and used regularly (at least 8 hours a day) by 10 (67%; 95% CI, 42% to 85%) of the 15 patients with a lower-limb amputation; 6 of the prosthesis users had a knee disarticulation, and 4 had a transtibial amputation. Four patients with a transfemoral amputation and one with a knee disarticulation did not use a prosthesis. Four prosthesis users needed a walking aid outside. Three of them had a knee disarticulation; one of the 3 needed a forearm crutch, one used a cane, and one used a walking frame with wheels. The fourth patient had a transtibial amputation, and this patient sometimes used a cane and sometimes used a walking frame with wheels. Four patients (3 with a knee disarticulation and one with a transtibial amputation) could walk ≥1 km. Five patients (3 with a knee disarticulation and 2 with a transtibial amputation) could walk 100 to 500 m. One patient with a transtibial amputation could walk <100 m. Prior to 9 of the 15 lower-limb amputations, the expectation was that the patient would use a prosthesis based on his or her age, physical condition, comorbidities, and motor skills. All 9 patients used a prosthesis daily. Another patient, who had not been expected to use a prosthesis because of a presumed lack of motivation, also used one daily. One of the 6 patients who had an upper-limb amputation had been expected, prior to the amputation, to use a prosthesis after the operation; however, that patient was not fitted with a prosthesis because of persistent residual limb pain. There had been doubts, before the operation, that 2 of the patients would use a prosthesis after their upper-limb amputation; one of these patients, who had a transradial amputation, used a prosthesis daily. None of the 4 patients who had a transhumeral amputation used a prosthesis.

### Level of Amputation

Five patients said that they would have preferred more precise information about the level of amputation, and 3 patients found the amputation to be too proximal. One patient had a knee disarticulation, which she said that she would not have preferred because of the cosmetic issue of length differences between her legs while she was sitting. The vascular surgeon and the physiatrist reported that detailed information concerning these topics had been given.

### Recurrence

Nine patients (43%) reported recurrence of CRPS-I in the residual limb, with one of them reporting that the recurrence was temporary. Four patients (19%) reported recurrence in another limb. All 21 patients allowed a physical examination, including the examiner touching the residual limb. On physical examination, 4 patients (19%; 95% CI, 8% to 40%)

fulfilled the criteria of Bruehl et al. (1): 3 of these patients (14%) had recurrence in the residual limb and one, in another limb. Another patient, with a lower-limb amputation, also had an upper-limb amputation in another hospital, 3 years after the first amputation, because of CRPS-I. Thus, in total, there was a recurrence in 5 patients: in the residual limb in 3 (14% of the 21) and in another limb in 2 (10%).

The patient who had the upper-limb amputation 3 years after the lower-limb amputation stated that both amputations improved her quality of life. She was able to walk while wearing a lower-limb prosthesis but did not use an upper-limb prosthesis. Two of the 3 patients who had recurrence in the residual limb reported that, despite the recurrence, they still had a major reduction in the level of pain and an increased mobility level after the amputation. The third patient indicated that the pain had worsened and the mobility level was reduced.

One patient required a shoulder disarticulation after a previous upper-limb amputation because of persistent pain that was unrelated to CRPS-I.

**Upper or Lower-Limb Amputation**
There were no significant differences between the data for the group with an upper-limb amputation and those for the patients with a lower-limb amputation.

# Discussion

An amputation may positively contribute to the lives of patients with long-standing, therapy-resistant CRPS-I. A reduction of pain as well as an improvement in mobility and sleep were reported by most patients in this study. Although they were not free from all symptoms, most patients were more actively participating in study, work, and sports activities. Quality of life was rated as good or very good by two-thirds of the patients. Twenty patients described their residual limb as ‘‘mine,’’ indicating that the residual limb was part of their body scheme again. A normal body scheme is a sign of recovery because most patients with CRPS-I describe the affected limb as foreign to their body scheme (17).

Despite the positive outcome, some patients still experienced CRPS-I symptoms (table 4) and some reported a deterioration in some aspects of their lives (table 2). The results of the WHOQOL-Bref in comparison with Dutch norm values showed that CRPS-I followed by an amputation had an impact on the physical health, psychosocial health, and environment domains. Despite several positive results, some patients had to deal with the adverse effects of an amputation. Some patients expressed that they felt less understood because people in their environment had expected all problems to be solved by the amputation.

Two-thirds of the patients with a lower-limb amputation and one of the 6 patients with an upper-limb amputation used a prosthesis regularly. Therefore, use of a prosthesis should be discussed with patients considering an amputation because of CRPS-I. The results of a systematic review showed that about 48%of the patients who had a lower-limb

Table 4

Symptoms According to Criteria of Bruehl et al. (n = 21)

| Symptoms | % (n) with Self-Reporting Symptom | % (n) with Symptom on Physical Examination |
|---|---|---|
| Continuing pain, disproportionate to any inciting event | 33% (7) | |
| Sensory | | |
| Reports of hyperesthesia | 52% (11) | |
| Evidence of hyperalgesia (pinprick) | | 38% (8) |
| Evidence of allodynia (light touch) | | 14% (3) |
| Vasomotor | | |
| Temperature asymmetry | 71% (15) | 29% (6) |
| Skin color changes | 19% (4) | 14% (3) |
| Skin color asymmetry | 52% (11) | 14% (3) |
| Sudomotor/edema | | |
| Edema | 19% (4) | 0% (0) |
| Sweating changes | 24% (5) | 0% (0) |
| Sweating asymmetry | 19% (4) | 0% (0) |
| Motor/trophic | | |
| Decreased range of motion | 24% (5) | 24% (5) |
| Motor dysfunction (weakness, tremor, dystonia) | 48% (10) | 14% (3) |
| Trophic changes (hair, skin) | 33% (7) | 5% (1) |

amputation and about 23% of the patients who had an upper-limb amputation because of CRPS-I used a prosthesis (13). In general, use of a prosthesis is more likely after lower-limb amputations than after upper-limb amputations (18). Although patients received extensive information about the level of amputation and possibilities of using a prosthesis, 5 patients said that they would have preferred more information. It may be that the patients did not remember all of the information that was provided (19,20).

Recurrence at the time of follow-up examination was diagnosed in 4 patients. An additional patient had already undergone an amputation in another hospital because of recurrence of CRPS-I in another limb. The recurrence rate was 14%, increasing to 24% if we take into account recurrence in another limb. This recurrence rate is low compared with the high rate (48%) reported in a recent systematic review (13). However, that high recurrence rate was strongly influenced by the results of one study (21). When that study was excluded from the systematic review, the recurrence rate dropped to 8%. Evidence-based guidelines state that there is insufficient evidence that amputation positively contributes to the lives of patients with CRPS-I (8). Our study showed a considerable percentage of patients with a general improvement (95%) and with a major reduction in pain (86%). The results of our retrospective study may contribute to the discussion when an amputation is considered for a patient with long-standing, therapy-resistant CRPS-I.

Amputation should be considered for therapy-resistant CRPS-I only when the patient has no major psychopathology and has a realistic point of view about the possible beneficial and adverse effects of an amputation. Therefore, this decision should be made with great care, and amputation is suitable for only a small group of patients. In 2003 and 2004, 197 and 175 patients, respectively, had a lower-limb amputation at our institution. In that same period, 8 patients with CRPS-I had a lower-limb amputation.

**Study Limitations**

A limitation of this research is the small number of patients. The duration of CRPS-I prior to the amputation may have been underestimated, as we relied on documentation from other hospitals for the estimates. The results of this study are influenced by selection bias because the study included only those patients selected for amputation by the team of professionals. We do not know the quality of life of the patients who were refused amputation. Another limitation is the cross-sectional design of this study. We have no information about the quality of life or the factors prior to and immediately after the amputation. Several investigators have searched for a specific psychological profile of individuals with CRPS-I but were unable to define one (22-24). The cross-sectional design and small sample size in this study prevented investigation of predictors of outcomes. Patients were asked to recall their situation before the amputation, giving rise to a substantial risk of recall bias. Most patients reported improvements in their lives. It is possible that a patient ‘‘must’’ feel improved to justify the amputation. Eight patients had met the psychologist in the pre-amputation assessment, which might have biased their answers. In order to evaluate determinants of the outcomes of amputation in cases of long-standing, therapy-resistant CRPS-I, prospective documentation including diagnostic criteria is needed. Future research should also focus on evaluating the timing of amputation.

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# 4

# Resilience in patients with amputation because of Complex Regional Pain Syndrome type I

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# Abstract

**Background**
Although controversial, an amputation for long-standing and therapy-resistant Complex Regional Pain Syndrome type I (CRPS-I) may improve quality of life and pain intensity. Resilience, the way people deal with adversity in a positive way may be related to these positive outcomes. This study focused on the relationship between resilience and post-amputation outcomes i.e. quality of life, pain and recurrence of CRPS-I, and psychological distress.

**Methods**
Twenty-six patients with an amputation related to CRPS-I filled in the Connor-Davidson Resilience Scale (CD-RISC), World Health Organisation – Quality of life Assessment (WHOQOL-Bref) and the Symptom Checklist-90 Revised (SCL-90-R). An interview was conducted and a physical examination performed. Results were compared with reference groups from literature and a control group from the outpatient rehabilitation clinic at our medical center.

**Results**
Resilience correlated significantly with all domains of the WHOQOL-Bref ($\rho$ ranged from 0.41 to 0.72) and negatively with all domains of the SCL-90-R ($\rho$ ranged from -0.39 to -0.68). Patients with an amputation because of CRPS-I have higher scores on resilience and quality of life than the control group. Resilience was lower in patients who reported CRPS-I symptoms compared to those who did not.

**Conclusions**
The results confirmed our hypothesis that patients with an amputation because of CRPS-I who have a higher resilience also have a higher quality of life and experience lower psychological distress. The prognostic value of resilience in this patient group requires further research.

# Introduction

Pain and swelling following a seemingly minor injury of wrist or ankle, do not recover in some patients within a normal timeframe. When pain intensifies and other symptoms occur and worsen (e.g. changes in sweating, colour or nail and hair growth) Complex Regional Pain Syndrome type I (CRPS-I) is likely to be present (1).

Guidelines offer evidence-based treatment options for CRPS-I such as medication, physical therapy and occupational therapy (2). However, not all patients respond to these therapies and in some patients CRPS-I may further develop into a dysfunctional limb with uncontrollable pain or life-threatening infection (3-5). Sometimes a patient requests an amputation of the affected limb as a last resort (6,7).

Amputation for long-standing, therapy-resistant CRPS-I is controversial and a rare intervention (8). Primarily, the aim of the amputation is to increase quality of life and mobility of the patient but also to decrease pain intensity. Outcome variables after an amputation such as quality of life have been infrequently reported (8). Previously, there was insufficient evidence that amputation positively contributes to the treatment of CRPS-I, with just a few published case studies with positive outcomes (2,7,9,10). Guidelines warn against amputation because of the risk of recurrence of the syndrome due to their referral to one or two larger studies with predominantly negative outcomes (5, 11-13). A systematic review on CRPS-I and amputation could not find enough evidence for or against amputation (8). Results from our recent study in a group of 21 patients who had an amputation because of long-standing, therapy-resistant CRPS-I did show an overall improvement of life in general and improvements in pain intensity, quality of life, mobility, use of a prosthesis and job or study enrolment (6). It is unknown why patients from this study have better results than most other patients described in literature (6,8). Patients faced physical disability and severe pain often several years prior to the amputation. After the amputation they seem to “bounce back” beyond what could be expected according to literature.

The ability to bounce back in times of adversity, including physical stress, is called resilience (14). Resilience is defined as “the process of adapting well in the face of adversity, trauma, tragedy, threats, or even significant sources of stress — such as family and relationship problems, serious health problems, or workplace and financial stressors” (15). It represents a person’s qualities that enable that person to thrive in the face of adversity (16). In patients with traumatic amputations psychological recovery and acceptance of limb loss were positively influenced, not only by social support or medical care, but also by higher resilience (17). Resilience may, in part, explain why patients are able to increase quality of life after amputation. Insight in resilience of patients with a limb amputation because of CRPS-I could guide patient selection and give reason for offering patients a program to increase their resilience before and after amputation.

Based on the results from our previous study on quality of life, we hypothesized that higher scores on quality of life and participation in daily life may be correlated with higher

resilience. The aim of this study was to analyze resilience and post-amputation outcome (CRPS-I symptoms, quality of life, psychological distress and participation in daily life) and to analyze how resilience relates to these outcome variables in patients with an amputation because of CRPS-I.

# Methods

### Participants and procedures

Patients with a request for amputation were referred to our outpatient clinic by their physiatrist, their general practitioner, or they came on their own initiative. Our outpatient clinic is situated in a university based medical center which serves as one of the referral clinics for people with long-standing, therapy-resistant CRPS-I in our country. Upon referral the patient was independently assessed by a physiatrist, vascular surgeon, physical therapist and psychiatrist or psychologist. CRPS-I was diagnosed according to the criteria of the International Association for the Study of Pain (IASP) and the criteria of Bruehl (18,19).

Patients were considered eligible for amputation if other diagnoses were ruled out, if (all) therapies for CRPS-I advised in guidelines were tried but failed (including infection and wound therapy), if quality of life was experienced as poor and participation in daily life activities was hindered excessively. In a multidisciplinary meeting the health care professionals discussed the pros and cons of an amputation together, and then later discussed these with the patient.

All patients (n=27) who underwent elective amputation because of CRPS-I at our center between 2000 and 2011 were contacted to participate in this cross-sectional explorative study. After agreement on participation, patients were sent information about the study, questionnaires and an informed consent form. Patients with insufficient knowledge of the Dutch language or younger than 18 years were excluded from the study. The study included several questionnaires, a semi-structured interview and a physical examination. The medical ethical committee approved the research (METc 2009/117).

### Questionnaires

Resilience was assessed with a Dutch version of the Connor-Davidson Resilience Scale (CD-RISC), a 25 item self-report measure that was developed to quantify current resilience (16,20). The score ranges from 0 to 100 with higher scores indicating a better resilience. Quality of life was evaluated with the World Health Organization – Quality of life Assessment (WHOQOL-Bref), a 26 item questionnaire covering four domains: physical health, psychological health, social relationships and environment (20). The scores range in each domain from 4 to 20; higher scores indicate better quality of life in a certain domain. The results of the WHOQOL-Bref of 21 patients included in this study have been described previously (6).

Psychological distress was assessed with the Symptom Checklist-90 Revised (SCL-90-R) (22). The SCL-90-R assesses self-reported psychological distress and multiple aspects of

psychopathology. It consists of 90 questions in 8 dimensions of psychological distress: anxiety, agoraphobia, depression, somatisation, insufficiency, sensitivity, hostility and insomnia. Patients report to which extent the symptoms of the checklist were present in the week preceding the completion of the questionnaire. Higher scores in the SCL-90-R indicate more problems. It can be used with single dimensions but also as a total psycho neuroticism. All questionnaires have five point Likert scales, scoring from 0 to 4 (CD-RISC) or 1 to 5 (WHOQOL-Bref and SCL-90-R).

### Interview and physical examination

A visit to the patient for an interview and physical examination by a psychologist and a physician was scheduled in a hospital close to or at the patient's home. Main results from these interviews have been published (6). Patients were asked if they still experienced CRPS-I related symptoms, stump pain and phantom pain in the 2 weeks before the visit. Stump pain and phantom pain were recorded on a visual analogue scale (VAS) in millimeters (mm).

After the interview, the physician performed a physical examination of the limbs for (recurrence of) CRPS-I (19) and the psychologist checked all questionnaires for missing answers and asked patients to fill in the missing answers.

### Analysis

The results of the CD-RISC and WHOQOL-Bref questionnaires were compared with results from a control group from our outpatient rehabilitation clinic. The control group exists of chronic pain patients selected from patients seen by the psychologist from our rehabilitation clinic between 2008 and 2013 (n=111; male 34%, mean age 45.9 years SD 13.4 years, female 66%, mean age 40.0 years SD 13.2 years). Patients in this control group experienced chronic pain (> 6 weeks) and social and psychological factors played a considerable role in maintaining the health related complaints.

The results of the CD-RISC were also compared with those of a non help-seeking general population sample (n=577) and primary care outpatients (n=139) in the United States of America (16). WHOQOL-Bref scores were additionally compared with scores found in the general Dutch population (n=218, male 41%, mean age 37.5 years SD 7.6, female 59%, mean age 37.4 SD 8.2) (23) SCL-90-R scores were compared with norm values for the Dutch population (n=2394, male:female 50%:50%, mean age 41.1 years SD 14.5) and for patients with chronic pain (n=2461, male:female 32%:68%, mean age 46.2 years SD 15.4) (22). Comparisons were made using Confidence Interval Analysis (CIA 2.2.0 University of Southampton) (24). Associations between resilience and the other outcome variables were analyzed. Non-parametric correlations (Spearman's ρ) and Mann Whitney U tests were used.

PASW Statistics version 18 for Windows was used for data analysis. Results are significant at $p \leq 0.05$.

# Results

## Patient characteristics

Of the 27 contacted patients, 26 agreed to participate: 23 women and 3 men, median age 44 years (Interquartile range (IQR): 34; 48). Patients underwent amputation between May 2000 and May 2010. Median duration of CRPS-I was 5.5 years (IQR: 3; 10). Median interval between amputation and study was 56 months (IQR: 25; 69). Twenty patients underwent amputation of a lower-limb (LL) and 6 patients of an upper-limb (UL). No patients were excluded. Previous failed therapies included combinations of e.g.: physical therapy including pain exposure physical therapy (25), occupational therapy, manipulation, sympathetic blocks or sympathectomy, medication such as morphine, anti-anxiety agents, and dimethylsulfoxide cream (50%) (12). Before amputation patients generally experienced their quality of life as poor and often referred to their affected limb as “paw”, “canon” or “obstacle”.

Table 1

Mean and standard deviation for CD-RISC and WHOQOL-Bref domain scores of patients who had a limb amputation because of long-standing, therapy-resistant Complex Regional Pain Syndrome type I (CRPS-I) compared to reference and control groups

| | CRPS-I | Reference and control groups | Difference (95% CI) |
|---|---|---|---|
| | | *Non help-seeking*[16] | |
| CD-RISC | 73.3 (11.7) | 80.4 (12.8) | 7.1 (2.1 ; 12.1)* |
| | | *Primary care*[16] | |
| | | 71.8 (18.4) | -1.5 (-8.9 ; 5.8) |
| | | *Outpatient rehabilitation clinic* | |
| | | 60.2 (12.3) | -13.1 (7.9 ; 18.4)* |
| WHOQOL-Bref Domains | | *Dutch norm values*[23] | |
| Physical | 12.7 (3.6) | 15.2 (2.6) | 2.6 (1.4 ; 3.7)* |
| Psychosocial | 14.4 (2.7) | 14.4 (2.0) | -0.1 (-0.9 ; 0.8) |
| Social | 15.1 (3.7) | 15.4 (2.9) | 0.3 (-0.9 ; 1.6) |
| Environment | 13.9 (2.8) | 15.8 (2.0) | 1.9 (1.0 ; 2.8)* |
| | | *Outpatient rehabilitation clinic* | |
| Physical | | 9.8 (2.4) | -2.9 (-4.0 ; -1.7)* |
| Psychosocial | | 12.8 2.3) | -1.6 (-2.6 ; -0.6)* |
| Social | | 13.7 3.5) | -1.4 (-2.9 ; 0.2) |
| Environment | | 13.6 (2.2) | -0.4 (-1.4 ; 0.7) |

*CD-RISC: Connor-Davidson Resilience Scale; reference values taken from Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC).[16] WHOQOL-Bref: World Health Organization Quality of Life–Bref questionnaire; reference values taken from Quality of life and psychopathology: Investigations into their relationship.[23] Control group: outpatient rehabilitation clinic: results from patients with chronic pain (> six weeks duration). CI: Confidence interval; * p ≤ 0.05.*

## Measures

CD-RISC. The mean CD-RISC was significantly higher than that of the control group at our outpatient rehabilitation clinic (table 1). CD-RISC scores were significantly lower compared to values for a USA non help-seeking general population sample and similar to patients seeking primary care (table 1) (16).

WHOQOL-Bref. Sixteen patients (62%) reported a good or very good quality of life; 4 patients (15%) reported good nor bad and 6 patients (23%) reported a poor or very poor quality of life. Patients scored significantly higher (=better) on the physical and psychosocial domain compared to patients in our control group (table 1). Patients scored significantly lower on the physical and environmental domain compared to Dutch norm values.

SCL-90-R. Patients scored significantly higher (=worse) on depression, somatisation, insufficiency, insomnia and psycho neuroticism compared to the Dutch norm values (table 2) (22). However, they scored similar to Dutch norm values for chronic pain patients (22).

Table 2

Mean (SD) SCL-90-R domain scores

of patients who had limb amputation because of long-standing, therapy-resistant Complex Regional Pain Syndrome type I (CRPS-I) compared with Dutch norm values

| | CRPS-I | Dutch norm values | Difference (95% CI) | Chronic Pain | Difference (95% CI) |
|---|---|---|---|---|---|
| Anxiety | 13.4 (5.4) | 12.8 (4.4) | -0.5 (-2.2 ; 1.2) | 15.4 (6.3) | 2.1 (-0.3 ; 4.5) |
| Agoraphobia | 8.7 (3.1) | 7.9 (2.3) | -0.9 (-1.8 ; 0.0) | 9.1 (4.0) | 0.3 (-1.2 ; 1.9) |
| Depression | 26.1 (12.0) | 21.6 (7.6) | -4.5 (-7.5 ; -1.6)* | 28.4 (11.4) | 2.3 (-2.1 ; 6.7) |
| Somatisation | 22.6 (8.6) | 16.7 (5.3) | -5.9 (-8.0 ; -3.9)* | 24.8 (7.9) | 2.2 (-0.9 ; 5.3) |
| Insufficiency | 16.9 (6.0) | 12.6 (4.3) | -4.3 (-5.9 ; -2.6) * | 17.9 (6.4) | 0.9 (-1.5 ; 3.4) |
| Sensitivity | 25.5 (8.9) | 24.1 (7.6) | -1.4 (-4.4 ; 1.5) | 25.2 (9.1) | -0.3 (-3.8 ; 3.2) |
| Hostility | 7.1 (1.5) | 7.2 (2.1) | 0.1 (-0.7 ; 1.0) | 8.2 (3.1) | 1.1 (-0.1 ; 2.3) |
| Insomnia | 7.0 (3.9) | 4.5 (2.2) | -2.5 (-3.4 ; -1.6)* | 7.4 (3.7) | 0.5 (-1.0 ; 1.9) |
| Psychoneuroticism | 138.7 (46.0) | 118.3 (32.4) | -20.4 (-33.0 ; -7.8)* | 148.6 (45.5) | 9.9 (-7.7 ; 27.5) |

*SCL-90-R: Symptom Checklist 90 Revised; Chronic Pain: Normal values for chronic pain patients. Reference values taken from Symptom Checklist.[22] * p < 0.05; CI: confidence interval*

## Interview and physical examination

Fifteen patients (56%) reported recurrence of CRPS-I-like symptoms. Twenty-three patients (88%) reported stump pain (median VAS score 31mm; IQR: 6; 63) and 20 patients (77%) reported phantom pain (median VAS score 25mm; IQR: 2; 51). Five patients (19%) met Bruehl's criteria (19) for recurrence of the syndrome in the stump and two patients (8%) for recurrence in another limb.

## Associations

The CD-RISC correlated positively with all domains of the WHOQOL-Bref (ρ ranged from 0.41 to 0.72) and negatively with all domains of the SCL-90-R (ρ ranged from -0.39 to -0.68) (table 3).

A positive, though not significant association (ρ =0.457, p=0.065) was found between CD-RISC score and frequency of prosthesis use for patients with a prosthesis (n=17). CD-RISC scores in patients who did not report persistence of CRPS-I related symptoms (n=11) (median: 81, IQR: 76; 83) was higher compared to patients who did report these symptoms (n=15) (median: 71, IQR: 64; 78) (Mann Whitney U: p=0.032). CD-RISC scores were significantly lower in patients reporting more stump pain (ρ=-0.508, p=0.008). For phantom pain such an association was not found (ρ=-0.297, p=0.14). CD-RISC scores did not differ significantly between patients with or without objectified recurrence of CRPS-I (Mann Whitney U: p=0.53).

Table 3

Correlations between CD-RISC and WHOQOL-Bref scores and between CD-RISC and SCL-90-R in patients with amputation because of long-standing, therapy-resistant CRPS-I

| | **Correlation Coefficient** | **p** |
|---|---|---|
| WHO-QOL-Bref21 | .549 | .004 |
| Physical | .454 | .020 |
| Psychosocial | .721 | <.001 |
| Social | .448 | .022 |
| Environmental | .407 | .039 |
| SCL-90-R22 | | |
| Anxiety | -.586 | .002 |
| Agoraphobia | -.405 | .040 |
| Depression | -.680 | <.001 |
| Somatisation | -.439 | .025 |
| Insufficiency | -.543 | .004 |
| Sensitivity | -.539 | .005 |
| Hostility | -.660 | <.001 |
| Insomnia | -.391 | .048 |
| Psychoneuroticism | -.668 | <.001 |

*WHOQOL-Bref: World Health Organization Quality of Life–Bref questionnaire. Resilience was measured with Connor-Davidson Resilience Scale (CD-RISC). Correlation Coefficient: between CD-RISC and SCL-90-R or CD-RISC and WHOQOL-Bref scores, calculated with Spearman's Rho.*

# Discussion

This research focused on resilience (the ability to bounce back from adversity) in a group of patients with an amputation because of long-standing, therapy-resistant CRPS-I. Resilience is an interactive concept concerning the combination of serious risk experiences and a relatively positive psychological outcome despite those experiences (26). Higher resilience is positively related to better physical functioning, higher quality of life and lower pain scores among patients with chronic conditions (27-29).

In a previous publication we showed relatively high quality of life scores in a group of patients with amputation due to long-standing, therapy-resistant CRPS-I (6). Based on the findings in literature and the results of our study (6) we hypothesized that patients with a CRPS-I related amputation who have relatively good results also score high on resilience. We found a positive association between resilience and quality of life, especially within the psychosocial domain. Despite living with CRPS-I for many years and experiencing an amputation, scores on the psychosocial domain are significantly better than patients with chronic pain who visit the psychologist at a rehabilitation outpatient clinic and similar to Dutch norm values (20). Even on the physical domain they score significantly better than the chronic pain patients.

The focus of most previous research on CRPS-I has been on risk factors. With an unknown cause of the CRPS-I, it is frequently assumed that psychological factors play an important role in the development of the syndrome. However, a systematic review showed that life events appear to be the only factor related to the development of CRPS-I; patients who experience more life events have a higher chance of developing CRPS-I (30).

Amputation because of CRPS-I is controversial due to clinicians' opinions on the negative outcome. Literature on amputation because of CRPS-I also focuses on reasons (risk factors) for amputation (8). Case studies on amputation due to long-standing, therapy-resistant CRPS-I are characterized by predominantly negative reporting on topics such as pain, quality of life, mobility and use of a prosthesis (8). Recurrence of the syndrome underlies most opinions about not to amputate in case of long-standing, therapy-resistant CRPS-I. However recurrence is often not (clearly) described in those case reports (8). Our clinical experience with these patients led us to believe in a more positive outcome after amputation regarding quality of life (6). Shifting the focus of research from identification of risk factors to this more positive approach on patients' competencies and strengths, offers a new perspective.

We are aware of the limitations of this study. Clinical relevance of differences in CD-RISC scores is not yet clear. A 7 point difference between our group and a non help-seeking population on a 0-100 scale (in which the upper and lower boundaries never occur) seems to be meaningful (table 1). Another limitation is that we do not have pre- and post-test measurements. This is also applicable for the results of the control group with chronic pain. Patients from this control group seek medical care for their (pain) problem, which is not necessarily the case for the CRPS-I and amputation population. Measurements

presented from this control group are scores at the beginning or during the rehabilitation process and not after the rehabilitation process which makes comparing the results difficult. We do believe that this control group is more or less comparable to our CRPS-I population since both groups have been dealing with pain for a longer period.

Several explanations for relatively high resilience scores can be thought of. First, the high resilience scores in our study may be related to patient selection. It is possible that the specialists who made the decision to amputate unknowingly selected patients on the basis of resilience; the patient's previous ability to bounce back from adversity. According to this explanation our patients were more likely to have better outcome than could be expected based on literature. Whether this phenomenon occurred is unclear since we have no information about the patients who were denied amputation. It may also be that only the most resilient patients with CRPS-I do not give up on looking for a solution in the face of repeated treatment failures. Another explanation for relatively high scores on questionnaires in general for this specific population years after amputation could be a phenomenon called response shift. Response shift means that, over time, the meaning of self-reported constructs are subject to change because of recalibration, reprioritization and reconceptualization (31,32).

Another factor that should be considered in explaining our results is the cognition of the patients. It is not unreasonable to assume that patients respond positively to their "last resort"; an amputation of their limb affected by long-standing, therapy-resistant CRPS-I. Additionally patients may feel understood or feel that their problems are being taken seriously when, at last a team of medical specialists is found willing to deliberate amputation. Although the mechanism is poorly understood, the positive effect of clinician-patient communication on outcomes has been found repeatedly in other pathologies (33). Another explanation of the score may lie in the intervening period between amputation and our study. Life experiences between these two points may also have given a raise in resilience scores and accounts for one of the limitations of this study.

Finally, cognitive dissonance could explain the relatively good results. Cognitive dissonance is the discomfort caused by holding conflicting cognitions. Based on that theory, patients will try to minimize regret of their irrevocable choice (34). These explanations should be taken into account in future research in this field.

The domain scores of the SCL-90-R correlated negatively with resilience. These findings indicate that participants with a better resilience experience less psychological distress which is in line with our hypothesis. This negative correlation between resilience and psychological distress was found previously in women with fertility problems (35). Not all associations were in line with our hypothesis. We expected that patients with a higher resilience score would improve in a larger number of topics. However, the association between resilience and the amount of topics patients improved upon was weak and not significant. Another "logical" hypothesis would be that those patients with a higher resilience score would use their prosthesis more often. The association between resilience and frequency of prosthesis use was not significant either ($p=0.065$). This lack of significance

could be attributed to lack of power due to the small sample size. However, it is very well possible that resilient patients find ways of participating without the use of a prosthesis. The direction of the association between resilience and quality of life remains unclear because of the study design. It is possible that the relatively good results encourage the patients to feel resilient rather than resilience leading to better results and the competency to restore parts of life. Programs for improving resilience are currently being developed and studied for effectiveness. The results of these programs substantiate that training can improve resilience (36). Resiliency training may indirectly lead to improvement in quality of life (37,38). When patients ask for an amputation for their therapy-resistant CRPS-I a training to improve resilience prior to the amputation might be considered. Medical care is known to influence a patient's quality of life, therefore rehabilitation after amputation plays an important role in the final results. Rehabilitation in our patient group, however, took place near patients' homes in different centers for rehabilitation in all parts of the country. Therefore, we cannot estimate the effect of it on the outcome. Despite our relatively positive results, amputation for CRPS-I remains controversial. Screening for psychopathology and assessment of resilience should be performed prior to amputation.

We think that resilience might be a key factor in helping patients to accept and adapt to their new situation. Longitudinal studies are needed to analyze the strength of resilience over time and to analyze its prognostic value. Exploring competencies offers a new perspective on why some patients report positive outcomes after amputation. We conclude that the results of this explorative study confirm our hypotheses.

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# 5

# Informed decision making in Complex Regional Pain Syndrome type I and amputation

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# Abstract

**Background**
Literature on Complex Regional Pain Syndrome type I (CRPS-I) discussing the decision to amputate or not, level of amputation or timing of the amputation is scarce, and decisions remain controversial. We describe informed decision making when amputation for CRPS-I is a last resort.

**Methods**
Retrospectively, we describe the decision making process of 36 patients with amputation at our university medical center between 2000 and 2012. Additionally we present the incident preceding CRPS-I, the reason for and the level of amputation, and outcome after amputation.

**Results**
Team members and the patient decide together whether or not to amputate and the level of amputation. Issues such as level of pain or allodynia, infection, desired length of the residual limb, range of motion of the joints, strength of all extremities, ability to use walking aids and "psychological green, yellow and red flags" are weighed in this process.

Outcome after amputation: no complications during surgery, 22% rate of complications (infection in all but one patient) immediately postoperatively (re-amputation not required), 72% phantom pain directly after amputation or developed phantom pain within the first 3 months after amputation; 77% phantom pain several years after amputation; CRPS-I was present in 27% of patients more than one year post-amputation; amputation through or below the level of allodynia did not relate to recurrence of CRPS-I.

**Conclusions**
Informed decision making in amputation for CRPS-I remains a difficult process in which only little evidence is present and patient specific outcome is not predictable. However, amputation should not be ignored as treatment option for long-standing, therapy-resistant CRPS-I.

# Introduction

Complex Regional Pain Syndrome type I (CRPS-I) is a disabling condition which can develop after an injury, surgical procedure or spontaneously and is characterized by severe pain in combination with sensory, autonomic, motor and dystrophic symptoms (1, 2) The etiology of CRPS-I has still not been clarified (1, 2). The incidence rate of CRPS-I is estimated at 26.2 per 100,000 person years (95% CI: 23.0 to 29.7) (3) with the majority of cases developing after fracture, sprain or surgery. CRPS type I should not be confused with CRPS type II, which develops after a nerve injury and requires different treatment.

Patients are treated in accordance with guidelines, which primarily recommend pharmacotherapy and physical therapy (4, 5). About 16% (95% CI: 9 to 22) of patients in a CRPS-I outcome study reported the syndrome to be severely progressive despite interventions (6). In a minority of cases treatment does not reduce or resolve pain and the affected limb may become non-functional preventing participation in daily life activities and work (6). As a last resort, some of these patients can reach a point where they request amputation.

Guidelines support amputation as a treatment only in the presence of wounds or infection. In general, guidelines warn against amputation due to the high recurrence rate of CRPS-I and poor usage of prostheses amongst this patient group. A large variation in recurrence rates has been published (7). The highest recurrence was 100% in a study of 28 patients (8). The lowest recurrence rate, 24%, was reported recently (9).

Amputation of the affected limb in patients with long-standing, therapy-resistant CRPS-I is an uncommon and much debated treatment option (5, 7, 10). In papers discussing amputation for CRPS-I, decisions regarding the amputation process such as level of amputation or timing of the amputation are lacking (7).

To help others prepare for an informed decision making process when amputation for CRPS-I is being considered, the aim of this paper is to describe the clinical procedures before amputation at our center. We present a process in which we consider the cause of CRPS-I, the reasons for amputation, the level of amputation and the (short-term) outcomes after amputation in a group of 36 patients at our university medical center between 2000 and 2012.

# Methods

Between May 2000 and September 2012, 36 patients (4 males, 32 females) with long-standing, therapy-resistant CRPS-I underwent an amputation at the University Medical Center Groningen, The Netherlands. CRPS-I was diagnosed using IASP and Bruehl criteria (1, 2). All patients had unbearable and therapy-resistant pain in a nonfunctional limb which negatively affected participation in daily life. All had repeatedly expressed a wish for amputation of the affected limb

Following the decision for amputation, patients were asked to participate in an observational study on CRPS-I. A retrospective review of these patients' medical records was performed. Medical Research Ethics Committee (METc) approval for this study was not required. Approval of a concurrent Quality of Life study was granted (METc 2009/117). Results from that study have been published (9).

Collected data from medical records concerned: incident preceding CRPS-I and duration of CRPS-I; treatments before amputation; reason for amputation; level of amputation; complications during amputation or post-operatively; presence of phantom pain and symptoms of CRPS-I post-amputation. Data on use of prostheses, recurrence of CRPS-I and presence of phantom pain at three months after amputation was also retrieved from medical records. Data regarding recurrence of the syndrome more than one year post-amputation was retrieved from the amended Quality of Life database (n=26), as well as information on phantom sensations, phantom pain and residual limb pain (n=35) (9). Data analysis was performed with IBM SPSS Statistics 20 for Windows.

### Clinical procedures before amputation

All patients were screened by a physiatrist, a psychologist or psychiatrist, a physical therapist and a vascular surgeon before any decision for amputation was made. The physiatrist diagnosed the syndrome as CRPS-I according to IASP and Bruehl criteria (1, 2). Alternate diagnoses such as (missed) fractures, possible nerve entrapments, CRPS-II and post-stroke shoulder-hand syndrome were considered and extra tests (x-rays or bloodflow tests) were performed if needed. Diagnoses other than CRPS-I were excluded for amputation and, if present, treated accordingly. Joint contractures and muscle strength were assessed and post-amputation goals discussed with the patient. Together with the vascular surgeon and the patient, the potential level of amputation was discussed. The choice was based on the level at which patients experienced no pain or allodynia, the presence and extent of infection and necrosis and the desired length of the residual limb with regards to motivation for rehabilitation (post-operative functioning of the limb) and motivation for use of a prosthesis. Co-morbidity and adiposity were also taken into account according to standard amputation and rehabilitation procedures (11).

The physical therapist measured joint range of motion, muscle strength of all extremities, tested the ability to use walking aids in case of an affected lower-limb and discussed post-amputation goals and presumed benefits with the patient.

The psychologist or psychiatrist assessed the patients for major psychopathology and ideas about beneficial and adverse effects of amputation. A semi-structured interview, developed since the start of amputation for this syndrome in our hospital, and several questionnaires (Hospital Anxiety and Depression Scale; Connor Davidson Resilience scale; SCL-90; World Health Organisation – Quality of Life Bref) are now used to support the interview. The psychologist used green, yellow and red flags indicating a tendency for positive or more negative amputation advice (table 1).

The professionals then discussed the findings of physical and psychological examinations with the patient. All possible effects of amputation (positive and negative) were discussed. Patients' expectations were further explored. Patients were asked to formulate Specific Measurable Attainable Realistic Time bounded (SMART) goals. Positive and negative effects of amputation for CRPS-I were derived from all known case studies and provided guidance for discussions with patients (7).

Adipose patients were strongly advised to lose weight prior to the amputation. In case of muscle weakness of the limbs not affected by CRPS-I, patients were referred to a physical therapist for muscle training prior to a possible amputation. In case of joint contractures of the limbs not affected by CRPS-I, an attempt to improve range of motion through training was made. Failed therapies were discussed and treatment options that were not yet tried but advised in guidelines were proposed to the patient (5, 10).

Table 1

Green, yellow and red flags in psychological assessment of patients requesting an amputation of an CRPS-I affected limb

| **Green flags**[1] | **Yellow flags**[2] | **Red flags**[3] |
|---|---|---|
| initiative of the amputation by the patient | mood or anxiety problems | mood disorder |
| internal locus of control | external locus of control | anxiety disorder |
| adequate social support | low resilience | automutilation |
| having a relationship | lawsuits regarding onset of the syndrome | somatization |
| behaviour intended for health promotion | passive coping | personality disorder |
| expectation of functional improvement | perfectionism | substance disorder |
| good learning capacity | worrying/catastrophizing | |
| regular sport activity | | |
| volunteering or having a job | | |

*[1]Green flags indicate a tendency towards a positive advice regarding amputation. [2]Yellow flags indicate issues that need to be addressed during the decision making process. [3]Red flags indicate a tendency for a negative advice regarding amputation.*

# Results

An amputation was performed on 6 upper-limbs (2 transradial, 4 transhumeral) and 30 lower-limbs (12 transtibial, 13 knee disarticulation, 5 transfemoral), after a median duration of CRPS-I of 4.5 years (Inter Quartile Range (IQR) 2 to 8 years). Patients had a median age of 39 years (IQR 27 to 45 years). CRPS-I occurred after sprain in 16 patients, after surgery or arthroscopy in 11 patients, after obvious over-use in 3 patients, after a skin burn in one patient and due to a needle stick injury in the hand in another patient. CRPS-I always occurred on the side of the inciting event. CRPS-I occurred spontaneously in 4 patients. All patients had been treated in other hospitals and came to our medical center on their own initiative with the wish for amputation. All patients reported unbearable, therapy-resistant pain in a dysfunctional limb as reason for amputation. Thirty patients had joint contractures affecting mobility and use of the limb. Eleven patients had non-healing wounds or infections of which 2 needed amputation because of fear of sepsis.

Before they requested amputation at our center, all patients had been treated elsewhere with a wide variety of therapies including e.g. physical therapy, occupational therapy and pharmacotherapy (9). Patients had been treated according to guidelines and beyond. Six patients had a surgical sympathectomy without satisfactory results on pain. Time contingent physical therapy, either abroad or in The Netherlands, had been given to 12 patients (33%) without satisfactory results.

In one patient muscle weakness of the leg not affected by CRPS-I was found by the physical therapist and the amputation was postponed. After sufficient increase in muscle strength the amputation was performed.

From 2006 onwards our center used a digital patient information system. Therefore we were able to trace medical records from patients who were referred to our center with a request for amputation (due to CRPS-I) from September 2006. Amputation was advised in one additional patient who returned to his referrer for amputation. Seven patients were denied amputation by the physiatrist. CRPS-I could not be diagnosed in 4 patients. Two patients were advised additional physical therapy. One patient expected her generalized dystonia would disappear after amputation which was not expected by the team.

No complications during surgery were reported in the medical files. Eight patients (22%) developed complications postoperatively of which 2 patients had therapy-resistant wounds prior to amputation. Infections in the residual limb occurred in 5 patients: 3 patients had infections in the residual limb during the hospital stay and 2 patients had to be re-admitted due to an infection of the residual limb. Treatment consisted of necrotomy and antibiotics. Re-amputation was not needed. One patient developed ischaemia in the distal part of the hamstrings which was then partly removed in a surgical procedure. Superficial skin infection at the epidural anaesthetics opening site occurred in 2 cases.

Twenty-six patients (72%) experienced phantom pain directly after amputation or developed phantom pain within the first three months after amputation. More than one

year after amputation 30 out of 35 patients (86%) experience phantom sensations, 27 patients (77%) experience phantom pain and 26 patients (74%) experience residual limb pain with a great diversity in frequency and impediment (table 2).

Recurrence of CRPS-I never occurred directly after amputation or 3 months post-amputation. From our Quality of Life database we know that CRPS-I recurred in 7 out of 26 patients (27%; Bruehl's criteria) more than one year post-amputation. Four patients developed recurrence in the residual limb, one patient had recurrence in another limb and one patient had recurrence in both the residual limb and in another limb. One patient was amputated on another limb due to CRPS-I in another hospital in the timeframe between the first amputation and our study (although we could not formally objectify recurrence of CRPS-I in this patient, we have considered it as a recurrence).

Twenty-nine patients (81%) were amputated above the allodynia level, 4 patients through the level of allodynia and 3 patients below this level. One patient with recurrence in the residual limb was amputated below the allodynia level. From the Quality of Life database we know that recurrence of the syndrome in the residual limb or in another limb did not relate to the level of amputation (above, at, or below the level of allodynia) (Fisher's Exact Test p=0.691 for recurrence in the residual limb and p=0.646 for recurrence in another limb).

Table 2

Occurrence of phantom sensations, phantom pain, residual limb pain and impediment due to these conditions in 35 patients with amputation because of CRPS-I.

| | **Phantom sensations n (%)** | **Phantom pain n (%)** | **Residual limb pain n (%)** |
|---|---|---|---|
| Frequency | | | |
| – never | 5 (14) | 8 (23) | 10 (29) |
| – several times a year | 6 (17) | 4 (11) | 3 (9) |
| – several times a month | 1 (3) | 5 (14) | 4 (11) |
| – several times a week | 2 (6) | 4 (11) | 3 (9) |
| – several times a day | 5 (14) | 7 (20) | 5 (14) |
| – several times per hour | 2 (6) | 1 (3) | 3 (9) |
| – continuously | 14 (40) | 6 (17) | 7 (20) |
| Impediment[1] | | | |
| – none | 9 (26) | 1 (3) | 1 (3) |
| – hardly any | 8 (23) | 10 (29) | 5 (14) |
| – moderate | 6 (17) | 7 (20) | 9 (26) |
| – much | 5 (14) | 5 (14) | 5 (14) |
| – very much | 2 (6) | 4 (11) | 5 (14) |

[1]*Impediment for patients who suffer from the condition. Due to rounding off percentages may not add up to 100%.*

In the group of patients with an amputation of the upper-limb (n=6), only one patient (17%) used a prosthesis. In the group of patients with a lower-limb amputation (n=30) 22 patients (73%) had a prostheses and 21 used it (Fischer exact test; p=0.029). No differences were found between prosthesis users and non user, regarding gender and age.

# Discussion

This manuscript describes the process of informed decision making in a group of patients who underwent amputation due to CRPS-I, and the (short-term) outcomes after amputation. Informed decision making concerns the issues of whether or not to amputate and the level of amputation, but also involves formulating SMART goals with the patient and treating specialists. All team members (physiatrist, vascular surgeon, physical therapist and psychologist or psychiatrist) and the patient make this decision together. Factors influencing the decision are level of pain or allodynia, presence of infection, desired length of the residual limb, motivation for use of a prosthesis, co-morbidity, adiposity, joint range of motion, strength of all extremities, the ability to use walking aids and "psychological green, yellow and red flags". The decision making process for amputation because of CRPS-I is very different from the decision making process for amputation in case of cancer, infections or vascular diseases. In the latter cases amputation may be a life saving option and the only obvious "choice". In case of CRPS-I, surgeons may have difficulty in disabling the patient purposely by amputating a limb. It should be kept in mind however that life with excruciating pain and a dysfunctional limb may be even more disabling.

Amputation for CRPS-I is an uncommon and debatable treatment (4, 7, 10). Amputation as a last resort treatment has led to positive as well as negative outcomes (7, 9, 12). Some important findings from the current study may help to inform the patient who requests an amputation because of CRPS-I: 26 patients (72%) experienced phantom pain directly after amputation or developed phantom pain within the first 3 months after amputation; phantom pain remains present in 77% of patients but impediment due to phantom pain varies (table 2); recurrence of the syndrome in the residual limb or in another limb may occur (27%) but it did not relate to the level of amputation regarding allodynia.

It is important to point out that both patient and clinician may feel frustrated after many years of failed treatments and that amputation of an affected limb may give reason for new perspectives as well as new problems. A majority of patients in our study came to our outpatient clinic on their own initiative with the (repeated) wish for amputation. Patients who were amputated were capable of formulating SMART goals and psychological assessment presented a picture of predominantly green flags. This manuscript does not address the question how patients came to the decision to request amputation initially. Rather, we consider the process of how health professionals came to a final decision together with the patient. Within the informed decision making process of patients and health professionals, one of the issues addressed is creating realistic expectations. Patients with other conditions, such as mangled foot after trauma, poliomyelitis or a Charcot foot, may also request an amputation. A retrospective cohort study among 18

patients with a transtibial amputation because of intractable foot and ankle pain showed similar outcomes: a decrease in overall disability, an increase in participation in sports and employment and a decrease in impediment due to pain (13). In a qualitative study among 6 patients with an elective amputation, it was stated that experiencing ongoing pain was the key reason for the wish of amputation (14). A lack of limb function, including problems with walking and wearing normal footwear, in combination with a desire to improve participation in daily life activities and sports appear to be the second and third most influential factors when patients decide to have an elective amputation (14). Patients stress that the decision to amputate should be the personal wish of the patient (14). Satisfaction with the result among patients with CRPS-I related amputation is greater when the initiative for amputation was taken by the patient (8). Patients' satisfaction with the result after amputation was related to how closely the results fit with their pre-amputation expectations (14). Therefore, close attention should be paid to the R(ealistic) in formulating SMART goals. Meeting with an amputee peer may also provide the patient with information (14). For example, one of the first patients with long-standing, therapy-resistant CRPS-I who was amputated in our center participated in the Paralympic Games and now serves as a role model for other patients with an amputation because of CRPS-I and ambitions to participate.

One of the major concerns in amputation for CRPS-I is the fear for recurrence of the syndrome. In literature, a high recurrence rate of CRPS-I symptoms after amputation has been reported (8, 15) and guidelines have warned against amputation as a treatment option (10). The latest guideline for CRPS-I mentions amputation only in a minor remark (4). However, in our center, the recurrence rate is much lower compared to other studies, with good outcomes reported in terms of quality of life, frequent prosthetic use and patient satisfaction (9). It has been assumed that recurrence of CRPS-I symptoms in the residual limb is more likely to occur when amputation is performed at a level in which CRPS-I symptoms are still present (8). We could not find evidence for this assumption. Although our findings do not support the idea of amputation above the level of allodynia in order to prevent recurrence, we do support the suggestion to amputate above the level of allodynia until more evidence is found regarding this phenomenom (8). A comparison of the residual limbs of patients with CRPS-I and other causes of amputation (e.g. trauma, vascular disease) following Bruehl's criteria (including pinprick and light touch) may provide information on normal patterns of residual limb pain, sensibility, edema and trophic changes.

General rationale regarding the rehabilitation process in the decision making process of amputation was followed (11). Other rationale for the level of amputation in CRPS-I patients has been mentioned once in literature and was reported as "proximal to the level of disturbance of skin sensation" (16). This remark should be taken into account when prosthesis fitting is considered.

Although an active stress loading program as a treatment for CRPS-I was described in 1987 (17), it was not until around 2003 before it became known that a similar approach was being used by one person in Macedonia. This treatment was implemented in The

Netherlands thereafter (18). Pain exposure physical therapy (PEPT) for long-standing CRPS-I now offers promising results in literature; some improvement in function was achieved in 95 of 106 patients with long-standing CRPS-I (18). PEPT is not (yet) advised in guidelines. From our cohort, 12 patients (1/3) received PEPT but none reported benefit from it. We do not know how many patients have avoided amputation by following PEPT. Others (roughly) estimated that nearly all amputations can be avoided (19).

Due to the contradictions found in literature on CRPS-I, guidelines advise not to amputate in this population. The aim of this research was to assist clinicians with the difficult task of providing evidence based advice to patients who present requesting amputation for CRPS-I. Specifically, we have provided insight to a cohort of patients who were amputated at our center and the accompanying decision making process our team applied. Informed decision making when considering amputation for CRPS-I is a team process involving health professionals as well as the patient. Amputation as a possible treatment option for long-standing, therapy-resistant CRPS-I may be considered after other evidence-based options have failed.

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# 6

# Peripheral nerve pathology in Complex Regional Pain Syndrome type I

Submitted

# Abstract

**Background**
Complex Regional Pain Syndrome type I (CRPS-I) is a chronic pain syndrome with no clinical evidence of nerve injury, however, recently changes in muscle tissue have been found in this case of CRPS-I. Our aim was to search for histological changes in peripheral nerves of amputated limbs from patients with CRPS-I that could justify muscle tissue changes.

**Methods**
Fifteen patients with CRPS-I (duration > 1 year) were included. Multiple nerve samples were taken, proximally and distally, from upper (n=4) and lower (n=11) amputated limbs. Histological changes (signs of nerve fiber loss and regeneration), fiber diameters, fiber diameter distribution, and fiber density were studied through microscopy and morphometry. Samples from 3 healthy sural nerves were used as control data as well as data from literature.

**Results**
All patients (93% of tissue samples) showed histological signs of nerve fiber loss and fiber regeneration, varying in severity. No specific preference was found for any nerve or the location within the nerve. Sural nerves showed loss of especially larger nerve fibers (>12 μm) in comparison control data. Sympathectomy did not influence this finding. The morphometric results of the other nerves are more difficult to interpret due to absence of good quality control data from literature. However, the percentages of nerve fibers >12 μm seem to lie within the normal range.

**Conclusions**
Besides the known pathology of thin nerve fibers innervating the skin or bloodvessels in CRPS-I, this study also shows pathological changes more proximal in the nerves, especially in the sural nerve.

# Introduction

In Complex Regional Pain Syndrome (CRPS), two types are distinguished: CRPS type I (CRPS-I) is considered a syndrome without nerve injury; CRPS type II (CRPS-II) is considered to develop after nerve injury (1). CRPS-I is characterized by (extreme) pain in a distal part of a limb, motor impairment and autonomic dysfunction. The intensity of the pain is disproportionate to the inciting event. The pathophysiology of CRPS-I is unknown, though several hypotheses have been proposed such as neurogenic inflammation, endothelial dysfunction and pathological sympathetic-afferent coupling (2-5). The presence of oxidative stress, hypoxia and inflammatory processes together with neuropathic pain mechanisms are currently the leading hypotheses (6, 7).

Changes in muscle tissue have been suggested based on motor impairment present in CRPS-I (8-10). Results from research on skin biopsies in patients with CRPS-I suggest nerve damage in CRPS-I, like CRPS-II, but assumes to be predominantly affecting small diameter fibers (11,12). Small fiber neuropathy can explain the pain and autonomic dysfunction (11,12). According to Van der Laan et al myelinated fibers did not show consistent abnormalities. However, in four of eight patients in their study a decrease in myelinated fiber density was found (13). A decrease of especially larger myelinated fibers (>9 μm) was found in an animal model (14). Pathology in large nerve fibers could explain recent findings in CRPS-I muscle tissue showing signs of denervation, reinnervation and again denervation (15). Based on those results we expect larger nerve fibers to be affected in CRPS-I too. Because of the differences between results of muscle tissue analyses of patients amputated because of CRPS-I and results from the literature, the aim of this study was to analyze samples of peripheral nerve tissue of patients amputated because of CRPS-I.

# Methods

## 2.1 Patients

In very few patients with CRPS-I, severe complications such as infections, ulcers, chronic edema and a dysfunctional limb may develop. These complications are difficult to treat (16,17). Amputation of the limb affected by CRPS-I is not a common procedure and whether or not it should be performed is debatable (18). Amputation of the affected limb is sometimes a patient's last resort in order to try to restore quality of life (19,20). Between May 2000 and March 2007, 18 patients with long-standing, therapy-resistant CRPS-I underwent an amputation at the University Medical Center Groningen, The Netherlands. CRPS-I was diagnosed according to IASP criteria (1). Re-evaluation of the patient files showed that CRPS-I would have been diagnosed according to Budapest criteria as well (21,22). All patients (n=18) requested amputation because of severe pain and a dysfunctional limb. Some (n=7) also had recurrent severe infections and wounds. No obvious clinical signs or history of nerve injury were present at the time of diagnosis. Limbs were dysfunctional for more than one year prior to amputation. All patients received many different (combinations of) treatments prior to their request for amputation including: exercise therapy, occupational therapy, manipulation and partial immobilization (by means of splints); medication including morphine, anticonvulsants, anti-anxiety agents, and antidepressants; electrotherapy, TENS, and Epidural Spinal Electro Stimulation (20). All treatments had been without satisfactory result. Six patients had a surgical sympathectomy, which did not result in pain reduction. Patients were seen by a team of specialists in this field (physiatrist, vascular surgeon, physiotherapist, and psychologist or psychiatrist). Patients were seen by a psychiatrist or psychologist in order to rule out severe psychiatric conditions such as body dysmorphic disorder.

After the decision to amputate was made, the patients were asked for permission to perform histopathological analysis of the amputated limb. After written consent was given, the medical history was retrieved from the medical records. The following data were collected: age at amputation, gender, duration of CRPS-I prior to amputation, affected limb, level of amputation, and whether or not a sympathectomy was performed. Duration of CRPS-I was calculated from the moment the patients met diagnostic IASP criteria in their medical record for the first time. The medical ethical committee was not involved. This scientific research does not involve treatment or intervention and therefore it is not bound to the law on scientific research with people (Dutch= Wet Medisch Wetenschappelijk Onderzoek met mensen).

## 2.2 Tissue collection and sampling

Results from previous studies indicated damage of motor nerve fibers (15). It was therefore logical to examine mixed, sensory and motor nerves: ulnar, median, proximal radial, tibial and peroneal nerves and evaluate the loss of myelinated nerve fibers. However, since CRPS-I is a pain syndrome with autonomic dysregulation we were also interested in evaluating nerves without motor fibers, namely, the sural and distal radial nerves. Moreover, of normal sural nerves good morphometrical data exists for comparison with our results (23).

Tissue samples from three patients were excluded: one patient suffered from diabetes which in itself can cause peripheral nerve pathology (e.g. decrease of fiber density) (24); 2 patients were excluded because of limited quality of tissue processing/osmiumtetroxide ($OsO_4$) postfixation/ impregnation.

Ultimately, tissue samples from 15 patients, 3 males and 12 females, median age 41 years (Interquartile range (IQR): 35; 47), were included. Four patients had an amputation of an upper-limb and 11 patients of a lower-limb. Median duration of CRPS-I was 4 years (IQR: 2; 9) (table 1). Nerve biopsies of 4 cm were taken directly after amputation. Biopsies of the ulnar, median and radial nerve were taken at wrist level. In case of more proximal

Table 1

Characteristics of patients who were amputated because of CRPS-I and site of tissue sampling

| Patient | Age at amputation (years) | Gender | Duration CRPS-I prior to amputation (years) | Affected limb | Level of amputation | Sympathectomy performed | Number of tissue samples | Tissue sample site[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | 47 | F | 9 | LL | KDA | - | 3 | tn(2), sn |
| 2 | 45 | F | 7 | UL | THA | + | 6 | rne, rnw, mne, mnw, une, unw |
| 3 | 41 | F | 2 | LL | TTA | - | 3 | pn(2), sn |
| 4 | 16 | F | 4 | LL | KDA | + | 1 | pn |
| 5 | 25 | F | 2 | LL | TFA | - | 3 | pn(2), sn |
| 6 | 52 | F | 2 | LL | TTA | - | 5 | pn(3), tn, sn |
| 7 | 48 | F | 13 | LL | TFA | - | 1 | tn |
| 8 | 38 | F | 2 | LL | KDA | + | 2 | pn, sn |
| 9 | 35 | F | 5 | LL | TFA | + | 3 | pn, tn, sn |
| 10 | 23 | M | 1 | UL | AF | - | 3 | rnw, mnw, unw |
| 11 | 42 | F | 7 | LL | TTA | + | 2 | pn, sn |
| 12 | 49 | M | 3 | LL | KDA | - | 3 | pn, tn, sn |
| 13 | 36 | F | 13 | LL | KDA | - | 2 | pn, tn |
| 14 | 39 | M | 3 | UL | AF | - | 1 | unw |
| 15 | 44 | F | 20 | UL | THA | + | 5 | rne, mne, mnw, une, unw |

*F = female; M = male; LL = lower-limb; UL = upper-limb; TFA = transfemoral amputation; KDA = knee disarticulation; TTA= transtibial amputation; THA = through humerus amputation; AF = amputation of forearm; + = yes; - = no; pn = peroneal nerve; tn = tibial nerve; sn = sural nerve; rne= radial nerve elbow; rnw = radial nerve wrist; mne = median nerve elbow; mnw = median nerve wrist; une = ulnar nerve elbow; unw = ulnar nerve wrist. () between brackets the number of samples if more than 1 sample.*

Table 2

Overview of morphometric data of peripheral nerves without evidence of peripheral nerve disease from literature and data from the current study on peripheral nerves from patients with CRPS-I and healthy[A] controls.

| Author, publication year | Participant characteristics (no of participants; age: mean and range) | Fiber diameter range | Nerve: Sural | Tibial | Peroneal | Radial | Median | Ulnar |
|---|---|---|---|---|---|---|---|---|
| O'Sullivan, 1968[23] | | 2-16;<br>peaks at 3-6 and 9-13<br>Proportion of large diameter fibers decreased with an increase of age in sural but not in radial nerves. | | | | | | |
| | 8; 43 yrs (26-57) | | 6015[C]<br>(5340-6760)<br>7.50±0.38 | | | | | |
| | 7; 41 yrs (26-54)[B] | | 6050[C]<br>(5340-6760)<br>7.40 ± 0.25 | | | | | |
| | 8; 40 yrs (17-57) | | | | | 7120[C]<br>(5410-10020)<br>7.42±0.81 | | |
| Ochoa, 1969[26] | 6; 22,5 yrs (15-34) | 2-14<br>peaks at 4-5 and 11 | 8000[D]<br>(7000-10000)<br>– | | | | | |
| Dyck, 1982[25] | 6; 32,5 yrs (20-54) | 1-13<br>peaks at 3-4 and 10 | 8100[C]<br>(7300-10000)<br>– | | | | | |
| | 2; 26 and 42 yrs | 1-14<br>peak at 4 and 10 | | –<br>(9300-10200)<br>– | | | | |
| | 3; 20, 26 and 42 yrs | 1-15<br>peaks at 4 and 9 | | | –<br>(10500 -12000)<br>– | | | |
| Jacobs, 1985[27] | 6; 40 yrs (21-58) | –<br>peaks at 3-5 and 9-12 | 8065 [C]<br>(7760-10190)<br>– | | | | | |

| Author, publication year | Participant characteristics (no of participants; age: mean and range) | Fiber diameter range | Nerve: Sural | Tibial | Peroneal | Radial | Median | Ulnar |
|---|---|---|---|---|---|---|---|---|
| Schröder, 1988 [28] | 2; 16 and 17 yrs | – | – | | | | | – |
| | | – | – | | | | | – |
| | | | 6.24; 6.68 | | | | | 6.47; 8.77 |
| Behse, 1990 [29] | 9; 33 yrs (17-54) | 2-14 | 7700 [C] (5500-8000) 6.74±0.30 | | | | | |
| Lindemuth, 2002 [30] | 6; 22-40 yrs | 1-16 | 8397 [D] | 8345 [D] | | | | |
| | | – | ± 1583 | ± 1118 | | | | |
| | | | 5.9 ± 0.4 | 5.9 ± 0.3 | | | | |
| Chentanez, 2009 [31] | 21; 36.6 yrs (14-58) | 1-16 | | | | 8873 [D] | | |
| | | – | | | | ±167.4 | | |
| | | | | | | 6.32± 0.09 | | |
| Current study Bodde et al | 3[A]; 32 yrs | 2-17 | 6062[C] | | | | | |
| | | – | (3989-9594) | | | | | |
| | | | 8.08 ± 3.4 | | | | | |
| | CRPS-I patients: 8; 41.5 yrs (25-52) | 2-17 | 7078 [C] | | | | | |
| | | – | (4299-8703) | | | | | |
| | | | 6.78 ± 2.8 | | | | | |
| | 6; 47.5 yrs (35-52) | 2-17 | | 5453 [C] | | | | |
| | | – | | (1887-8388) | | | | |
| | | | | 7.38 ±3.4 | | | | |
| | 9; 38 yrs (16-52) | 2-21 | | | 7025 [C] | | | |
| | | – | | | (2306-8388) | | | |
| | | | | | 7.03 ± 3.6 | | | |
| | 3; 23, 44 and 45 yrs | 2-17 | | | | 4823 [C] | | |
| | | – | | | | (4194-7025) | | |
| | | | | | | 8.49 ± 3.3 | | |
| | 3; 23, 44 and 45 yrs | 2-17 | | | | | 6920 [C] | |
| | | – | | | | | (5662-8284) | |
| | | | | | | | 8.12 ± 3.3 | |
| | 4; 23, 39, 44 and 45 yrs | 2-17 | | | | | | 5400 [C] |
| | | – | | | | | | (3670-8179) |
| | | | | | | | | 8.31 ± 3.4 |

*All manuscripts included patients without evidence of peripheral nerve disease except the current study. The authors derived the data from the appendices, tables or text of the manuscripts cited. If information could not be derived this is marked with: -. Regarding "nerve data cells": in each cell the first row represents mean or median fiber density: fibers/mm²; the second row indicates the range, between brackets or standard deviation ; the third row represents mean fiber diameter and standard deviation. Fiber diameters, fiber diameter range and peaks (in case of bimodal fiber diameter distribution) are expressed in µm. [A] facial nerve paralysis, but otherwise healthy controls. [B] data from these subjects were used for comparison in current manuscript. [C] median fiber density. [D] mean fiber density.*

amputation, biopsies were also taken at the level of the elbow. Biopsies of the tibial and peroneal nerve were taken at transtibial level and from the sural nerve just above the lateral malleolus. No other biopsies were taken in case of more proximal amputation of the lower limb. Biopsies were fixed in 2% glutaraldehyde with buffer for one week. Care was taken not to touch the nerve biopsies in the middle in order to prevent mechanical damage or artifacts. After the fixation period a 1mm thick section from the middle of the biopsy was taken, again to exclude material, which might have been damaged during sampling (mostly found at the edges of biopsy specimen) (25). This 1mm thick tissue specimen was postfixed in $OsO_4$ for 2 days, embedded in Epon resin and finally cut in semi-thin sections with a glass knife on a microtome at a thickness of 0.5µm. The sections were mounted on glass slides and stained with toluidin blue for evaluation of nerve fiber loss and regeneration as well as morphometry.

### 2.3 Healthy sural nerve control group

Literature on morphometric analysis of human nerve fibers (nerve fiber diameters, density and distribution) from healthy subjects is scarce. A list of most common cited literature and its details is presented in table 2 (23,26-31). Most biopsies of the current study came from sural nerves (n=8). We compared our results with results from a sample of sural nerves from persons with approximately the same age as our patients from the study of O'Sullivan and Swallow et al (1968) (First 7 patients in Appendix II from that study: median age 41 years (23)).

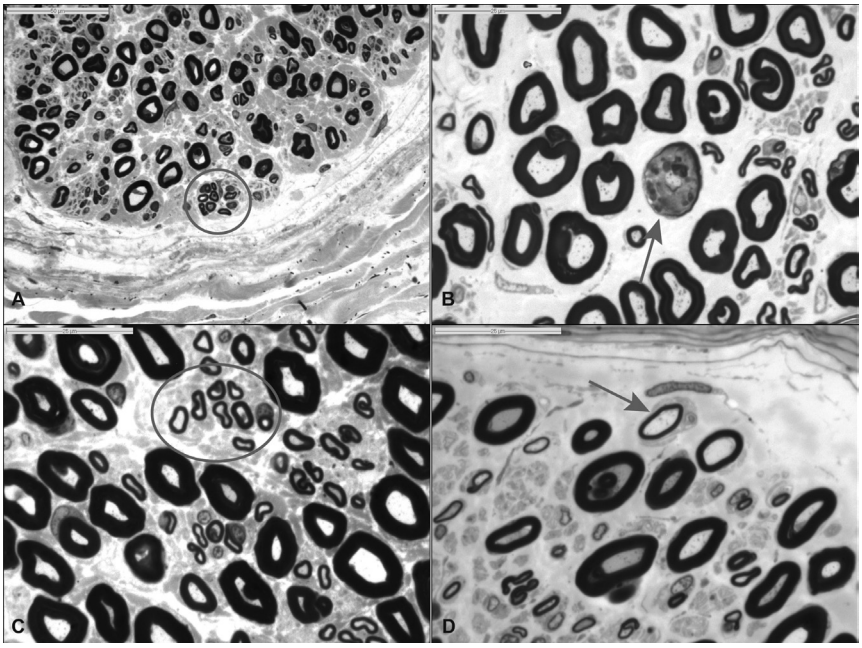
In addition, we obtained healthy sural nerve biopsies from 3 patients undergoing cross face nerve grafts for a facial nerve paralysis, median age 32 years. Patients in this control group did not have other peripheral nerve problems than their facial nerve paralysis. The same method of preparation was used for these healthy sural biopsies (paragraph 2.2). These biopsies were evaluated to verify if our results in CRPS-I patients might be the result of our research and laboratory methodology.

### 2.4 Microscopic and morphometric analysis

All biopsies (table 2) were assessed by MB and WdD together, using microscopy and morphometry. The biopsies were assessed for histological changes of the peripheral nerves (figure 1). Nerve injury causes Wallerian degeneration and fiber loss distally from the injury site followed by fibrosis and possible nerve fiber regeneration. Therefore, the tissue characteristics assessed were fiber loss and degeneration (figure1B) and regeneration (figure 1A, 1C and 1D). Fiber loss and degeneration were determined to be present if collapsed fibres or myelin balls were found. Regeneration was determined to be present if clusters of small myelinated fibers or normal size axons with a thin myelin sheath were found.

For morphometric analysis a magnification of x400 was used to count all myelinated fibers within one standard area (9536.9$\mu m^2$). Several standard areas per nerve were evaluated and the results averaged. The areas were chosen randomly. In order to analyze fiber loss and regeneration in morphometry, all fibers with a myelin sheath per standard area were measured twice. First, the surface area of the total fiber was measured. Second, the axon

Figure 1




*1A Overview of a peripheral nerve of a CRPS-1 patient (bar represents 50 micron). The circle indicates a small regeneration cluster. In 1B a degenerating nerve fiber is shown (arrow). 1C shows a regeneration cluster (circle). The arrow in 1D indicates an regenerated nerve fiber with a relative thin myelin sheath. Bars in B to D: 25 micron.*

surface area of the myelinated nerve fibers was measured. The fiber and axon diameter were calculated assuming circularity. Then, the g-ratio was calculated as the ratio between axon diameter and total fiber diameter (32,33). The g-ratio represents the myelinisation of an axon and it is a measure of maturity of the regenerating nerve. Regenerating fibers have thinner myelin sheaths resulting in higher g-ratios (33-36). We hypothesized a slightly higher g-ratio in our CRPS-I group because of regeneration of a relatively small number of fibers (15).

### 2.5 Statistics/Analytical approach

Descriptive data analysis was performed using PASW for Windows version 18.0. Fiber density and g-ratios will be presented as means with standard deviation and parametric tests will be applied.

Microscopical variables (fiber loss and regeneration), axon and fiber diameters will be presented as median values with interquartile range (IQR) and nonparametric tests (Mann Whitney U) will be applied.

# Results

### 3.1 Nerve pathology in CRPS-I

Forty-three biopsies of nerve tissue were microscopically analyzed. In 35 biopsies (81%) fiber loss was found; in 37 biopsies (86%) regeneration was found. In three biopsies (7%) no signs of nerve pathology were found (samples taken from the median nerve at the elbow and radial nerve at the wrist in patient 2 and one sample from the peroneal nerve in patient 3; table 1), however, in other nerve samples from these patients signs of pathology were present. Therefore, in all patients some pathological changes were found during microscopic analysis (nerve fiber loss or regeneration). In sural nerve biopsies from our control group no signs of nerve fiber loss or regeneration were found.

### 3.2 Fiber density in CRPS-I and controls

A mean (sd) of 58.4 (16.9) myelinated fibers per standard area was found in CRPS-I tissue, corresponding with 6128 fibers/mm$^2$. Fiber densities of all CRPS-I and control nerves are presented in table 2. Fiber densities ranged considerably: the highest fiber density was found in a sural nerve sample of patient 6 (8703 fibers/mm$^2$) and the lowest fiber density was found in a tibial nerve sample of patient 1 (1887 fibers/mm$^2$) who also showed the most severe degenerative changes in the microscopical analysis.

### 3.3 Fiber diameters and distribution in CRPS-I and controls

Myelinated fiber diameters ranged from 2 to 21µm. The median axon diameter of myelinated fibers was 3.3µm (IQR: 2.3µm; 4.7µm) and the median fiber diameter of myelinated fibers was 7.1µm (IQR: 4.3µm; 10.3µm). No significant differences in fiber size were found between biopsies taken at the elbow or at the wrist, therefore biopsies taken from these two levels in the ulnar and median nerve were taken together. Median fiber diameters of CRPS-I and control nerves are presented in table 2; line diagrams of fiber distribution of all nerves are presented in figures 2 and 3. The percentage of fiber diameters >12 µm are as follows: 33.7% radial nerve, 21.6% ulnar nerve, 15.9% median nerve, 15.4% tibial nerve, 11.6% peroneal nerve and 2.4% sural nerves. In our healthy controls this percentage was 18.9% (sural nerves).

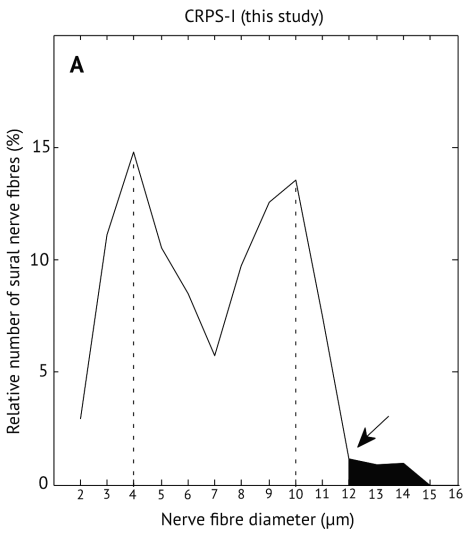
### 3.4 g-ratios

The mean (sd) g-ratio of all nerve fibers was 0.50 (0.1); the mean g-ratio of the radial nerve biopsies was 0.53 (0.1). The mean g-ratio of the healthy controls was 0.49 (0.1). The g-ratio of the sural nerves of CRPS-I patients, (n=500 fibers; 0.50 (0.1)) was significantly lower (p=0.02) than the g-ratio in our healthy control group, (n=724 fibers; 0.49 (0.1)). This indicates slightly thinner myelin sheaths in the CRPS-I group, in turn pointing in the direction of nerve fiber regeneration.

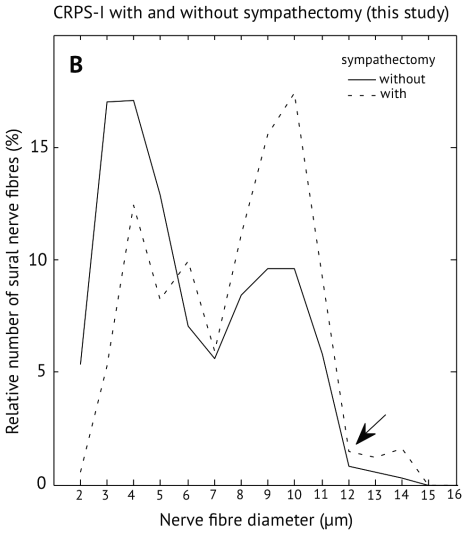
### 3.5 Influence of sympathectomy

The samples of patients with (n=24) and without (n=19) sympathectomy were compared (figure 2B). Results were in line with what could be expected since in sympathectomy smaller nerve fibers are affected and a larger percentage of large nerve fibers will remain.

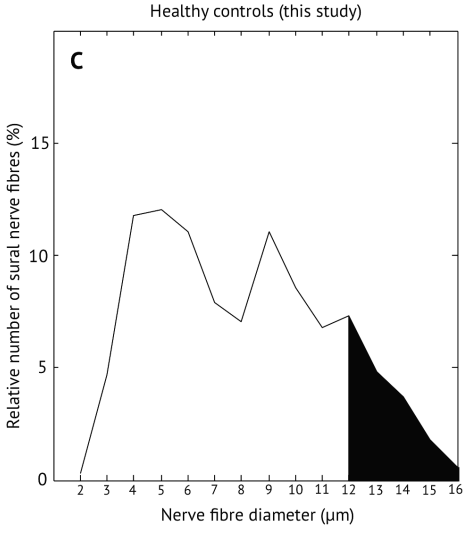
Figure 2



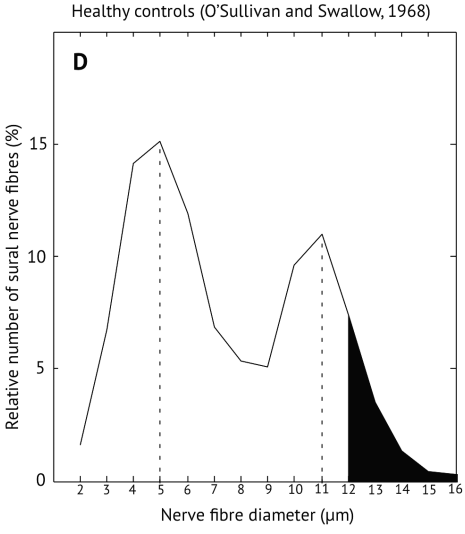

*2A Diameter distribution of myelinated nerve fibers from sural nerve biopsies in our patient group (8 patients, median age 41.5 years) in percentages. Arrow: decrease of large fibers is visible ≥ 12µm. The black area under the curve shows the amount of large fibers present.*




*2B Diameter distribution of myelinated nerve fibers from sural nerve biopsies in our patient group, comparing patients with and without sympathectomy. Patients with a sympathectomy have relatively smaller amounts of small myelinated nerve fibers and more large myelinated nerve fibers. Arrow: in both groups a decrease of larger fibers is present from about 12µm.*



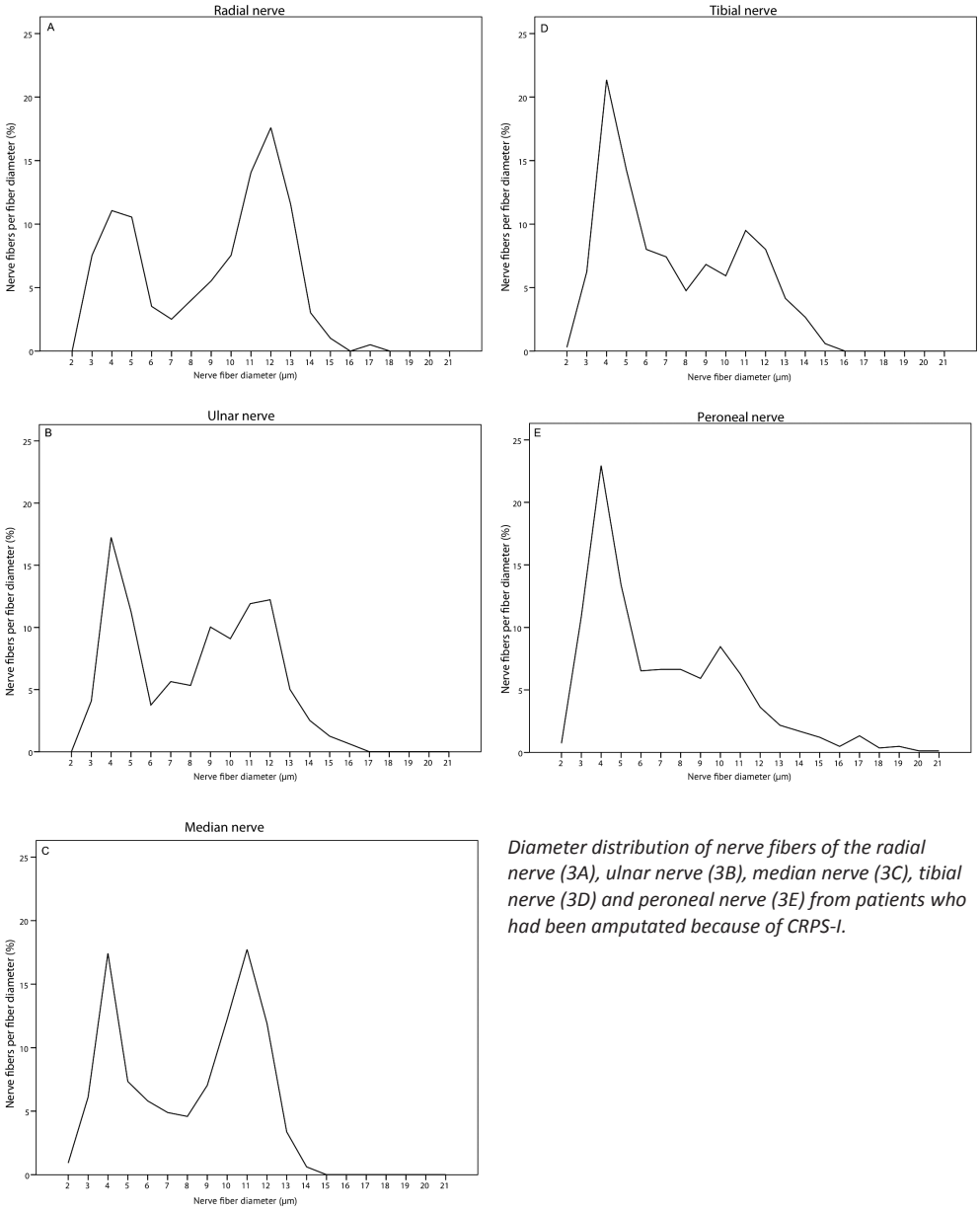

*2C Diameter distribution of myelinated nerve fibers from sural nerve biopsies from our healthy control group (nerves biopsies taken from patients undergoing a cross facial nerve graft because of facial nerve paralysis). The black area under the curve shows the amount of large fibers (≥ 12µm ) present.*




*2D Distribution of diameter of myelinated nerve fibers from sural nerve biopsies from literature (O'Sullivan and Swallow, 1968: 7 patients median age 41 years). The black area under the curve shows the amount of large fibers (≥ 12µm ) present. A larger area under the curve is seen in 2D compared to figure 2A.*

*Nerve fiber diameters in sural nerves in literature show a bimodal distribution (figure 2D). Distribution of nerve fiber diameters in our small healthy sural nerve control group showed less clear peaks (figure 2C), however, the bimodal distribution is present in the CRPS-I group (figure 2A).*

Figure 3




*Diameter distribution of nerve fibers of the radial nerve (3A), ulnar nerve (3B), median nerve (3C), tibial nerve (3D) and peroneal nerve (3E) from patients who had been amputated because of CRPS-I.*

# Discussion

CRPS-I is defined as a syndrome without nerve injury (1). However, our results indicate that peripheral nerve damage is present in most of our CRPS-1 nerve tissue. Whether nerve damage triggers the syndrome or occurs in the course of the syndrome remains unknown from this study. These results are in line with the signs of a process of repetitive denervation and reinnervation of muscle tissue found previously and that has been suggested by others (11-13,15).

All CRPS-I patients showed, to a varying extent, histological changes including nerve fiber loss and regeneration. These histological changes were also found by Van der Laan et al (13). These histological abnormalities were not observed in the sural nerve biopsies from our healthy controls, although it has been described that some structural abnormalities may be found in healthy controls (25,29). Our microscopic findings suggest that peripheral nerve degeneration and regeneration does occur in the course of CRPS-I, at least in those who had their limb amputated. It has been suggested that CRPS-I is a syndrome in which distally located peripheral nerve fibers (for instance the nerve endings in the skin) are damaged (11, 37). Our findings indicate that nerve damage is also present more proximally in the nerves. Several hypotheses for this damage at a more proximal level can be formulated. The nerve may be damaged through local pressure from edema in the affected limb. An animal model of rats with chronic loose ligatures of the sciatic nerve shows a deficit in large myelinated nerve fibers (>9µm) at the end of the observation period at ten weeks when swelling had disappeared and the total number of myelinated fibers was close to normal (14). Nerves may also be damaged through other local symptoms of autonomic dysfunction and trophic changes. These changes can lead to endothelial dysfunction and the production of free radicals, which in turn induce histopathological changes caused by oxidative stress (6). Yet another hypothesis in the pathophysiology of CRPS-I is the concept of neurogenic inflammation in which local or systemic “products” such as neuropeptides and cytokines may cause (local) damage of the nervous system (2,4,7). Finally, nerve degeneration and regeneration may also be the result of retrograde degeneration of the nerve after damage more distally in an extremity.

Morphometric characteristics of peripheral nerve fibers were independent of age in a group from 14-58 years (mean 36.6) (31). Fiber density stays relatively constant until the age of 60 years. Thereafter it tends to decrease (27). Therefore, the results from these studies can be used for comparison with our data. Fiber densities reported in literature range considerably from approximately 5300/mm$^2$ to 12000/mm$^2$, depending on the nerve in question (table 2). The fiber density in the sural nerves of our control group matched those from O’Sullivan, but was smaller when compared with Dyck (25), Jacobs (27) and Behse (29) (table 2). Because of the wide range of sural nerve control data in literature, our CRPS-I data have to be evaluated with caution. In our CRPS-I patient group, the fiber density also varied considerably, and was lying within the range of our control group. Therefore, hard conclusions cannot be drawn from these data comparisons. Most likely this means that even though nerve fibers pathology can be found in all our patients, the number of nerve fibers that are affected is too small to cause significant changes in nerve

fiber density measurements. Besides the sural nerve, control data for the other nerves from literature is even scarcer (table 2) and therefore conclusions cannot be drawn. Completed maturation of axon and myelin sheath is considered to occur around the age of 17 years (28). Nerve fiber diameter ranges from 2 to approximately 21 µm (34). Sural nerves are known to have a bimodal fiber diameter distribution with peaks at 3-5 µm and at 9-12 µm at adult age (figure 2.D) (27). However, others found a decrease in the proportion of large diameter fibers with increasing age in the sural nerve but not the radial nerve (23). To make adequate comparisons of our data with data from literature we used data from sural nerves from patients with a similar age range. Some analysis methods allow counting nerve fibers <1 µm (30,31,38), resulting in smaller mean fiber diameters (table 2) and making adequate comparisons difficult.

Distribution of nerve fiber diameters from the sural nerve of our control group show less clear peaks (figure 2C), however, the bimodal distribution is present in the CRPS-I group (figure 2A). Interestingly, the area under the curve at >12µm shows a loss of large myelinated nerve fibers in the CRPS-I group (figure 2A). This loss of larger myelinated nerve fibers cannot be explained by artifacts due to surgical removal or different fixation and measuring techniques, because the same methods were applied in our control sural nerves. Theoretically, a sympathectomy would cause a combination of diminished numbers of unmyelinated and thin myelinated nerve fibers due to Wallerian degeneration and this will influence the mean nerve fiber diameter. The decrease at 12µm exists in both the CRPS-I group with and without sympathectomy. This means that this form of therapeutic intervention does not cause the decrease of nerve fibers >12µm.
Based on the findings in the sural nerves described here, as well as the previously reported skeletal muscle pathology, we expected a similar loss of large myelinated fibers in the mixed sensory-motor nerves. However, the percentages of fiber diameters >12 µm in the other nerves were much higher. Therefore it seems that our findings from the CRPS-I sural nerves cannot be translated to the other CRPS-I nerves.

A limitation of this study is the small sample of control sural nerves and lack of control samples from mixed (motor) nerve fibers. As stated data from literature are difficult to compare when samples are not taken and measured following an identical procedure (23). Morphometric data of healthy nerves is scarce and often not extensive enough for good comparison (table 2). Limbs are generally amputated due to vascular problems, which may cause impaired and changed vascularisation of peripheral nerves, or due to oncological reasons. In those cases changes in nerve tissue may have occurred due to systemic or local chemotherapy. Thus the above mentioned limbs are not suitable to serve as “healthy” control material. In the Netherlands, bodies available for anatomical research are anonymous. Consequently, the medical backgrounds are unknown and we cannot reliably use them as healthy controls. This is a common problem in morphometric research, although others may choose to use post-mortem samples (24).

**Future research**

As the sural nerve samples showed more dramatic changes in the morphometrical evaluation than the other nerves studied here, fiber typing by immunohistochemy could be interesting. Furthermore, the evaluation of the motor nerve fibers and end-plates in the skeletal muscle tissue could lead to additional information concerning the pathophysiology of the muscular changes in CRPS-I.

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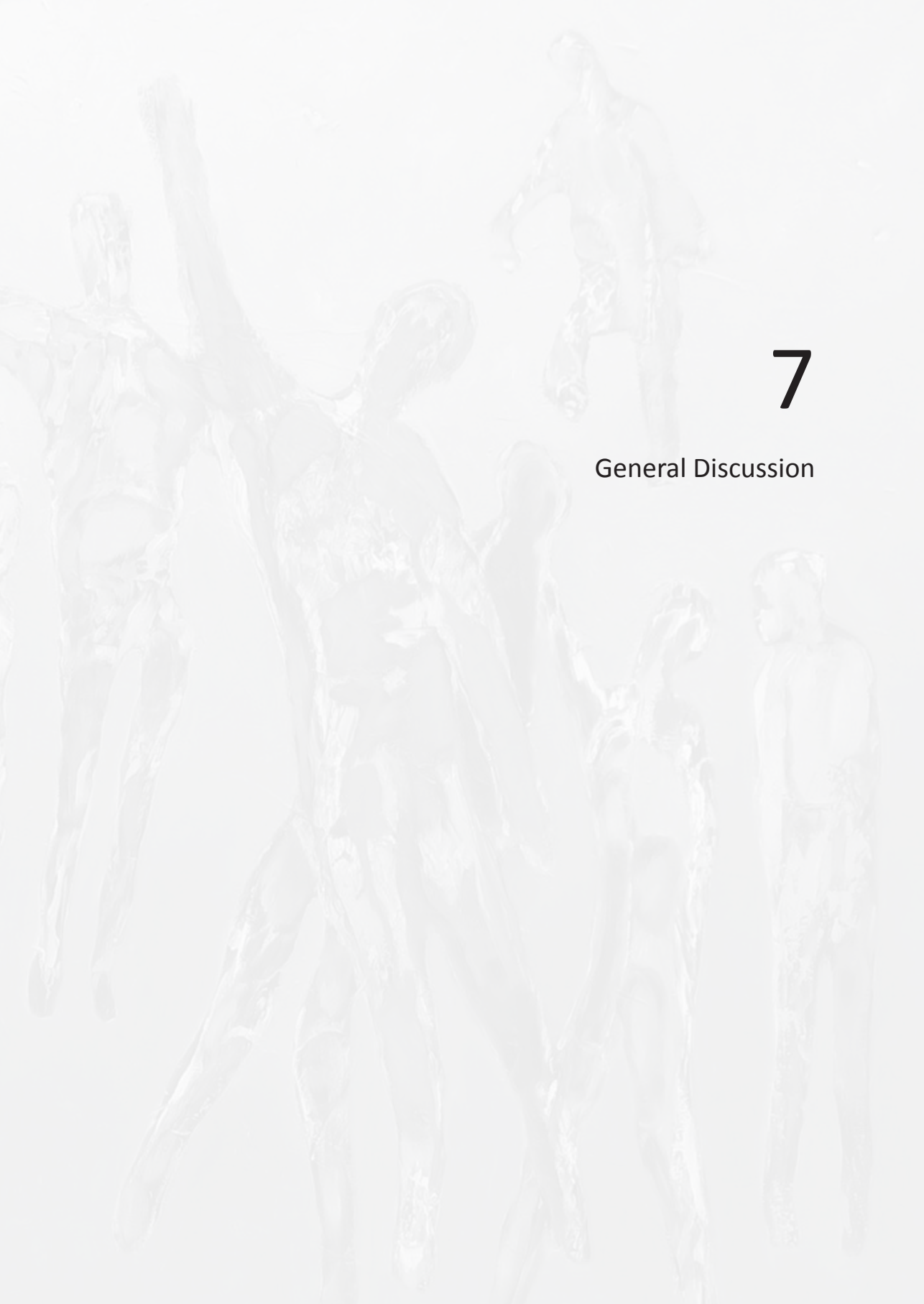

# 7

# General Discussion

# General Discussion

In this thesis, the focus was on the agonizing decision to amputate in case of long-standing, therapy-resistant CRPS-I. The case of Mrs. X will serve as a thread in this general discussion and will help to reflect on effects on quality of life of people who choose to be amputated, what is known in literature about this decision, why people amputated in the University Medical Center Groningen (UMCG, The Netherlands) seem to do better than patients amputated in other centers and on aspects of nerve tissue samples from CRPS-I affected amputated limbs.

> *"Since Mrs. X's knee disarticulation in 2000, almost a decade had passed when she was invited to participate in a quality of life study among patients with CRPS-I related amputations."*

Retrospectively, it can be argued that Mrs. X should not have been amputated for CRPS-I based on negative opinions and advices in guidelines in those days (1, 2). Both studies (3, 4) on which the advices in guidelines were based were part of the systematic review (26 studies, 111 amputations in 107 patients), (chapter 2). Beneficial and adverse effects of an amputation in case of CRPS-I could not be clearly delineated from the results of the systematic review. Effects of the amputation on quality of life were also difficult to derive from the included studies. Based on the findings from the systematic review no advice could be given for alteration of the guidelines regarding amputation for CRPS-I. It remains awkward that guidelines and media base their negative opinion on one paper in particular in which it is not always clear what the unit of research was, amputation (n=34), limb (n=31) or person (n=28) (4). Percentages are therefore difficult to interpret. However, it also clearly stated in that study that the majority of patients (86%) is satisfied with the results, even though CRPS-I recurred in 28 out of 34 amputations (82%) and relief of pain was achieved in a minority of patients (32%?) (4).

> *"Mrs. X does not experience stump or phantom pain, nor is she affected by recurrence of CRPS-I. She uses her prosthesis daily and qualifies as a K-level 3: a community ambulator (she has the ability to use a prosthesis for basic ambulation and the ability to adjust for most environmental barriers; she may walk at varying speeds) (5). Although she had been working as a housecleaner in the years before CRPS-I affected her leg, she has never been able to restore her working life."*

Mrs. X is one of few patients who do not experience any residual limb or phantom pain. Most patients in our study report a major reduction in pain following amputation (18/21 patients, 86%), but still experience pain in the residual limb (18/21 patients, 86%) (chapter 3). A large proportion of the study group (26/36 patients, 72%) experienced phantom pain

directly after amputation or developed phantom pain within the first 3 months after amputation. One year post-amputation only 6 patients never experienced phantom pain (6/36 patients, 23%), another 6 patients (23%) always experienced phantom pain (chapter 5). Seven patients (27%) experienced phantom pain several times a day and the others (27%) experienced phantom pain several times per year (chapter 5). Compared to the percentage of patients experiencing phantom pain found in the systematic review (41%) this is rather high (chapter 2). However, it is in line with results from Dielissen et al (71%) (4). Impediment due to phantom limb pain varied from none and hardly any (6/20 patients, 30%) to much or very much (9/20 patients, 45%) (chapter 5). Recurrence of CRPS-I never occurred within 3 months after amputation. Following Bruehl's criteria for CRPS-I (6), the syndrome recurred in 7 out of 26 patients (27%) more than one year post-amputation. Four patients developed recurrence in the residual limb, one patient had recurrence in another limb and one patient had recurrence in both the residual limb and in another limb. One patient had an amputation of another limb due to CRPS-I in another hospital in the timeframe between the first amputation and our study (although we could not formally objectify recurrence of CRPS-I in this patient, we considered it to be a recurrence). The differences in recurrences of CRPS-I after amputation between this study (27%) and the study by Dielissen et al (4) (82% of the amputations) may lie in the more stringent criteria for CRPS-I which were developed after the date of their publication (1995). Regular use of a prosthesis (more than 8 hours per day) was found in our study in 10 of 15 patients (67%) for lower-limb amputees and only in one of 6 patients with an upper-limb amputation. Participation improved. The percentage of paid employees increased from 3 patients (14%) before amputation to 8 patients (38%) at the time of this research project. The percentage of students increased from 3 patients (14%) to 6 (29%).

> *"Mrs. X is happy with her choice for amputation and wished the amputation had been performed a few years earlier. It would have saved her many years of pain and sleep deprivation."*

Under similar circumstances, 86% of patients (18/21) would choose amputation again and nearly all patients reported an improvement in their life (95%, 20/21) (chapter 3). It was therefore concluded that an amputation may positively contribute to the lives of patients with long-standing, therapy-resistant CRPS-I (chapter 3).

In contrast to results from other studies which were the basis of guidelines, Mrs. X showed remarkably positive results after amputation, as did many others in the study population of this thesis. The difference with patients with more negative outcomes in literature might be related to resilience: the patient's ability to bounce back from adversity (chapter 4). A positive association between resilience and quality of life, especially within the psychosocial domain was found (chapter 4).

Several hypotheses regarding the relatively high resilience scores and more positive quality of life outcomes can be thought of. They reflect the limitations of this thesis. It is possible

that team members unknowingly selected patients on the basis of resilience. The lack of information on patients who were denied amputation at the UMCG, introduces another limitation of this thesis. Also, quality of life and resilience were not measured before amputation or directly after amputation, which makes results difficult to interpret. Recall bias, response shift and cognitive dissonance may also have influenced results.

**Comments from reviewers on submitted and published manuscripts in this thesis and comments in general**

*I do not think that the authors have understood the pathophysiology of CRPS .*

(Unpublished response of authors: "Who does?")

*Amputations for CRPS-I are serious disabling interventions and can be avoided with current new treatment strategies.*

*In the US this surgery is rarely if ever considered an option.*

*It is not clear if it is the pain intensity that drove to the decision to amputate or if this draconian decision has been taken for other reasons such as the diffusion of infection, gangrene or acute vascular problems.*

*It should be stated that amputation is no standard therapy of CRPS and not recommended by the IASP. It is really astonishing how many amputations were performed during the recruitment for that study, especially since data to amputation is very scarce in the literature.*

*The decision to amputate in these cases can be agonizing for the surgeon as well as the patient & family.*

*Certainly there will be strong reactions to this data as the results are surprising given the prior literature and clinical experience of some providers.*

*This is a complex issue for patients – while some of the problems got better, amputation certainly does not solve all of the issues – and creates a new set of issues for people to overcome.*

*This paper offers data that suggests that one extreme treatment, namely, amputation of a limb, may be an appropriate and effective one.*

Five studies on CRPS-I and amputation are included in this thesis. Every manuscript has a long history of contradicting and emotional comments from reviewers resonating the negative advice in guidelines regarding CRPS-I.

It has been suggested that we most likely must have misdiagnosed CRPS-I. In 1994, the International Association for the Study of Pain (IASP) published its own criteria (7) followed by the criteria according to Bruehl in 1999 (6) and the Budapest criteria in 2007 (8). Generally diagnostic criteria for CRPS-I are poorly described in literature (9), especially regarding CRPS-I and amputation (chapter 2). Patients studied in this thesis were always diagnosed according to IASP and Bruehl criteria (6, 7). CRPS-I may in general be over-diagnosed using IASP (7) or Veldman criteria (10), since those criteria are very broad (6, 11, 12). Over-diagnosing CRPS-I seems to be less likely in our research population since retrospectively, during chart review, all patients fulfilled the recent and more stringent Budapest criteria (8, 13). Alternate diagnoses should always be considered e.g. CRPS-II, (missed) fractures, possible nerve entrapments and post-stroke shoulder-hand syndrome (chapter 5). Further, it is important to identify if (psychiatric) disorders, e.g. body integrity identity disorder (BIID), are present in CRPS-I patients. Patients with BIID may face the same reluctance among clinicians regarding the wish for amputation. The discussion on whether or not to amputate in case of BIID, patients with a wish for amputation of a healthy limb, goes beyond the scope of this thesis. However, it is important that clinicians realize that patients with BIID may go extreme ways (freezing methods, gunshot, guillotine) in order to get an amputation. Diagnoses which have been mistaken for CRPS-I in the past include osteochondral lesions or underlying synovial sarcoma (14, 15). Unfortunately, having another diagnosis than CRPS-I may still require an amputation as treatment (15).

CRPS-I is defined as a syndrome without clinical evidence of a nerve injury (7). However, our research results indicate that at least some peripheral nerve damage is present in nerve tissue of most of our patients (chapter 6). One reviewer commented that, since we found nerve pathology, it was most likely that our patients were wrongly diagnosed with CRPS-I instead of CRPS-II. However, no clinical evidence of nerve injury was present in the patients or could be derived from their medical history. The small number of patients and the absence of a substantial control group are limitations of this study. Whether nerve damage triggers the syndrome or occurs in the course of the syndrome remains unknown (chapter 6). The results were in line with the signs of a process of repetitive denervation and reinnervation of muscle tissue (16).

### Current opinions on amputation as last resort treatment for CRPS-I

Prior to amputation we strongly suggest and recommend patients with long-standing and therapy-resistant CRPS-I to try all therapies recommended in guidelines (and beyond). Our intention to publish on amputation for CRPS-I has always been to provide evidence to promote “evidence-based practice”. As stated before, it has appeared that manuscripts from this thesis ran into rather pre-made-up minds on several occasions. It is unknown why clinicians and researchers are reluctant regarding amputation as a last resort therapy/ treatment for CRPS-I. We believe this reluctance is based on two papers in particular in

### Amputation in guidelines on therapy for CRPS-I

In 1998, when amputation as treatment for CRPS-I had been described several times (chapter 2, table 2), international guidelines for the therapy of CRPS-I were published (17). Amputation was not mentioned in those guidelines. In 2010, amputation was mentioned in another guideline for the treatment of CRPS-I: "Amputation is sometimes performed with the aim to improve quality of life of CRPS-I patients with severe complications, such as life threatening sepsis or severe functional impairment"(2). This guideline notes that 24 patients remained satisfied with their amputation even though CRPS-I recurrence occurred in 28 of 34 amputations (2). Two retrospective studies (3, 4) were the basis for that guideline which, in conclusion, stated that: "there is insufficient evidence that amputation positively contributes to the treatment of CRPS-I". In 2012, guidelines in the United Kingdom on the treatment of CRPS-I were published, stating that "amputation may worsen CRPS, with CRPS recurring in the stump", "amputation should not be used to provide pain relief in CRPS" and "amputation may be considered in rare cases of intractable infection of the affected limb" (18). The most recent international guidelines only state: "Rare CRPS patients have severe edema in an arm or leg that can painfully distort their tissues and compromise tissue oxygenation and nutrition, potentially leading to skin ulceration, infection, and need for amputation in the worst cases" (19). Amputation is also not mentioned in a recent Cochrane study on treating pain and disability in CRPS-I (20).

which negative results were published (3, 4). Amputation for CRPS-I has been called a "bad practice" therapy (21) and also "a slow, painful, gradual suicide" (22), based on those other, more negative, studies.

Clinicians' reluctance might be based on their belief of "primum non nocere", the negative opinions in literature and media or their belief of own failure in the treatment of their CRPS-I affected patients. In order to inform other clinicians on the procedure followed by the team of specialists in the UMCG, the information decision making process in the wish for amputation in case of CRPS-I was described (chapter 5). Informed decision making concerns the issues of whether or not to amputate and the level of amputation. It also reflects the process of formulating "SMART" goals with the patient and treating specialists (chapter 5). Factors influencing the decision to amputate are level of pain or allodynia, presence of infection, desired length of the residual limb, motivation for use of a prosthesis, co-morbidity, adiposity, joint range of motion, muscle strength of the extremities, the ability to use walking aids and "psychological green, yellow and red flags".

*"Amputation is totally unnecessary and should never be performed. Just simple weight bearing under the effect of a strong analgesic such as Stadol or Buprenorphine (Buprenex) along with the use of moist, warm water and epsom salt, exercise and massage for the extremity to reverse the vasoconstriction on the surface and to increase the circulation in the deep structures corrects this situation without the need for amputation. Amputation in CRPS is a slow, painful, gradual suicide "* (22).

Other studies found positive results for pain and function in case of amputation for intractable foot or ankle pain (23, 24). One study identified key factors in the decision making process in case of elective amputation and divided these factors into factors with maximum influence on the decision making process (pain, function and participation), factors with minimal or no influence (body image, self identity and physical self and opinions of others) and other factors (information and mental state) (24). Satisfaction of the outcome of amputation was related to how closely the results fit with the expectation of life with an amputation (24). This emphasizes the need for clinicians to discuss life with an amputation and prosthetic devices in the process of decision making (24). Meeting with an amputee peer should also be considered in creating realistic expectations on life after amputation (24).

### Clinical implications and future research

Information on patients who were denied amputation should be stored in a database including the (main) reason for denial for the benefit of future research. At this moment denial of amputation often takes place during a patient's first visit at the physiatrist at the UMCG regarding this request. It is to be expected that patients who were denied amputation, will continue their search for a surgeon who is willing to amputate their limb (24). Inquiring after previous failed requests for amputation should be part of the procedure when patients visit the outpatient clinic at the UMCG or elsewhere.

In order to prevent recall bias and make better comparisons, all patients with a wish for amputation should complete several questionnaires (at least the CD-RISC and WHOQOL-Bref). Patients with CRPS-I may be compared to a group of patients with another diagnosis who also wish to have their limb amputated. Whether they should complete these questionnaires before or after the decision for amputation is made, is up for debate. Completed questionnaires may help facilitate the choice for amputation. However, it can be questioned whether patients fill in true or desirable answers. What can be defined as 'a desirable answer' is still unknown in case of CRPS-I. Even after partly unraveling the black box of the process of informed decision making in amputation for CRPS-I, it remains relatively unclear how all information gathered by the professionals is weighed during that process. The role of 'exploration of a patient's competencies' offers a new perspective and should be evaluated. Future qualitative research may help further unraveling of this process, making it more transparent and better reproducible.

Patients with a wish for amputation, who were diagnosed with CRPS-I elsewhere, but who are diagnosed differently in the UMCG should be recorded. CRPS-I should be diagnosed using the Budapest criteria (8, 13). The Groningen Questionnaire Problems after Arm Amputation (GQPAA) (25) and the Groningen Questionnaire Problems after Leg Amputation (GQPLA) (25) may help in gathering specific information on amputation-related problems and should be added to the list of questionnaires following amputation.

Further research on amputated limbs from patients affected by CRPS-I is justifiable considering the findings in research into muscles (16) and nerves (chapter 6). After our previous studies it would be logical to further examine the peripheral nerves (fiber typing, the evaluation of the motor nerve fibers and end-plates in the skeletal muscle tissue). It may not solve the etiology-issue on CRPS-I, but it may clarify differences with other conditions that (may) lead to amputation. It is therefore suggested that future research should not only focus on amputated limbs from patients with long-standing and therapy-resistant CRPS-I, but should also include other diagnoses leading to amputation. Clinical aspects of the limb need to be carefully documented. It would be interesting to examine all limbs according to the Budapest criteria, including the patients with other diagnoses.

From the quality of life study it was clear that patients report better sleep, better mobility and less pain (chapter 3). Relatively simple questionnaires for comparison of these topics before and after the amputation could be implemented to generate more specific information on just these topics. Usage of medication (e.g. narcotics) and especially the change in use of medication could be an interesting addition to these topics.

As a last suggestion for future research it should be stated again that priority in the research of CRPS-I should be given to finding the cause of the syndrome (etiology), prevention and early treatment. “Miraculous” results have been expected from Pain Exposure Physical Therapy (26), Graded Motor Imagery (27, 28) and spinal cord stimulation (29), but all fail to do so thus far.

Research on (the quality of life of) patients who needed amputation as a last resort treatment is only of interest as long as better treatments are not available through evidence-based medicine.

### What may be learned from this study for other diagnoses?

A different diagnosis for which amputation could be a (last resort) treatment is epidermolysis bullosa (EB). In patients with EB repeated blistering and scarring may cause painful and dysfunctional limbs. Surgery in order to correct deformities may be recommended by clinicians, but literature on amputation for EB is scarce. Whether or not an amputation in EB is considered only in case of (squamous cell) carcinoma is unknown. Successful prosthetic fitting in a patient with EB and a transtibial amputation was described in 1988 (30). Oral rehabilitation of patients with EB and implants/prostheses has been described more often and lessons may also be learned from those case studies on performing surgery in that group of patients (31, 32). It is unknown if amputation may be beneficial to patients with EB and if amputation adds quality of life. It would be for the

**Example : The treatment of Mrs. Y**

*Based on Mrs. X and the results in this thesis a more positive approach to patients with a request for amputation in case of long-standing and therapy-resistant CRPS-I is justifiable. In the decision making process regarding Mrs. Y, the next Mrs. X, the patient and the team should follow the next steps:*

a A physiatrist diagnoses CRPS-I according to the Budapest criteria. Information on patients with other diagnoses is recorded. Those patients are referred back to their referring medical doctor (MD) or patients are referred to another medical specialist.
b In case of CRPS-I, Mrs. Y is asked whether she has made a request for amputation elsewhere. She completes questionnaires (WHOQoL-Bref, CD-RISC).
c A medical history is compiled by the physiatrist.
d Each member of the team of specialists gathers information in their own field and performs an assessment (see clinical procedures in chapter 5).
e In order to formulate "SMART" goals it is possible for Mrs. Y to meet with a peer with CRPS-I-related-amputation.
f Both the team and the patient take time to make a decision.
g 1 In case of a positive advice for amputation, the amputation is planned.
  2 In case of doubt, resilience may be trained to raise the odds of a positive outcome.
  3 In case of a negative advice for amputation, Mrs. Y is referred back to her MD.
h The amputation is preferably performed above the level affected by allodynia.
i The amputated limb is notified to the pathologist and standardized biopsies are taken from muscles, nerves and blood vessels.
j The following questionnaires are completed at 3, 6, 12 and 24 months post-amputation: WHOQOL-Bref, CD-RISC, GQPAA/GQPLA. Mrs. Y is followed up by a physiatrist who examines her and applies the Budapest criteria in order to diagnose the absence or recurrence of CRPS-I.

benefit of the patient group to consult with a physiatrist when amputation is considered and to report about these patients in literature.

## General conclusion

The research questions of this thesis aimed at providing evidence for clinicians who are faced with requests for amputation from patients who are affected by CRPS-I. The research population was small (<40 patients) and limitations of the study included selection bias and information bias. However, amputation may positively contribute to the life of patients with long-standing and therapy-resistant CRPS-I and should no longer be ignored in guidelines. For the interest of the patients suffering from long-standing, therapy-resistant CRPS-I and a wish for amputation it is to be hoped that it does not take another 15 years or more for the results of this theis to find their way into the guidelines.

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# Summary

Complex Regional Pain Syndrome type I (CRPS-I) is characterized by severe pain in the distal part of an extremity that may develop spontaneously or after a noxious event. The intensity of the pain is disproportionate to the inciting event. The pain is described as burning and continuous, and it may worsen with movement, touch, or stress. The pathophysiology of CRPS-I is (still) unknown. Patients with CRPS-I may require long, intensive treatment (in accordance with national or international guidelines). In a small number of patients, the syndrome is therapy-resistant and persist for months or years. The dysfunctional limb may cause difficulties with daily life activities and the ability to work. After long series of failed treatment some of these patients request an amputation of the affected limb as a last resort therapy.

Amputation for long-standing, therapy-resistant CRPS-I is topic for debate among medical specialists. This thesis aimed at providing evidence for clinicians who are faced with requests for amputation from patients who are affected by CRPS-I. What is known in literature on beneficial and adverse effects of amputation in case of CRPS-I is described and discussed in the systematic review of the literature in *chapter 2*. The impact of an amputation on pain, participation in daily life activities, and quality of life is described in *chapter 3*. The use of a prosthesis, recurrence of CRPS-I and occurrence of phantom pain after amputation are also described in that chapter. The association between resilience and post-amputation outcome of patients amputated because of CRPS-I is described in *chapter 4*. In *chapter 5* aspects of the process of informed decision making in amputation for CRPS-I are described. In *chapter 6* results from histopathological research on nerve tissue from the CRPS-I affected amputated limbs are described. A summary and conclusion of all findings are presented in *chapter 7*, the general discussion.

Amputation for the treatment of long-standing, therapy-resistant CRPS-I is controversial. An evidence-based decision regarding whether or not to amputate is not possible on the basis of current guidelines. A literature search (*chapter 2*) included 26 original papers, involving 111 amputations in 107 patients with CRPS-I. Studies were assessed with regard to the criteria used to diagnose CRPS-I, level of amputation, amputation technique, rationale for the level of amputation, reason for amputation, recurrence of CRPS-I after the amputation, phantom pain, prosthesis fitting and use, and functional ability, satisfaction, and quality of life. The primary reasons for amputation were pain (80%) and a dysfunctional limb (72%). Recurrence of CRPS-I in the stump occurred in 31 of 65 patients, and phantom pain occurred in 15 patients. Thirty-six of 49 patients were fitted with a prosthesis, and 14 of these patients used the prosthesis. Thirteen of 43 patients had paid employment after the amputation. Patient satisfaction was reported in 8 studies, but the nature of the satisfaction was often not clearly indicated. Changes in quality of life were reported in 3 studies (15 patients); quality of life improved in 5 patients and the joy of life improved in another 6 patients. The conclusion of the study was that previously published studies did not clearly delineate the beneficial and adverse affects of an amputation performed for CRPS-I. However, the study did provide information used for comparisons in the other chapters.

That amputation may positively contribute to the lives of patients with CRPS-I was concluded from a study among 21 patients (*chapter 3*). From May 2000 to October 2008, in the UMCG, 22 patients underwent an amputation of a dysfunctional limb because of therapy-resistant CRPS-I. Twenty-one of these patients were included in that study. The median age was 46 years (interquartile range [IQR], 37 to 51 years), the median duration of CRPS-I was 6 years (IQR, 2 to 10 years), and the median interval between the amputation and the study was 5 years (IQR, 3 to 7 years). Twenty patients (95%) reported an improvement in their lives. Nineteen patients (90%) reported a reduction in pain, seventeen patients (81%) reported an improvement in mobility, and 14 (67%) reported an improvement in sleep. Eighteen patients stated that they would choose to undergo an amputation again under the same circumstances. Ten of the 15 patients with a lower-limb amputation and one of the 6 with an upper-limb amputation regularly used a prosthesis. Recurrence of CRPS-I symptoms occurred in the residual limb of 3 patients (14%) and in another limb in 2 patients (10%) (adding up the risk of recurrence to 24%).

In the previous chapter it was concluded that amputation may improve quality of life and decrease pain intensity in patients with CRPS-I. Resilience, the way people deal with adversity in a positive way, may be related to these positive outcomes. Twenty-six patients with an amputation related to CRPS-I participated in this study (*chapter 4*), which focused on the relationship between resilience and post-amputation outcomes, i.e. quality of life, pain and recurrence of CRPS-I and psychological distress. Resilience, measured through the Connor-Davidson Resilience Scale (CD-RISC), correlated significantly with all domains of the World Health Organisation – Quality of life Assessment (WHOQOL-Bref) (ρ ranged from 0.41 to 0.72) and negatively with all domains of the Symptom Checklist-90 Revised (SCL-90-R) (ρ ranged from -0.39 to -0.68). Patients with an amputation because of CRPS-I had higher scores on resilience and quality of life than a control group with patients with chronic pain. Resilience was lower in patients who reported recurrence of CRPS-I symptoms compared to those who did not. The results confirmed our hypothesis that patients with an amputation because of CRPS-I who have a higher resilience also have a higher quality of life and experience lower psychological distress.

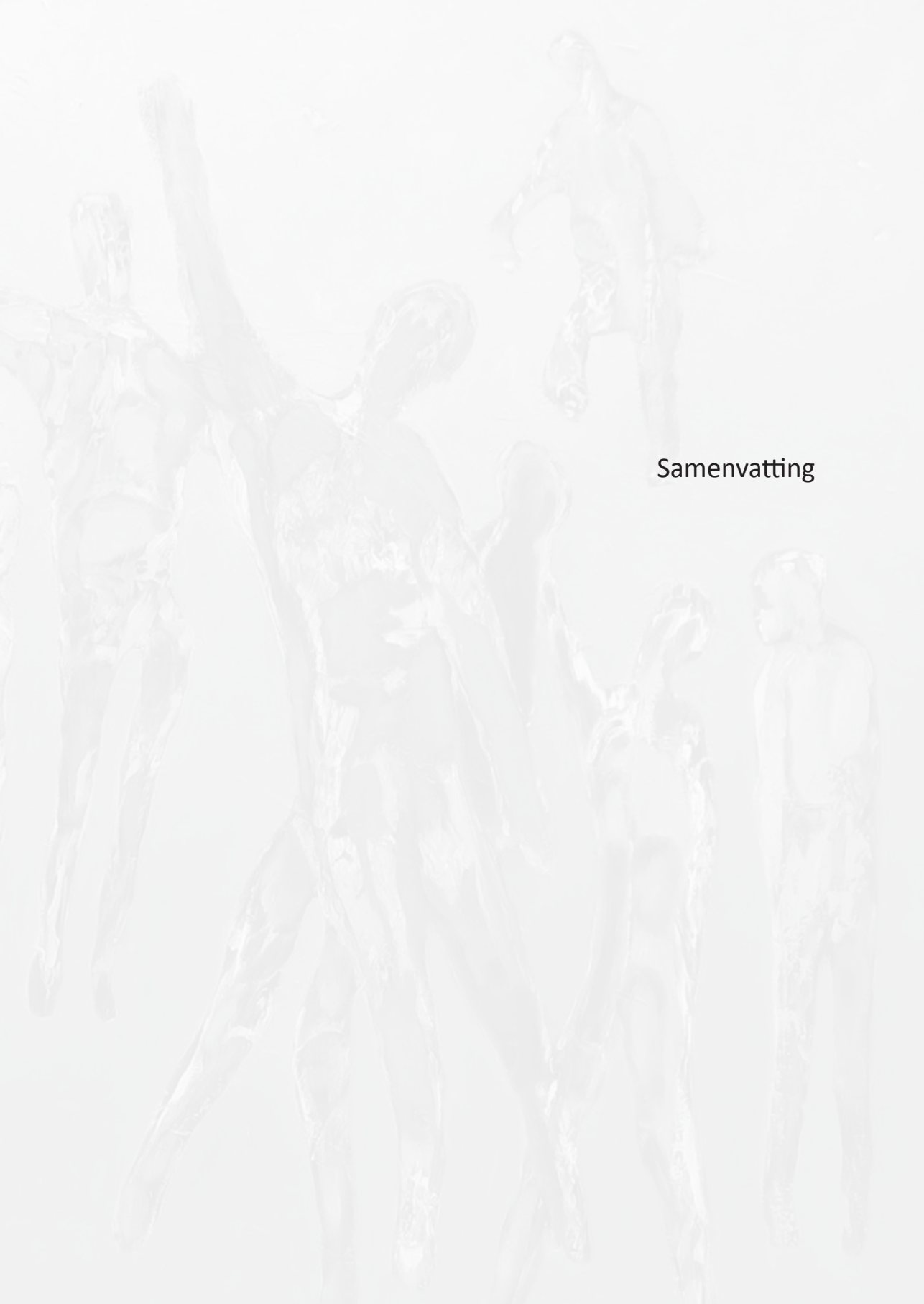
In line with the absence of solid information on the outcome after amputation in case of CRPS-I, information involving the decision to amputate is equally scarce. In *chapter 5* this process, as performed in the UMCG, is described. Team members and the patient decided together whether or not to amputate and on the level of amputation. Issues such as level of pain or allodynia, infection, desired length of the residual limb, range of motion of the joints, strength of all extremities, ability to use walking aids and “psychological green, yellow and red flags” were all weighed in this process. The study provided additional information: no complications during surgery, 25% complications (infection) immediately postoperatively (re-amputation not required), 72% phantom pain directly after amputation or developed phantom pain within the first three months after amputation; 77% phantom pain several years after amputation; CRPS-I was present in 27% of patients, more than one year post-amputation; amputation through or below the level of allodynia did not relate to recurrence of CRPS-I.

The study described in *chapter 6* described pathological changes more proximal in the nerves, especially in the sural nerve, in addition to the damage other researchers have found in more distal nerve fibers innervating the skin or bloodvessels. Previous results from research on muscle tissue had led to the hypothesis that peripheral nerve pathology was likely to be found. Fifteen patients with CRPS-I (duration > one year) were included in this study. Multiple nerve samples were taken, proximally and distally, from upper (n=4) and lower (n=11) amputated limbs. Histological changes (signs of nerve fiber loss and regeneration), fiber diameters, fiber diameter distribution, and fiber density were studied through microscopy and morphometry. Samples from three healthy sural nerves were used as a control data as well as data from literature. All patients (93% of tissue samples) showed histological signs of nerve fiber loss and fiber regeneration, varying in severity. No specific preference was found for any nerve or the location within the nerve. Sural nerves showed loss of especially larger nerve fibers (>12 µm) in comparison with control data. Sympathectomy did not influence this finding. The morphometric results of the other nerves are more difficult to interpret due to absence of good quality control data from literature. However, the percentages of nerve fibers >12 µm seem to lie within the normal range.

This thesis provides relevant information for clinicians who are faced with requests for amputation from patients who are affected by CRPS-I. Based on the findings from the studies in this thesis it may be concluded that amputation may positively contribute to the life of patients with long-standing, therapy-resistant CRPS-I and should no longer be ignored in guidelines. When interpreting the data it should be taken into account that the research population was small (<40 patients) and all studies in this thesis have their limitations.

Future research should include further examination of the amputated limbs.

Research on (the quality of life of) patients who asked and received an amputation as a last resort treatment is only of interest as long as better treatments are not available through evidence-based medicine.



# Samenvatting

Bij het Complex Regionaal Pijn Syndroom type I (CRPS-I) is er sprake van hevige pijn in een arm of been, die zich zonder aanwijsbare oorzaak of na een letsel ontwikkelt. De ernst van de pijn is disproportioneel in verhouding tot het uitlokkende moment. De aard van de pijn wordt ervaren als continu en brandend, en de intensiteit van de pijn neemt toe bij beweging, aanraking of stress. De pathofysiologie van CRPS-I is nog onbekend. De behandeling van patiënten met CRPS-I is intensief en duurt vaak lang. Bij een klein deel van de patiënten zijn de symptomen therapieresistent en de symptomen kunnen maanden tot jaren voortduren. Het aangedane ledemaat kan het doen van activiteiten van het dagelijks leven en arbeidsparticipatie fors negatief beïnvloeden. Wanneer alle geprobeerde behandelingen niet effectief zijn, komen sommige patiënten met het verzoek om een amputatie van het aangedane ledemaat.

Amputaties bij therapieresistente CRPS-I zijn een onderwerp van discussie onder medisch specialisten. Dit proefschrift heeft als doel behandelaars die geconfronteerd worden met patiënten met CRPS-I die vragen om een amputatie van goed gefundeerde informatie te voorzien. In *hoofdstuk 2* wordt, op basis van een systematische literatuurstudie, beschreven wat er bekend is over de positieve en negatieve effecten van een amputatie bij CRPS-I. In *hoofdstuk 3* wordt de impact van een amputatie op pijn, ADL- activiteiten en kwaliteit van leven beschreven. Het gebruik van een prothese, het risico op terugkeer van CRPS-I en het optreden van fantoompijn worden ook beschreven in *hoofdstuk 3*. De relatie tussen “veerkracht” en de uitkomsten na amputatie bij patiënten die vanwege CRPS-I een amputatie hebben ondergaan, wordt beschreven in *hoofdstuk 4*. In *hoofdstuk 5* komen diverse aspecten betreffende het proces van geïnformeerde besluitvorming tot amputatie bij CRPS-I aan bod. In *hoofdstuk 6* worden de resultaten beschreven van een histopathologische studie waarin de karakteristieken van zenuwweefsel van de door CRPS-I aangedane en geamputeerde armen en benen werden onderzocht. In *hoofdstuk 7* worden resultaten samengevat, bediscussieerd en aanbevelingen gedaan voor de praktijk en verder wetenschappelijk onderzoek.

Amputatie van een arm of been bij chronische, therapieresistente CRPS-I is controversieel. Het nemen van een op wetenschap gefundeerd besluit om wel of niet te amputeren is op grond van de huidige richtlijnen niet mogelijk. Een systematische literatuurstudie, beschreven in *hoofdstuk 2*, leverde 26 oorspronkelijke publicaties op, aangaande 111 amputaties bij 107 patiënten met CRPS-I. Deze studies werden beoordeeld op de aan/afwezigheid en kwaliteit van de volgende items: criteria waarop de diagnose CRPS-I was gesteld, niveau van amputatie, amputatietechniek, rationale voor niveau van amputatie, reden van amputatie, terugkeer (recidief) van CRPS-I na de amputatie, fantoompijn, prothesegebruik, functioneren, tevredenheid en kwaliteit van leven. De voornaamste redenen om te amputeren waren pijn (80%) en een disfunctionele extremiteit (72%). Recidief van CRPS-I in de stomp trad op bij 31 van de 65 patiënten, en bij 15 was er sprake van fantoompijn. Zesendertig van de 49 patiënten kregen een prothese en 14 van deze patiënten gebruikten de prothese. Dertien van 43 patiënten hadden betaald werk na de amputatie. De patiënttevredenheid werd in 8 studies gerapporteerd, maar een precieze beschrijving wat deze tevredenheid inhield, werd meestal niet gegeven. Verandering in kwaliteit van leven werd beschreven in 3 studies (15 patiënten); kwaliteit van leven verbeterde bij

5 patiënten en levensvreugde nam toe bij 6 patiënten. Op basis van eerder gepubliceerde studies werd geconcludeerd dat er geen duidelijk omlijnd beeld bestond van de positieve en negatieve effecten van een amputatie tengevolge van CRPS-I. Toch leverde deze studie informatie op die in de overige hoofdstukken werd gebruikt ter vergelijking.

Dat amputatie een positief effect kan hebben op het leven van patiënten met CRPS-I, blijkt uit een studie onder 22 patiënten, die in de periode mei 2000 tot oktober 2008 in het UMCG een amputatie van een afunctionele arm of been ondergingen vanwege therapie-resistente CRPS-I. Eenentwintig van deze patiënten werden geïncludeerd in deze studie. De mediane leeftijd was 46 jaar (interkwartielafstand [IQR], 37 tot 51 jaar], de mediane duur van CRPS-I symptomen was 6 jaar (IQR, 2 tot 10 jaar) en het mediane tijdsinterval tussen de amputatie en de studie was 5 jaar (IQR, 3 tot 7 jaar). Twintig patiënten (95%) rapporteerden een verbetering van hun leven. Negentien patiënten (90%) gaven aan minder pijn te ervaren, 17 patiënten (81%) rapporteerden een verbeterde mobiliteit en 14 (67%) een verbetering van nachtrust. Achttien van de 21 patiënten (86%) verklaarden dat zij er opnieuw voor zouden kiezen een amputatie te ondergaan, in een vergelijkbare situatie. Tien van de 15 patiënten met een amputatie van de onderste extremiteit en één van de 6 met een amputatie van de bovenste extremiteit gebruikten regelmatig een prothese. Drie patiënten (14%) kregen een recidief CRPS-I in de stomp en 2 andere patiënten (10%) kregen een recidief in een andere extremiteit (totaal recidief risico van 24%).

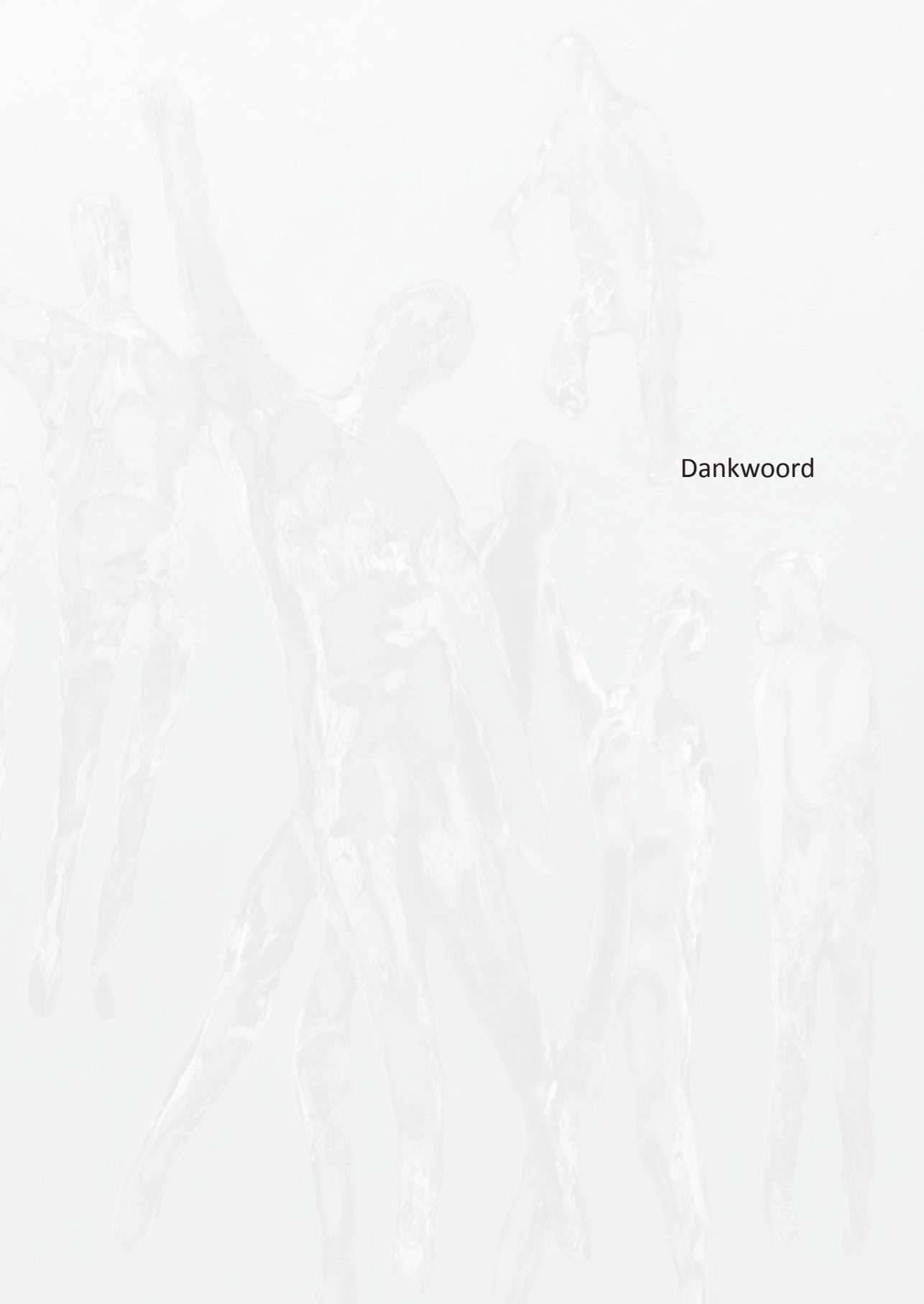
In het vorige hoofdstuk, *hoofdstuk 3*, werd geconcludeerd dat amputatie bij CRPS-I patiënten de kwaliteit van leven kon verbeteren en tot vermindering van pijnintensiteit leidde. Er werd verondersteld dat veerkracht, de manier waarop mensen op een positieve manier met tegenslag omgaan, mogelijk een rol bij deze positieve bevindingen speelde. Zesentwintig patiënten met een amputatie vanwege CRPS-I namen deel aan een studie, waarin de relatie tussen veerkracht en uitkomsten na amputatie, te weten kwaliteit van leven, pijn, recidief CRPS-I symptomen en psychologische problemen en symptomen van psychopathologie werden onderzocht. Deze studie werd beschreven in *hoofdstuk 4*. Er was een significante positieve correlatie tussen veerkracht, gemeten met de Connor-Davidson Resilience Scale (CD-RISC) en alle domeinen van de World Health Organisation – Quality of life Assessment (WHOQOL-Bref) (Spearman's ρ varieerde van 0.41 tot 0.72) en er was een significante negatieve correlatie met alle domeinen van de Symptom Checklist-90 Revised (SCL-90-R) (ρ varieerde -0.39 tot -0.68). Patiënten met een amputatie vanwege CRPS-I scoorden hoger op veerkracht en kwaliteit van leven dan de controle groep (patiënten met chronische pijn die bekend zijn bij de polikliniek Revalidatiegeneeskunde in het UMCG). Veerkracht scores waren lager bij patiënten die CRPS-I symptomen rapporteerden vergeleken met hen die, na amputatie, geen CRPS-I symptomen rapporteerden. Deze resultaten bevestigden de hypothese dat patiënten met een amputatie vanwege CRPS-I met een betere veerkracht, ook een betere kwaliteit van leven hadden en minder psychologische problemen en symptomen van psychopathologie ervoeren.

Net als het ontbreken van goede informatie over de uitkomsten na amputatie vanwege CRPS-I, was er nauwelijks informatie beschikbaar over het proces van besluitvorming tot amputatie. In *hoofdstuk 5* werd dit proces, zoals het in het UMCG wordt toegepast,

beschreven. Leden van het behandelteam kwamen samen met de patiënt tot de beslissing om wel of niet te amputeren en bepaalden samen het niveau van de amputatie. Factoren als ernst van de pijn of allodynie, infectie, gewenste lengte van de stomp met het oog op functionaliteit en mogelijkheden voor prothesefitting, bewegingsuitslagen van de gewrichten, spierkracht van de extremiteiten, mogelijkheid om hulpmiddelen bij het lopen te gebruiken in geval van een been amputatie, en psychologische "groene, gele en rode vlaggen" werden afgewogen bij dit proces. Uit deze studie kwamen nog een aantal andere kenmerken van deze patiëntengroep naar voren: 25% van de patiënten had direct postoperatieve complicaties (infecties) (re-amputatie niet nodig); 72% had fantoompijn direct na de amputatie of gedurende de eerste drie maanden na de amputatie; 77% had fantoompijn enkele jaren na de amputatie; recidief CRPS-I ontstond bij 27% van de patiënten meer dan een jaar na de amputatie; amputatie op of onder het niveau van allodynie had geen relatie met de kans op recidief CRPS-I.

De studie beschreven in *hoofdstuk 6* toonde aan dat er bij patiënten met CRPS-I pathologische veranderingen aanwezig zijn in het meer proximale deel van de zenuwen. Andere onderzoekers beschreven eerder al pathologische veranderingen in de meer distale zenuwvezels die huid en /of bloedvaten innerveren. Onderzoeksbevindingen vanuit studies in spierweefsel bij CRPS-I leidden tot de hypothese dat er perifere zenuwpathologie bij CRPS-I kon worden aangetoond. Vijftien patiënten met CRPS-I (duur > een jaar) werden geïncludeerd in deze studie. Meerdere zenuwbiopten werden afgenomen, zowel proximaal als distaal, in geamputeerde bovenste (n=4) en onderste (n=11) ledematen. Histologische veranderingen (tekenen van zenuwvezelverlies en regeneratie), vezeldiameter, vezeldiameterverdeling, en vezeldichtheid werden onderzocht door middel van microscopie en morfometrie. Controlemateriaal was moeilijk te verkrijgen. Vooral controledata uit de literatuur werden gebruikt met daarnaast biopten van 3 gezonde "suralissen". Alle patiënten toonden histologische tekenen van zenuwvezelverlies en vezelregeneratie, variërend in ernst. Vergeleken met de controledata lieten de "suralissen" van de patiënten met CRPS-I een verlies van vooral de grotere zenuwvezels zien (>12 µm). Vanwege een gebrek aan kwalitatief goede controledata in de literatuur zijn de morfometrische resultaten van de andere zenuwen moeilijker te interpreteren. Het percentage zenuwvezels > 12 µm leek echter binnen het normale spectrum te vallen.

Dit proefschrift levert belangrijke nieuwe informatie voor behandelaars die te maken krijgen met het verzoek om amputatie van een arm of been door patiënten met chronische, therapieresistente CRPS-I. De resultaten moeten met enige voorzichtigheid worden geïnterpreteerd want de onderzochte populatie was relatief klein (<40 patiënten) en alle studies hadden hun beperkingen. Desondanks kan geconcludeerd worden dat een amputatie een positieve bijdrage kan leveren aan de kwaliteit van leven van patiënten met chronische, therapieresistente CRPS-I. Deze behandeling kan dan ook niet langer buiten de behandelrichtlijnen voor CRPS-I worden gehouden. Toekomstig onderzoek zal zich onder meer moeten richten op verdere bestudering van de geamputeerde extremiteiten. Onderzoek naar (de kwaliteit van leven van) patiënten met CRPS-I waarbij een amputatie de laatste behandeloptie is, is alleen zinnig zolang er nog geen betere evidence-based behandeling beschikbaar is.



# Dankwoord

# Dankwoord

Zonder onderwerp, geen proefschrift. Onderwerp van dit proefschrift waren allen die vanaf 2000 in het UMCG een amputatie hebben ondergaan vanwege CRPS-I. Mijn dank gaat uit naar jullie voor de bereidwilligheid deel te nemen aan het onderzoek en de interesse die jullie erin toonden.

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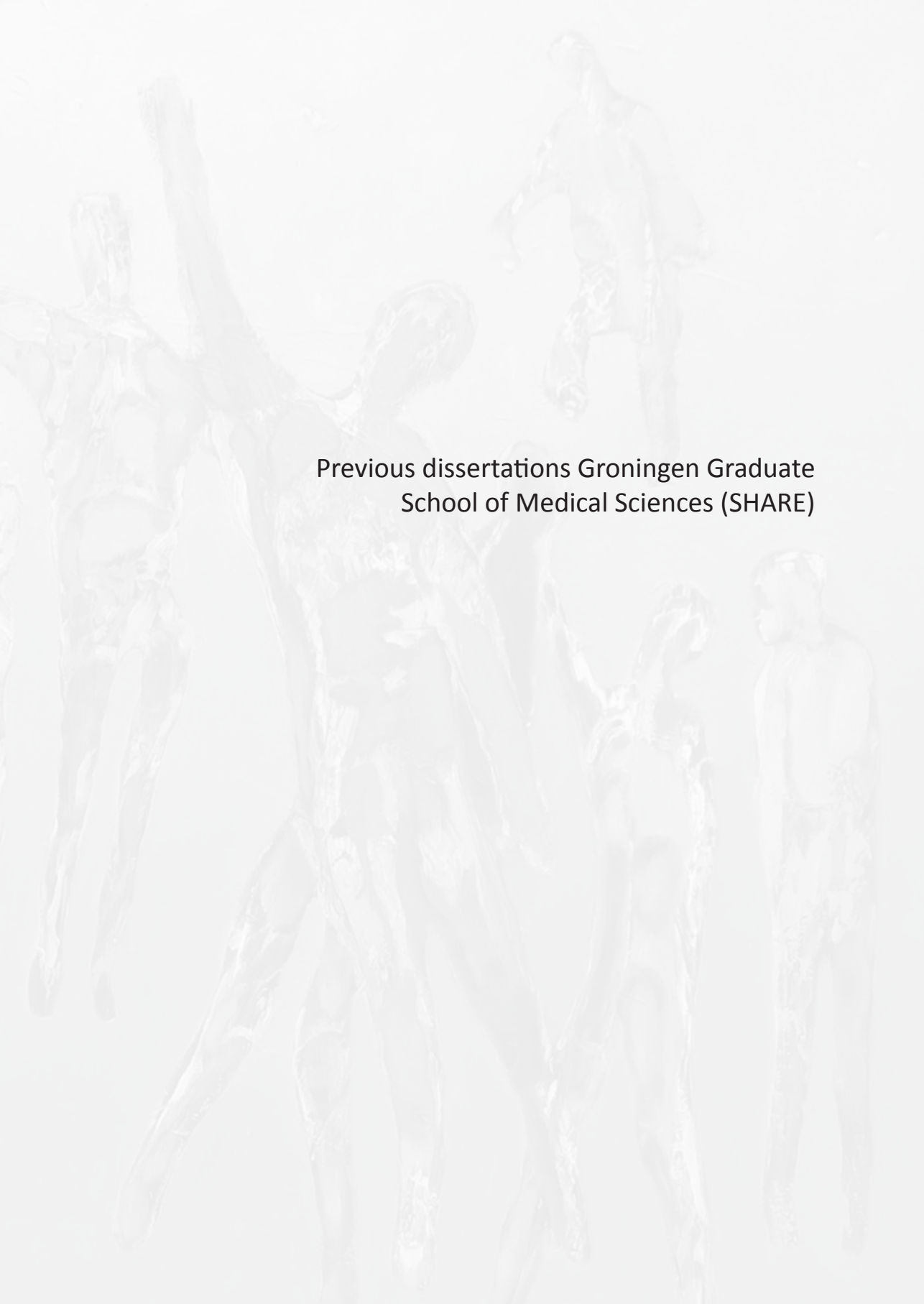
Nu is het tijd om te dansen!



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