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SELF-REPORTED PAIN IN SLE

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune, rheumatic disease, potentially affecting most organ systems. The disease is commonly considered to be chronic and occurs in often unpredictable flares, with alternating low and high disease activity. SLE predominantly affects females, but incidence and prevalence differs across different populations. Pain in SLE is reported to be a common symptom, and has a complex relationship with impaired health-related quality of life and other symptoms, such as fatigue, anxiety and depression. These may individually öor together influence a patient's ability to perform daily activities. Modified treatment regimens and new potentially active drugs for patients with SLE have been developed over the last decade. Considering these changes in medical care, as well as the heterogeneous nature of SLE, the question of whether SLE-related pain is still common remains unanswered. An updated and more detailed knowledge about the extent of pain and pain characteristics are therefore required.

Aim: The overall aim of this thesis was to investigate to what extent patients with SLE report disease-related pain, and also to investigate pain characteristics and pain complexity regarding disease duration and disease activity in a cohort of patients with SLE. Fatigue, anxiety, depression and health-related quality of life were investigated in patients recording higher scores of pain intensity, compared to those with lower scores of pain intensity.

Method: In this cross-sectional cohort study, 84 patients with SLE and 91 age and sex-matched controls from the general population completed self-assessment measures and questionnaires regarding pain (VAS and SF-MPQ), fatigue (MAF), health-related quality of life (SF-36), and anxiety and depression (HADS). In addition, data on age, disease duration, disease damage and disease activity were collected, as well as treatment with glucocorticoids. Based on pain intensity scores through VAS, the patients were dichotomized into two groups, the low-pain group and the high-pain group. A cut-off value, 40 millimetres, was chosen due to the distribution of scores in VAS.

Results: The high-pain group constituted 24% of the SLE-cohort and was characterized by significantly shorter disease duration and higher disease activity compared to the low-pain group. In the high-pain group, 70% scored

present pain as *distressing*. The high-pain group also used significantly more words in SF-MPQ compared to the low-pain group. The words most used to describe ‘moderate and severe’ pain were *aching*, *burning*, *tender* and *stabbing*. The most common pain location in both groups was joints. Treatment with glucocorticoids did not differ between the two groups, and patients treated or not treated with glucocorticoids did not differ in pain-intensity scoring. The high-pain group reported significantly impaired quality of life, higher scores of fatigue, anxiety and depression compared to the low-pain group and control group. The low-pain group did not differ significantly from controls regarding pain, fatigue, anxiety and depression.

Conclusion: The results show that pain in SLE is still a significant problem for a substantial proportion of patients. Higher levels of disease-related pain from SLE indicate great symptom burden regarding impaired health-related quality of life, fatigue, anxiety and depression, despite mild to moderate disease activity. Identification and focusing on patients with higher scores of self-reported pain, especially patients with short disease duration, seems crucial in order to reduce symptom burden and alleviate suffering.

LIST OF PUBLICATIONS

I. Waldheim E, Elkan AC, Bergman S, Frostegård J, van Vollenhoven R, Welin Henriksson E. Extent and characteristics of self-reported pain in patients with systemic lupus erythematosus. *Lupus* 2013; 22: 136-143

II. Waldheim E, Elkan AC, Pettersson S, van Vollenhoven R, Bergman S, Frostegård J, Welin Henriksson, E. Patients with SLE expressing higher levels of pain also report impaired health-related quality of life, fatigue and mood compared to controls and patients with lower levels of self-reported pain. (Manuscript).

CONTENTS

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
GFI	Global Fatigue Index
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
IQR	Inter Quartile Range
MAF	Multidimensional Assessment of Fatigue
PPI	Present Pain Index
Q3	Third Quartile
QoL	Quality of Life
SF-36	Medical Outcomes Survey-Short Form 36
SF-MPQ	Short-Form McGill Pain Questionnaire
SLAM	Systemic Lupus Activity Measure
SLE	Systemic Lupus Erythematosus
SLEDAI	SLE Disease Activity Index
SLICC/ACR	Systemic Lupus International Collaborating Clinics Damage Index, the American College of Rheumatology
VAS	Visual Analogue Scale

1 INTRODUCTION

Persons living with chronic diseases meet a range of challenges, especially in those with unpredictable courses such as systemic lupus erythematosus (SLE) [1]. SLE had previously been considered a life-threatening condition. Due to improved medical care and treatment, morbidity as well as mortality has decreased considerably. Mostly, SLE is no longer considered a life-threatening disease, but is still chronic. Due to its prolonged course, efforts should be made to help and support patients to maintain or gain control over their lives and experience health.

The focus of this thesis was self-reported pain, since pain in SLE is described as a common and burdensome symptom that may affect several dimensions in humans life, such as impaired quality of life, increased fatigue, anxiety and depression [2, 3]. This means that pain, when present, may constitute a great symptom burden for patients with SLE. Despite advancement in medical care and treatment of SLE, reports exist where patients with the disease express dissatisfaction with how pain is met by the healthcare service [4]. Feelings of not being understood may create indignity and suffering [5].

Preventing and alleviating suffering is described as the primary objective of nursing [6] and patients' experiences and reactions in different life contexts constitute the basis of nursing. Pain is not the same as suffering, but there are close links between the terms [7]. From that perspective, it seems essential for nursing research to investigate if pain in SLE is still common and thus a potential cause of suffering. The results will contribute to an updated and extended knowledge of patients' experiences of pain in SLE and point out if further research and interventions regarding SLE-related pain are needed.

2 BACKGROUND

2.1 SYSTEMIC LUPUS ERYTHEMATOSUS AND IMPACT ON LIFE

Systemic lupus erythematosus (SLE) is a potentially life-threatening autoimmune rheumatic disease, which can affect most organ systems. The disease, considered mostly as a chronic condition, occurs in often unpredictable flares, with periods of high disease activity followed by periods of lower disease activity. Symptoms of the disease vary widely in severity and depend on which organ is affected by inflammation. The skin is a common site for inflammation, as well as the musculoskeletal system. Nephritis indicates disease activity in the kidney and is a serious condition. Also, neurological symptoms such as seizure and psychosis may occur and indicate that the brain is affected.

SLE is also highly connected with general symptoms like pain, fatigue and malaise. The presence of auto-antibodies is typical of the disease, particularly anti-double-stranded DNA, which is known to be associated with lupus nephritis [8, 9]. The etiology is not yet fully understood, but is considered to be multifactorial involving genetics, age and sex hormones, as well as environmental factors such as viruses and ultraviolet radiation [8, 9]. Survival rate has improved considerably over the past half-century, but mortality is still high compared to the general population [8,10]. Data on incidence and prevalence from previous studies is inconsistent, possibly due to genetic and environmental factors, as well as different methodologies [9].

Worldwide incidence of SLE ranges from 1-8.7/100000 per year, while in Sweden it ranges from 4-4.8/100000 per year. Prevalence worldwide ranges from 28.3-149.5./100000, and in Sweden from 38.9-42/100000. Overall, the disease is more common among females, with a ratio of approximately 10:1. In Sweden, the median incidence age is reported to be 47 years, but the peak incidence age differs between countries [10, 12]. To identify patients with SLE in research settings, the American College of Rheumatology (ACR) has developed disease-specific criteria [13] (Table 1).

Table 1. 1982 revised ACR criteria, for identification of patients with SLE in clinical studies, four or more of 11 manifestations should be present [13].

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
7. Renal disorder
8. Neurological disorder
9. Hematological disorder
10. Immunologic disorder
11. Anti-nuclear antibody (ANA)

To meet the criteria for SLE in a research setting, four of 11 criteria in Table 1 must be met.

Modified treatment regimens and new potentially active drugs have been developed over the last decade. Pharmacological treatment to reduce disease activity comprises immunosuppressive drugs, including glucocorticosteroids and biologics [14, 15].

Patients with SLE may deal with a lot of challenges due to the disease, not only of physical nature. Pharmacological treatment has, as described, decreased morbidity and mortality, but also led to patient-reported concerns about toxicity and side effects [16]. Concerns still exist about the prognosis and severity of the disease, as well as its unpredictable course. Changes in body image, mainly from the skin in presence of hair loss, rash and scaring as well as weight gain due to treatment with glucocorticosteroids, may constitute a challenge for many patients [16, 17]. Photosensitivity may limit the ability to stay outdoors [17].

Boomsma et al. [18] investigated 114 patients with SLE and found that 54% reported that daily life in general was compromised ‘moderately to severely’ by the disease. In that study, employment status was also reported to be affected of SLE, with absence from work, changes of duties, and reduced working hours. Impact on employment status is also reported by Yazdany and Yelin [19], who showed how unemployment increased after SLE diagnosis. Both

Boomsma et al. [18] and McElhone et al. [16] reported negative impacts on relationships with partners, family members and others. Even the role of parenting may be affected. Poole et al. [20] showed that symptoms from SLE influenced women's parenting roles, due to a lack of energy to talk and listen to a child, difficulties with maintaining discipline, playing games, shopping and doing household chores. Contrastingly, there were patients who reported positive impacts of the disease, such as it bringing the family closer together [18] and being a legal reason to leave a job they did not like [16].

There are several studies reporting mutual relationships between subjective symptoms in SLE, like pain, fatigue, anxiety and depression, as well as health-related quality of life (HRQoL) [3, 21, 22, 23, 24]. In a study by Danoff-Burg and Friedberg [25], patients with SLE reported dissatisfaction concerning help with fatigue, pain and depression from healthcare services. Moses et al. [4] found that patients with SLE and pain may experience insufficient attention from healthcare providers and that directed interventions were scarcely initiated.

By reducing or not confirming a person's experience, indignity and suffering may be felt by the patient [26, 27, 28]. Therefore, the central themes of this thesis were pain, HRQoL, fatigue, anxiety and depression. Due to the reported impact of SLE and mutual associations, pain, HRQoL, fatigue, anxiety and depression constitute a challenge in rheumatology nursing and are topics for further interventions.

2.2 PAIN

Pain, in general, is a complex experience that may affect several dimensions of a person's life. Pain is not only negative, but is the body's defence against potentially threatening inflammation and damage.

The International Association for the Study of Pain (IASP) defines pain as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". *Note. "…* Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life…." [29].

Pain can be classified under different perspectives [30]:

- **Intensity**: mild, moderate and severe.
- **Duration**: acute, long-standing, transient and breakthrough pain.

- **Origin**: postoperative/post-traumatic pain, cancer-related pain, long-standing pain.
- **Etiology**: physiological pain, physiological inflammatory pain, pathological inflammatory pain (nociceptive), neuropathic pain and somatic pain.

Nociceptive pain is generated by noxious stimulation of nociceptors located in peripheral nerve endings [31], while neuropathic pain emerges from injury or disease in a peripheral or central nerve [32].

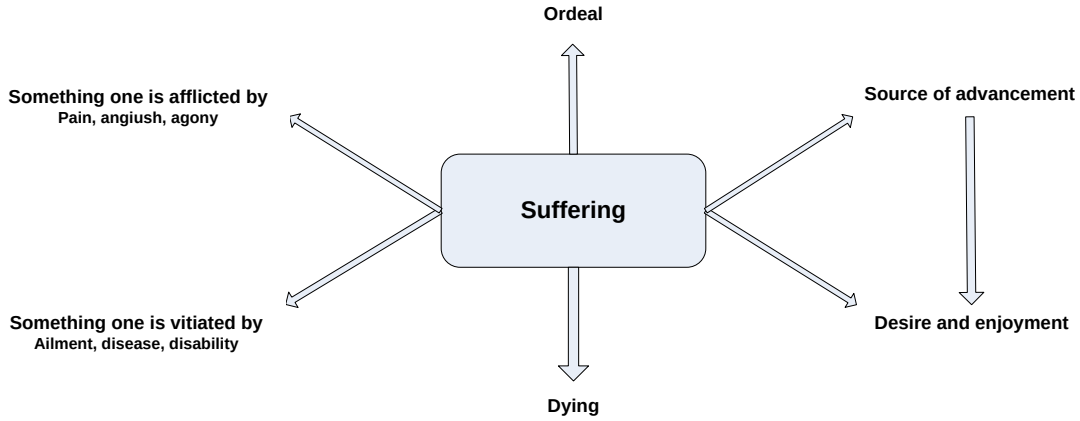
Long-standing pain or persistent pain is defined as pain that persists beyond the expected healing time or pain that persists beyond three months [33]. The prevalence of long-standing pain in the adult general population is approximately 19-53% [34, 35, 36].One cause of this can be injury or inflammation that remains or does not heal as expected, which may be the cause, for example, of rheumatic diseases. Another cause may be in the complex pain processing. Central sensitization means an up-regulation of peripheral afferent nerve transmission into the spinal cord, and may emerge from prolonged and intensive in-put of peripheral signals. Central pain processing also includes inhibiting mechanisms. Different parts and networks of the central nervous system (CNS), including central sensitization and pain inhibitory mechanisms (together called neuro-matrix), cooperate in pain processing. The development of acute pain to long-standing pain is considered to be due to pathological changes in the neuro-matrix, and is believed to be a separate disease entity [33,35].

Patients with different types of long-standing pain should primarily be treated multi-professionally and, in addition, pharmacological treatment such as analgesics, antidepressants and anticonvulsants may be beneficial [35]. Non-pharmacological treatments constitute a prominent role in reducing/alleviating pain and impairment of long-standing musculoskeletal pain. Studies of non-pharmacological treatments include cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT), physical activity/exercise, patient education (in group or individual), as well as complementary alternative medicine (CAM; acupuncture, massage, yoga). The majority of non-pharmacological treatments provide beneficial outcomes when used in combination with pharmacological treatment [35, 37].

2.3 PAIN AND SUFFERING

Rodgers and Cowles [7] defined the concept of suffering as “an individualized, subjective and complex experience that involves the assignment of an intensely negative meaning to an event or a perceived threat.” Suffering is considered to be a natural and important part of human life [6, 26] (Figure 1).

Figure 1. Dimensions of suffering according to Eriksson.
Adapted from Eriksson K. *Den lidande människan.* Liber utbildning, 1994, p 20 [5].
With permission from professor Eriksson.



In this context, the experience of ‘health’ can be interpreted as being able to endure suffering. Health and suffering are two, more or less, always present dimensions of human life, and suffering includes the possibility of growth and development [26].

Pain and suffering are not synonymous, but there are relationships between the two words [6, 7]. This is because pain and possible consequences of pain, such as fatigue and psychological distress, may contribute to suffering [38]. Suffering may also be caused by healthcare providers, and this is described by Eriksson [5] as *suffering related to care*. Eriksson asserts that this can be summarized into four main categories; violation of the patient’s dignity, condemnation, punishment, and loss of care.

2.4 PAIN IN SLE

Pain, especially from the musculoskeletal system such as arthralgia, arthritis and myalgia [1, 2, 3, 39], in the abdomen and head [2, 40, 41] is common in patients with SLE. However, not all patients with SLE experience pain [2]. Although many patients cope well with pain, a considerable proportion exhibit pain-related distress [2, 42]. Pain in SLE, as well as in other conditions, has a complex impact on psychological state, impairs HRQoL [22, 24], and reinforces the effect of fatigue [21, 23]. These negative impacts of pain contribute to limitations on daily living, like exercise [43], household chores, gardening, and even occasionally personal hygiene [16, 17, 44, 45].

Except for pharmacological analgesia, treatment interventions for SLE-related pain have been sparsely investigated. Greco et al. [46] demonstrated the positive effect of acupuncture in a pilot randomized controlled study, while a self-management course by Songh [47] provided benefits for several dimensions but not for pain. Yuen et al. [48] demonstrated the alleviation of pain, fatigue, anxiety and depression through a home-exercise program based on an interactive video system. Paradoxically, in a study by Mancuso et al. [49], pain was reported as a barrier for physical exercise

2.5 HEALTH-RELATED QUALITY OF LIFE IN SLE

The concept quality of life (QoL), is frequently used in nursing, as well as in medical, social, economic and behavioural research, as an outcome variable. The concept is often described as a subjective perception, not yet fully defined, described or understood [50]. In a review of conceptualization of QoL among several nursing theorists, Plummer and Molzahn [51] defined QoL as “an intangible, subjective perception of one’s lived experience”. They also suggested that QoL may replace the metaparadigm health in nursing, due to the interconnection between the two concepts. Typically, QoL is defined as a multidimensional term [50]. Other terms include well-being, health, satisfaction with life, and social and economic satisfaction. Health-related quality of life (HRQoL) implies quality of life in connection with health and is more specifically focused on well-being and functioning [50, 52]. Many definitions of HRQoL are based on the definition of health by the World Health Organization [53] “health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity” [54]. HRQoL is reported to be reduced in

patients with SLE compared to controls [55, 56, 57, 58], irrespective of the measurement used [39, 56]. There are many factors that influence HRQoL in patients with SLE; the disease itself, treatment and the patient's ability to cope with illness. Support from significant others seems to be an important factor [59, 60]. Other factors that promote HRQoL include a strong sense of coherence, feeling rested after sleep, a good sleep structure, as well as having the capacity to work [59]. Most studies found no considerable correlation between HRQoL and disease activity, which suggests that HRQoL in SLE is a separate entity [56].

2.6 FATIGUE IN SLE

The concept fatigue is not fully understood or defined. Usually, fatigue is not defined synonymously with tiredness, but more often defined as an uncontrolled, untreatable physical and mental exhaustion [61]. In a study by Petterson et al. [3], the participants described the character of SLE-related fatigue as controlling, unbeatable and beyond words. Fatigue is reported to be a common symptom of SLE [3, 62], as well as in other rheumatologic conditions and its cause is unclear. The prevalence of fatigue in SLE is estimated to be approximately 53-80% [63]. In all probability, a multifactorial pathogenesis exists [63], where both peripheral and central mechanisms contribute [64]. In a previous study, elevated levels of IL-1β in cerebrospinal fluid were found in patients with rheumatoid arthritis, which provided a correlation between IL-1β and assessment of fatigue. No correlation between levels of IL-1β and the assessment of pain and tender joints was found [65]. However, there are reports of associations between SLE-related pain and fatigue [21, 63].

2.7 ANXIETY AND DEPRESSION IN SLE

Self-reported anxiety and depression are common outcomes in studies of SLE. They are usually overall terms including different psychiatric sub diagnosis. Both anxiety and depression are reported to be more common among patients with SLE compared to the general population [62,66] and are reported to be present in 28-65% of patients with SLE [66, 67, 68]. Bachen et al. [66] found that self-reported disease activity was a predictor for depression. In contrast, Jarpa et al. [67] found no association between anxiety/depression and disease

activity, but suggested a reaction to the patient's experience of a chronic disease. In line with that, Phillip et al. [69] found that the chronic nature and unpredictable course of the disease, together with a poor understanding of lupus, may generate a higher degree of depression. Kozora et al. [62] provided a physiological explanation. They found a strong correlation between cognitive impairment and depression, pain and fatigue in patients with neuropsychiatric SLE, suggesting global changes in the central nervous system.

3 RATIONALE FOR THE STUDY AND AIMS

Advancements in medical care and pharmacological treatment for patients with SLE have been developed over the last decade, leading to decreased morbidity and mortality [9]. Despite this, some studies report that pain in SLE is still present [1, 2, 3, 39, 40, 41]. In some studies, patients report feeling that healthcare providers do not pay enough attention to pain, fatigue, anxiety and depression in SLE [4, 25]. In respect of these studies, as well as other studies reporting various prevalence and severity of SLE within different populations potentially impacting the outcomes [70], an update and more detailed knowledge of pain in SLE was required. Pain is also reported to be common in the general population [34, 35], thus this study investigated if there were any differences between patients with SLE and controls from the general population.

Therefore, the overall aim of this thesis was to investigate to what extent patients with SLE report disease-related pain.

The aim for study I was:

- to investigate intensity and characteristics of SLE-related pain
- to measure disease activity and disease duration

The aim for study II was:

- to investigate overall pain, health-related quality of life, fatigue, anxiety and depression in patients with SLE and age and sex-matched controls from the general population

4 METHODS

4.1 STUDY POPULATION

In this study, a cross-sectional design was chosen as a first step to investigate the possible existence of pain in patients with SLE. The subjects were recruited from an on-going cohort study [71] in which patients with SLE, according to the 1982 revised ACR criteria [13] (Table 1), aged 18 to 70 years participated. In the cohort study, potential study participants were identified by diagnosis code in the electronic medical record system at the department of rheumatology, Karolinska University Hospital, Huddinge, Stockholm, Sweden. Identified patients were mailed letters with an invitation to participate in the study (n=160). They were also invited by telephone and in connection with routine visits at the clinic (n=10). Of the invited patients, 118 (69%) agreed to participate in the study. Four patients were later on excluded. Three did not meet the diagnosis criteria for SLE and one patient had on-going psychosis precluding further participation in the study. The main reasons for not participating were lack of time and the extensive amount of time already spent on visits to medical care. For comparison, 121 sex and age-matched controls were randomly identified from the general population through the Swedish population register. These were from the same greater urban area as the patients. The identified controls were invited to participate in the study by mail. Over a period of 13 months, 84 patients and 91 controls were asked to participate in this present study. All agreed to participation.
In this work, the term patient is used rather than person, as it is within our profession at a hospital that the meetings take place. This choice does not intend to reduce the human being behind the term.

4.2 DATA COLLECTION

The participants were invited to respond to questionnaires regarding pain, HRQoL, fatigue, anxiety and depression in connection to the inclusion visit in the cohort study. The study was conducted at an outpatient clinic in the rheumatology department at the Karolinska University Hospital, Huddinge, Stockholm, Sweden, enabling questions from the participants when in doubt and to avoid missing data.

In addition characteristics such as age, disease duration and current treatment with glucocorticoids were collected. Disease damage and disease activity were measured by a physician.

4.3 QUESTIONNAIRES STUDY I

4.3.1 Pain

Visual analogue scale (VAS) [72, 73] was used to measure self-reported overall pain and for the patients only self-reported SLE-related pain. The scale consists of a 100 millimetre (mm) long horizontal line symbolizing a continuum of increasing pain. The beginning of the line represents *no pain* and the end of the line represents *worst imaginable pain*. The study participants rated their pain during the past week by placing a transverse line on the 100 mm horizontal line. The scales were connected to the questions *how much pain have you experienced in average the last week*? and for the patients only *how much pain due to SLE have you experienced in average the last week*?

The short-form McGill Pain Questionnaire (SF-MPQ) [74] was used to describe the character of the self-reported pain. The instrument has previously been tested for validity and reliability in Swedish patients with fibromyalgia [75] and in Turkish patients with rheumatoid arthritis [76]. In the first part of the questionnaire, the participants graded the intensity of perceived pain during the most recent week (0=none, 1=mild, 2=moderate, and 3=severe) using a number of describing words. This provided a total score (0-45), as well as scores for sensory (0-33) and affective (0-12) indices. In the second part of the questionnaire, the participants estimated their current pain using VAS, and in the third part of the questionnaire, the participants were asked to choose the word most accurate to describe their present pain (present .pain index (PPI)).

4.3.2 Damage and disease activity

To capture disease damage, SLICC/ACR (Systemic Lupus International Collaborating Clinics Damage Index, the American College of Rheumatology) was used [77, 78]. This physician-rated index consists of 41 items covering 12 organ systems. Manifestations persisting continuously over six months after onset of SLE were recorded as damage, regardless of disease activity.

Furthermore, SLE-specific co-morbidities as well as morbidity due to treatment for SLE were captured. Scores ranged from 0-47.

SLAM (Systemic Lupus Activity Measure) and SLEDAI (SLE Disease Activity Index) were used to measure disease activity [78, 79]. Both SLAM and SLEDAI are physician-rated indices frequently used in research settings and shown to be valid, reproducible and correlate well with other disease-activity indices. SLAM records objective and subjective symptoms that have been present during the preceding month. Its scores range from 0-84 and a score of seven or more is considered clinically important. SLEDAI records objective symptoms of disease activity over the previous 10 days. Its scores range from 0-105 and a score 0 indicate no activity, 1-5 indicate mild activity, 6-10 moderate activity, 11-19 high activity and $\geq$20 very high activity. Both the physician and the patients estimated disease activity on the visual analogue scale (VAS) within the activity index SLAM. SLAM was also used to identify the most common location of pain related to SLE [78].

As a supplement to measure disease activity, the Erythrocyte Sedimentation Rate (ESR*)* according to Westergrens method was used [80]. The ESR is also included in SLAM.

4.4 QUESTIONNAIRES STUDY II

Besides pain assessment with VAS and disease activity indices as in study I, additional self-assessment questionnaires were used in study II.

4.4.1 Health-related quality of life (HRQoL)

The Medical Outcomes Survey-Short Form 36 (SF-36) Standard Swedish Version 1.0 [81, 82, 83] was used to measure self-reported HRQoL in patients and controls. This measurement has previously been tested for validity and reliability in the Swedish population [82, 83] and has also been validated and used in patients with SLE [58, 81, 84]. It is the most used measurement of HRQoL in SLE [56]. The instrument measures physical and mental health, and consists of questions whose answers are compiled in eight dimensions; PF=physical function, RP=role physical, BP=bodily pain, VT=vitality (fatigue), GH=general health, SF=social function, RE=role emotional, and MH=mental health. Scores range from 0-100 and a higher score indicates better health.

4.4.2 Fatigue

The Multidimensional Assessment of Fatigue (MAF) [85] was used to measure self-reported fatigue over the past week in patients and controls. Reliability and validity for this measurement had previously been established for patients with rheumatoid arthritis [86] and in a pilot study in Swedish patients with systemic sclerosis [87].The measurement contains 16 items and measures four dimensions of fatigue; severity, distress, degree of interference in activities of daily living, and timing. In items 1-14, the study participants grade the impact of fatigue from one to 10. Item 15 and 16 consist of multiple-choice responses. Items 1-15 can be used to calculate a global fatigue index (GFI). GFI scores of 50 account for severe fatigue.

4.4.3 Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) [88] was used to measure anxiety and depression during the past week in patients and controls. The measurement has been tested in different contexts and in different populations; somatic, psychiatric and primary care patients, as well as the general population [89]. Lisspers et al. [90] found strong reliability and validity in a Swedish population sample. The measurement consists of seven questions concerning anxiety and seven questions concerning depression. Each question has four response options. The answers are summarized into two scales, anxiety and depression total index, which ranges from zero (no symptoms) to 21 (maximum distress). A score from 8-10 is defined as mild to moderate inconvenience, and score above 10 justifies deeper diagnostics and possible treatments in both anxiety and depression dimensions of HADS.

4.5 STATISTICAL METHODS

Descriptive analysis was performed and due to non-normal distribution of collected data and ordinal data, non-parametric statistical methods were used in both study I and II. The data was presented as median and interquartile range (IQR). The sources of comparative statistics were Chi-2/Fischer's exact test, the Sign Test, and the Mann-Whitney U Test. Spearman rank correlation was used for univariate analysis. Significance value was set to $p<0.05$.

Power analysis was calculated post hoc between the whole patient group and the controls, between the low-pain group and the high-pain group, and between the controls and the low and high-pain group respectively (Table 2). Non-parametric power was conducted by the software nQuery Advisor 4.0 (Statistical Solutions, USA) and corresponding parametric power by STATISTICA 10 (Stat Soft Scandinavia AB, Uppsala, Sweden). Other statistical analyses were performed in STATISTICA 10.

Table 2. Power calculation.

	Patients versus controls		Low-pain group versus controls		High-pain group versus controls		Low-pain group versus high-pain group	
Sample size (n)	74	91	56	91	18	91	56	18
Power	0.63	0.72	0.08	0.10	0.99	0.99	0.99	0.99
Number of observations (in each group) to achieve a minimum power of 0.80	111		1362		7		6	
Number of observations (in each group) to achieve a minimum power of 0.90	148		1823		10		8	

When the intensity score for SLE-related pain on VAS (n=84) was analysed, the median was 10.5 mm and the interquartile range (IQR) was 1-35.5 mm. Values above 40 mm constituted the scores beyond Q3 (>Q3) (Figure 2a). When dichotomized with the cut-off value of 40 mm, two groups appeared which did not overlap (Figure 2b). Thus the cut-off value, 40 mm, was chosen in order to divide the patients into two groups for comparative analyses. This

cut-off value also coincides with the value often used to denote the threshold for moderate pain [91]. The group scoring SLE-related pain 0-39 mm was named low-pain group and the group scoring 40-100 mm was named high-pain group.

Figure 2a. Distribution of self-reported SLE-related pain on VAS in the patient group n=84.

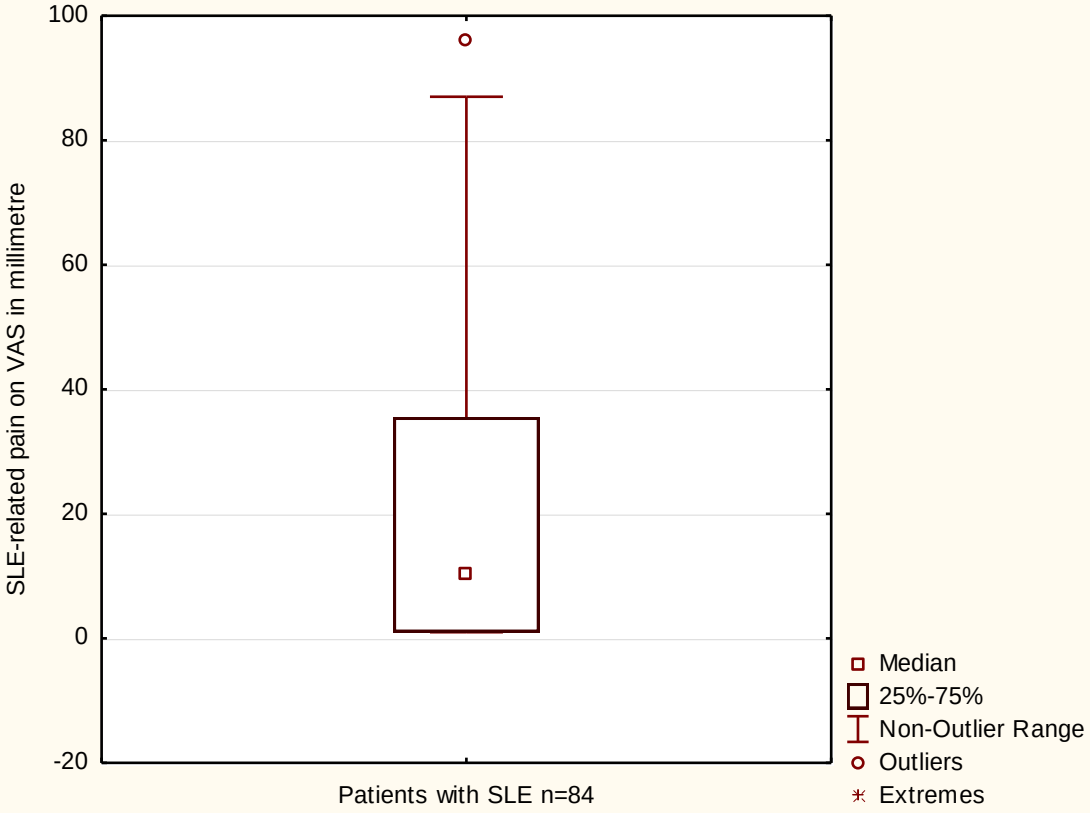
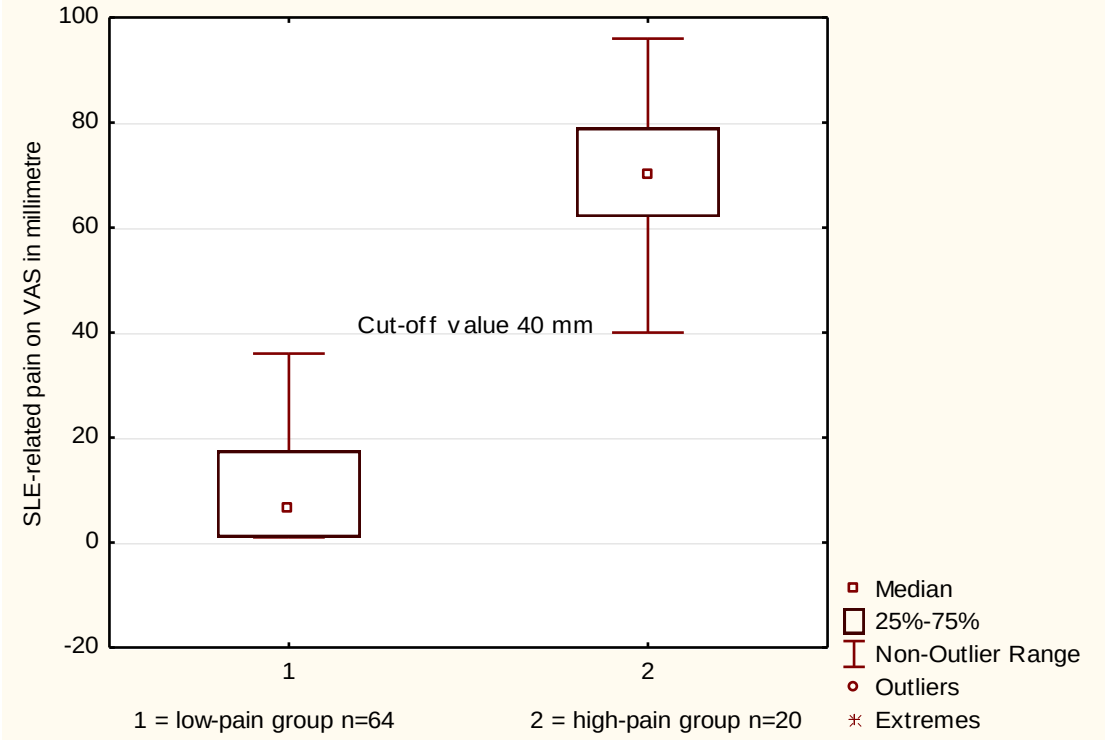


Figure 2 b. Distribution of self-reported SLE-related pain on VAS in the low-pain group and in the high-pain group.



5 ETHICAL CONSIDERATIONS

The study was approved by the Stockholm Regional Ethical Review Board. All patients and controls who were asked to participate in the study received oral information about the study and the procedures. They were also informed that participation was voluntary and could be discontinued at any time. If those questioned were still interested in participating in the study after the oral information, then they were supplemented with written information. The participants were given the opportunity to read through the information in peace and quiet, mostly in their home but in some cases at the hospital. The participants were also provided with telephone numbers to the study nurses, for questions and other issues. All participants provided written informed consent. Participants completed the questionnaires at the clinic, which made it possible to ask questions regarding ambiguities. There was also time for questions and advice during meetings with the study nurses and physicians. For medical issues that emerged at the study visit, the controls were referred to appropriate healthcare providers. Feedback was also provided on results from the investigations. Medical issues in the patient group were managed at the clinic in agreement with the patient's regular treating physician and nurse. All participants were encouraged to contact the study nurses for questions that may arise regarding participation and procedures in the study, even after completion.

The professionals in the study were aware of the risk of unspoken pressure that participation can mean. Another identified negative risk was the questions within the questionnaires that could be considered as personally intrusive.

In order to minimize these risks, it was emphasized that rejecting participation in the study would not in any way impact future care and treatment.

6 RESULTS

6.1 STUDY I

The study population (n=84) consisted of 72 (86%) females and 12 (14%) males. There were no differences between the low and high-pain groups in proportion to females and males, nor in relation to age. For characteristics of patients see Table 3.

Table 3. Characteristics and differences between the low and high-pain group.

	Low-pain group, n=64	**High-pain group, n=20**	**p-value**
Female, n / %	54 / 84%	18 / 90%	0.42
Male, n / %	10 / 16%	2 / 10%	NA
Age, yrs, median, (IQR)	45.9 (32.3-56.95)	45.95 (37.05-58)	0.71
Disease duration, yrs, median, (IQR)	10 (5-17.5)	5.5 (3-9.5)	*0.008*
Current treatment with oral glucocorticoids, n / %	39 / 61%	14 / 70%	0.32
Current dose of oral glucocorticoids, mg / day, median, (IQR)	3.44 (0-6.25)	5.63 (0-10)	0.14
Disease activity (SLAM), median, (IQR)	5.5 (4-8)	10.5 (8-14)	*<0.001*
Disease activity (SLEDAI), median, (IQR)	2 (0-4)	4.5 (2.5-9.5)	*0.014*
ESR, mm/h, median, (IQR)	17 (12-26)	27 (13.5-43)	*0.044*
Disease activity measured by physicians (VAS mm/SLAM), median, (IQR), n=27	7 (3-11)	25.5 (13-30)	*0.029*
Disease activity measured by patients (VAS mm/SLAM), median, (IQR), n=81	13 (8-23)	52.5(41-68.5)	*<0.001*
Disease damage (SLICC), median, (IQR)	1 (0-2)	1 (0-3.5)	0.21

6.1.1 Pain intensity, disease duration and disease activity

The high-pain group accounted for 24% of the study population and reported significantly higher scores of SLE-related pain on VAS (median 70 mm, IQR, 62-79 mm) compared to the low-pain group (median 6.5 mm, IQR, 1-17.5 mm) ($p<0.001$). The high-pain group also differed significantly from the low-pain group regarding shorter disease duration and higher disease activity measured by SLAM, SLEDAI and ESR (Table 3). SLAM scores in the high-pain group indicated clinically important disease activity. SLEDAI scores indicated mild disease activity in both low and high-pain groups. The correlation (r) between SLE-related pain and SLAM and SLEDAI was 0.44 and 0.35 respectively.
Global assessment of disease activity was reported by the physicians and the patients on VAS, and there was a significant difference between the low and high-pain groups (Table 3). The whole patient group reported significantly higher disease activity (median 19 mm, IQR, 10-50 mm) compared to the physicians (median 12 mm, IQR, 4-23 mm) ($p=0.007$).
The majority of all the patients (63%) were currently being treated with oral glucocorticoids. There were no significant differences between the low-pain group and the high-pain group in proportion treated with glucocorticoids or dose of glucocorticoids (Table 3). Neither were there any differences in scores of self-reported SLE-related pain in patients treated or not with glucocorticoids (data not shown).

6.1.2 Pain characteristics

The high-pain group scored significantly higher for the SF-MPQ total intensity score of descriptive words, as well as sensory and affective index (Table 4).

Table 4. Total intensity score for descriptive words, sensory and affective indices in SF-MPQ for the low and high-pain group.

	Low-pain group median (IQR)	**High-pain group median (IQR)**	**p-value**
The total intensity score for descriptive words	2 (0-5)	14.5 (5.5-20.5)	*<0.001*
The sensory index	2 (0-4)	13 (7-17)	*<0.001*
The affective index	0 (0-1)	2 (0-3.5)	*0.002*
Descriptive words (n)	2 (0-4)	8.5 (4-10.5)	*<0.001*

IQR=inter quartile range

There was a positive correlation (r) between self-reported SLE-related pain and the number of descriptive words used (0.78). The high-pain group used significantly more descriptive words in SF-MPQ (Table 4). The descriptive words most reported in the high-pain group as moderate were *stabbing, burning* and *aching* and as severe *tender*, *heavy* and *exhausting* (Table 5).

Table 5. The most frequently used describing words as moderate and severe in the low and high-pain group. Presented as numbers (n) and proportion (%) of patients who used the words.

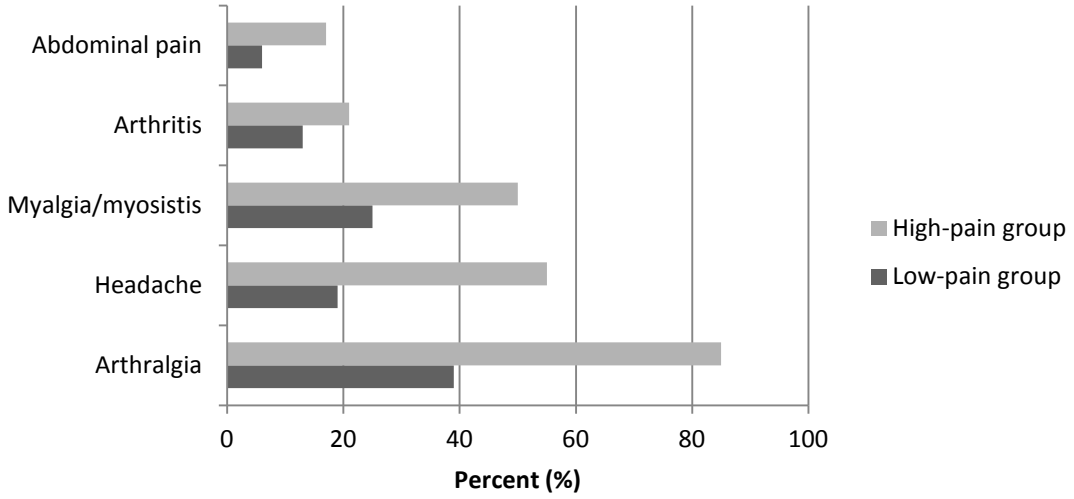
	LPG moderate	**HPG moderate**	**LPG severe**	**HPG severe**
Stabbing n/%	***7/11%***	***6/30%***	2 / 3%	4 / 20%
Burning n/%	5 / 8%	***9/45%***	0 / 0%	3 / 15%
Aching n/%	5 / 8%	***10/50%***	***5/8%***	3 / 15%
Heavy n/%	1 / 2%	3 / 15%	0 / 0%	***5/25%***
Tender n/%	***8/13%***	5 / 25%	2 / 3%	***8/40%***
Exhausting n/%	***7/11%***	5 / 25%	1 / 2%	***5/25%***

LPG=low-pain group, HPG=high-pain group

And in the low-pain group the words *tender*, *stabbing* and *exhausting* were the most common words as moderate and *aching* as severe (Table 5). In the present pain index (PPI), most patients (70%) in the high-pain group recorded their present pain as *distressing* and in the low-pain group most patients (55%) recorded *no pain*.

Joints were the most frequently reported pain location according to SLAM in both the low and high-pain groups (Figure 3).

Figure 3. Distribution of pain location due to SLAM in the low and high-pain group.



Most of the patients in the low-pain group (42%) had no pain location according to SLAM. In the high-pain group, most of the patients (32%) had three pain locations (Figure 4a+b).

Figure 4a. Proportions of pain locations in the low-pain group in percent.

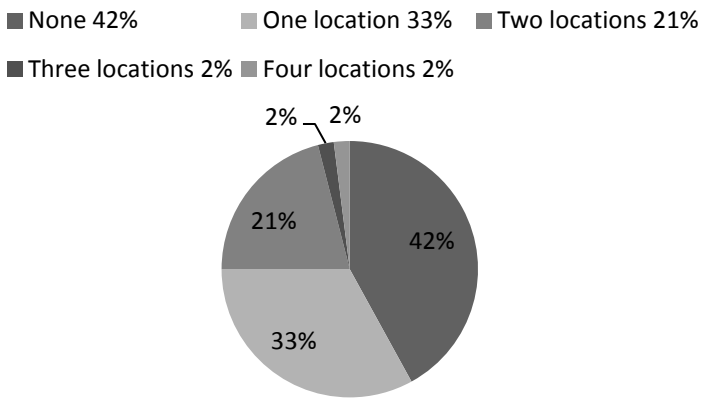
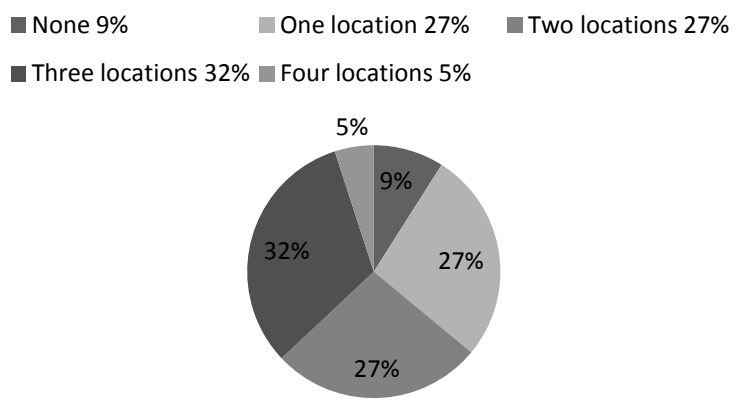


Figure 4b. Proportions of pain locations in the high-pain group in percent.



Patients with arthritis confirmed by the physician at the study visit had significantly shorter disease duration (median 3 years, IQR, 1-11 years) compared to patients with no confirmed arthritis (median 9 years, IQR, 5-17.5 years) (p=0.03).

6.2 STUDY II

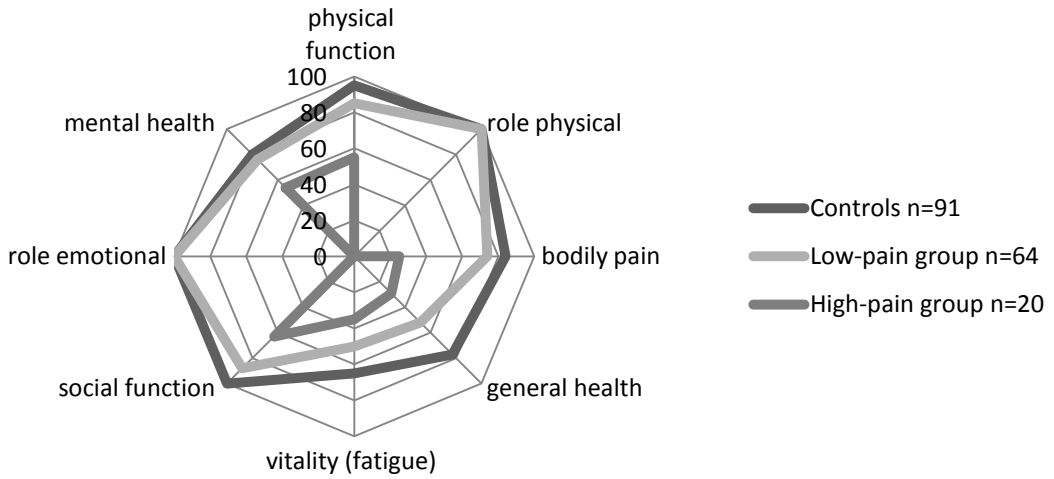
6.2.1 Pain

In addition to study I, the low and high-pain groups were compared to 91 age and sex-matched controls. For appropriate comparisons with controls we chose to use overall pain instead of SLE-related pain in the patient group. Overall pain exhibited the same pattern as SLE-related pain with significant difference between the low-pain group (median 11 mm, IQR, 2–22 mm) and the high-pain group (median 72 mm, IQR, 64–80 mm) ($p<0.001$). There were no differences between SLE-related pain and overall pain in the low and high-pain group ($p=0.15$ and $p=0.06$ respectively). The overall pain score for the controls (median 5 mm, IQR, 0–36 mm) differed significantly from the high-pain group ($p<0.001$) but not from the low-pain group ($p=0.65$).

6.2.2 Health-related quality of life

The high-pain group reported significantly lower scores in SF-36 compared to both the low-pain group ($p<0.001$-0.005) and the controls ($P\leq0.001$) (Figure 5).

Figure 5. Health-related quality of life (SF-36) expressed as median in the controls, the low and high-pain group**.**



There were significant differences between the low-pain group and the controls in the dimensions *physical function* (p<0.001), *general health* (<0.001), *vitality* (p=0.02) and *social function* (p=0.02). No significant differences were found between the low-pain group and the controls regarding *role physical* (p=0.10), *bodily pain* (p=0.22), *role emotional* (p=0.11) and *mental health* (p=0.07) (Figure 5).

For correlations (r) between the dimensions in SF-36 and pain and disease activity, see Table 6.

Table 6. Health-related quality of life. Correlations (r) between dimensions in SF-36, pain and disease activity [92].

	PF (r)	**RP (r)**	**BP (r)**	**GH (r)**	**VT (r)**	**SF (r)**	**RE (r)**	**MH (r)**
Overall pain patients n=73	-0.54	-0.51	-0.85	-0.51	-0.37	-0.32	-0.42	-0.29
Overall pain controls n=91	-0.51	-0.51	-0.77	-0.44	-0.56	-0.3	-0.31	-0.41
SLE-related pain patients n=83	-0.54	-0.58	-0.81	-0.43	-0.44	-0.43	-0.48	-0.43
SLAM	-0.52	-0.57	-0.41	-0.45	-0.44	-0.39	-0.39	-0.26
SLEDAI	-0.38	-0.34	-0.32	-0.30	-0.33	-0.26	-0.17	-0.25

LPG=low pain group, HPG=high-pain group, **r=**Spearman's rank correlation coefficient

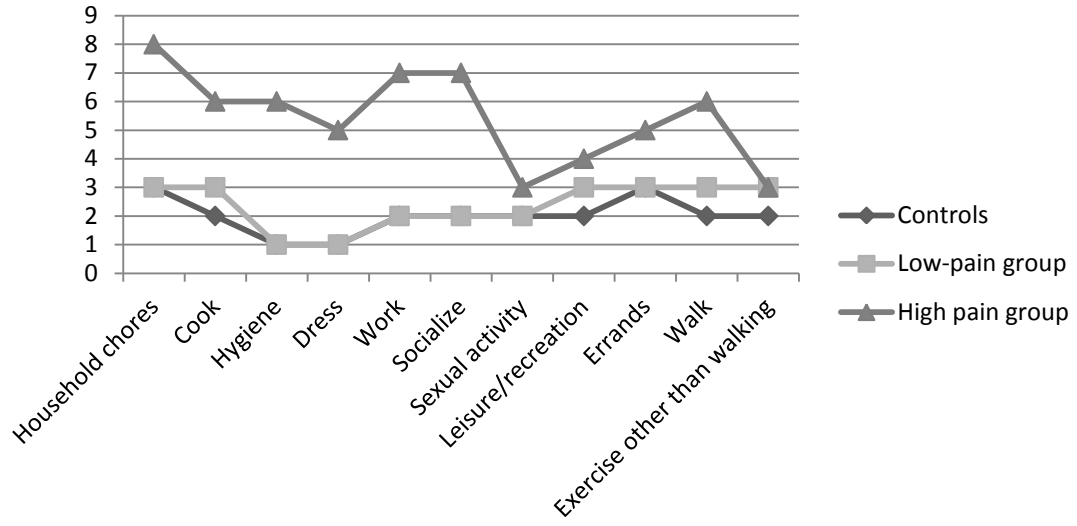
6.2.3 Fatigue

The MAF/GFI for the high-pain group was significantly higher (median 36.5, IQR, 32.5–39.7) than for the low-pain group (median 23, IQR, 14.6–34.1) ($p<0.001$) and for the controls (median 19.4, IQR, 11.63–29.05) ($p<0.001$). The difference between the low-pain group and the controls was not significant ($p=0.09$).

In the high-pain group, 50% experienced fatigue every day compared to 33% in the low-pain group and 24% in the controls.

In the high-pain group, fatigue interfered mostly with the activities of daily living, such as *household chores*, *work* and *socialize with friends and family*. Least affected by fatigue was *engage in sexual activity* and *exercise other than walking* (Figure 6).

Figure 6. Interference of fatigue on activities of daily life (MAF item 4-14) expressed as median, score range 1-10.



Regarding interference of fatigue on activities of daily living, there were significant differences ($p<0.001$-0.02) between the high-pain group and the low-pain group except for the items *engage in sexual activity*, *engage in leisure and recreational activities*, *walk* and *exercise other than walking*. The high-pain group differed significantly from the controls in all items of interference of fatigue on activities of daily living ($p<0.001$-0.04) except for engage in *sexual activity* and *exercise other than walking*.

The low-pain group did not differ significantly from the controls in any items of MAF. The correlation (r) between MAF/GFI and SLE-related pain was 0.53 and between MAF/GFI and overall pain in the patient group 0.49. Regarding relationship between MAF/GFI and disease activity indices SLAM and SLEDAI the correlation (r) were 0.48 and 0.29 respectively. In the control group the correlation (r) between MAF/GFI and overall pain was 0.40.

6.2.4 Anxiety and depression

The anxiety index for the high-pain group indicated symptoms of mild to moderate inconvenience (median 9, IQR, 6.5-11.5), but not in the depression index (median 7.5, IQR, 5.5-9). The HADS scores in the low-pain group indicated no symptoms regarding anxiety (median 4, IQR, 3-8) or depression (median 3, IQR, 1-5), as well as for the controls' anxiety (median 4, IQR, 2-7) and for depression (median 2, IQR, 1-4).

The high-pain group showed significantly higher values for both depression and anxiety indices, compared to the low-pain group ($p<0.001$) and the controls ($p<0.001$).

The low-pain group did not differ significantly from the controls regarding anxiety ($p=0.81$) or depression index ($p=0.19$). For correlations (r) between anxiety and depression and pain and disease activity, see Table 7.

Table 7. Correlations (r) between anxiety/depression (HADS) and pain and disease activity in patients with SLE and controls.

	Patients		**Controls**	
	Anxiety (r)	**Depression (r)**	**Anxiety (r)**	**Depression (r)**
SLE-related pain	0.43	0.52	NA	NA
Overall pain	0.38	0.43	0.24	0.27
Disease activity (SLAM)	0.24	0.31	NA	NA
Disease activity (SLEDAI)	0.28	0.25	NA	NA

HADS=Hospital Anxiety and Depression Scale, NA=Not Applicable.

7 DISCUSSION

7.1 METHODOLOGICAL CONSIDERATIONS

The cross-sectional design in this study, as well as the relatively small sample, may limit the generalization of the results. However, despite the sample size, several significances were found. On the other hand, because of the sample size, further significances may have been undetected. The small proportion of males to females did not allow comparison between sexes.

For ethical reasons no data was collected from potential participants who denied participation. Thus, comparisons between participants and those who declined to participate in the study were not conducted.

The statistical approach was mainly descriptive, but comparative analyses were also performed using nonparametric methods due to non-normal distributed and ordinal data.

The self-assessment questionnaires used in this study were generic, but have frequently been used in patients with SLE [21, 22, 23, 44, 48, 62, 78, 93]. More specifically, the SF-36 was the only measurement that previously had been validated in SLE [58, 81, 84]. However, SLE is regarded as an uncommon disease and in the scope of this study it was not possible to test reliability and validity for each questionnaire in patients with SLE.

There are both advantages and disadvantages of using VAS in measuring pain. Among the advantages emerges simplicity to implement. One disadvantage regarding VAS is its one-dimensional nature. In the current study, VAS was used to measure pain intensity over the previous week, but in addition SF-MPQ was used for more detailed information about pain; and through the descriptive words used displayed a picture of the patient's experiences. SF-MPQ is preferred for long-term pain [91], but on the other hand score on VAS was convenient to use when dividing into two groups. VAS is also frequently used in clinical practice and known by most patients. The measurement of fatigue, health-related quality of life, anxiety and depression contributed to the multidimensional perspective of pain and enabled insight into the perspectives individually.

Because the questionnaires were completed at the clinic, there were few missing data. Regarding missing data among descriptive words in the SF-MPQ, professor Ronald Melzack who constructed the measurement was

contacted for advice. In dialogue with professor Melzack, we first tried to determine if the missing values were meant to be zero (no pain) depending on the other replies. Upon suspicion that the reply was not zero (no pain), we took the average of the other descriptors, and added this to the incomplete subtotal. Since most patients with SLE in Sweden should be affiliated with a rheumatologist [94, 95, 96], the cohort was considered to be representative of the disease. Both the patients with SLE and the sex and age-matched controls were from the same greater urban area and therefore comparisons between patients and controls were appropriate.

7.2 DISCUSSION OF THE RESULTS

7.2.1 Pain

Results from this study address self-reported pain in SLE, which was recorded as a significant symptom in a substantial proportion (24%) of the patients. Despite progress in pharmacological treatments and medical care, as well as liberal access to healthcare and medication due to the health insurance system in Sweden, nearly one quarter of this study population expressed moderate to severe disease-related pain. This group was also burdened with a higher degree of fatigue, anxiety and depression, as well as impaired HRQoL. There is a close connection between pain and suffering [7] and Eriksson [6] argued that the basis of nursing is to alleviate suffering. Therefore, the extensive experience of SLE-related pain reported in this study presents a challenge in nursing and nursing research, suggesting the development of strategies for pain management.

Previous studies have shown similar results regarding self-reported pain in SLE [1, 2, 42] but except for Pettersson et al. [3], in other populations an in different medical care settings. Due to the heterogeneous nature of SLE, incidence and prevalence in different populations [8, 9, 11, 12], different health insurance systems and organization of medical care [70] as well as improved drug therapy [14, 15], we judged that an update and a more detailed investigation of this topic was necessary.

As in the study by Kozora et al. [62], the patients in this study reported higher degree of pain compared to the controls. The identification of patients into the low and high-pain groups, made it possible to accomplish comparative statistical analysis between the two groups regarding fatigue, HRQoL, anxiety

and depression, and thus provided more detailed knowledge regarding self-reported pain and accompanying symptom burden. The results from the present study also highlight that all patients with SLE do not have pain, as previous reported by Greco et al. [2]. Actually, pain scores in the low-pain group, did not differ significantly from scores in the controls of the general population. Therefore, a challenge for health professionals will be to identify and focus on patients with higher levels of pain, which probably indicate great symptom burden. The median VAS for the high-pain group was 70 mm, which commonly counts as severe pain [91]. The high-pain group had significantly higher disease activity measured by SLAM, SLEDAI and ESR, however both SLEDAI and SLAM indicated mild to moderate disease activity. Due to higher scores of fatigue, anxiety and depression as well as impaired HRQoL in the high-pain group, a higher degree of pain may be a marker for great symptom burden despite low disease activity.

The lack of differences between the two groups regarding treatment with oral glucocorticoids is in line with results from previous studies [23,62] and does not support the impact of glucocorticoids on pain in SLE.

The patients in this study were asked to report SLE-related pain over the previous week, which probably comprised both persistent as intermittent and acute pain. In other words, the results from this study did not distinguish between these types of pain.

The high occurrence of fibromyalgia in SLE is shown by Staud [97] in a comprehensive review where up to 47% of patients with SLE fulfilled the criteria for fibromyalgia. The expanded understanding of central pain-processing and the contemplation of long-standing pain as a separate disease entity [33, 35] may imply modified regimes regarding pain in SLE. Differentiating between diverse pain conditions in SLE appears necessary in view of their different medical management [35, 37]. It should also be said, that at the time of this study, no patient had a known fibromyalgia syndrome diagnosis. On the other hand, the patients in this study were not investigated regarding fibromyalgia.

As reported elsewhere, the most common pain location according to SLAM was the joint [2, 39]. The shorter disease duration in the high-pan group as well as in patients with arthritis suggest that the disease is not yet controlled. In line

with that, there is reported to be a progressive remission of the disease that usually follows over time in many patients [10].

The scores in SF-MPQ also showed significant differences regarding greater pain intensity and greater numbers of describing words used in the high-pain group. These results regarding pain characteristics from SF-MPQ, together with a greater numbers of identified pain locations according to SLAM, suggest diverse experiences of pain in SLE, especially in the high-pain group. The variation in pain experience was also confirmed in a recent study from Sweden by Mattsson et al. [98], where the study participants described pain in SLE as unpredictable in intensity and location which created uncertainty.

7.2.2 Health-related quality of life

The scores in SF-36 indicated, as expected, impaired HRQoL in the high-pain group. The pattern provided when comparing low-pain group and the controls is more difficult to interpret. The two groups differed significantly from each other in one half of the dimensions and not in the other half. Nevertheless, the difference in scores in *bodily pain* between the groups support the results from pain scores on VAS and SF-MPQ indicating no significant difference between the majority of patients with SLE and the general population. The remarkable low scores in *role emotional* and *role physical* in the high-pain group raises questions regarding impact of disease on self-perception. These results appears consistent to the study by McElhone et al. [16], where the participants reported emotional difficulties as anger, poor self-esteem, frustration and anxiety, but also dependence on others regarding everyday tasks such as practical household chores. In general, the results from SF-36 are in line with previous studies in other populations showing impaired health-related quality of life in patients with SLE compared to controls [39, 55, 56, 58]. McElhone et al. [56] demonstrated the mixture of results regarding the dimensions in SF-36 most affected. However, the identification of the patients into the low and high-pain groups showed that not all patients with SLE differ from the general population regarding HRQoL. Thus, the results suggest that lower HRQoL comes with higher degree of pain. But in contrast, the correlation between overall pain and dimensions in SF-36 were low to moderate, suggesting even other contributing factors. The correlations between HRQoL and disease

activity indices were low to moderate and may be in line with Griffiths et al. [78] indicating HRQoL as a separate entity independent of disease activity.

7.2.3 Fatigue

As previous reported [3, 62, 63], fatigue was largely present in this study, particularly in the high-pain group. The moderate correlation between MAF/GFI and pain indicates a likely relationship between fatigue and pain. This is probably by the mutually reinforcing effect between pain and fatigue as described in previous studies [3, 21, 44, 99]. Activities of daily life least influenced by fatigue in the high-pain group were *engage in sexual activities* and *exercise other than walking*. Actually, there were no significant differences between the three groups in those activities. Impact of SLE on sexual functions seems to be a rather uninvestigated field. Nevertheless, Tseng et al. [100] found no impact of SLE on sexual functioning except for vascular factors, but this study investigated the impact of fatigue on sexual functioning. Curry et al. [101] reported a higher degree of sexual abstention in patients with SLE compared to controls. However, they investigated nor relationship to fatigue. Activities most influenced by fatigue were *household chores*, *work* and *socialize with friends and family.* This is in line with the study by Pettersson et al. [99] where the participants reported impact of fatigue on work, family relations, social contacts and leisure activities.

To the best of our knowledge, no previous study has investigated fatigue by identifying patients with SLE into low and high-pain groups except for Burgos et al. [21]. They used the median of pain scores on VAS as a reference point and showed that patients with higher levels of pain also had worse values of fatigue. The results from Burgos et al. [21] are consistent with the results of this present study. However, this study provides a more detailed understanding by studying patients with the highest level of pain (>Q3) and by not using the median as a reference point.

7.2.4 Anxiety and depression

In the light of previous studies [62, 66, 102], reporting a high prevalence of anxiety and depression, the patients in this study seemed to feel quite well regarding anxiety and depression measured by HADS. Despite significantly higher scores in the high-pain group, it was only in the anxiety index the high-

pain group reached scores indicating symptoms of mild to moderate severity. That means that neither the patients with SLE nor the controls where afflicted with anxiety or depression to the extent that detailed diagnostics and possible treatments were considered. Yet, the scores for the high-pain group were significantly higher compared to the low-pain group and may reflect worries about the future, prognosis of the disease and less knowledge of SLE [16, 17, 69]. In that case, educational interventions could be beneficial in order to reduce the symptom burden. The correlations between anxiety and depression and disease activity were weak and thereby in line with results from the study by Jarpa et al. [67]. Seawell and Danoff-Burg [68] concluded in theirs review that there are mixed results regarding associations between anxiety and depression and disease activity, and this study does not support such association. Similarly for HRQoL and fatigue in this study, there were moderate correlations between pain and anxiety and depression in the patient group, suggesting an impact of pain in SLE even if other factors may interact. Nevertheless, the significantly higher scores in the high-pain group of anxiety and depression probably mean a greater symptom burden, even in the absence of psychiatric illness.

7.2.5 Global disease activity on VAS

Assessment of global disease activity on VAS, within SLAM, by the physicians was available in only 27 patients. This may limit the comparison between the patient's and the physician's estimated disease activity. Nevertheless, the results from this study reinforce similar studies indicating that patients and healthcare providers may evaluate disease activity in different ways and on different basis [103, 104]. Yen et al. [105] showed that higher degree of pain correlates to a higher degree of discord in assessment of disease activity between patients and physicians. The professional role for healthcare providers includes interpretation of objective and measurable signs and symptoms of diseases. Healthcare providers` assessments should not be limited to objective measurable signs, which might reduce the patient's experience of subjective symptoms and thereby cause suffering [5] and misunderstandings. Disparities between patients and healthcare providers in assessment of disease activity would rather serve as a basis for discussion. Through presenting underlying motives for the assessment of disease activity mutual understanding may arise.

Chambers et al. [106] reported different concerns regarding adherence to medical treatment in SLE and raised the importance of communication between patients and healthcare providers. Nurse-led rheumatology clinics providing drug monitoring and focus on individual needs and experiences [107, 108] constitute a valuable organization in overcoming communication problems that could lead to suffering [26]. Eriksson [26] means that the experience of not being understood or not being taken seriously can for the patient mean “suffering caused by caring”.

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8 SUMMARY, CONCLUSIONS AND CLINICAL IMPLICATIONS

The approach for identification of the patients into the low and high-pain group clearly proves that patients in SLE are a heterogeneous group regarding pain, HRQoL, fatigue, anxiety and depression.

Almost one fourth of the patients in this study reported moderate to severe disease-related pain. This group had shorter disease duration and higher disease activity, even if the activity scores only indicated mild to moderate disease activity. Due to the significantly higher disease activity in the high-pain group, disease activity may indicate higher degree of pain and extended symptom burden. But disease activity cannot be regarded as the only indicator of pain and greater symptom burden, as disease activity in the high-pain group was mild to moderate. The patients in the high-pain group used more describing words for their pain and identified several pain locations indicating varying pain experience.

Furthermore, the high-pain group was also burdened with significantly more fatigue, anxiety, depression and impaired health related quality of life.

Special attention to pain should therefore be directed to especially recently diagnosed patients and patients with short disease duration, who might need more comprehensive and multidimensional interventions to reduce the symptom burden and for pain management.

Differences in the assessment of disease activity between patients and healthcare providers indicate different perspectives and focus. This should be taken into account in communication between healthcare providers and patients to avoid indignity and suffering.

9 FUTURE RESEARCH

Taking into account the chronic course of SLE and the heavy symptom burden associated with pain, further studies regarding SLE-related pain and its nature seems important. Previous reports regarding reductions in employment [19] and relationships between pain and impaired work capacity [19, 111, 112], which add economic burden to patients with SLE and society are also incentives for further investigations.

Also in the light of reported co-morbidity to fibromyalgia in SLE, where other interventions are required in addition to immune-modulating and anti-inflammatory treatment in SLE [97, 109, 110], further research would be critical.

As reported in a review by Calvo-Ale'n and Alarcon [113] outcomes in SLE from different populations are also influenced by cultural and socioeconomic considerations, which should justify investigations of different populations and contexts for updates and evaluations.

The development and evaluation of interventions, such as pain management techniques and educational programs, to alleviate pain in SLE is pivotal. This could be connected to research and development of nurse-led rheumatology clinics [107, 108] and it`s utility as a part of multi-professional management.

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