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PIA ELFVING

INCIDENCE, MORTALITY AND DISEASE BURDEN IN SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Systemic lupus erythematosus (SLE) has an individual race-dependent occurrence and disease course. The disease is systemic, targets many organs and along the continuing activity causes irreversible damage. The objectives of this thesis were to evaluate incidence, survival, initial drug therapy and impact on work ability in incident SLE patients in Finland.

The incidence cohort was based on new reimbursement decisions on SLE medication in the years 2000-2007 in the nationwide register maintained by the Social Insurance Institution (SII). The 599 patients identified were linked by their personal identity code to the official death certificate statistics of the Statistics Finland and the drug purchase, the sickness allowance and pension registries of the SII until the end of year 2008. The second supplementary incidence study cohort consisted of all 72 new adult patients with connective tissue disease and 14 new adult patients with vasculitis patients in Northern Savo Hospital District in year 2010.

The incidence of SLE in adults was 1.7/100 000 by the nationwide register-based method and 3.4/100 000 in 2010 in Northern Savo. The peak incidence occurred in females aged 40-59 years. Incidence of SLE in children was 0.4/100 000. Their mean age at disease onset was 13 years. Disease-modifying anti-rheumatic drugs (DMARDs) were used in 90% of the patients in the first-year drug therapy. The most used drug was hydroxychloroquine in a three -quarters of adult patients, followed by azathioprine (15%), and methotrexate (13%). SLE patients more commonly used medication for preselected concomitant comorbidities (cardiovascular diseases, dyslipidemia, diabetes mellitus, hypothyroidism, and obstructive pulmonary diseases) than the background population. During the observation time work disability (WD) pension was granted to 27 working- aged (18-64 years old) patients. The main cause was SLE itself (59%), followed by musculoskeletal and psychiatric diseases. The cumulative incidence for SLE-related WD was 3.4% (95% CI 1.9 to 5.8) in 5 years and 5.0% (95% CI 3.0 to 8.5) at the end of follow-up, and for all cause WD 5.8% (95% CI 3.9 to 8.7) and 8.6 % (95% CI 5.6 to 13.1), respectively. The age- and gender- stratified incidence ratio for all cause WD pension was 5.4 (95% CI 3.7 to 7.9) compared to the background population. Thirty adult patients died until the end of 2008. In females the mean age at death was higher (67.8 ± 17.2 years) than in males (62.3 ± 15.2 years). The five-year survival rates for females and males were 94.8% (95% CI 92.0 to 96.6%) and 88.2% (95% CI 76.5 to 94.3%), respectively. The main underlying causes of death were cardiovascular diseases (37%), malignancy (17%) and SLE itself (13%). The age- and gender-stratified standardized mortality ratio (SMR) was 1.48 (95% CI 1.01 to 2.12).

The incidence of SLE has remained stable over the decades. It was highest in females close to menopausal age. Initial drug therapy is active in Finland and reflects international recommendations. The disease itself is a risk for concomitant comorbidities and WD. Survival is inferior to the population and cardiovascular diseases are the most common causes of death in these patients.

National Library of Medicine Classification: WA 900, WA 950, WB 330, WD 375, WD 380

Medical Subject Headings: Connective Tissue Diseases; Lupus Erythematosus, Systemic; Incidence; Mortality; Cause of Death; Drug Therapy; Cost of Illness; Comorbidity; Disability Evaluation; Work; Pensions; Cohort Studies; Registries; Finland

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TIIVISTELMÄ

Systeeminen lupus erythematosuksen (SLE) ilmaantuvus ja taudinkulku on yksilöllinen ja rotusidonnainen. Tauti on systeeminen, useisiin elimiin kohdistuva, ja pitkäkestoinen taudin aktiivisuus johtaa pysyviin elinvaurioihin. Tässä väitöskirjatyössä arvioitiin taudin ilmaantuvuutta, eloonjäämisennustetta, alkuvaiheen lääkehoitoa ja vaikutusta työkykyyn tuoreilla SLE potilailla Suomessa.
Uuden erityiskorvauspäätöksen SLE lääkityksiin saaneet potilaat vuosina 2000- 2007 muodostivat ilmaantuvuusotoksen maanlaajuisen Kansaneläkelaitoksen (KELAn) rekisterin pohjalta. Tunnistetut 599 potilasta yhdistettiin sosiaaliturvatunnuksen avulla Suomen Tilastokeskuksen ylläpitämään kuolinsyytilastoon ja KELA:n ylläpitämiin lääkeosto-, sairasloma- ja eläkerekistereihin vuoden 2008 loppuun saakka. Toinen täydentävä ilmaantuvuustutkimusotos sisälsi 72 uutta, aikuista sidekudostauti- ja 14 vaskuliittipotilasta Pohjois-Savon sairaanhoitopiirin alueella vuonna 2010.
Maanlaajuisella rekisteripohjaisella menetelmällä SLE:n ilmaantuvuus aikuisilla oli 1.7/100 000 ja Pohjois-Savossa 3.4/100 000 vuonna 2010. Ilmaantuvuus oli suurinta 40- 59 – vuotiailla naisilla. Lapsilla SLE:n ilmaantuvuus oli 0.4/100 000. Heidän keski-ikänsä taudin puhjetessa oli 13 vuotta. Antireumaattista lääkitystä käytettiin 90% :lla potilaista ensimmäisen vuoden lääketerapiassa. Käytetyin antireumaatti oli hydroksiklorokiini kolmella neljäsosalla potilaista ja seuraavia olivat atsatiopriini (15%) ja metotreksaatti (13%). SLE potilaat käyttivät taustaväestöä enemmän lääkitystä ennalta valittuihin samanaikaisiin perussairauksiin (sydän- ja verisuonisairaudet, rasva-aineenvaihdunnan häiriöt, diabetes, kilpirauhasen vajaatoiminta ja ahtauttavat keuhkosairaudet). Tarkasteluaikana työkyvyttömyyseläke myönnettiin 27 työikäiselle (18-64- vuotiaalle) potilaalle. Tärkein syy oli tauti itse (59%) ja toissijaisena olivat tuki- ja liikuntaelinsairaudet ja psykiatriset syyt. Jatkuvan SLE:sta johtuvan työkyvyttömyyden ilmaantuvuus oli viiden vuoden kohdalla 3.4% (95% CI 1.9, 5.8) ja seurannan päättyessä 5.0% (95% CI 3.0, 8.5) ja vastaavat luvut kaikista syistä johtuvalle työkyvyttömyydelle olivat 5.8% (95% CI 3.9, 8.7) ja 8.6 % (95% CI 5.6, 13.1). Ikä- ja sukupuoli vakioitu ilmaantuvuustiheyksien suhde kaikista syistä johtuvalle työkyvyttömyydelle oli 5.4 (95% CI 3.7, 7.9) taustaväestöön nähden. 30 aikuista potilasta kuoli vuoden 2008 loppuun mennessä. Kuolleiden keski-ikä oli naisilla korkeampi (67.8 ± 17.2 vuotta) kuin miehillä (62.3 ± 15.2 vuotta). Viiden vuoden eloonjäämisaste naisilla oli 94.8% (95% CI 92.0, 96.6%) ja miehillä 88.2% (95% CI 76.5, 94.3%). Tärkeimmät peruskuolinsyyt olivat sydän- ja verisuonisairaudet (37%), maligniteetti (17%) ja SLE (13%). Ikä- ja sukupuolivakioitu kuolleisuussuhde oli 1.48 (95% CI 1.01, 2.12).
SLE:n ilmaantuvuus on säilynyt samankaltaisena vuosikymmenten ajan. Taudin ilmaantuvuus oli suurinta naisilla lähellä menopaussi-ikää. Alkuvaiheen lääkehoito on Suomessa aktiivista ja heijastelee kansainvälisiä suosituksia. Tauti itsessään on riski samanaikaisille muille perussairauksille ja työkyvyn säilyttämiselle. Eloonjäämisennuste on muuhun väestöön nähden alhaisempi ja sydän- ja verisuonisairaudet ovat tavallisin kuolinsyy näillä potilailla.

Luokitus: WA 900, WA 950, WB 330, WD 375, WD 380

Yleinen suomalainen asiasanasto: reumataudit; punahukka; ilmaantuvuus; kuolleisuus; kuolemansyyt; lääkehoito; työkyvyttömyys; työkyvyttömyyseläkkeet; kohorttitutkimus; rekisterit; Suomi

We don't see things as they are,

we see them as we are.

-Anais Nin

Dedicated to my late grandmother Tyyne

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Pia Elfving
Kuopio, October 2017

List of original publications

This dissertation is based on the following original publications:

I Elfving P, Puolakka K, Kautiainen H, Virta LJ, Pohjolainen T, Kaipiainen-Seppänen O. Incidence of Systemic lupus erythematosus in Finland, 2000-2007, nationwide study. *Clin Exp Rheumatol 2014; 32:953-5.*

II Elfving P, Puolakka K, Kautiainen H, Virta LJ, Pohjolainen T, Kaipiainen- Seppänen O. Mortality and causes of death among incident cases of systemic lupus erythematosus in Finland 2000-2008. *Lupus 2014;23: 1430-4*

III Elfving P, Puolakka K, Kautiainen H, Virta LJ, Pohjolainen T, Kaipiainen-Seppänen O. Drugs used in incident systemic lupus erythematosus – results from the Finnish nationwide register 2000- 2007. *Lupus 2016;25:666-670.*

IV Elfving P, Puolakka K, Rantalaiho V, Kautiainen H, Virta LJ, Kaipiainen-Seppänen O. Impact of early systemic lupus erythematosus on work disability - results from the Finnish nationwide register 2000-2007. *Submitted*

V Elfving P, Marjoniemi O, Niinisalo H, Kononoff A, Arstila L, Savolainen E, Rutanen J, Kaipiainen- Seppänen O. Estimating the incidence of connective tissue diseases and vasculitides in a defined population in Northern Savo area in 2010. *Rheumatol Int 2016;36:917-24.*

Contents

Abbreviations

Ab	Antibody
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
AIHA	Autoimmune hemolytic anemia
AM	Antimalarial
ANA	Antinuclear antibody
anti-ds-DNA	Anti-double-stranded deoxyribonucleic acid
anti-Jo	Anti-histidyl-t-ribonucleic acid-synthetase
anti-Sm	Anti-Smith
Anti-RNP	Anti-ribonucleoprotein
APC	Antigen presenting cell
ARA	American Rheumatology Association
ATC	Anatomical Therapeutic Chemical- code
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator
BMI	Body mass index
C	Complement
CD	Cluster of differentiation
CI	Confidence Interval
CLE	Cutaneous lupus erythematosus
CRP	C-reactive protein
CTD	Connective tissue disease
CVD	Cardiovascular disease
DC	Dendritic cell
DIL	Drug-induced lupus
DM	Dermatomyositis
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
EBV	Ebstein-Barr virus
ECLAM	European Community Lupus Activity Measure
EPC	Endothelial progenitor cell
ERV	Endogenous retrovirus
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EXPLORER	Exploratory Phase II/III Evaluation of Rituximab trial
FoxP3	Forkhead Box P3
GC	Glucocorticoid
GI	Gastrointestinal
GSTM1	Glutathione-S-transferase- M1
HCQ	Hydroxychloroquine
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
IC	Immune complex
ICD	International classification of disease
Ig	Immunoglobulin
IFN	Interferon
IL	Interleukin
IMPDH	Inosine monophosphate dehydrogenase
IQR	Interquartile ranges
IRAK 1	Interleukin- 1 receptor associated kinase 1
IRF	Interferon regulatory factor
IRR	Incidence rate ratios
KLK	Kallikrein-related peptidase
LAPS	Lupus Atherosclerosis Prevention Study
LDL	Low-density lipoprotein
LE cell	Lupus erythematosus cell
LMW	Low-molecular-weight
LUNAR	Lupus Nephritis Assessment with Rituximab
MCTD	Mixed connective tissue disease
mDC	Myeloid dendritic cell
miR	Micro RNA
MMF	Mycophenolate mofetil
MTX	Methotrexate
NET	Neutrophil extracellular trap
NF-κB	Nuclear factor kappa B
NHL	Non-Hodgkin's lymphoma
NSAID	Non-steroidal anti-inflammatory drug
pDC	Plasmacytoid dendritic cell
PCB	Placebo
PM	Polymyositis
PP2A	Protein phosphatase 2A
pSS	Primary Sjögren's syndrome
RCT	Randomized controlled trial
RELESSER	Spanish Rheumatology Society Systemic lupus erythematosus Registry
RNA	Ribonucleic acid
RR	Rate ratios
SD	Standard deviation
SDI	Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index
SII	Social Insurance Institution
SLAM	Systemic Lupus Activity Measure
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus Activity Index
SLICC	Systemic Lupus International Collaboration Clinics

SMR	Standardized mortality ratio	TNF	Tumour necrosis factor
SNP	Single-nucleotide polymorphism	TLR	Toll like receptor
SSc	Systemic sclerosis	Treg	Regulatory T cell
SRI	Systemic lupus erythematosus Responder Index	TREX	Transcription and export complex
		UCTD	Undifferentiated connective tissue disease
STAT	Signal transducer and activator of transcription	UV	Ultraviolet
		VAS	Visual analog scale
Th cell	T helper cell	WD	Work disability

1 Introduction

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease in which disturbance in immune system precedes the clinical disease by years and wide autoantibody and immune complex production eventually leads to organ damage (1). The science is far from understanding the immunopathology of SLE, but steps forward have been made especially in the roles of genetics, epigenetics, immune signaling and associated accelerated atherosclerosis (2,3). The increased knowledge of the disturbances in the immune system has connected many risk factors like sun light exposure and fluctuation of female hormone levels to disease development at a theoretical level (2,4).

The disease course is heterogeneous and individual, and the diagnosis is often challenging. The recognition of the disease has been improved by the autoantibody testing and updated classification criteria (5,6). Earlier diagnosis is thought to pick up milder cases, but also lead to better prognosis of the disease (7-9). Although work ability levels and the life expectancy of SLE patients is shown to be inferior to the general population (10,11), the efficacy of early scheduled diagnosis and treatment has yet to be clarified in high-quality studies (8,9,12). Multidimensional disease features make it difficult to create therapeutic agents or uniform treatment strategy. Most of the drugs used in therapy have been either designed for or used first in the treatment of rheumatoid arthritis (13). The data on strategies in initial drug therapy is almost lacking (12,14,15).

SLE itself is a disease targeting multiple organs. If the disease continues to be active, the damage accrual progresses over time (16). Moreover, disturbances of the immune system, persistent inflammation and drug therapy can cause other comorbidities to patients (12,16). As the treatment of disease and infections have shown advance, the focus has turned into the excess of cardiovascular diseases (17). In western countries cardiovascular causes remain to be the most important cause of death, whereas in developing countries active disease associated with infection can be a lethal combination (18,19). The recent report has suggested that the risk of cardiovascular disease is elevated already in the early course of disease, possibly antedating the appearance of clinical disease (17).

The characteristics of the disease vary depending on race and social environment (11,20,21), and therefore the studies have to be performed locally. As Finland is a sparsely populated country and SLE is a rare disease, the results of the present thesis were based on valuable information from health care registries. The epidemiologic approach assessed the incidence, survival and causes of death in the patients recently diagnosed with SLE identified from the special drug reimbursement register in years 2000-2007. The outpatient

drug therapy during the first year and work disability levels of working-aged SLE patients were determined until the end of year 2008. The incidence of SLE was also evaluated prospectively in a defined population-based cohort in Northern Savo in the year 2010.

2 Review of literature

2.1 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

2.1.1 Evolutions of the concept of SLE

The history of systemic lupus erythematosus has many breakthroughs. The term lupus was initially used in the Middle Ages for all erosive skin changes that looked like bite of a wolf (22). Laurent Theodore Biett with the help of his student Pierre Cazenave was the first who documented skin lesions of lupus erythematosus reliably in 1833. Ferdinard von Hebra illustrated in 1866 the image of butterfly in the malar rash on the face of a patient (5). A systemic disease course was observed for the first time by Moriz Kaposi in 1872. Sir William Osler created the current term systemic lupus erythematosus and found that SLE can occur without cutaneous involvement (5,22). Recognition of a lupus erythematosus (LE) cell by Malcom Hargraves in 1948 started a new era in the history of SLE. Later in the 1950s antinuclear antibodies (ANAs) were discovered, and this widened the understanding of the autoimmune features of the disease (5). Recently, animal models have provided insights into the pathogenesis and genetics of SLE (22).

2.1.2 Classification

The preliminary criteria for the classification of SLE were published in 1971. Since those criteria did not include antibody profile in disease, the criteria were revised for the first time in 1982 by American Rheumatology Association (ARA82 criteria also later used as American College of Rheumatology, ACR82 criteria). The original idea of classification criteria was to separate a disease with an autoimmune profile from other diseases (23). Later in 1997 ARA82 criteria were again revised by replacing "positive LE cell preparation" by the definitions of antiphospholipid antibodies (24). These ACR97 criteria (25) along with the latest Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (6) are the basis for the classification of SLE in nowadays studies. ACR97 criteria are shown in detail in Table 1 and the SLICC classification criteria in Table 2. The classification criteria are not the same as diagnostic criteria and they do not work that well in early and in incomplete disease, in which the treatment decisions have to be made on clinical grounds (1,8).

Table 1. Classification of systemic lupus erythematosus according to ACR 1997 revised classification criteria. The disease can be classified as SLE if 4 of the 11 criteria below are fulfilled (24,25).

Classification criteria
1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis Non-erosive arthritis involving ≥ 2 peripheral joints characterized by tenderness, swelling or effusion
6. Serositis Pleuritis Pericarditis
7. Renal disorder Persistent proteinuria >0.5 grams per day or 3+ if quantitation not performed OR cellular casts- may be red cell, haemoglobin, granular, tubular or mixed
8. Neurological disorder Seizures - *in the absence of offending drugs or known metabolic derangements* Psychosis - *in the absence of offending drugs or known metabolic derangements*
9. Hemotologic disorder Hemolytic anemia- with reticulocytosis OR leukopenia < 4000/mm^3 on 2 or more occasions OR lymphopenia <1500/mm^3 on 2 or more occasions OR thrombocytopenia < 100,000/mm^3 *in the absence of offending drugs*
10. Immunologic disorder Anti-DNA antibody to native DNA in abnormal titre OR anti-Smith; presence of antibody to Sm nuclear antigen OR positive finding of antiphospholipid antibodies based on -abnormal concentration of IgG or IgM anticardiolipin antibodies or -positive lupus anticoagulant test using a standard method or -false-postive serologic test for syphilis
11. Antinuclear antibody *in the absence of drugs known to be associated with a "drug-induced lupus" syndrome*

ACR = American College of Rheumatology; SLE = systemic lupus erythematosus

Table 2. SLICC classification criteria for systemic lupus erythematosus. Requirements of 4 or more criteria (at least 1 clinical and 1 laboratory criteria) or biopsy-proven lupus nephritis with positive ANA or Anti-dsDNA-Ab. Modified from Petri M et al. 2012 (6).

Clinical Criteria	**Immunologic Criteria**
1. Cutaneous Lupus including: Lupus malar rash Bullous lupus Toxic epidermal necrolysis variant of SLE Maculopapular lupus rash Photosensivity lupus rash *in the absence of dermatomyositis* or subacute cutaneous lupus	1.ANA level > laboratory reference range 2.Anti-dsDNA-Ab level > laboratory reference range 3.Anti-Sm:presence of antibody to Sm nuclear antigen 4.Antiphospolipid antibody positivity by any of the following: Positive test for lupus anticoagulant False-positive test result for rapid plasma reagin Medium- or high-titer anticardiolopin antibody level (IgA,IgG or IgM) Positive test for anti-β2-glycoprotein I (IgA,IgG or IgM) 5.Low complement Low C3 Low C4 Low CH50 6.Direct Coomb's test in the absence of haemolytic anemia
2. Chronic cutaneous lupus, including: Classic discoid rash (localized/generalized) Hypertrophic lupus Mucosal lupus Lupus erythematosus tumidus Chillblains lupus Discoid lupus/ lichen planus overlap	
3. Oral ulcers Buccal, Tongue or nasal *in the absence of other cause*	
4. Nonscarring alopesia *in the absence of other cause*	
5. Synovitis or tenderness in joints and at least 30 minutes of morning stiffness	
6. Serositis Typical pleurisy for > 1 day or pleural effusions or pleural rub Typical pericardial pain for > 1 day or pericardial effusion or pericardial rub or pericarditis by electrocardiography *in the absence of other cause*	
7. Renal involvement Urine protein-to-.creatinine ratio (or 24-hour urine protein) representing 500mg protein/24 hours or red blood cell casts	
8. Neurologic involvement Seizures Psychosis Mononeuritis multiplex *in the absence of other cause* Pheripheral or cranial neuropathy *in the absence of other cause* Acute confusional state *in the absence of other cause*	
9. Hemolytic anemia	
10. Leukopenia (<4000/mm^3 at least once) or Lymphopenia (<1000/mm^3 at least once)	
11. Trombocytopenia (<100,000/mm^3 at least once)	

SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus; ANA = antinuclear antibody; anti-ds- DNA-Ab =anti-double-stranded DNA antibody

2.2 EPIDEMIOLOGY

The incidence and prevalence figures are dependent on the method of identification, classification and study (21). In general, studying the entire population is not possible, and the studies are based on samples of the population. The clinical picture of SLE is not always clear at the onset of the first signs of the disease (1). Figure 1 presents early stages in SLE disease process.

The occurrence of SLE is strongly related to gender, race, age at disease onset and socioeconomic class (26,27). Because twin studies on SLE patients have reported a higher concordance in monozygotic contrast to dizygotic twins (28), genetic factors most likely influence the incidence of SLE. SLE is more prevalent in females. About 80-90% of the patients are females (21). This preponderance is already seen in children, although not as strongly as in adults (29). The impact of race on the epidemiology of SLE is hard to separate from socioeconomic factors (27). Age at disease onset varies between races. In people of African- American background SLE is 2-4 more prevalent than in white people and the highest peaks of incidence are seen in females at childbearing age. In contrast, in Europe the highest incidence rates in females are reported after 40 years of age. ANA testing and improved classification criteria enable more precise case ascertainment nowadays (16,27). Division of SLE patients into adults and children by the age differs between studies (30). SLE in children is not as common as in adults, but is more aggressive already at diagnosis (30,31).

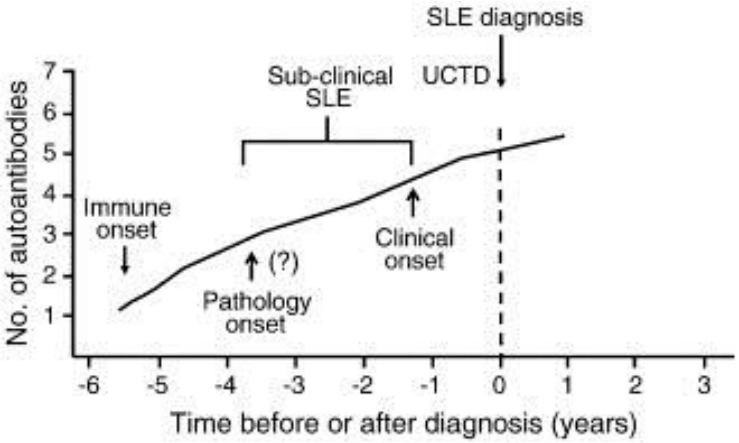


Figure 1. The early stages of systemic lupus erythematosus preceding clinical diagnosis. (Reprinted from Autoimmun Rev 10 (1), Doria et al., SLE diagnosis and treatment: When early is early, p.55-60, Copyright (2010), with permission from Elsevier).

2.2.1 Incidence

2.2.1.1 Meta-analysis of the incidence studies in adult SLE

2.2.1.1.1 Search process, case definition and analysis of incidence SLE studies

A search of all publications concerning the incidence of adult SLE was performed using PubMed and Medline Ovid. All abstracts including data on incidence and SLE were reviewed from 1962 to April 2016. Articles written in English were included. Inclusion criteria for meta-analysis included the articles reporting only one specific rate for incidence for the study period and reliable definition of the disease. The studies reporting incidence rates only by the old method by Fries and Homan were excluded. The present two incidence studies were excluded. Studies were analyzed in three categories according to the classification method used: ACR 97 (A), ACR 82 (B) and others (C) in which the case identification based on the codes of the international classification of diseases 9 (ICD- 9) and 10 (ICD-10) or clinical evaluation. The search process is described in figure 2. As Eilertsen et al reported incidence rate from the earlier years using ACR 82 and from the later years using ACR 97 classification, the study was included in both categories according to the used method (32). Some studies that used several methods in the classification were pooled only into the category A, if the study used also ACR 97 criteria (33-37). Studies using only ACR 82 criteria were pooled into the category B (38). The remaining studies in category C used only clinical and ICD- 9 and 10 disease codes for case definition. Only one study used the latest SLICC criteria for SLE along with ACR 97 classification criteria (34). The case inclusion in the analyzed studies dated between years 1950 and 2014.

Pooled proportions and 95% CIs were computed using random- effects model with the DerSimonian and Laird method. In all meta-analyses, between-study heterogeneity was tested by the Cochran's Q statistic and quantified by the I^2 value. Low heterogeneity was defined as an I^2 value of 0%–25%, moderate heterogeneity as an I^2 of 25%–75%, and high heterogeneity as an I2 of 75%–100%.

2.2.1.1.2 Results of the meta-analysis

The meta-analysis of incidence studies consisted of 41 studies with a total of 38 675 SLE patients (32-72). Sample sizes varied from a minimum of 6 to a maximum of 12 789 SLE patients. The highest numbers of SLE cases were reported in Asian studies (33,63,67,68), studies taking advantage of either medical records or health insurance databases (33,65,67,68,71,72) and the studies identifying SLE cases according to ICD-9 or 10 disease codes (63,67,68,71,72). All analyzed incidence studies showed clear female predominance with 76-93 percentages of female SLE patients (32-72). The mean age at SLE diagnosis was

reported in 19 studies and was 42.4 years (32,35-38,43,44,46,48-51,54-56,58,60,63,66). Incidence studies from Scandinavia showed a higher mean age at diagnosis than other countries (21,51,66).

Figure 3 shows meta-analysis of the incidence rates of SLE according to ACR 97 (A), ACR 82 (B) and others (C). The random effect estimates of incidence rate of SLE were 4.6 (95% CI: 3.8 to 5.48), 3.3 (95% CI: 2.6 to 3.8) and 7.4 (95% CI: 5.7 to 9.0) per 100 000, respectively.

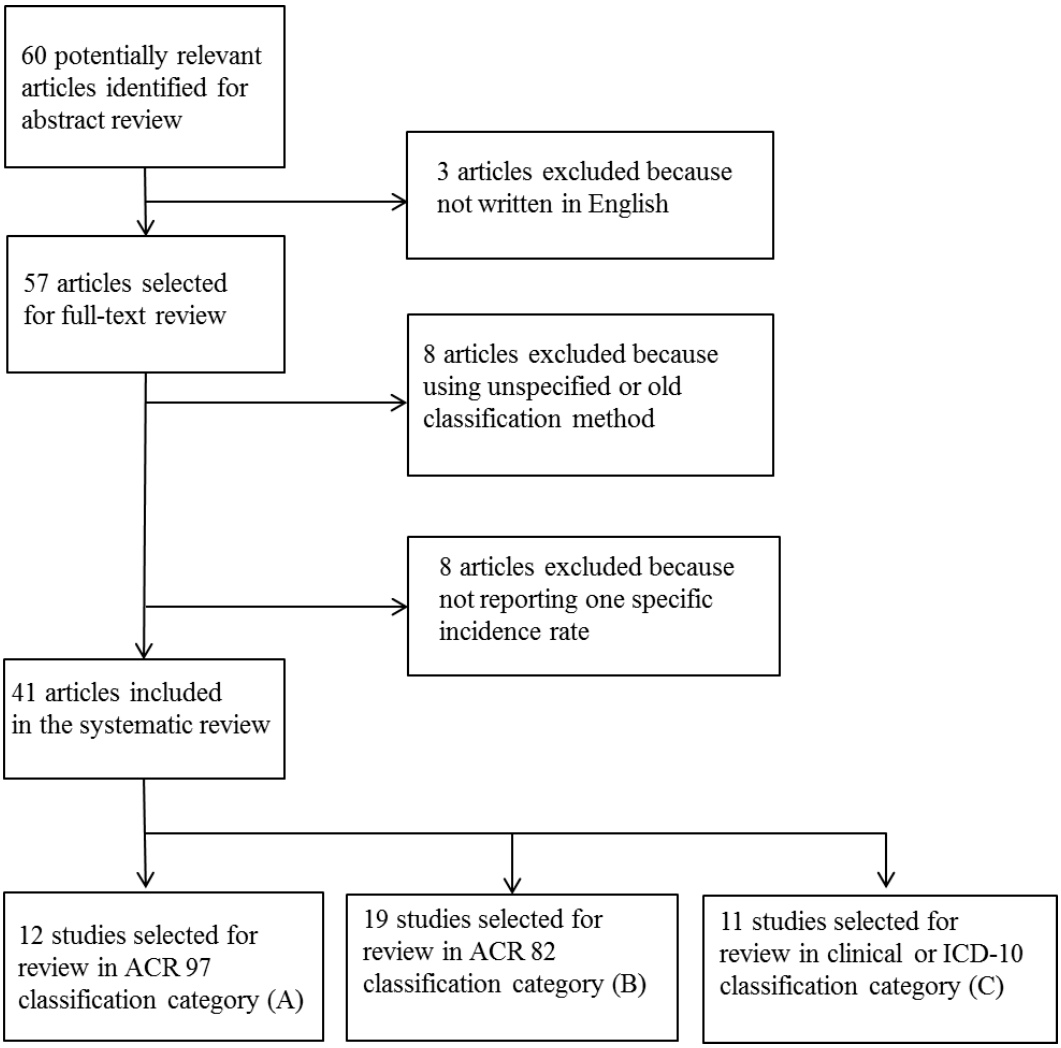
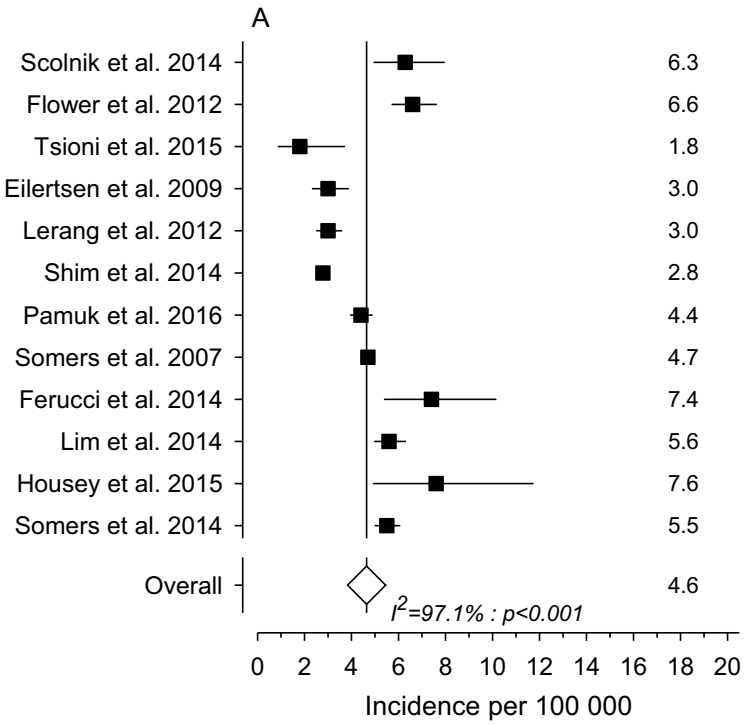
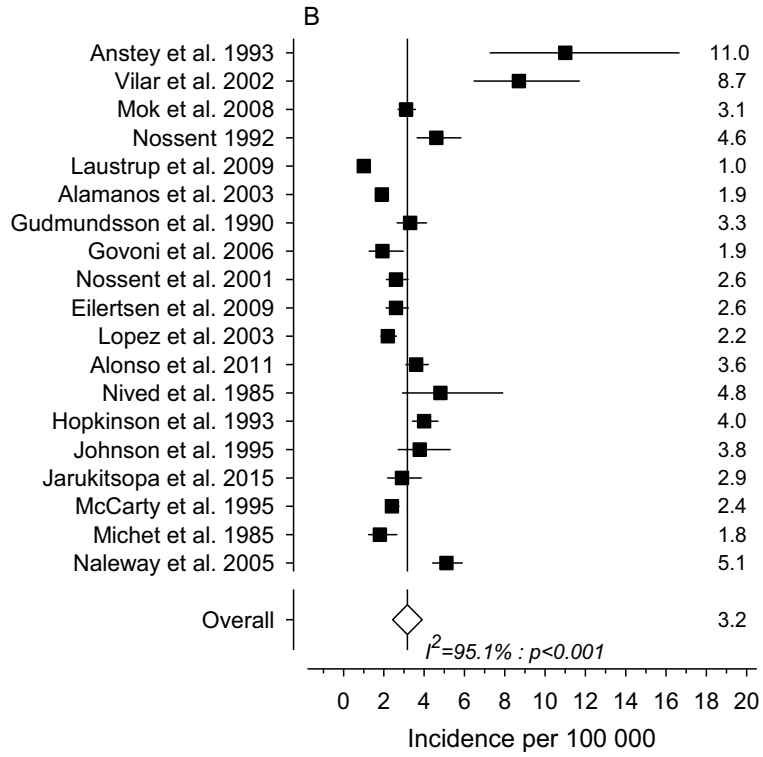


Figure 2. Flow-chart of the meta-analysis on incidence studies in adult SLE

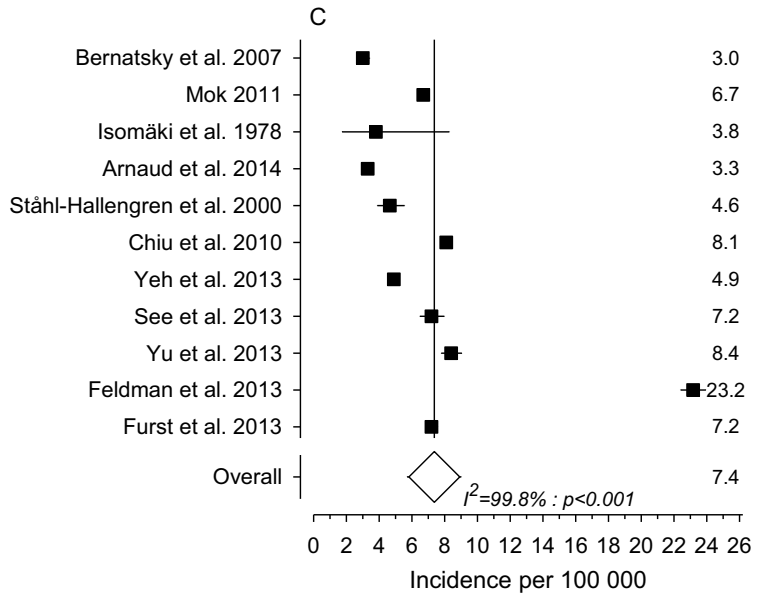
Figure 3. Meta-analysis of the studies on incidence of systemic lupus erythematosus. Results are classified according to the primarily used case identification method: ACR 97 (A), ACR 82 (B) and others (C).



ACR97 Overall 4.6 (95% CI: 3.8 to 5.48)



ACR82 Overall 3.2 (95% CI: 2.6 to 3.8)



OTHERS Overall 7.4 (95% CI: 5.7 to 9.0)

2.2.1.2 Previous incidence studies in Scandinavia

Studies in the Scandinavian countries generally included small numbers of patients, and all the studies represented samples from the population. Few studies have been carried out since the turn of millennium and most of the studies have used old classification methods or clinical evaluation in case ascertainment. The reported incidence rates in the Scandinavian countries range between 1.0 and 4.8/ 100 000 (32,38,42,49,51,53,64,66, 73-76). The one and only previous Finnish study dates back to 1974-75 in Heinola and constitutes of two patient series: a prospective follow-up survey of arthritis and a retrospective case-finding study. The patients were ≥ 16 years of age. The estimated incidence was 3.8/100 000 (64). Table 3 shows a summary of studies performed in the Scandinavian countries.

Table 3. The incidence studies on systemic lupus erythematosus in Scandinavian countries

Country, time period	Incidence per 10^5	Case definiton	Number of cases	Population (%)	Case finding / Age adjustment +/-	Mean age	Author
Denmark, 1980-94	1.1-3.6	ACR 82, method by Fries and Holman	127	387 841 (9%)	HR, physician evaluations, register for autoimmune tests NS	39.2	Voss et al. 1998 (73)
Denmark, 1995-2003	1.0	ACR 82, method by Fries and Holman	109	386 844 (9%)	HR, physician evaluations, register for autoimmune tests NS	38.9	Laustrup et al. 2009 (49)
Denmark, 1995-2011	2.4	ICD-10 + >365 days follow-up	1644	100%	Danish National Patient Registry +	47 median	Hermansen et al. 2016 (76)
Finland, 1974-75	**3.8**	**Clinical**	**6**	**260 000 (7%)**	**HR, physician survey, case finding study NS**	**-**	**Isomäki et al. 1978** (64)
Iceland, 1975-84	3.3	ACR 82	76	239 498	HR, physicians survey -	46.6	Gudmundsson et al. 1990 (51)
Norway, 1978-96	2.6	ACR 82	83	222 403	HR, mortality database -	-	Nossent et al. 2001 (53)
Norway, 1978-95 1996-2006	2.6 3.0	ACR 82 ACR 97	81 58	226 898 (5%)	HR NS	41.7 39.4	Eilertsen et al. 2009 (32)
Norway, 1999-2008	3.0	ACR 97	116	459 535	CTD and cause of death register, rheumatology services, hospital SLE cohort +	-	Lerang et al. 2012 (42)
Sweden, 1981-82	4.8	Preliminary ARA 71, ACR 82	15	156 924	HR NS	39	Nived et al. 1985 (38)
Sweden, 1981-86	4.0	method by Fries and Holman	38	158 572	Prospective follow-up, clinical HR, physician survey NS	40 median	Jonsson et al. 1990 (74)
Sweden, 1981-86 1987-91	4.5 4.8	Clinical	121	172 300	HR, DR, LD +	49 47	Ståhl- Hallengren et al. 2000 (66)
Sweden 1981-2006	3.9	method by Fries and Holman, ACR 82	174	176 460	HR, central laboratory database, diagnosis register +	48.6	Ingvarsson et al. 2016 (75)

NS =not specified, + figures age-adjusted, - figures crude rates, ARA = American Rheumatic Association, ICD = International Classification of Disease, ACR = American College of Rheumatology, CTD = connective tissue disease, HR = hospital records, DR = diagnosis register, LD = laboratory database

2.2.1.3 Comparison of incidence rates of other connective tissue diseases

Many autoimmune connective tissue diseases (CTDs) share similarities in disease presentation and immunology. This may result overlapping between diagnoses. It has been debated that the classification criteria of CTDs do not perform well in separating different CTDs from each other (77). Table 4 shows the comparison of reported incidence rates for other CTDs.

Table 4. Comparison of incidence rates for other connective tissue diseases

Diagnosis Country	Incidence / 100 000	Mean age in years	Time period	Method	Criteria	Author
Idiopathic inflammatory myopathies						
Finland	0.37	-	1990	IRB, HR	Bohan and Peter	Kaipiainen-Seppänen et al. 1996 (77)
Taiwan	0.7 (DM) / 0.4 (PM)	44 (DM) / 49 (PM)	2003-2007	IRB, DR	ICD-9	Kuo et al. 2011 (78)
USA/ Minnesota	0.4 (PM)	59	1981-2000	HR	Bohan and Peter	Wilson et al. 2008 (79)
USA/ Minnesota	0.96 (DM)*	-	1976-2007	CBS	Definitions by Gerami et al for DM	Bendewald et al. 2010 (80)
USA	5.8	-	2003-2008	IRB	ICD- 9	Furst et al. 2012 (81)
Argentina	1.1	-	1999-2009	HMO, HR, LD	Bohan and Peter	Rosa et al. 2013 (82)
Japan	0.99- 1.34	-	2003-2010	RB	Local diagnosis code	Ohta et al. 2014 (83)
New Zealand	0.87	-	1989-2001	HR	Bohan and Peter	Lynn et al. 2005 (84)
USA	4.27, 5.23	-	2004-2008	IRB	ICD-9	Smoyer-Tomic et al. 2012 (85)
Taiwan	1.5*	-	2000-2008	IRB	ICD-9	Yu et al. 2013 (70)
Systemic sclerosis						
Finland	0.37	-	1990	IRB, HR	Criteria by Masi et al.	Kaipiainen-Seppänen et al. 1996 (77)
USA/ Detroit	1.9	52	1989-91	HR, PP, PC	ACR80	Mayes et al. 2003 (86)
Italy	4.3	59.7				Lo Monaco et al. 2011 (87)
Argentina	2.1	66	1999-2004	HMO	ACR80 or LRM	Rosa et al. 2011 (88)
Spain	2.3	-	1988-2006	HR	ACR80 or LRM	Arias-Nuñez et al. 2008 (89)
Greece	1.1	-	1981-2002	HR, PP	ACR80	Alamanos et al. 2005 (90)
Taiwan	1.1	51.3	2002-2007	IRB	ICD- 9	Kuo et al. 2011 (91)
USA	5.6	-	2003-2008	IRB	ICD -9	Furst et al. 2012 (92)
Australia	1.5	-	1993-2002	HR, PP, LD, DR	ACR80	Roberts-Thomson et al. 2006 (93)
Sweden	1.9	-	1998-2010	HCR	ACR80 and ACR/EULAR	Andréasson et al. 2014 (94)
Netherlands	0.89	-	2005-2007	SC, QST	ACR80, LRM	Vonk et al. 2009 (95)

(./..)

Table 4. Comparison of incidence rates for other connective tissue diseases (./..)

MCTD						
Finland	0.84	-	1990	IRB, HR	Clinical + antibodies	Kaipiainen-Seppänen et al. 1996 (77)
Norway	0.21	-	2005-2008	HR	# 4 level definition	Gunnarsson R et al. 2011 (96)
Sjögren's syndrome						
Greece	5.3	55	1982-2003	HR, PP	AES	Alamanos et al. 2006 (97)
USA/ Minnesota	3.9	59	1976-1992	HR	Clinical	Pillemer et al. 2001 (98)
Taiwan	6.0	53/58 F/M	2005-2007	IRB	AES	Weng et al. 2011 (99)
Sweden	3.1	-				Kvanström et al. 2015 (100)
Slovenia	3.9	51.3	2000-2002	HR	EC	Plesivcnik Noljan et al. 2004 (101)

MCTD = mixed connective tissue disease; DM = dermatomyositis; PM = polymyositis; F = female; M = male;
IRB = Insurance register- based; DR = death records; ICD = International Classification of Disease; RB = register- based; CBS = Community- based study; HMO = Health maintenance organization; HR = hospital records; LD = Laboratory database; *included also juvenile patients; PP = Private practice, PC = patient cohort ; ACR = American College of Rheumatology criteria, LRM = Le Roy and Medsger criteria; ACR/EULAR = the proposed American College of Rheumatology- European League Against Rheumatism classification criteria; HCR = Health care register; SC = Study cohort; QST= Questionnaire; # 4 criteria obligatory: clinical diagnosis of MCTD, positive anti-ribonucleoprotein antibody testing, fulfilment of at least one of three of following criteria sets: the modified Sharp's criteria, the criteria of Alarcón- Segovia and Villareal and those of Kasuwaka and exlusion of other connective tissue diseases; AES = American-European consensus criteria for Sjögren's syndrome; EC = European classification criteria for Sjögren's syndrome

2.2.1.4 Incidence of pediatric SLE

SLE is more common in adults than in children. The female predominance is seen already in children (103). The peak of incidence in girls occurs in teenage (104). Practically all studies on incidence in pediatric SLE are in line with each other, showing rates between 0.4 and 0.9 /100 000 (41,61,105-113). The only exception is the incidence study by Lim et al. that found a rate of 2.5/100 000 in Atlanta, presumable reflecting racial differences (114). Table 5 summarizes the available data on the incidence of pediatric SLE.

Table 5. Incidence studies on pediatric systemic lupus erythematosus

Country, years, first author	Incidence per 100,000	Number of cases	Female to male ratio	Age group	Mean age at onset (years)
USA, Baltimore, 1970-77, Hochberg (105)	0.53	10	4.3:1	0-14	-
Finland, 1983-86, Pelkonen (106)	**0.37**	**15**	**4:1**	**0-15**	**13.1 (8-15)**
USA, Southern New England, 1984-92, Denardo (107)	0.4	~6.4	5:1	4.6-22	12.6
Canada, 1991-93, Malleson (108)	0.36	52	6.4:1	0-16	12.1 (3.2-16.8)
Japan, 1984-94, Fujikawa (109)	0.47	906	5.2:1	0-16	-
Austria, 1997-98, Huemer (110)	0.48	6	5:1	0-16	12.4
USA, Wisconsin, 1991-2001, Naleway (61)	0.9	2	2:0	0-19	-
UK, 1992-98, Nightingale (111)	0.73	20	9:1	0-19	-
USA, Atlanta, 2002-04, Lim (114)	2.5 (0.5 White)	31	23:6	0-19	-
Australia, 2009-11, Mackie (112)	0.32	30	4:1	0-15	12.6 (2.8-14.8)
Japan, 1977-2013, Kawasaki (113)	0.34	37	26:11	-	-
Italy, 2009-2012, Tsioni (41)	3.8	2	2:0	0-13	-

2.2.2 Prevalence

In the Scandinavian countries the prevalence rates of adult SLE range between 22 and 85 / 100 000 (38,42,49,51,53,66,73-76,115)). The lowest figures 22-28/100 000 are shown in Denmark (49,73) and 28/100 000 in Finland (116). Earlier Danish studies covered 9% of the entire population and were based on hospital records, physician evaluations and the register for autoimmune tests (49,73). The recent nationwide Danish study used the Danish National Patient Registry and reported higher rate of 45/ 100 000 (76). The only Finnish study from the year 1978 identified SLE patients through nationwide hospital discharge registers (116).

The highest prevalence rates, 42-85/100 000, were reported in three Swedish studies. The first collected patients from diagnosis registers and laboratory databases in the years 1986

and 1991, and the second was nationwide and took advantage of multiple national registries in the year 2010 (66,115). The latest southern Swedish study identified patients from a diagnosis register, hospital records and the laboratory database (75).

Elsewhere, the lowest prevalence figures of 9-21/100 000 since the millennium have been reported from the Eastern European countries and Spain (55,117,118). In contrast, the highest prevalence rate since the millennium, 178/100 000 was from Alaska in the American Indian and Alaska native population (44). A similarly high prevalence rates of SLE, 159/100 000 has been reported in Puerto Rico (119). Prevalence rates of 98/100 000 in Taiwan based on the National Health Insurance Research Database and 65-97/100 000 in the United Kingdom from the Clinical Practice Research Datalink have also bees reported (68,120). In the literature, the spectrum of prevalence rates for adult SLE have generally been reported between 20-70/100 000 (27).

2.3 ETIOPATHOGENESIS

Despite extensive efforts, information on complex pathogenesis of SLE is still sketchy. Immune system dysregulation, genetic, hormonal and environmental exposures have key roles in the etiopathology (2). The mechanisms differ between individuals and even between organs of the same individual. As a consequence of the loss of immunological tolerance, inflammatory cells identify self-antigens as intruders and start the full - spectrum of defense. The pathologic immune process is self-amplifying and proceeds to irreversible clinical disease (8,121).

2.3.1 Genetic factors

Clustering of SLE cases in families reflects the role of heredity in the disease. In Finland, familial SLE was studied in the 1990s nationwide, and 53 families were found with two or three affected family members. Four pairs of twins, including 3 female monozygotic twins, were found. The clinical picture was similar in familial and sporadic SLE patients (122). Genome- wide association studies have demonstrated that genetic susceptibility to SLE is polygenic and only in very few cases related to a defect in a single gene like in complement components of C1q and C4 (4,123,124).

C1q is a starter of the classical pathway and essential in interaction with innate and adaptive immune system. C1q works in the clearance of apoptotic material by opsonizing dying cells. A defect in this gene increases susceptibility to repeated encapsulated bacterial infections. The inheritance is recessive in C1q deficiency, and this rare defect is the strongest known genetic risk factor for SLE (4,124). The resulting disease differs from the

sporadic SLE by earlier age of disease onset, more prevalent oral ulcers and discoid rash and less prevalent arthritis and anti-dsDNA (121,124,125).

Almost 80 genes are so far revealed to be involved in SLE, and about 20 of them are associated with T cell activity. Several of the single-nucleotide polymorphisms (SNPs) are located in noncoding parts of DNA in genes associated with the immune system (126,127). The candidate genes have been divided into four groups by the molecular function of the genes concerned: lymphocyte activation (HLA DR, STAT4, PP2A), innate immune signaling (NF-κB activation, IFN signaling), immune complex clearance (DNAase1, TREX1) and others/intrarenal signaling (ACE, KLK). Some of the genes may have many roles (123,128). Moreover, in most patients, interferon (IFN) -targeting genes are distinctly overexpressed in peripheral blood cells, forming a so- called IFN signature (129).

2.3.2 Environmental factors

2.3.2.1 Epigenetics

Epigenetic mechanisms influence gene function by regulating DNA accessibility and gene expression in a reversible way without changes in the nucleotide sequences. They are suggested to connect genes and environment in the disease process (130). Dysregulated epigenetic mechanisms in SLE consist of DNA methylation, histone modifications and noncoding RNA (126,131). The first two mechanisms modulate the chromatin in either a facilitating or averting manner at the time of transcription. In contrast, microRNAs work post-transcriptionally in gene silencing (126). Hypomethylation of DNA especially in CD4+ T cells leads possibly through type I IFN release to overproduction of IgG by B cells and global activation of transcription and disease (126,130). Sun exposure with ultraviolet radiation, procainamide and hydralazine may also result in impaired DNA methylation. The aforementioned drugs are related to drug-induced lupus syndrome (2,126). Biochemical changes in histones may have a role in the pathogenesis of SLE especially in CD4+ T cells in SLE patients (132). A decreased amount of microRNA miR-146a in genes IRF5 and STAT-1 has been found in SLE patients. This is the type of microRNA that prevents expression of type I IFN, and decreased miR-146a increases levels of type I IFN. Estrogen has a role in expression of certain microRNAs like downregulation of miR-146a and upregulation of miR-223. Moreover, microRNAs interplay in maturation and action of regulatory T cells (Tregs) (133).

2.3.2.2 Sun exposure

Ultraviolet (UV) exposure can exacerbate pre-existing SLE disease (134). In a small Finnish study, the disease activity scores by European Community Lupus Activity Measure (ECLAM) test were greater during spring and summer compared to winter season (135).

In a Swedish retrospective case-control study females with type I/II sun-reactive skin (always burn, never/sometimes tan) had 2.9-fold increased odds for future SLE compared to females with other skin types. Being more than once seriously sunburnt was related to increased risk for developing SLE (136). Other studies have focused on occupational sunlight exposure with mixing results. A Canadian case-control study found a connection with the development of SLE in those persons that had an outdoor work preceding 12 months before disease onset (≥20h/week, ≥2months/year). However, the total amount of sun exposure in years did not increase the odds for SLE (137). On the contrary, a large population-based study on recent SLE, which measured cumulative months of sun exposure in work, did not find an increased risk for SLE. Yet, Caucasians with the glutathione-S-transferase-M1 (GSTM1) null genotype and ≥24 months of sun exposure in work had an over 3 times higher risk for SLE (138).

Experimental studies support the role of UV exposure in the pathogenesis of lupus. UV radiation effects on the regulation of Th1 and Th2 cells and production of Tregs leading to the increase of IL-10. Especially UV-B causes apoptosis by several mechanisms, including reactive oxygen radicals (139). When patients with cutaneous lupus erythematosus (CLE) were predisposed to a single dose of UV-A (60-100J/cm^2), a significant accumulation of apoptotic material was detected in skin biopsies after 3 days of exposure compared to healthy controls. Yet, one day's of exposure, resulted in no difference. The increased dying cells, indicated ineffective apoptosis in the CLE patients (140).

2.3.2.3 Life style manners and exposure at work

Many studies have demonstrated an increased risk for SLE in current smokers. In a Japanese study, the risk was dose -dependent – the higher the exposure of cigarette smoking the greater the probability of future SLE. Mild or moderate alcohol consumption seems to slightly protect against SLE (136,141). A large matched-control cohort study suggested a higher risk of SLE in persons with sleeping difficulties (142). Work-related exposure to crystalline silica, mercury, poultry processing and mixing pesticides may increase the odds for future SLE (143,144).

2.3.2.4 Vitamin-D levels

There is increasing evidence for the role of vitamin D in the immune system. Possible immunomodulatory effects are diverse. Low levels of vitamin D have been measured in many SLE patients and are also related to disease activity (145). Calcitriol is an active form of vitamin D. It has shown to prevent antigen presentation, differentiation of monocytes into dendritic cells and expression of HLA class II, CD40, CD86 and IL-6. Vitamin D also

works as an inhibitor in production of antibodies (146,147). One study found that with higher vitamin D levels, the likelihood to develop autoimmune disease was lower (148).

2.3.2.5 Drugs

Some drugs may cause a condition similar to SLE. The clinical picture and immunological profile of the adverse reaction varies greatly according to the causative drug. Certain drugs either reveal the underlying SLE or create as a rule reversible drug-induced lupus (DIL). There are no diagnostic criteria for DIL. No history of earlier SLE, enough exposure to the drug, minimum one symptom of SLE and quick recovery after ending the exposure to drug has been proposed as guidelines (149,150). An increased erythrocyte sedimentation rate (ESR), hematological cytopenias, homogenous ANA and antihistone antibodies are common in DIL (150). Over 80 drugs are connected to DIL. The most reliable associations for DIL have been demonstrated with hydralazine, procainamide, isoniazid, methyldopa, quinidine, minocycline and chlorpromazine. Anti-TNF-α therapy may rarely induce lupus-like syndrome (149,150).

2.3.2.6 Infections

Lupus patients are susceptible to infections due to many deficiencies in the immune system, immunosuppressive agents, disease activity and permanent organ damage (151). Furthermore, many viral and bacterial infections have been suggested to influence the pathogenesis of SLE. The potential role of Epstein-Barr virus (EBV) has been justified by the similarities of certain EBV proteins with SLE self-antigens and autoantibodies, which can cause cross-reactivity and therefore induce SLE. Secondly, EBV has an ability to stimulate development of B cells after infection (152). Human parvovirus B19 may also mimic and possibly aggravate SLE disease (153). It has been proposed that endogenous retrovirus (ERV) proteins create a link between genetically predisposed individuals and infection viruses (like EBV) in development of lupus. As ERVs are integrated into the human genome, they are safe from immune defenses. These genes accumulate in the process and in the end together with infection viruses trigger synthesis of ANA, anti-DNA antibodies and type I IFN. Viral DNA or RNA stimulates type I interferon gene transcription through pattern-recognition receptors like TLRs (153,154).

2.3.3 Gender and sex hormones in SLE

As SLE occurs predominantly in females, the possible mechanisms behind the predisposition to develop the disease are under abundant ongoing research. The incomplete inactivation of the second X chromosome has been suggested to impact on disease pathogenesis. The role of the second X chromosome is supported by the observation that individuals with Klinefelter's syndrome (47,XXY) have 10 times more

frequently SLE compared to males with normal genotype 46, XY (155). It has been hypothesized that excess active X- chromosome leads to double the amount of X- encoded proteins. The X- chromosome contains many possible risk genes for SLE, like IRAK1 encoding a protein kinase involved in IL-1 signaling, FoxP3 important in transcription of Tregs, TLR 7 encoding toll-like receptor (TLR) 7, essential in innate immune response, and CD40 ligand, which is a costimulatory molecule on the T cell surface (155,156). At the moment, the X chromosome is known to contain 113 microRNAs, while 2 microRNAs have been found in the Y chromosome. Some of these microRNAs in X chromosomes like miR-223 and miR-106a have key regulatory roles in innate immunity (157).

The literature on sex hormones in SLE (estrogen, progesterone, prolactin, testosterone and dehydroepiandrosterone) suggests many possible theories behind the excess prevalence in females and increased disease activity (155,158,159). Estrogen is essential in immunology, and estrogen receptors can be identified in cells central in the immune response. In some studies, polymorphism of estrogen receptor α has been connected into the pathogenesis of lupus (157,159). Otherwise the age of menarche, irregular menstrual cycles, total years of menstruation, surgical and early menopause have been correlated with the risk for SLE. It has been suggested that the changes in the levels of the sexual hormones may predispose to SLE (115,155). Prolactin and estrogen participate in maturation of DCs from monocytes (158,160). Activation of monocytes is higher in females than in males and further activated in SLE females than in healthy females. Monocytes are the most important source of pro-inflammatory cytokines like IL-6 in SLE (158). Whereas estrogens have been proposed to increase the probability of future SLE, androgens may decrease the risk (155).

2.3.4 Immunological mechanism

2.3.4.1 General aspects

Characteristic for the disease is a wide dysregulation of the immune system. Both the innate and adaptive immune system are activated, and there is an increased production of cytokines like IFN- α, IL-17, IL-6 and IL-21, the breakdown of tolerance in B and T cells causing activation of autoreactive B and T cells and further strengthening inflammation, overexpression of antigen presenting cells (APCs), overproduction of autoantibodies, e.g. anti-dsDNA- antibodies, development of immune complexes (ICs) in the milieu of excess autoantigens and autoantibodies, activation and deficiency of the complement system, increased apoptosis and endothelial activation (3,161,162). Figure 4 demonstrates the immunopathology of SLE.

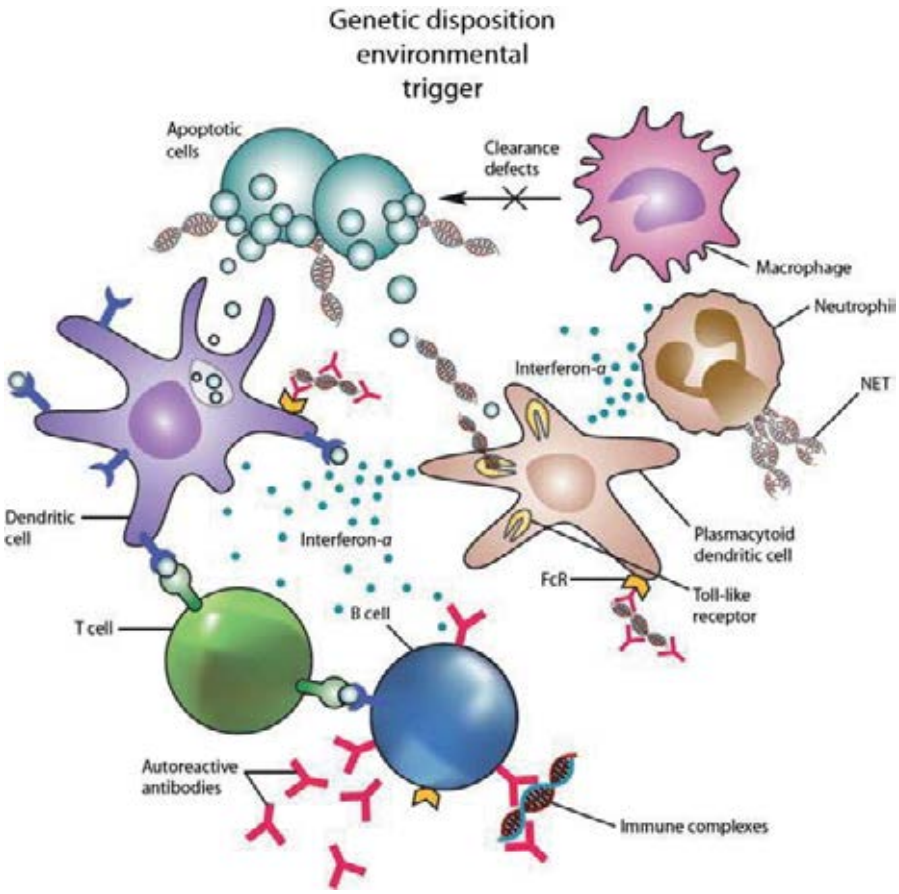


Figure 4. Schematic view of the pathogenesis in systemic lupus erythematosus. (Reprinted from Autoimmun Rev 12(5), Luijten et al.,The use of glucocorticoids in systemic lupus erythematosus after 60 years still more an art than science, p.617-628, Copyright 2013, with permission from Elsevier).

2.3.4.2 Failure in tolerance in B- and T- cells

At the moment it is believed that besides the overload of apoptotic material, dendritic cells (DCs) have a crucial role in the loss of immune tolerance. They work as APCs and in controlling T and B cells (163). Inactive DCs maintain immune tolerance in the presence of self-antigens. Apoptotic material and processed chromatin can stimulate myeloid DCs (mDCs) through overexpression of the co-stimulatory molecules CD40 and CD86 (essential for T cell proliferation) and pro-inflammatory cytokines like IL-6, IL-1β, and TNF α (162,163). The immune stimulatory milieu further triggers autoreactive T cells to act and excrete cytokines IL-2, IL-17 and IFN-γ (164). Especially mDCs include a variety of TLRs essential in innate immune signaling (163). TLRs are adherent also to B cells (165)

and plasmacytoid DCs (pDCs) (2). Plasmacytoid DCs are able to produce large amounts of type I IFN, which further leads to stimulation of both B and T cells and differentiation of B cells into plasma cells responsible for antibodies (162,163,166). Type I IFN made by pDCs also promotes DC maturation. Stimulated DCs are impaired in regulation of proliferating Tregs and autoreactive T cells (163). Also the balance of IL-2, IL-6, IL21, IFN-γ and IL-17 affects whether naive T cells develop into pro-inflammatory (Th17, Th1) or suppressive cells (Treg) (162,165). Circulating immune complexes are able to trigger pDCs through TLR-7/9-signalling, leading to overproduction of IFN α. Both IFN α and ICs can induce NETosis. Neutrophil extracellular traps (NETs) on the other hand, promote further IFN α production in pDCs (162,164). The excess IFN α promotes maturation of mDCs to assist self-reactive B cells in epitope shifting and autoantibody synthesis (164). B lymphocyte stimulator (BLyS) and IL-17, which are abnormally abundant in SLE patients, influence the stage where self-reactive B cells should at the latest to be destroyed (2,134,167).

2.3.4.3 Autoantibodies in SLE

The presence of autoantibodies especially against structures of the nucleus is a diagnostic hallmark of the disease. ANAs are a defined category of antibodies directed to cytoplasmic and nuclear antigens. These self-antigens interplay with ANAs in steps of gene expression and the cell cycle and cause tissue damage through damage to proteins in the cell frame and inflammation. Over 100 different ANAs are found in SLE patients, and they precede disease onset sometimes by years (161,168,169). The intracellular self-antigens are normally unachievable, but due to different ways of cell death they become accessible to the immune system (162,164).

Anti-dsDNA Abs are one of the most specific antibodies in SLE, but not that sensitive since they fluctuate and can be detected in approximately 50-60% of SLE patients (168). They precede the disease and are related to the pathogenesis of lupus. The pathogenicity of dsDNA Abs is multifactorial, but the main things involved are high affinity to antigen, stimulation of complement by IgG, and binding to Fc receptors (161,162,170). Increased levels of anti-dsDNA antibodies indicate activation of disease and are found also in target tissues (168,170). They are associated with lupus nephritis, lupus dermatitis and certain forms of neuropsychiatric lupus (162).

Anti-Smith (anti-Sm) antibodies in high titers are specific antibodies in SLE. They are present in 5-30 % of SLE patients and appear approximately 1.5 years before the clinical disease. The occurrence of these antibodies is higher in Black Americans than in Caucasians. A subgroup of antibodies, anti-SmD1, is closely related to lupus nephritis. It is not clear whether titer fluctuations reflect disease activity (168,171).

Antibodies against ribonucleoprotein (anti-RNP) often coexist in myositis and Raynaud's phenomenon. The value of anti-Ro and anti-La antibodies in lupus is not entirely clear. Anti-La occurs commonly in combination with anti-Ro. Anti-Ro antibodies are recorded in about half of SLE patients. They are present practically in every mother carrying a child with neonatal lupus, which is a critical situation in a new born, and may include cytopenias, skin manifestations, hepatitis, and autoimmune-mediated congenital heart block. Both these antibodies are common in Sjögren's syndrome among others and are therefore not specific to SLE (168).

Anti-ribosomal P protein antibodies have the ability to intrude into living cells and engage with T cells, monocytes, neurons, and hepatocytes. In that way they stimulate pro-inflammatory cytokine production, leading to inflammation and tissue damage. Anti-ribosomal P protein antibodies in SLE are related to liver, kidney and neuropsychiatric involvement, and their level correlates with disease activity (168,172).

Antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin and β-2-glycoprotein are closely, although not specifically related to SLE. Characteristic of these antibodies is an increased risk of thrombosis, miscarriage, preterm delivery, pre-eclampsia and antiphospolipid syndrome (168,173,174).

Autoantibodies against different players of complement have been found. C1q- antibodies are not disease-specific, but can be measured in proliferative lupus nephritis. The raise in titer predicts activation of the disease (175). Autoantibodies targeting histones have also been detected in lupus and their level may have some prognostic value concerning disease activity (168).

2.3.4.4 Complement system and immune complexes

The complement cascade has a crucial importance in the normal innate immune system, but complement also works as a link to the adaptive immune system by stimulating B and T cells. Almost all complement components are found in plasma, which allows measurement of the crucial components (C3,C4) as markers of disease activity. For the same reason complement system is exposed to autoantibodies. The complement cascade can be turned on by several factors like immune complexes, autoantibodies and the general Fcγ-receptor-mediated immune reaction. Although the complement system initially prevents onset of lupus, after a certain point of the disease process, it fortifies the pathogenic process (125,176,177). Autoantibodies engage with self-antigens and create ICs (178). The most important task of complement is the clearance of apoptotic material and ICs. Disturbance in this work leads to overexposure to self-antigens served to B cells, accumulation of apoptotic mass and deposition of ICs into vascular beds. This further

exacerbates local inflammation and results in long-term vasculitis or organ damage (125,178). The deposition of ICs is in particular seen in the glomerular capillary bed during lupus nephritis (134). In the normal development of B cells, in order to achieve negative selection for self-reactivity, complement supplies self-antigens to immature B cells. It has been suggested that deficiency in the complement level is partly behind the breakdown of tolerance in SLE (125,176).

2.3.4.5 Apoptosis and NET formation

Cells mainly die by necrosis or apoptosis. Necrotic cell death starts by a sudden mechanical, physical, or chemical event and continues by a cascade with rapid metabolic changes, swelling of cytoplasm and finally cell rupture. Emancipated intracellular material causes local inflammation (178). Apoptosis, on the other hand, is a programmed process, which can be initiated by external (like Fas ligand binding into its receptor) or internal (for example by DNA damage) causes. During the process there are many chromatin structure alterations like cleavage by proteases, caspases, and endonucleases, citrullination and methylation (164,178,179). As apoptotic cells loose integrity of cellular membrane, they may release intracellular material for self-antigens (140). Inefficient function of complement, DNase I in serum, DNase II in lysosomes of phagocytes, and other disorders in phagocytosis and signaling lead (140,178) eventually to gathering of dying cell debris into apoptotic blebs, and also secondary necrosis. The unrecognized modified nuclear components are interpreted as intruders, causing an alarm signal (164,178,179). In SLE, apoptosis is accelerated, and more importantly clearance of apoptotic material is deficient (177,179).

Lately, a new form of cell death has been detected concerning mainly neutrophils, called NETosis (128). In the process, NETs including also chromatin components are emancipated outside the cell, which is thought to accelerate IFN secretion and the autoimmune process. In SLE patients NETs are created more abundantly and clearance is worse than in healthy individuals partly due to impaired activity of DNase 1 (128,164). The fibers of the NETs are partly responsible for the increased thrombosis. In addition, NETs may induce endothelial damage (3).

2.3.4.6 Atherosclerosis in SLE

Atherosclerosis in SLE patients, although not fully understood, is different and more robust from the earlier known disease process (180). Immune responses in SLE itself and in atherosclerotic process share similarities. In both processes there is a loss of tolerance either against oxidized LDL cholesterol antigens or self-reactive antigens, sterile inflammation and imperfect clearing of apoptotic material (3). The recent data highlights

the role of neutrophils. Low- density granulocytes, known to be more prevalent in SLE patients, are more potent in developing NETs, which in turn initiate IFN 1-mediated immune responses, through the activation of matrix metalloproteinase 9 (MMP-9) promote cytotoxic endothelial injury and may induce thrombosis (3,181). Stimulated oxidative enzymes released from NETs have the ability to change protective high density lipoprotein (HDL) cholesterol into proatherogenic and proinflammatory forms (181). Type 1 IFN disturbs the function of vascular repairing cells like endothelial progenitor cells (EPCs) and enhances the accumulation of lipids into monocytes and macrophages, and in that way also formation of excess foam cells. Moreover, type 1 IFN prevents CRP upregulation, which results in poor predictive value of CRP in dysregulated lipid synthesis and inflammation of SLE (3,180).

When IFN α stimulates Th1 CD4+ cells inside the plaque, it comes more unstable and vulnerable to rupture (180). Tregs, which could theoretically control the inflammation, are few in number in SLE patients (3, 182). In SLE patients T cells are also more likely to be activated in response to lower stimuli than in the normal population, and the overexpression of certain co-stimulatory molecules like CD40 ligand is more abundant. Signaling through the CD40 ligand is involved in interplay with B cells and in atherosclerosis (3).

2.4 DISEASE COURSE

2.4.1 Clinical picture

The clinical spectrum of SLE is wide and differs between individuals. Typically, active and quiescent phases fluctuate along with disease flares (27). Fatigue is characteristic, affecting over half of the patients and not necessarily correlating with disease activity (183). Fever is often seen at onset, but also in later active stages (104). Skin and mucocutaneous involvement are very common, and their different features are explained with more details in the SLICC classification criteria (6). Erythematous malar rash is a typical diagnostic and acute hallmark of the disease (184). Discoid lupus, on the other hand, is a chronic and specific sign of the disease. The centrum of this lesion may be scarring in older manifestations (185). Sun light may trigger SLE, especially skin lesions (16).

Musculoskeletal involvement is very common and comprises of arthralgia, arthritis, avascular osteonecrosis and myalgia, but very infrequently myositis. Arthritis is typically non-erosive and non-deforming (183), except in Jaccoud's arthropathy, which can be seen in 5% of patients. Typical presentations are swan neck and thumb subluxation, ulnar deviation and hallux valgus (186). Erosive arthritis (mainly in the wrists and hands) is uncommon (183).

Serositis is common and can manifest as pleurisy or exudative pleural effusion, pericarditis, or peritonitis (6, 181,187). Pericarditis is the most common primary cardiac manifestation (11%). Conduction disorders, arrhythmias, myocarditis, valvular dysfunction and endocarditis are seen more seldom (188). Besides pleurisy, other pulmonary manifestations may include alveolar hemorrhage with cough and hemoptysis, pneumonitis, pulmonary hypertension and shrinking lung syndrome with dyspnea (189,190).

Renal involvement is ordinary along the disease course, but the symptoms can be silent until nephrotic syndrome or renal failure (191). Signs of the renal disease are proteinuria, microscopic hematuria, increasing anti-DNA and anti- C1q antibody levels, and low complement C3 level (192,193). Renal biopsy is needed for the classification of lupus nephritis. The International Society of Nephrology/ Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis is shown in the Table 6 (194).

Table 6. International Society of Nephrology/ Renal pathology Society (ISN/RPS) 2003 classification of lupus nephritis Modified from Weening et al. 2004 (194).

Class I	**Minimal mesangial lupus nephritis** Otherwise normal glomeruli, but mesangial immune deposits by IF
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by LM, with mesangial immune deposits
Class III	**Focal lupus nephritis** Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations *Subclassification according to the activity of lesions (A, A/C, C)*
Class IV	**Diffuse lupus nephritis** Active or inactive diffuse, segmental or global endo-, extracapillary lomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. *Subclassification into segmental (IV-S) lupus nephritis when ≥50% of the glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Subclassification also according to activity of lesions (A, A/C, C)*
Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits or their morphologic sequelae by LM and by IF or electron microscopy, with or without mesangial alterations *May occur in combination with class III or IV* *Shows advanced sclerosis*
Class VI	**Advanced lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

IF = immune fluorescence; LM = light microscopy; A = active lesions; A/C = active and chronic lesions; C = chronic lesions

Cytopenias are common and incorporated in the classification criteria (6,25). One of the initial marks can be leukopenia (181,195), which can be seen almost in half of the patients. Leukopenia can appear as neutropenia, lymphopenia or as a mixture of them (196). Leukopenia or rather lymphopenia can reflect active lupus. Anemia may result from different reasons: chronic inflammation, bleeding, secondary reasons, or drug toxicity. The most severe form is autoimmune hemolytic anemia (AIHA), which is mostly the warm type disease (197). Hemolytic anemia, pancytopenia and antiphospholipid antibodies may be accompanied by thrombocytopenia. Thrombocytopenia can also occur independently, presumably due to anti-platelet antibodies (198).

Antiphospholipid antibodies have a crucial role in increased rate of thrombosis, neurological manifestations and complicated pregnancies (168,199,200). Neuropsychiatric involvement is multidimensional. Patient may have headache, cognitive problems, depression, anxiety, paresis, seizures or psychosis. Nervous system manifestations with estimated prevalences are presented in table 7 (201).

Table 7. Neuropsychiatric manifestation of lupus and estimated prevalences. Modified from Voss et al. 2012 (201).

PNS/muscle		**CNS**	
Manifestation	**Prevalence**	**Manifestation**	**Prevalence**
Polyneuropathy	5-22 %	Cerebrovascular disease	2-39 %
Cranial neuropathy	2-7 %	Seizures	16-84 %
Guillan Barré syndrome	Rare	Aseptic meningitis	Rare
Plexopathy	Rare	Demyelinating syndrome	Rare
Mononeuropathy	3-8 %	Movement disorder	Rare
Autonomic disorder	Rare	Acute confusional state	7-13 %
Myastenia gravis	Rare	Anxiety disorder	5-24 %
		Headaches	11-57 %
		Myelopathy	Rare
		Cognitive dysfunction	5-43 %
		Mood disorder	12-51 %
		Psychosis	5-22 %

PNS = peripheral nervous system; CNS = central nervous system (Modified from Voss E et al. 2012)

Pregnant patients experience frequent miscarriages, fetal losses, preeclampsia, and premature births (16). From the fetal perspective SLE may predispose to restricted growth and neonatal lupus along with congenital heart block (202).

Gastrointestinal (GI) manifestations are commonly seen (50%), but the symptoms are mostly moderate. Patients may complain of nausea, anorexia, and abdominal discomfort or pain (203). The spectrum of GI involvement is wide, including esophageal disease, gastric involvement counting peptic ulceration, mesenteric vasculitis and thrombosis, serositis, inflammatory bowel disease, pancreatitis, hepatitis, and hepatomegaly (204). The

occurrence of intestinal vasculitis is highest in patients with active SLE associated with abdominal pain. These patients may suffer from mild to severe pain, vomiting and bleeding (203).

2.4.2 Assessment of SLE

The EULAR recommendation for SLE monitoring consists of 10 domains: patient assessment, evaluation of cardiovascular risk factors, other comorbidities (cancer, osteoporosis), evaluation of infections and their risk, frequency of monitoring, recommendations for laboratory tests, evaluating mucocutaneous lesions, kidney manifestations, neuropsychiatric involvement and eye monitoring. Patient assessment should include evaluation of organ involvement at least once a year, assessment of quality of life at each visit either by interview or by patient global scale, observing comorbidities and drug toxicity and measuring of disease activity by a validated indicator in every visit. At onset of disease the recommended autoantibodies to monitor are ANA, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm, anti-phospholipid and in addition complement components C3 and C4. Patients with stable disease should be monitored in every 6-12 month visits for complete blood count, urinalysis, creatinine or glomerular filtration rate, serum albumin, urine protein/creatinine ratio, ESR, C- reactive protein and safety laboratory tests according to the current therapy (205).

2.4.3 Measures for the disease activity, damage and treatment response

Persistent disease activity over time may lead to permanent organ damage in lupus (206). Sorting permanent damage out of the disease activity is also essential and affects the selection of therapy (207). Many specific tools are available to assess disease activity in lupus: the British Isles Lupus Assessment Group (BILAG), Systemic Lupus Activity Measure (SLAM), European Community Lupus Activity Measure (ECLAM) and the SLE Disease Activity Index (SLEDAI) (208-211). The accumulation of damage can be quantified objectively by the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI). It collects information on especially irreversible organ damage since the SLE diagnosis. SLE-associated damage has been related to higher age in adults, younger age in children, longer disease course, certain ethnicity (African, Hispanic, Chinese), frequent flares, presence of antiphospholipid antibodies, immunosuppressive therapy, and daily prednisolone doses over 7.5 mg (206,212). The SLE Responder Index (SRI) is the most used index in randomized controlled trials (RCTs) for quantifying treatment response (213).

2.5 TREATMENT

2.5.1 Immunotherapy

As SLE is a heterogeneous disease with multiple and fluctuating manifestations, and still not fully understood immunopathology may differ between SLE patients and target organs, there are difficulties to elaborate therapy that serves every patient (214). Although some guidelines have been established, the therapy must always be individualized, and several things concerning disease process, prognostic factors, side effects, fertility, interactions and economics have to be evaluated carefully (215-218). The adherence to a long-term drug therapy has an impact on treatment results (219). So far, the drug treatment of SLE has been from the glucocorticoids era (214).

2.5.1.1 Glucocorticoids

Glucocorticoids (GCs) are essential in the therapy of SLE due their ability to work regardless of the target organ (216,220). GCs are lipophilic, and move effortlessly across cellular surface into cytosol and proximity of nucleus (220). They act mostly as a complex with a GC receptor either through a genomic or more rapid non-genomic pathway (221). The main immunomodulatory and anti-inflammatory properties are expressed mainly by the genomic pathway (220). After the drug is bound to specific GC receptor, the gene expression is either inhibited with suppression of pro-inflammatory molecules or stimulated. The latter process lies behind unwanted adverse effects of GCs like osteoporosis and metabolic disturbances (221). In SLE, GCs can be administrated orally, with intra-articular injection, topically or intravenously (222,223). Wide profiles of side effects of GCs which increase along with the accumulative dose expose patients for premature co-morbidities and restrict their use. GCs can predispose patients among other things to hypertension, obesity, osteoporosis and osteonecrosis, cataracts, hyperglycemia, infections, insomnia, psychological, and mood disorders (221,224). The efficacy of CGs is best documented in lupus nephritis although they are widely used with other organ involvement. Intravenous methylprednisolone pulses are justified in life-threating exacerbations. There is a lack of high-quality randomized controlled trials (RCTs) evaluating GC dosing in different manifestations. At the moment the clinical decisions are made more in an experimental than an evidence-based manner (223).

2.5.1.2 Hydroxychloroquine

Hydroxychloroquine (HCQ) belongs to the antimalarial drug group along with chloroquine. HCQ has replaced chloroquine due to a less toxic profile. Antimalarials (AMs) have a good safety profile and multiple advantageous influences in SLE and are therefore considered as a standard therapy for SLE (225). Their exact mechanisms of action

are not clear. It has been suggested that AMs suppress the processes in self-antigen presentation and toll-like receptor signaling (TLR3, TLR7 and TLR9) by interfering lysosomal stability (226). AMs have also a role in decreasing the synthesis of IL-1 and IL-6 in monocytes and macrophages (227).

The daily oral dosage of HCQ is 200-400mg and at maximum of 6,5mg/kg. There is an option to follow adherence to medication by measuring HCQ blood concentration (228). Side effects are usually mild, abdominal or skin symptoms and headache. Regular ophthalmologist visits are recommended after five years of cumulative therapy to detect possible drug-induced retinopathy, which is normally reversible (227). HCQ is beneficial for pregnant SLE patients in order to maintain remission and potentially to avoid fetal cardiac complications (229,230).

HCQ has a clear protective effect on disease activity (225). A Canadian double-blind RCT demonstrated a significant increase in disease activity during a half year period among those SLE patients who received placebo instead of HCQ (231). Moreover, HCQ is shown to improve survival in SLE (225). A case-control study on multiethnic LUMINA cohort of 244 SLE patients confirmed the protective effect of HCQ on survival with odds ratio 0.32 (232). In addition, HCQ has potential, favorable influences on lipid profile (225), thrombosis (233), lupus nephritis (27) and damage accrual (234).

2.5.1.3 Cyclophosphamide

Cyclophosphamide is a prodrug for active cytotoxic alkylating metabolites. It targets both proliferating and resting lymphocytes and inhibits DNA replication (235). It has a robust, well-documented role in treatment of severe SLE, especially lupus nephritis (216). Accumulative doses increase toxicity (13). Infections and malignancies, myelotoxicity, infertility and hemorrhagic cystitis are the most striking adverse effects (13,216). The drug can be administrated either orally or intravenously. Mesna and appropriate liquefaction are recommended at time of cyclophosphamide pulse therapy to avoid toxicity in the urinary bladder (216). Cyclophosphamide is teratogenic and contraindicated for pregnant patients (13).

Treatment of lupus nephritis with cyclophosphamide is widely studied. Earlier data has revealed that cyclophosphamide is more efficient than GCs alone in achieving remission (236). On the other hand, intravenous cyclophosphamide is suggested to be better tolerated than the orally administered drug (237). Optimal dosing is under discussion. In a multinational RCT on lupus nephritis 90 patients were allocated to receive either high-dose or low-dose cyclophosphamide. Induction therapy was followed by azathioprine up to 30 months after entering the study. The remission rates were equal (238).

2.5.1.4 Methotrexate

Methotrexate (MTX) is a folate antagonist, which inhibits competitively dihydrofolate reductase and thus possibly blocks de novo pyrimidine and purine production crucial for RNA and DNA. This action further limits development of lymphocytes (239,240). Due to this feature MTX was designed originally as anti-tumor therapy (241). Although the precise mechanisms of multiple anti-inflammatory effects are not known, it has been suggested that a crucial part of immunosuppression is mediated via an increased release of adenosine. MTX has an inhibitory effect on certain central pro-inflammatory cytokines like IL-1, IL-6 and TNF-α. It may also promote apoptosis in T cells (239,240). MTX is administered either orally, subcutaneously or intramuscularly up to 25mg once a week, and folic acid substitution is preferred in order to avoid side effects. The most common of those are gastric, hematological, and hepatic symptoms (13,216). MTX is contraindicated for those planning pregnancy or carrying a child (13).

MTX has a well-documented efficacy alone and in combination therapy in rheumatoid arthritis (239,242). In contrast, evidence concerning use of MTX in SLE is almost lacking. There are two double-blind placebo- controlled RCTs with a limited number of non-renal SLE cases (243). The first double-blind PCB RCT in SLE showed significant improvements in disease activity (SLEDAI), joint pain (VAS) and lower glucocorticoid doses with MTX 15-20mg per week for 6 months (244). The latter 6 months Canadian double-blind placebo-controlled trial (PCT) in SLE confirmed that MTX up to 20mg weekly can decrease disease activity and simultaneously work as a GC-sparing agent with a tolerable safety profile (245). In addition, there are some follow-up data from cohort studies (243). The established data suggest that MTX is favorable in the treatment of synovitis and skin manifestations in SLE (246,247).

2.5.1.5 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is modified into an active metabolite mycophenolic acid, which inhibits inosine 5-monophosphate dehydrogenase (IMPDH) enzyme. This results in suppression of de novo purine synthesis, which is central in late-phase of B and T cell proliferation (248). MMF was originally designed for immunosuppression after organ transplantation and has become more common in the therapy of SLE, especially in resistant disease (226). MMF is administrated orally 2-3 g per day (249) and is well tolerated. Side effects are mostly mild gastrointestinal tract symptoms (250). MMF is not recommended for childbearing females (251).

MMF provides a good option in therapy of lupus nephritis for cyclophosphamide-resistant patients and preserves childbearing potential (12). MMF and cyclophosphamide

in combination with prednisolone showed similar efficacy in diffuse proliferative lupus nephritis (252). Later Ginzler et al compared induction therapy of active lupus nephritis with MMF and monthly intravenous cyclophosphamide in an open-label randomized non-inferiority study design and found MMF had slightly better in remission rate and tolerance (253). Similar results were established in an RCT on induction therapy of proliferative lupus nephritis with MMF and intravenous cyclophosphamide (254). In contrast, in a bi-phase multinational RCT on active lupus nephritis, MMF was not superior in achieving remission compared to monthly pulses of intravenous cyclophosphamide. Also the tolerance and infection rates were similar in both categories (255). Azathioprine and MMF were studied in maintenance of remission in lupus nephritis in a double-blind RCT after the aforementioned induction therapy. MMF protected better from renal relapses (256). The MAINTAIN study was an investigator-initiated study on maintenance therapy in proliferative lupus nephritis. Patients were randomized to receive after induction therapy to either MMF or azathioprine. There was no statistical difference between regimens, although there were less treatment failures in MMF group (257). MMF seems to have potential also in non-renal SLE, although the most data is derived from low-quality cohort studies (243). The preliminary results of studies suggest that MMF may be useful in hematological and cutaneous manifestations in refractory disease. There is no support for the usage of MMF in neuropsychiatric manifestations (250,258).

2.5.1.6 Azathioprine

Azathioprine is a purine analogue and is converted into the active metabolites 6-mercaptopurine and 6- thioguanine nucleotides. The latter metabolite suppresses leukocyte DNA synthesis and has a potential anti-proliferative role in T cells (259,260). Many other immunosuppressive mechanisms have been proposed. The oral daily maintenance dosage is up to 2.5mg/kg (260). Common side effects include nausea, abdominal symptoms, myelosuppression and hepatic reactions (259).

A small open-label RCT on induction therapy in lupus nephritis showed that azathioprine combined with methylprednisolone was inferior to intravenous cyclophosphamide in prevention of chronic renal changes (261), renal exacerbations in long-term follow-up and in predisposing to herpes zoster virus infections. In both trial groups patients received also oral prednisone (262). In spite of earlier results azathioprine is a drug of choice also in induction therapy in selected lupus nephritis patients (263). In maintenance therapy azathioprine is a good alternative (264). In non-renal SLE the literature on azathioprine is limited (242). Despite lacking RCT data, azathioprine maintains its role as a valuable immunosuppressant in SLE during pregnancy (243,265).

2.5.1.7 Cyclosporine A

Cyclosporine A is a T-helper cell-specific calcineurin inhibitor, which inhibits transcription of certain cytokines like IFN–γ and IL-2, further suppressing development of lymphocytes (266). In addition of suppressing synthesis of immune complexes and their glomerular deposition, cyclosporine A assists in maintaining glomerular barrier function (267). Cyclosporine A is administered 2-5 mg/kg/day and taken twice daily. Cyclosporine A is not cytostatic, and it may be considered to use in child-carrying females as a second option (13,266). Nephrotoxic side effects are normally reversible if the daily dose is limited under 5mg/kg (266). Other possible adverse effects are an increase in blood pressure, mild gastrointestinal and renal dysfunction, numbness, gingival hypertrophy and hair growth (268).

The BILAG multicenter open-label RCT analyzed cyclosporine A and azathioprine in severe SLE. Both drugs were equally efficient in steroid-sparing, and withdrawal due to side effects was similar in both therapy regimens (269). A small study on mostly conventional therapy resistant lupus nephritis patients, found cyclosporine A effective in lowering disease activity (270). A Chinese study on lupus nephritis (WHO class IV) also showed cyclosporine A to be useful in a cohort in which over half of the patients were resistant to earlier therapy (271). The efficacy of cyclosporine A in non-renal SLE requires more high-quality studies (243).

2.5.1.8 Biological agents

Belimumab is the first drug individually designed for SLE therapy. This human monoclonal antibody targets B lymphocyte stimulator (BLyS), which affects the proliferation, differentiation, and survival of B lymphocytes. Increased levels of BLyS have been measured from SLE patients (272). Belimumab is approved for therapy of conventional treatment-resistant and serologically active (either positive anti-DNA-Ab, ANA or low complement levels of C3 and C4) SLE without renal and neuropsychiatric lupus manifestations. It is administrated intravenously starting 10mg/kg fortnightly 3 times and after that once in 4 weeks (214,273). The most common side effects are increased infections and mild infusion reactions (273).

Rituximab is a chimeric monoclonal antibody directed against CD20 in B cells. It has efficacy in non-Hodgkins lymphoma and rheumatoid arthritis (274). Some case reports have shown rituximab also beneficial in severe refractory SLE (275). However, large double-blind, RCTs in moderate or severe SLE (EXPLORER) and class III or IV lupus nephritis (LUNAR) did not show superior efficacy of rituximab compared to placebo when added to conventional therapy (276,277).

2.5.1.9 Other therapies

In mild SLE, non-steroidal anti-inflammatory drugs (NSAIDs) may be symptom relieving in combination with AMs (222). Tacrolimus can be used in other therapy resistant patients with severe disease. It shares similarities with cyclosporine A in mechanism of action and in side effects (216).Thalidomide and dapsone are mainly used for cutaneous manifestations in second line (13). Plasmapheresis along with glucocorticoids is a routine therapy of rare, life threatening thrombotic thrombocytopenic purpura. Intravenous immunoglobulin is the drug of choice for the most severe forms of immune neutropenia and thrombocytopenia. Splenectomy can also be considered for resistant thrombocytopenia (197).

2.5.2 Adjuvant therapy

2.5.2.1 Life style manners

Adjuvant therapy is a vital part of the treatment. Ultraviolet protection with appropriate clothing and topical sun screen with blocking rate of 25-50 should be recommended for all patients in order to prevent disease relapses and skin manifestations (222). Patients are also encouraged to life style changes like cessation of smoking, increasing exercise, controlling weight, adequate vitamin D and calcium intake, since they may benefit in the later disease course (12,278).

2.5.2.2 Therapy targeting anti-phospholipids

The SLE patients with concomitant anti-phospholipid antibodies are guided to take low-dose aspirin (accompanied with HCQ) for primary prevention against thrombosis and fetal loss. In situations where the risk of thrombosis is further elevated (pregnancy, operation) low-molecular-weight (LMW) heparin should be added. If a patient has an earlier history of multiple thromboses, oral anticoagulant therapy should be considered for secondary prevention, except in pregnant patients, for whom a combination of either unfractionated or LMW heparin and low-dose aspirin is recommended (12,279).

2.5.2.3 Atherosclerosis and osteoporosis

Due to increased atherosclerosis and excess cardiovascular events among SLE patients, the traditional risk factors like elevated blood pressure, hyperglycemia and dyslipidemia should be regularly monitored and adequately treated according to the guidelines tailored for the general population in great risk for cardiovascular events (12,278). Disease-related factors and excess usage of glucocorticoids predispose patients to osteoporosis. Bisphosphonates, denosumab, raloxifene, and teriparatide are used along with relevant calcium and vitamin D intake to protect from bone fractures (217).

2.5.2.4 Exogenous oestrogen

Therapy with oestrogen should be used only under careful risk consideration due to the risk of thrombosis and possible effect on disease relapses (12). However, oral contraceptives compared to placebo did not increase the amount of severe disease flares in carefully selected patients (280). In parallel, in an RCT on mild or moderate SLE, the disease activity and SLE exacerbations did not differed significantly between patients on hormone replacement therapy (HRT) and control group. Nevertheless, the risk of thrombosis was higher in HRT than in the placebo group (281).

2.5.2.5 Vaccines

SLE patients are in an increased risk for infections due to impaired immune system and immunosuppressive therapy (282). Vaccines are one way to protect from infections. Vaccinations, however, should be timed to inactive periods of the disease and live virus vaccines should not be injected in immunosuppressive patients. In general, influenza and pneumococcal vaccines are considered safe and advisable (283), although the efficacy is not always satisfactory (151).

2.5.3 Initial drug therapy

Only a few studies have explored the initial drug therapy for SLE. First-year drug treatment has been described in a multinational inception cohort of 200 patients collected from 14 European academic rheumatology centers over 5 years until the end of year 2005. A third of the patients received GCs intravenously and 83% orally. Less than half of the patients were on AMs and a quarter of them on azathioprine or cyclophosphamide (oral and intravenous administration pooled together) (284).

An incidence study taking advantage of the General Practice Research Database from the United Kingdom in years 1990-1999 reported pharmacotherapy of incident patients along with other issues of interest. Glucocorticoids were prescribed for over half, AMs for 38% and azathioprine for 14 % of the patients (43).

2.6. WORK ABILITY

2.6.1 General aspects

Work ability is related to work requirements on one hand and health-related and professional competence on the other hand (285). Mismatch between requirements and personal capability results in loss of work production. The number of days off work, i.e. absenteeism, is an easy way to measure work time loss. Presenteeism is defined as lost work productivity while still working (286). The ability to work can be reduced by the

disease activation or by the permanent organ damage (285). As SLE is a systemic disease with increasing damage accrual along the time and occurring predominantly among working aged individuals, diminished working capacity is a substantial outcome. Work disability (WD) causes significant indirect costs to society, and in addition to income loss, has an adverse effect on patients' social life and self-esteem (287,288).

2.6.2 Predictors of work disability

Work ability is multifactorial and influenced by the age, educational level, socioeconomic factors, working culture, employment level of the country, demands of the work and disease-related factors. Regarding total work withdrawal many studies have reported African- American ethnicity, lower educational level, high physical and cognitive demands of work (286), longer disease course, greater disease activity, damage accrual, neuropsychiatric involvement, and fatigue as predictors for a worse outcome (289-291). Some evidence shows that patients with SLE < 55 years of age have more problems especially in work entry than in maintaining the work place at least in the United States (292). On the other hand it has been shown that particularly total withdrawal from work is responsible for declined working time, not the diminished working hours (293).

2.6.3 Measures on work participation

The impact of SLE on work has been studied by the number of days off work (sick leave), WD and level of employment. Study settings differ greatly, most studies are small and cross-sectional, and the data on the background population often is either lacking or is limited. Most previous studies on WD are based on self-reports (291). Also the social security systems between different countries vary abundantly and do not allow results to be generalized (294).

2.6.4 Sick leaves and WD days

All studies on SLE-related sick leaves show uniformly increased level of work time loss. The recent Finnish study on 181 SLE females available in workforce showed that a mean of 25 working days were lost in the preceding year in contrast to 10 days among age- and residence- matched controls (295). In parallel, a study from the United States found that 21% of 198 early SLE patients versus 11% of controls had sick leaves over 14 days in the preceding year (10). Moreover, a German cross-sectional study reported sick leave in 36% of 1248 patients during the past 12 months antedating study (296). On the other hand, a Dutch study showed that 81% of those SLE patients who had reported a continuous 6-week work loss due their disease were still unable to work after a half year since that period (297).

2.6.5 Employment level

Employment level is one way to measure work participation, but it does not explain the reasons beyond unemployment like shortage of work, local work circumstances, health problems and working attitudes. The study that utilized the Georgians Organized Against Lupus cohort of 511 patients, found that the patients had 3.6 times higher overall ratio of unemployment than the general population (298). Another Dutch study on 147 SLE patients showed 59% of unemployment level after a mean disease duration of 6.3 years (288).

2.6.6 WD levels

The earlier reported WD levels in SLE patients range from 13 to 43% and disease durations from 3 to 18 years (table 11) (10,286,289,290,294,295,297,299-304). It is evident that along with time, co-morbidities, damage accrual and WD levels increase (295,298,304-306). In a Canadian early SLE cohort WD rates within 2, 5 and 10 years since diagnosis were 13, 19, and 21%, respectively (304). Similarly, in a Finnish hospital- based female SLE cohort WD percentage was at 5 years 13, at 10 years 22 and at 20 years 47 (295). No data exist whether there have been any changes over decades.

Table 11. Studies on work disability in systemic lupus erythematosus

First author, year	Number of cases	Mean age at dg (y)	WD (%)	Disease duration (mean,y)	Method	Country
Partridge, 1997 (299)	159	31.6	40	3.4	self-report	USA, Boston
Boomsma, 2002 (297)	114	31	23	10	self-report	Netherlands
Bertoli, 2007 (300)	273	36.5	19	4.7	self-report	USA
Nived, 2007 (301)	71	-	13	-	self-report	Sweden
Mok, 2008 (302)	105	38.1	37	10.0	self-report	China, Hong Kong
Utset, 2008 (289)	132	40.4	43	9.2	self-report, chart review	USA, Chicago
Yazdany, 2008 (303)	830	-	32	-	self-report	USA, San Francisco
Baker, 2009 (290)	1137	50	19	18	self-report	Canada
Campbell, 2009 (10)	198	39	26	4.0	self-report	USA
Dhannani, 2009 (304)	432	35.9	23	7.3 median	self-report	Canada
Zhu, 2012 (294)	125	31.0	16	9	self-report	China, Hong Kong
Ekblom-Kullberg, 2015 (295)	**181**	**31.3**	**34**	**12.7**	**self-report, chart review**	**Finland**
Utset, 2015 (286)	344	-	31	9.0	self- report, chart review	USA

WD = workdisability, dg = diagnosis, y= years

2.7 MORTALITY

2.7.1 General

SLE patients have a shortened lifespan. Over the recent decades early mortality due to active disease has decreased probably due to more advanced treatment and broader knowledge of SLE-related conditions like infections and excess risk of cardiovascular diseases (CVD) (11).

2.7.2 Prognostic factors

Poor survival in SLE is strongly associated with renal failure, coincidental infection and disease flare, disease onset after 50 years of age, use of intravenous cyclophosphamide, secondary antiphospholipid syndrome, active disease, male gender, low complement levels, hemolytic anemia, serositis as initial manifestation of disease and poor adherence to medication (19,307-311). In addition, African-American race, low income, neuropsychiatric manifestation, heart involvement, and high damage scores have been related to less favorable prognosis (18,307,312,313). Age under 16 years at onset and male gender are especially connected to deaths at an early course of the disease (309).

2.7.3 Survival

Table 8 summarizes studies on survival rates in SLE. Few of them have analyzed inception cohorts (17,32,40,50,53,60,66,314-316). A small study from the United States in years 1950-79 reported 5- year and 10- year survival of 75% and 63%, respectively (60). In studies started in the seventies, 5- year survival rates have ranged between 84-92% and 10- year survival rates between 75-81% (32,51,53). Later studies before the millennium have reported 5-, 10- and 15- year survival rates of 88-97%, 74-92% and 64-80%, respectively (17,32,50,61,66,314). Only two studies on survival in incident SLE have started case inclusion after the turn of millennium. One of those showed 5- year survival rate of 80% over 2000-2009 in the mainly African- Caribbean population of Barbados. Lupus nephritis was highly prevalent (47%) at the disease onset (40). The larger study on 665 Chinese patients admitted to hospital in 2006-2009 reported 5 and 10 -year survival rate of 91% and 80%, respectively (315). At least the short-term survival has increased during the decades, although survival rates diverge markedly.

Studies on established SLE show similar results. The lowest survival rates of 5 – and 10-year survival date back to the 1970-80s (48,317). Three studies have reported 20 –year survival with rates of 53-80% (307,318,319).

Table 8. Survival studies on systemic lupus erythematosus

Country	Survival % (y)				Time period	Cases/ deaths (n)	Year, first author
	5	10	15	20	(y)		
Canada (Toronto)	75	63	53	-	1970-74	81/11	1976, Urowitz (317)
USA (Rochester, MN)*	75	63	-	-	1950-79	25/-	1985, Michet (60)
Iceland*	84	78	-	-	1975-84	76/17	1990, Gudmundsson (51)
Curacao	60	46	-	-	1980-89	68/25	1992, Nossent (48)
USA (Rochester, MN)*	95	72	-	-	1980-92	48/-	1999, Uramoto (316)
Denmark	91	76	64	53	1975-95	513/122	1999, Jacobsen (318)
Sweden (South)*	93	83	-	-	1981-91	81/-	2000, Ståhl- Hallengren (66)
Norway (North)*	92	75	-	-	1978-96	83/18	2001, Nossent (53)
USA	86	-	-	-	1994-97	288/34	2001, Alarcón (320)
Germany	97	90	-	-	1985-99	338/35	2002, Manger (312)
Europe (Euro-Lupus Cohort)	95	92	-	-	1990-2000	1000/68	2003, Cervera (184)
Greece (Nortwest)*	97	90	-	-	1982-2001	178/12	2003, Alamanos (50)
Tunisia	86	83	-	-	1987-2001	100/15	2004, Houman (321)
USA (rural Wisconsin area)*	88	76	-	-	1991-2001	44/8	2005, Naleway (61)
China (Hong Kong)*	92	83	80	-	1991-2003	285/29	2005, Mok (314)
USA (Hopkins Lupus Cohort)	95	91	85	78	1987-2004	1378/118	2006, Kasitanon (307)
Italy (Padova)	96	93	76	-	40 years	207/17	2006, Doria (322)
Saudi Arabia	92	69	-	-	6 years	93/8	2007, Heller (309)
Norway (North)*	91	81	-	-	1978-95	81/25	2009, Eilertsen (32)
	95	92			1996-2006	58/5	
Spain (Northwest)	94	87	80	-	1987-2006	150/19	2011, Alonso (55)
China”	80	57	32	-	1995-2009	158/64	2012, Lin (311)
Barbados*	80	-	-	-	2000-09	183/24	2012, Flower (40)
Denmark (Funen)	94	87	73	-	1995-2010	215/38	2013, Voss (323)
Taiwan	93	-	-	-	2000-08	671/41	2013, Yu (70)
Turkey	96	92	89	-	1996-2012	428/19	2013, Pamuk (310)
Iran	93	90	90	80	1992-2011	417/35	2014, Fatemi (319)
China (Zhengzhou)*	91	80	-	-	2006-09	665/81	2014, Wu (292)
Norway (Oslo)	95	90	-	-	1999-2009	127/12	2014, Lerang(324)
USA	+99	98	-	-	1970-2011	795/14	2014, Merola (325)
	.5 “95	90	-	-		133/12	
USA (Wisconsin)*	~90	74	~64	-	1991-2008	70/19	2014, Bartels (17)
Turkey (Thrace)	95	90	-	-	2003-2014	331/17	2016, Pamuk (34)

*Inception cohort, %= percentage, + diagnosis <50 years, ” diagnosis ≥ 50 years, y=years, n= number, ~estimated from the survival curve

2.7.4 Standardized mortality ratio

The standardized mortality ratio (SMR) is the ratio between observed deaths in a study cohort and expected deaths in the general population. Studies on SMR in SLE are gathered into table 9. All these studies uniformly demonstrated excess mortality due to SLE. In the Scandinavian countries, SMR figures have ranged between 1.3 and 4.6 (49,53,318,323,324,326), the highest figures dating back to the seventies (53,318). In incident cohorts SMRs have been 1.3-2.7 (50,316). The highest figure of 7.9 is from China (47,327). Especially high SMRs were demonstrated in patients aged under 40 years and less than 12 month disease duration in a multinational cohort of 9547 SLE patients (18).

Table 9. Studies on standardized mortality ratio in systemic lupus erythematosus

Country	SMR	Time period	Mean age at death	Mean disease duration (years)	First author, year
Denmark	4.6	1975-95	-	7.3	Jacobsen, 1999 (318)
USA (Rochester)*	2.7	1980-92	-	-	Uramoto, 1999 (316)
Norway	1.3-3.9	1978-96	59.2	110 months	Nossent 2001 (53)
Germany	2.7	1985-99	-	7.8	Manger, 2002 (312)
UK	4.0	1978-2000	52.6	15.8	Moss, 2002 (328)
Greece (Nortwest)*	1.3	1982-2001	-	-	Alamanos, 2003 (50)
Sweden	3.6	1964-95	-	-	Björnådal, 2004 (326)
South Korea	3.0	1992-2001	-	-	Chun, 2005 (329)
International cohort	2.4	1958-2001	-	-	Bernatsky, 2006 (18)
China (South)	2.2-7.9	2000-2006	43.8	5.1	Mok, 2008 (47)
Denmark (Funen)	1.9	1995-2003	62.6	12.0	Laustrup, 2009 (49)
China (Hong Kong)	5.3	1999-2008	-	-	Mok, 2011 (327)
Denmark (Funen)	2.2	1995-2010	64.2	17.0	Voss, 2013 (323)
Taiwan	2.9	2000-08	-	-	Yu, 2013 (70)
Norway	3.0	1999-2009	*63.0	-	Lerang, 2014 (324)

SMR = standardized mortality ratio, *Inception cohort

2.7.5 Causes of death

Causes of death in SLE vary over the disease course and between the races and societies (53,317,320). Urowitz et al were the first to recognize the bimodal mortality according to disease course in the 1970s. Causes behind the early deaths were mostly related to disease activity with concomitant infection. On the other hand, patients who died later had atherosclerotic coronary disease, leading to lethal myocardial infarction (317). Early mortality has declined presumably due to improved drug and renal replacement therapy (330), but CVDs are highly overrepresented already in the early deaths. The proportions of deaths due to CVDs have not decreased over time (18,326,331).

Infection, disease activity, organ dysfunction, CVDs and malignancy are the leading causes of death (18,307,308). Table 10 shows the latest and most relevant previous studies on the proportions of the primary causes. Predominant role of infection is in particular seen in Asia and in Arabic countries (34,315,319,332). Renal, pulmonary or CNS involvement and multiple concomitant organ dysfunction are essential behind the excess mortality due to SLE itself (322,330,332). Inflammation also promotes atherosclerosis (3). The proportion of CVD -deaths is high particularly in the western world (17,323,333,334).

The literature on SLE-associated malignancy is controversial. A large multinational study on 16 409 SLE patients reported a marginally increased risk for all malignancies (335), and a Canadian study on 297 patients between years 1975-1994 discovered an increased number of cancers. In particular, non-Hodgkin's lymphoma (NHL) and cervical cancer

were more frequent than expected (336). In contrast, a study of an unselected cohort of 238 Icelandic patients in years 1957-2001 did not discover a relationship between SLE and overall malignancies (337).

Besides NHL and cervical cancer, the risk for cancer in liver, vulva, thyroid and lungs (in particular small cell lung cancer) has been shown to be higher. On the contrary, some evidence suggests that SLE may decrease the risk for breast and prostate malignancies (335,338). However, the risk of malignancy-related death compared to the general population has been relatively low in many studies (339,340). It has been speculated that the excess mortality due to other causes in early SLE reduces the impact of malignancy later in life (341).

Table 10. The most important studies on causes of death in systemic lupus erythematosus

Country, time	Three main causes of death and percentage of deaths			Cases/ deaths (n)	Mean age at death	Disease duration (y)	First author, year
Canada, 1970-74	Active SLE and infection 36%	CVD 36%	Active SLE 18%	81/11	44	4.2	Urowitz, 1976 (317)
Finland, 1972-78	**SLE 52%**	**CVD 21%**	**Infection 17%**	**1427/142**	**-**	**6.0**	**Helve, 1985** (116)
Europe (Euro-Lupus Cohort), 1990-2000	SLE 26.5%	Thrombosis 26.5%	Infection 25%	1000/68	44	9.5	Cervera, 2003 (184)
Sweden, 1964-95	CVDs including stroke 42%	SLE 21%	Malignancy 12%	4737/2314	-	-	Björnådal, 2004 (326)
Europe (multinational), 5 years since 1999	CVD 48%	Infection 30%	Malignancy 7%	~2500/91	-	10.2	Nossent, 2007 (331)
Barbados*, 2000-09	Nephritis and sepsis 42%	Nephritis 29%	CVD 13%	183/24	-	-	Flower, 2012 (40)
Brazil^, 1985-2007	SLE 65%	CVD 10%	Infection 4%	-/4815	35.8 #	-	Souza, 2012 (341)
Brazil, 2005-2009	SLE related organ failure 38%	Infection 38%	Active SLE 8%	179/13	44.8	9.6	Telles, 2013 (19)
Italy, 1976-2008	CVD 55%	Malignancy 23%	Infection 18%	535/22	-	-	Cartella, 2013 (333)
China, 1986-2012	SLE 52%	Infection 37%	CVD 4%	268/3831	37.5	6.0	Fei, 2014 (332)
Iran, 1992-2011	SLE 43%	Infection 29%	CVD 20%	394/35	34.2	5.4	Fatemi, 2014 (319)
Norway, 1999-2009	Malignancy 20%	CVD 16%	Active SLE 12%	325/50	63	F 13.5 M 7.0	Lerang, 2014 (324)
USA, 1970-2011	SLE 23%	CVD 15%	Infection 15%	928/26	-	-	Merola, 2014 (325)
USA, 1991-2008	CVD 32%	Renal failure 16%	Infection 16%	70/19	-	-	Bartels, 2014 (17)
Malaysia, 2006-2013	Active SLE 38%	Infection 26%	Active SLE + infection 21%	633/58	-	-	Teh, 2015 (308)
UK, 1989-2010	Infection 38%	CVD 27%	Malignancy 14%	382/37	53.7	6.9	Yee,2015 (334)
Turkey*, 2003-2014	Infection 29%	CVD 24%	Renal failure 12%	331/17	-	-	Pamuk, 2016 (34)

*Inception cohort, ^ based on death certificates, n = number, y = years, SLE = systemic lupus erythematosus, CVD = cardiovascular disease, # mean age at death when SLE is the underlying cause, F = female, M = male

2.8 FINNISH SOCIAL SECURITY SYSTEM

The Finnish health care services are publicly arranged and financed mainly by general taxation. Hence, the services are available for all citizens. All Finns who reside permanently in Finland are insured by the National Health Insurance and are included in a register of insurances of the Social Insurance Institution (SII) since birth when the identity code is created. The SII provides financial support to compensate expenses resulting from illnesses (342-344).

2.8.1 Drug therapy

The standard imbursement level in years 2000-2008 was 42 % of the expenses of the outpatient medication prescribed by a doctor. Persons with certain chronic and severe diseases are entitled into higher reimbursement level (either 72 or 100 % in study years) if predefined criteria are met. Based on a common settled policy this benefit is usually applied at diagnosis. The act of granting is independent of patient's residence or socioeconomic status. The process is two-stepped. First the specialist treating a patient makes a medical certificate, which has to be based on proper diagnostic procedures and have a treatment plan in accordance with good clinical practice. Secondly, the diagnosis and the medical certificate are re-evaluated by an insurance physician of the SII. Certificates are handled within one month. The patient will receive a new personal health insurance card with a respective code, when the special reimbursement decision is awarded. In pharmacies all purchases of the reimbursed drugs are documented in detail (patient, Anatomical Therapeutic Chemical (ATC) - code, date, amount and cost of the drug as well as the reimbursed sum). These data are collected into nationwide registers, maintained by the SII. Individuals with different diagnoses can be identified by the international disease codes (ICD-10) (342).

2.8.2 Compensation of work disability

All Finnish working aged citizens are eligible for compensated sick leave if they are incapable of working due to illness. Employers are responsible for paying salary over the day on which the illness begins and the next nine weekdays. Then, the SII starts paying sickness allowance for at most 300 weekdays. The patients with partly limited work ability are eligible to apply for a partial sickness benefit to facilitate the return to work. In case of continuing WD over 300 days, the individual can apply for WD pension, either full-time or part-time. The temporary WD pension (so called temporary rehabilitation allowance) can be granted instead of permanent disability pension, when the prospects for returning to labor market are favorable after treatment or rehabilitation. A medical certificate is an absolute requirement for the sickness benefit and temporary or permanent WD pension. The data on the sickness benefits and temporary and permanent WD pensions are collected into the registries maintained by the SII and the Finnish Centre for Pensions. The amount of pension consists of earnings over the previous years. If the earnings are small or non-exist, the SII pays national guarantee pension (343,344).

3 Aims of the present study

1. To evaluate the incidence of SLE in Finland by using nationwide data from the registry of the SII.

2. To study mortality and causes of death in adult incident SLE patients in Finland.

3. To explore the initial outpatient anti-rheumatic medication and the purchases of drugs for certain comorbidities in incident SLE patients compared to the general Finnish population.

4. To find out whether incident SLE has an impact on work participation in Finland.

5. To estimate the incidence and distribution of autoimmune CTDs including SLE in a defined population in the Northern Savo area in the year 2010.

4 Patients and methods

4.1. THE FINNISH EARLY SLE REGISTER STUDIES (I, II, III, IV)

4.1.1 Background

At the end of year 2007, Finland had a total population of 5 300 484 residents and of them 1 028 872 were children aged 0-16 years. Over 98% of the residents were Caucasians. The number of working aged 18-64 years old adults was 3.4 million in year 2008. The nationwide data on the official death certificates was gathered into the register maintained by Statistics Finland. The three-stepped cause-of-death determination comprises of underlying causes, causes leading to death and immediate causes of death. Causes of death are documented conforming to the ICD-10 codes and supplemented with contributory causes of death. In the years 2000-2008 an autopsy was carried out for 31% of the deaths (345).

4.1.2 Patient cohorts

Reimbursement decisions for SLE are individualized by the international disease code (ICD-10) of M32. The data from the reimbursement register between January 1st, 2000 and December 31st, 2007 were screened through computerized searches to form a nationwide incident SLE cohort. The date of the reimbursement decision for SLE medicines was determined as the index day. Patients who were 0-16 years of age at the index day were defined children and were included in the pediatric cohort. The patients who were over 16 years of age formed the adult SLE cohort for incidence, mortality and initial drug therapy studies. In the work disability study SLE patients aged 18-64 years available for labor market were analyzed. Thus, patients aged 18-64 years, who were already on permanent work disability pensions were excluded from the study.

4.1.3 Medications

The medication of the adult incident SLE cohort was explored from the drug purchase register. The drug purchase register includes all purchased reimbursed drugs with detailed information of Anatomical Therapeutic Chemical (ATC) - code, amount and date of purchase. All the anti-rheumatic drugs the patients had purchased from one month before and until a year after the index day were evaluated. The drug was considered to be part of the initial drug therapy if a patient had purchased the drug at least once during the follow-up time. The patients were categorized into four groups according to year of the first reimbursement decision date (2000-01, 2002-03, 2004-05 and 2006-07). The data of the purchases of glucocorticoids was incomplete in years 2006-07, since the prednisolone 5mg

was not reimbursed at that time. The purchases of drugs for predefined comorbidities (cardiovascular diseases, dyslipidemia, diabetes mellitus, hypothyroidism, obstructive pulmonary disease and female sex hormones) were analyzed within the first year after the index day. The proportions of drugs used in incident SLE patients were compared to calculated average annual medication per patient-year in the general population during the follow-up time.

4.1.4 Work disability

The working-aged SLE patients available for the labor market at the index date were linked to the national sickness insurance and pension registries maintained by the SII and to the earnings-related pension register maintained by the Finnish Center for Pensions. The data was analyzed until the end of follow-up on December 31st, 2008. The data on the incidence of premature WDs in the Finnish age- and sex matched population was received from the same institutions.

The annual WD days for any cause were assessed in 365-day cycles from the index day and calculated per patient year. The WD data contained all sick leaves lasting > 10 working days, temporary rehabilitation allowances (temporary disability pension) and disability pensions, which all can be part- or fulltime. The leading causes of the permanent WD were evaluated by the ICD-10 codes on the pension register data.

WD pension was defined to include all permanent WD pensions since the index day and long-term temporary rehabilitation allowances that continued beyond the end of the observation time on December 31st, 2008. The follow-up of incident SLE patients ended at the first manifestation of the followings: death, after a patient became 65 years old, the beginning of WD for a cause other than SLE, normal old-age pension or the end of year 2008.

4.1.5 Mortality

The patient cohort was linked into the death certificate register by the personal identity code until the end of year 2008. Time and age at death and causes of death were determined from the death certificate register from January 1st, 2000 until December 31st, 2008. In the cause of death analysis accidental and suicidal causes were pooled together.

4.1.6 Ethical aspects

There was no legal requirement for ethical approval, since only register data were used, and patients were analyzed anonymously. The permission to use register data was obtained from the Finnish SII, the Population Register Center and the Finnish Center for Pensions (32/26/2007).

4.2 NORTHERN SAVO 2010 POPULATION-BASED INCIDENCE STUDY (V)

4.2.1 Background

The Northern Savo 2010 incidence study was conducted in 2010 in the Northern Savo hospital district, where there are five publicly funded rheumatology centers and all of them took part in patients' retrieval. The mid-year adult population (≥ 16 years) in the study year in that area was 206 441 citizens. This was about 4.7% of the general adult population in Finland at that time (345). The study protocol and results concerning CTDs are dealt in more detail.

4.2.2 Patient cohort

All adult patients aged ≥ 16 years in the Northern Savo area who were diagnosed a new connective tissue disease (CTD) were asked to enter into the incidence study. The study consisted of two components: a limited study that collected only the diagnosis, gender, age and date of diagnosis, and a broader study in which the patients were evaluated more intensively. Only one patient refused participation in the study. The patients' follow-up lasted one year. At the end of follow-up the diagnosis was re-evaluated.

4.2.3 Methods

The patients were studied in daily clinical practice with similar detail as normally. Height, weight, waist circumference and blood pressure were measured. Prevalent chronic diseases along with current medicines, duration of the rheumatic symptoms, smoking habits, family history of rheumatic diseases (first-degree relatives) and profession were determined in a questionnaire. The basic laboratory tests contained urinalysis, creatinine, alanine aminotransferase, alkaline phosphatase, fasting glucose, lipid levels, ESR, CRP and blood count. Depending on the clinical picture of the disease, supplementary tests were monitored when appropriate including antiphospholipid antibodies, creatinine kinase, complement 3 and 4 levels, radiological studies, nailfold capillaroscopy, electrocardiograms, respiratory function tests, electromyograms, histopathological tests and synovial fluid examination. Rheumatoid factor and relevant autoantibody tests (ANA, anti-dsDNA, anti-U1-RNP, anticentromere, antitopoisomerase I, anti-Sm, anti- Ro, anti-La, anti-Jo-1 and antineutrophil cytoplasmic antibodies) were evaluated at diagnosis.

The classification of diseases was originally made using the international classification criteria as described in the following: ACR97 revised criteria for SLE (24,25), the 1988 LeRoy classification of systemic sclerosis (SSc) (346), revised American-European classification criteria for Sjögren's syndrome (347) and criteria proposed by Bohan and

Peter for dermato- and polymyositis (348,349). In the analysis dermato- and polymyositis were pooled together and named as idiopathic inflammatory myopathies. Diseases that had clinical and immunological features corresponding to CTD, but not fulfilling the defined criteria for classification in a certain class of CTD were designated as undifferentiated connective tissue diseases (UCTDs). In Sjögren's syndrome the classification was not precisely followed and subjective symptoms of dry eyes and mouth were recognized as sign for keratoconjunctivitis sicca or failure of salivation. An associated other disease or treatment leading to similar symptoms was excluded. In the end the ascertainment of diagnosis was clinical. Later all CTD patients were reviewed according to the SLICC classification criteria for SLE (6) and the revised 2013 systemic sclerosis criteria (350). The date of the CTD diagnosis was defined as index day in incidence calculations.

4.2.4 Ethical aspects

The study was evaluated and approved in advance by the Ethics Committee of Kuopio University Hospital. Only volunteer patients were accepted into the study, and those entering the study signed informed consent.

4.3 STATISTICAL ANALYSES

The data were expressed as means with standard deviations (SDs), medians with interquartile ranges (IQRs) or counts with percentages. The main results were presented with 95% confidence intervals (95% CIs) assuming a Poisson distribution, except for annual WD days the 95% CIs were determined by bias-corrected bootstrapping and the linearity across year cohorts was tested by bootstrap-type analysis of covariance with an appropriate contrast. The mean annual incidence rates were counted by dividing the number of incident SLE patients in years 2000-2007 by the general population at risk (345) in the register study and by dividing the number of patients in certain CTD class by the mid-population in year 2010 in Northern Savo incidence study. Age-adjustment was made with direct method using the Finnish general population in the year 2010 as a reference, and the method invented by Yazici et al for the rare diseases (351) was used in the evaluation of incidence in the situation where there was no patient in certain CTD among the other gender in Northern Savo incidence study. Standardized estimates of incidence rate ratios (IRRs) and crude and standardized estimates of the rate ratios (RR) of the drug users were obtained by using Poisson or negative binomial regression models when appropriate.

The Kaplan-Meier method was used in time-to-event analysis to estimate and illustrate cumulative survival and cumulative incidence of continuous WD. In the study III, statistical significance for the hypotheses of periodic linearity was tested by using

generalized linear model with a logit link and a binomial distribution. The probability of drug therapy was determined based on gender-, age- and calendar-period-specific rates in the general population. P-value <0.05 was considered statistically significant. The standardized incidence ratio for a premature WD pension was calculated as the ratio of observed and expected numbers of WD pensions in the age-, sex- and calendar year-matched general Finnish population. Age-adjusted risk for mortality between the genders was estimated by advancing Cox proportional hazard model. The standardized mortality ratio (SMR) was calculated as the ratio of observed and expected numbers of deaths, where the expected number of deaths was based on the gender-, age- and calendar-period-specific mortality rates in the Finnish general population (345).

5 Results

5.1 EPIDEMIOLOGY AND OUTCOMES OF THE FINNISH INCIDENT SLE

5.1.1 Patients (I)

A total of 599 incident SLE patients were found in the nationwide special reimbursement register in the years 2000-2007. There were 566 adult patients and 33 children. There was a female predominance with 492 (87%) adult females. The figure 4 shows the number and percentage of incident SLE patients years 2000-2007 by gender and age class. The latter image demostrates the age distribution of the population among females and males in different age classes in the same years (vertical line). In pediatric incident SLE the overrepresentation of girls was not as prominent (73%).

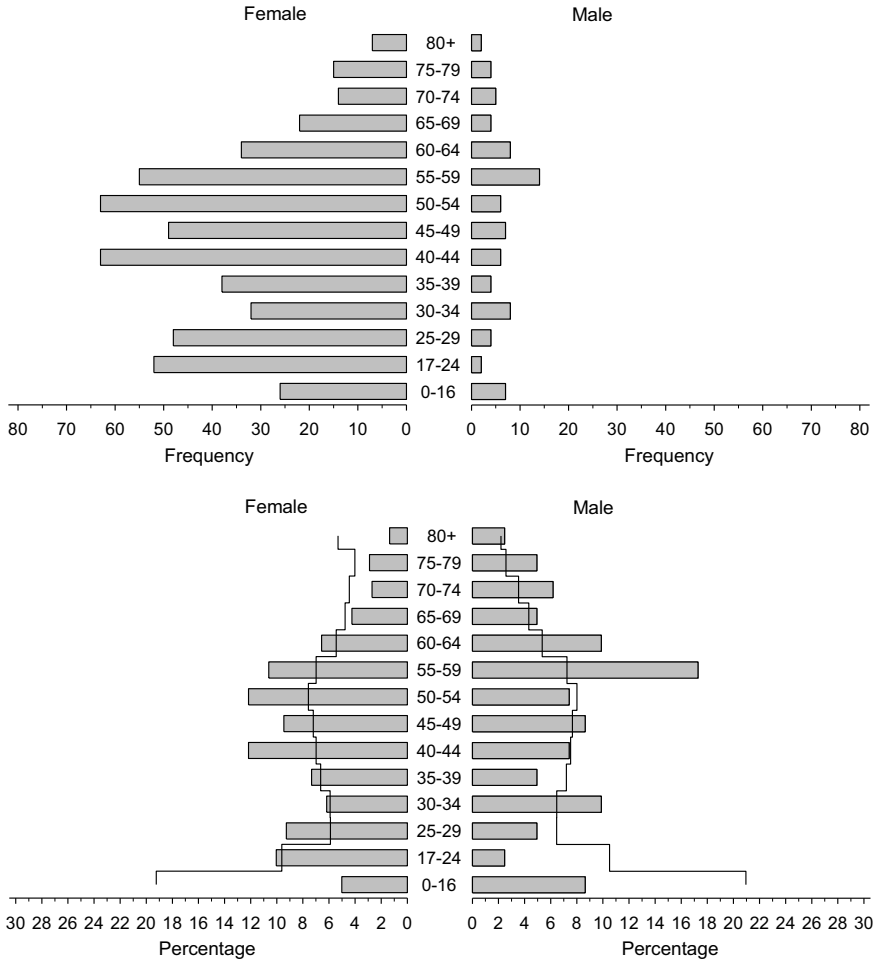


Figure 4. Distribution of incident SLE patients in years 2000-2007 by gender and age class. The upper image describes the number and the latter image the percentage of patients. The vertical line in the latter image shows the distribution of the general population measured in percentages among females and males in different age classes in the same years **(I)**.

The mean age at diagnosis in adults was 46.5±15.9 years; 45.7±15.8 years for females and 51.8±15.2 years for males (P =0.002). Pediatric SLE occurred in 33 children (26 girls, 7 boys) with mean age at diagnosis 13.0±3.0 years. Figure 5 represents the number of incident pediatric SLE cases by age and gender.

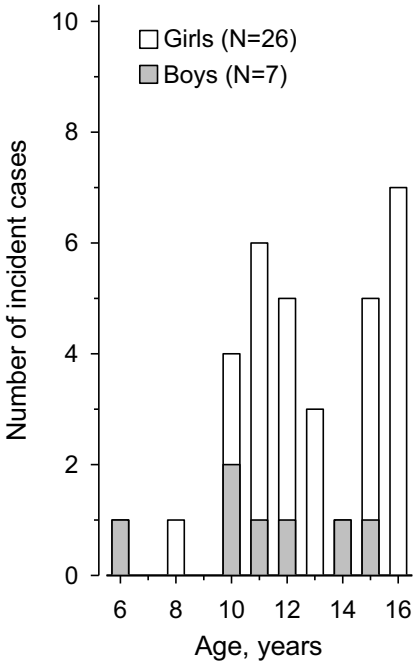


Figure 5. Number of incident pediatric SLE cases by age and sex **(I)**

5.1.2 Incidence (I)

In Finland, the mean annual incidence rate of SLE for adults was 1.69 (95% CI: 1.56 to 1.84)/100 000 in years 2000-2007. In females the incidence rate was 2.85 (2.60 to 3.11) with statistically significant changes in the incidence between age groups (P<0.001). The incidence rates were the highest in the 40-59-year-old females and lower peaks were also seen among young females aged 17 to 29 years.

In males the incidence rate was 0.46 (0.36 to 0.57) and there was no clear difference in the incidence according to the age at diagnosis (P=0.80). The gender incidence rate ratio was 6.43 (95% CI: 5.06 to 8.26, age-adjusted). Age-and gender-specific incidence rates are presented in Figure 6.

The mean annual incidence rate of pediatric SLE was 0.39 (0.27 to 0.55) during the eight-year follow-up; for girls 0.63 (0.41 to 0.93) and for boys 0.16 (0.07 to 0.34).

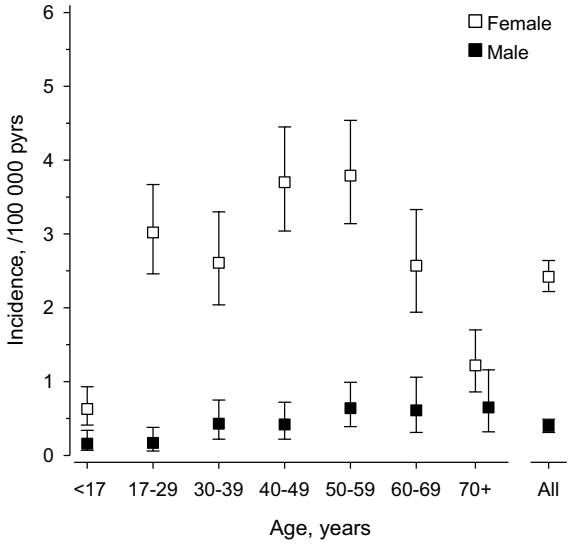


Figure 6. The Finnish mean annual incidence rates of systemic lupus erythematosus in a nationwide register study years 2000-2007 displayed by age and gender **(I)**

5.1.3 Initiation treatment strategies (III)

Table 12 demonstrates in two-year calendar periods the number and percentages of incident SLE patients buying anti-rheumatic drugs at least one time in the first year since special reimbursement decision for SLE. Almost all 538 of 566 (95%) adult incident SLE patients had purchased some anti-rheumatic medication and 507 (89.6%) of them had purchased disease modifying anti-rheumatic drugs (DMARDs). Oral cyclophosphamide was not purchased for early SLE after the year 2004. Purchases of mycophenolate mofetil instead increased significantly during the observation time, but the numbers were low. Otherwise proportions of purchases of anti-rheumatic drugs remained constant. Over the periods of 2000-2001, 2002-2003 and 2004-2005 use of oral glucocorticoids (66-70%) stayed stable (2006-2007 not analyzed). Throughout the study periods, 73-80% of the patients purchased hydroxychloroquine (HCQ), which was the most commonly used DMARD. Azathioprine was the second most frequently purchased DMARD (10-19% of patients) and was followed by methotrexate (9-17%).

Table 12. The proportions of purchased anti-rheumatic medications in outpatient therapy in Finnish SLE patients within the first year of diagnosis divided into two-year calendar periods by the disease onset (**III**)

Medication	**Years**				**P for linearity**
	2000-01 N=176 N (%)	2002-03 N=155 N (%)	2004-05 N=124 N (%)	2006-07 N=111 N (%)	
Hydroxychloroquine	140 (80)	116 (75)	95 (77)	81 (73)	0.25
Azathioprine	23 (13)	26 (17)	13 (10)	21 (19)	0.45
Methotrexate	20 (11)	14 (9)	21 (17)	19 (17)	0.059
Cyclophosphamide	2 (1)	8 (5)	0	0	-
Cyclosporin A	4 (2)	4 (3)	3 (2)	1 (1)	0.49
Mycophenolate	0	3 (2)	3 (2)	7 (6)	<0.001
No DMARD	18 (10)	17 (11)	16 (13)	8 (7)	0.64
Glucocorticoid	121 (69)	108 (70)	82 (66)	NA	-
None	6 (4)	7 (5)	9 (7)	6 (5)	0.25

DMARD = disease modifying anti-rheumatic drug, NA = not available, None = no DMARD or glucocorticoid

5.1.4 Comorbid medication (III)

The proportions of comorbid medication of SLE patients were higher in all selected categories compared to the general population. Table 13 shows the age- and gender-stratified rate ratios of the proportions of purchased drugs in preselected comorbidities in incident SLE patients in the first year since diagnosis compared to the average annual drugs in the general population in years 2000- 2007. The rate ratios were the highest for beta-blockers, drugs affecting the renin-angiotensin system and also sex hormones in female patients.

Table 13. Proportions of users for preselected medications with the rate ratios among incident SLE patients compared to average annual medication in the general Finnish population in 2000-2007. Rate ratios are age- and sex-stratified. **(III)**

Medication for	**Anatomical Therapeutic Chemical code**	**SLE patients N (%)**	**Rate ratio (95% CI)**	**P -value**
Diabetes	A10	35 (6)	1.64 (1.20 to 2.45)	0.02
Cardiovascular diseases				
Arrhythmia and glycosides	C01	74 (13)	3.57 (2.94 to 4.32)	<0.001
Diuretics	C03	122 (22)	5.14 (4.37 to 6.05)	<0.001
Beta-blockers	C07	164 (29)	7.83 (6.72 to 9.12)	<0.001
Calcium-channel blockers	C08	130 (23)	5.03 (4.24 to 5.96)	<0.001
Renin-angiotensin system	C09	164 (29)	7.78 (6.67 to 9.07)	<0.001
Other antihypertensive drugs	C02	8 (1)	0.38 (0.19 to 0.75)	<0.001
Lipid lowering drugs	C10	79 (14)	3.52 (2.87 to 4.32)	0.006
Hypothyroidism	H03A	90 (16)	4.69 (3.83 to 5.75)	<0.001
Obstructive pulmonary diseases	R03	112 (20)	4.81 (3.90 to 5.94)	<0.001
Sex hormones*	G03	174 (31)	8.30 (7.22 to 9.55)	<0.001

*only females

5.1.5 Work disability (IV)

The study found 446 working-aged (398 females, 48 males), non-retired incident SLE patients with median (IQR) follow-up time 5.3 (3.0,7.0) years. Mean age at diagnosis for the total cohort was 42±13 years, for the females 42±13 years and for the males 46±12 years.

In the years 2000-2008, 257 (58%) SLE patients were on WD days. WD days consisted of sick leaves lasting > 10 weekdays (criterium of eligibility for sickness allowance) and days on WD pensions after the SLE diagnosis. The mean number of WD days per patient year was 32 (95% CI 28 to 35) days. The annual number of WD days (shown in the figure 7) increased along the observation time (P for linearity = 0.007).

The WD pension was granted for 27 patients by the end of year 2008. WD was highest during the first year, but increased again at the end of the observation time (figure 8).

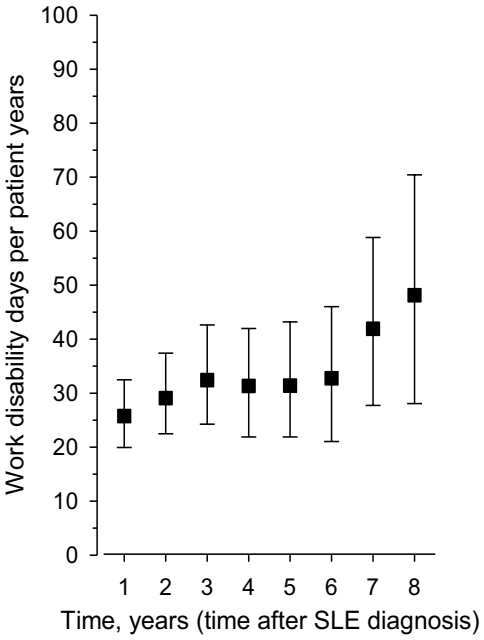


Figure 7. The number of work disability (WD) days for any cause in Finnish incident systemic lupus erythematosus patients during the years 2000-2008. The WD days are calculated per patient- year since diagnosis. **(IV)**

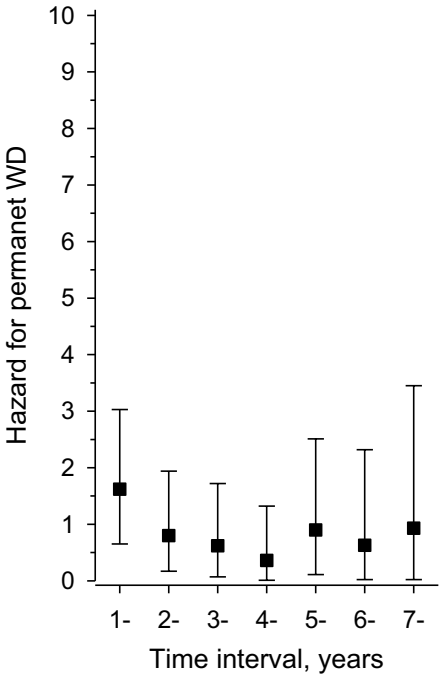


Figure 8. The hazard for permanent WD along with year intervals since diagnosis among incident SLE patients years 2000-2008 in Finland

The primary cause of WD pension was SLE itself (16 patients, 59%). The following two most common causes were musculoskeletal and psychiatric diseases with 5 (19%) patients in each group. In the rest of the patients the cause was breast cancer, heart failure, or muscular dystrophy.

Figure 9 illustrates SLE-associated cumulative incidence for WD pensions. Five years since diagnosis 3.4% (95% CI 1.9 to 5.8) and at the end of observation 5.0 % (95% CI 3.0 to 8.5) of the patients were granted WD pension due to SLE. The respective numbers for all-cause WD pensions were 5.8% (95% CI 3.9 to 8.7) and 8.6 % (95% CI 5.6 to 13.1). In the comparison to the general population in Finland age- and sex-stratified incidence ratio for WD pension due to all cause in incident SLE patients was 5.4 (95% CI 3.7 to 7.9).

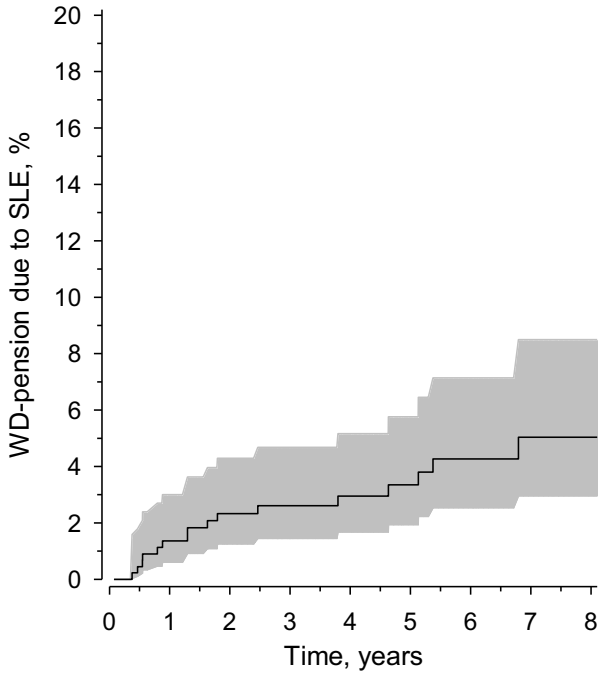


Figure 9. Systemic lupus erythematosus (SLE) -associated cumulative incidence for work disability with the 95% confidence intervals (grey area) since diagnosis in 446 working-aged incident SLE patients in Finland years 2000-2008 **(IV)**

5.1.6 Mortality (II)

There were 30 deaths among the incident SLE cohort during the median follow-up time of 5.4 (IQR 3.3, 7.1) years in 2000-2008. The mean age at death among 23 females was 67.8 ± 17.2 years and among 7 males it was 62.3 ± 15.2 years. Figure 10 illustrates the survival of the incident SLE cohort by gender. In females the five-year survival rate was 94.8% (95% CI 92.0% to 96.6%) and the eight year survival rate was 93.5% (90.2% to 95.7%). In males the respective figure after 5 years was 88.2% (76.5% to 94.3%) and because there were no additional deaths among the male cohort since 5 years after diagnosis, the survival rate stayed the same at 88.2% (76.5% to 94.3%) after 8 years. The age-stratified hazard ratio for females compared with males was 0.69 (95% CI: 0.29 to 1.62), P=0.39. The age- and gender stratified standardized mortality ratio (SMR) was 1.48 (95% CI 1.01 to 2.12); 1.65 (1.04 to 2.47) in females and 1.12 (0.45 to 2.30) in males.

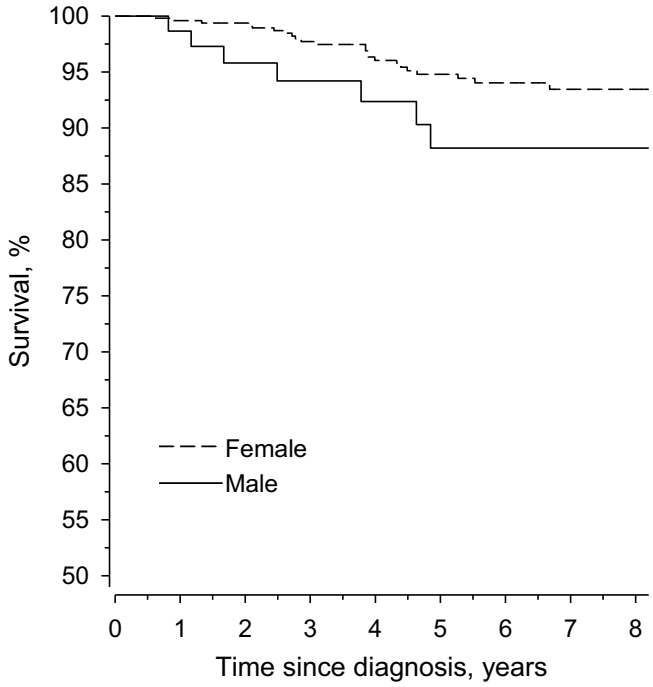


Figure 10. The Kaplan-Meier estimated survival function for Finnish incident SLE patients 2000-2008 captured since diagnosis **(II)**

Primary causes of death in 30 incident SLE patients were as follows: cardiovascular causes 11 (36.7%), malignancy 5 (16.7%), SLE 4 (13.3%), accidental/suicidal causes 4 (13.3%), gastrointestinal causes 2 (6.7%), renal failure 1 (3.3%), pulmonary interstitial disease 1 (3.3%), hematological disorder 1 (3.3%), and dementia 1 (3.3%). Multiple causes-of-death analysis of each patient is presented in table 14. One fifth of the deaths had an infection as an immediate cause of death and in half of them SLE was classified as an underlying cause. The lethal infections were 3 pneumonias, 2 septicemias, 1 acute cholecystitis and one acute peritonitis.

Table 14. Multiple causes-of-death analysis in 30 deceased incident SLE patients during 2000-2008 in Finland **(II)**

Underlying cause	Causes leading to death	Immediate cause	Contributory cause
SLE		Septicemia	
SLE			Grand-mal epileptic seizure
SLE		Acute peritonitis	
SLE		Pneumonia	
Myocardial infarction		Thrombosis in coronary arteries	
Myocardial infarction			Pneumonia
Myocardial infarction			SLE
Myocardial infarction		Pericardial bleeding	
AHD		Heart failure	Hypertension
AHD			Diabetes, SLE, AHD
AHD		Heart failure	SLE
AHD			Atrial fibrillation, asthma
Rheumatic valve disorder		Heart failure	SLE
Cerebrovascular ischemia			
Multiple cerebral bleeding			
Lung cancer			
Lung cancer		Intoxication	Pneumonia
Cervix cancer			
Gall bladder malignancy		Acute cholecystitis	
Cancer of unknown origin			
Suicide	Suffocation		Inebriation
Accident	Hypothermia		Intoxication, Falling
Accident		Carbon monoxide intoxication	Inebriation
Accident	Local brain injury		
Ileus		Septicemia	AHD
Autoimmune hepatitis			SLE, diabetes, sarcoidosis
Renal failure		Unspecified fever	
Pulmonary interstitial disease			AHD, hypertension, asthma
Hemotological disorder			Acute tubulointerstitial nephritis
Dementia			SLE

SLE = systemic lupus erythematosus, AHD = atherosclerotic heart disease

Cardiovascular drugs and systemic infection agents were responsible for 36% of the total cost of medication in outpatient therapy among these patients. Table 15 describes the distribution of total medical costs used in outpatient drug therapy in deceased SLE patients since diagnosis until death. The proportions of costs for cardiovascular and anti-rheumatic drugs are shown in detail.

Table 15. Distribution of the total cost of medication in outpatient therapy with detailed information for medicines in cardiovascular and antirheumatic categories in deceased SLE patients during the years 2000-2008 in Finland

Medicine category	**Medicine**	**Proportion (%)**	**Total (%)**
Cardiovascular			18,3
	Diuretics	27,3	
	Renin-angiotensin system inhibition	18,0	
	Beta-blockers	16,4	
	Nitrates	15,3	
	Calcium antagonists	8,2	
	Statins	8,2	
	Digoxin	5,5	
	Others	1,1	
Systemic infection agents			17,2
Antirheumatics			13,0
	Corticosteroids	42,3	
	Hydroxychloroquine	27,7	
	Azathioprine	13,8	
	Methotrexate	7,7	
	Cyclophosphamide	2,3	
	Mycophenolate mofetil	2,3	
	Others	3,8	
Analgesics			9,1
Gastroenterological			9,1
Psychiatric			7,8
Local dermatological			6,1
Bone metabolism			4,7
Others			14,7

SLE = systemic lupus erythematosus

5.2 INCIDENCE AND CHARACTERISTICS OF THE NORTHERN SAVO-2010 COHORT (V)

5.2.1 Patients

A total of 72 patients (56 females) were diagnosed with a new autoimmune CTD in 2010 in the Northern Savo hospital district. Table 16 presents the number of incident patients in certain CTD classes, gender distribution, mean age at diagnosis and median diagnostic delay from the first symptoms to diagnosis.

Table 16. Number of new cases of autoimmune connective tissue diseases, gender distribution, mean age at diagnosis and median delay from the first symptoms to diagnosis in Northern Savo in year 2010 (**V**)

Disease	Number of cases (females)	Mean age at diagnosis, years ±SD	Median delay to diagnosis months, IQR
SLE	7 (4)	48.7±14.1	6.0 (3.0,16.0)
Dermato/polymyositis	4 (2)	68.7±10.4	2 (1.3,5.0)
Systemic sclerosis	9 (7)	65.1±9.9	72.0 (40.5,186.0)
Sjögren's syndrome	22 (21)	48.9±15.3	12.0 (5.8,27.0)
MCTD	2 (2)	50.4±12.3	9.0 (6.0,12.0)
UCTD	28 (20)	49.4±14.3	6.5 (3.3, 18.0)

SD = standard deviation, IQR = interquartile range, SLE = systemic lupus erythematosus, MCTD = mixed connective tissue disease, UCTD = undifferentiated connective tissue disease

The mean ages of CTDs were around 50 years of age, except for SSc 65 years and for idiopathic inflammatory myopathies 69 years. Diagnostic delays from the initial symptoms into definite diagnosis of CTD in general were between 2 to 12 months, with exception of SSc. The median diagnostic delay in SSc was 72 months. Fifty-nine patients with CTD were continued into the larger study protocol. Altogether, 47% of 59 CTD patients had positive family history with other rheumatic autoimmune disease at least in one first- degree relative. Six (10%) patients had an earlier history of smoking and 11 (22%) patients were current smokers. Thirty-six patients (60%) were overweight at diagnosis and nine (15%) were obese, BMI >30 kg/m^2. Table 17 presents the characteristics of incident SLE patients in Northern Savo in year 2010. All except one of the seven new SLE patients fulfilled four ACR97 criteria for SLE (24,25) and one patient fulfilled seven criteria. When all new connective tissue diseases were classified according to the SLICC classification criteria for SLE (6) one additional patient was found from the UCTD group, and three patients fulfilling the ACR97 criteria for SLE did not meet the recent criteria for SLE.

Table 17. Characteristics of incident SLE patients in Northern Savo in year 2010 (**V**)

Manifestation	**Number of patients n=7**	**Percentage %**
Malar rash	6	86
Discoid rash	5	71
Photosensitivity	4	57
Oral ulcers	2	29
Arthritis or arthralgia	5	71
Serositis	-	-
Renal disorder	2	29
Neuropsychiatric disorder	1	14
Hematologic disorder	1	14
Immunological disorder	2	29
ds-DNA-Ab	2	29
Sm-Ab	2	29
Low levels of C3/C4	4	57
Antinuclear antibodies	7	100
Smoking history	4	57
Current	3	43
Ex- smoker	1	14
BMI ≥ 25	6	86
BMI ≥ 30	3	43
Rheumatic disease in relative*	3	43

SLE = systemic lupus erythematosus, ds- DNA-Ab = double-stranded DNA antibodies, Sm-Ab = Smith antibodies, C = complement, BMI = body mass index, *only first degree relatives counted

5.2.2 Incidence

The overall crude annual incidence rate was for systemic CTD 34.9 (27.3-43.9) and age-adjusted 35.0 (33.3-36.8) per 100 000. Table 18 shows the amount of new connective tissue diseases in various classes and the annual incidence figures with crude and age-adjusted rates.

Table 18. Number of new cases with various connective tissue diseases in Northern Savo in 2010 and annual incidence rates per 100 000 presented with 95 % confidence intervals. Incidence rates are age-adjusted with the Finnish 2010 population. **(V)**

Disease	**Number**	**Incidence**	
		Crude	**Age-adjusted**
SLE	7	3.4 (1.4-7.0)	3.6 (3.0-4.2)
females	4	3.8 (1.0-9.7)	4.0 (3.5-4.7)
males	3	3.0 (0.6-8.7)	3.1 (2.6-3.6)
DM/PM	4	1.9 (0.5-5.0)	1.8 (1.4-2.2)
females	2	1.9 (0.2-6.9)	1.5 (1.2-1.9)
males	2	2.0 (0.2-7.1)	2.1 (1.7-2.5)
SSc	9	4.4 (2.0-8.3)	4.1 (3.5-4.7)
females	7	6.6 (2.7-13.7)	5.8 (5.1-6.6)
males	2	2.0 (0.2-7.1)	1.8 (1.4-2.3)
MCTD	2	1.0 (0.1-3.5)	1.0 (0.7-1.3)
females	2	1.9 (0.2-6.9)	2.0 (1.6-2.5)
males	0	< 3.0 (0.6-8.7)	
Sjögren's syndrome	22	10.7 (6.7-16.1)	10.8 (9.9-11.8)
females	21	19.9 (12.3-30.5)	21.9 (20.5-23.3)
males	1	1.0 (0-5.5)	0.02 (0-0.13)
UCTD	28	13.6 (9.0-19.6)	13.9 (12.8-15.0)
females	20	19.0 (11.6-29.3)	16.9 (15.7-18.2)
males	8	7.9 (3.4-15.6)	7.4 (6.6-8.2)

SLE = systemic lupus erythematosus, DM = dermatomyositis, PM = polymyositis, SSc = systemic sclerosis, MCTD = mixed connective tissue disease, UCTD = undifferentiated connective tissue disease

6 Discussion

6.1 CASE IDENTIFICATION AND METHODS

6.1.1 Incidence studies

The basic element of a reliable epidemiological or clinical study is proper patient identification with decent disease classification, ensuring that the study concentrates on the right patients and may thereby offer valuable information (352). In this Finnish early SLE register study, the patient identification was based on the reimbursement decisions for the SLE treatment. The method used does not confirm whether all the patients fulfilled the criteria for classification of SLE. Nevertheless, the reimbursement decision required diagnosis verified both by a specialist treating SLE and by an official in the SII. Moreover, the sensitivity of the present method has been evaluated to be 95% when assessing the incidence of inflammatory arthritides (353).

It is possible that the method misses some patients with a silent clinical condition with no need for drug therapy, those patients who are in an early stage of the disease and are classified initially under the category of undifferentiated CTD, and those who die soon after diagnosis, before the reimbursement application is made. In the present study selection bias caused by the patient's socioeconomic status or residence is minimized because the benefit is available to all permanent Finnish residents. In contrast, in many studies identifying patients through insurance databases, lower socioeconomic classes are underrepresented (71,72).

Great strengths of the present study are the nationwide coverage and the longitudinal setting. Nationwide studies on incidence, drug therapy, WD and mortality are sparse (67,76,106,116,291,354). In addition to representing a comprehensive sample of an entire population, they at the same time identify unselected patients. The longitudinal setting reveals any secular trend of the disease. An inception cohort allows observation of early events in the disease course. This register study lacks clinical data. This limitation excludes disease characteristics and activity, hospital-based drug therapy and predictors for prognosis.

In contrast, in the Northern Savo 2010 incidence study SLE patients could be classified by both the ACR97 and the recent SLICC criteria (6,24,25), and clinical characteristics and concomitant medication were available. On the other hand, in the Northern Savo 2010 incidence study, the data collection period was too short leaving the possibility of chance and hiding fluctuation of incidence over time. The number of total cases was small and the

inadequate, partly clinically-based case definition of primary Sjögren's syndrome (pSS) may have led to overlapping between classifications of pSS and UCTD. Strengths of the Northern Savo study are that it gathered cases without a definitive diagnosis during the one- year observation. The study simultaneously compared the incidence of SLE with other autoimmune connective disease categories.

6.1.2 Other aspects of the Finnish early SLE register study

In this study the evaluation of the drug usage was based on drug purchases in contrast to studies which based on patients' prescriptions (43,354). The present method better accounts for primary non-compliance. This method, however, neglects the medicines used only in hospitals like intravenous cyclophosphamide and those sold over- the- counter like acetylsalicylic acid. It is worthwhile to recognize that the present method does not demonstrate if a patient maintained the therapy after the first purchase. Rather, the results reflected the general view of the initial treatment strategy in Finland. The most ideal way to study drug treatment in a multidimensional disease like SLE would also account for the clinical features and activity of the disease, but the available data did not allow that kind of approach.

The SII carefully ensures that patients are alive and that reimbursements are not paid to the heirs. Also in the present study the patients who died during the follow-up were excluded from the analysis further on.

The study cohort was compared with the total population in terms of the drug usage in preselected comorbidities, incidence of WD and mortality rates, increasing the value of the results. However, shorter sick leaves lasting ≤ 10 days are not covered. Thus, the results represent an underestimate of the real absenteeism. Considering mortality and WD the follow-up time is rather short and a longer follow-up could have better revealed trends in work participation and in mortality.

The structure of the death certificates is based on multiple cause of death analysis in Finland. This enables more precise evaluation on multi-dimensional disease process in the most severe form of SLE in the present study (339). Some studies are still reporting only one primary cause of death. Multi-cause analysis results in that, all infections are placed under the immediate or the contributory cause of death, not among the underlying cause of death on the contrary to the studies demonstrating only one primary cause of death (18,308,334).

6.2 INCIDENCE IN FINLAND

In the present two studies, the incidence of SLE in Finland in this millennium was estimated by two different methods. The figures on the incidence in those studies are close each other and in line with the earlier Finnish study from the 1970s reporting the rate of 3.8/100 000. It seems that the incidence of SLE has remained stable during the last decades (64). The comparison of the results between the Finnish early SLE register study and Northern Savo 2010 incidence study is difficult as the study designs were completely different. In short, in the Finnish early SLE register study the strengths were comprehensive coverage of patients and a sufficiently long collection period whereas Northern Savo 2010 incidence study identified patients more reliably with clinical characteristics. As the occurrence of SLE is clearly related to race, the most reliable way to assess the results is to compare them with populations of similar background like in Nordic countries.

The Icelandic incidence study on SLE from the years 1975-84 had a nationwide design. The patients were collected from hospital records and physician surveys and classified according to the ACR82 criteria. The study reported an incidence rate of 3.3/ 100 000 (51). Also one recently published Danish study has reported nationwide incidence figures (76). All the other previous Scandinavian incidence studies on SLE are based on patient cohorts in a defined region of a country (32,38,49,53,64,66,73-75). There are three earlier Norwegian studies (32,42,53). The most recent study was performed in Oslo in the years 1999-2008. The study identified patients with ACR97 classification criteria from a systemic connective tissue disease and vasculitis register, rheumatology services from hospital and private practice, cause of death register, an earlier hospital SLE cohort and reported an incidence rate of 3.0 (42). The other Norwegian hospital register-based study included two SLE cohorts from time intervals 1978-95 using ACR82 classification criteria and 1996-2006 using ACR97 criteria. The incidence in the earlier cohort was 2.6 and in the latter 3.0 (32). The third study from years 1978-1996 identified patients from hospital registries and mortality database, used ACR82 criteria and estimated the incidence rate at 2.6 (53).

There are three Danish incidence studies. Two of them relied on ACR82 criteria and the old method by Fries and Holman and identified the patients from the hospital records, private sector, general practitioners and the register for autoimmune tests (49,73). The first evaluation was made in 1980-94 and reported rates between 1.1-3.6 (73) and the second study with a rate of 1.0 from the years 1995-2003 was also made in the Funen area, representing 9% of the entire Danish adult population (49). The latest Danish study identified SLE patients in the Danish National Patient Registry using ICD-10 codes during the years 1995-2011. The patients had to have at least one year of follow-up with the same

diagnosis corresponding SLE. The overall incidence rate was 2.4 in this nationwide study (76). In Sweden, there are four incidence studies on SLE. The collection of patients in the first study was done in 1981-82 from hospital and primary care registers, and the study used preliminary ARA71 and revised ACR82 criteria for classification. The estimate of the annual incidence was 4.8 (38). The later studies from Sweden used either a clinical definition or the old method by Fries and Holman for classification of SLE patients and retrieved the patients from hospital records, diagnostic registries, primary care units and the central laboratory database in the Lund-Orup health care district. The incidence figures from years 1981-91 were between 4.0-4.8 (66,74). The most recent study from years 1981-2006 reported a rate of 3.9 and confirmed the classification also with ACR82 criteria (75).

In a comparison of Scandinavian studies and the present work to studies made worldwide, the figures are clearly lower (35,37,46,63,70,120). When concentrating on the studies in which the data collection has been made mostly since the year 2000, the highest incidence figure of 8.7/100 000 is reported from Brazil in a study classifying cases by ACR82 criteria and collecting cases from public and private health units and laboratory databases (46). Other high rates of incidence (up to 8.4) have been reported from Asia in studies that relied on national health insurance databases and identified cases by ICD-9 codes (67,70). The incidence figures in the latest European studies (0.3-4.9) have been close to figures in the present two reports (34,41,52,65,116,120).

One European study has taken advantage of the national insurance database. The French study collected the patients in the year 2010 using ICD-10 codes, confirmed the diagnosis of insured patients by the hospital discharge registers and reported an incidence rate of 3.3 (65). In contrast, the latest US studies have shown uniformly higher rates of incidence ranging from 5.5 to 7.6 (35-37,44,72). The higher rates in the USA seem to be reliable as the methods in those reports have been different, but the results were similar. The US studies have collected SLE patients from multiple sources, including hospital records, specific lupus registries and insurance claim codes and identified patients with ACR82, ACR97 and ICD-9 codes (35-37,44,72). Differences in the race distribution may be attributable at least partly to the divergence between US and European reports (35-37,41,44,65,72,120).

An interesting phenomenon in Scandinavia is the highest peaks of incidence in older women close to menopausal age (38,51,66). The finding was repeated also in the present study. Nevertheless, the most recent report from Sweden was different. Whereas in the first Swedish SLE cohort from years 1981-93 incidence was highest in 45-54 years old females, in the latter cohort from years 1994-2006 females were most likely to develop SLE at the age of 25-34 years (75).

There is not much research simultaneously comparing the incidence of different connective tissue diseases in the same area (69,78). A Taiwanese study identified the CTD patients from the national health insurance database in years 2005-2009 by ICD- 9 codes and found incidence rates as follows: Sjögren's syndrome 11.8 /100 000, SLE 7.2, systemic sclerosis 1.1, dermatomyositis 0.7 and polymyositis 0.6. Rates for MCTD and UCTD were not assessed. The order of frequency of CTDs in the present Northern Savo 2010 incidence study was similar to the Taiwanese study (69).

6.3 USE OF INITIAL ANTIRHEUMATIC AND COMORBID MEDICATIONS IN FINLAND

6.3.1 Initial drug therapy in SLE

In 2000-2008, the majority of SLE patients (90%) received some DMARD during the first-year after the index day, and three -quarters hydroxychloroquine. The use of antimalarials was stable from year to year. The coverage of the AMs could have been better. Guidelines advise to prescribe AMs to all SLE patients who can tolerate it and have no contraindications to the drug (9,12,227). AMs have beneficial effects on drug tolerance, skin manifestation, survival, and lipid and glucose metabolism, and they protect from damage and flares (9,156,225,227,232). In severe SLE, AM therapy alone is not sufficiently efficacious (225).

Glucocorticoids have been and still are invaluable therapeutic agents in SLE, especially for the most serious manifestations (223). However, they have many dose- and duration-dependent adverse effects like hyperglycemia, hypertension, an increased risk of infection, osteoporosis and mood disorders. Therefore, their dose and treatment time should be minimized. DMARDs help in sparing glucocorticoids (12,221). In the present study, the proportions of various DMARDs were similar throughout the study periods, with exception of an increase in purchases of MMF and a cessation in the use of oral cyclophosphamide in early therapy. The promising results on the use of MMF since the turn of millennium are reflected most probably in the increased purchases of the drug in Finland (250,256,264). Azathioprine was the most commonly prescribed (15%) immunosuppressive agent. Azathioprine can also be used during the reproductive years (264). The second common immunosuppressive drug was methotrexate known to be beneficial especially in arthritis (216).

Few studies have focused on early drug therapy in SLE (43,284,354), and most of them deal with lupus nephritis (14,15). Early treatment strategies differ between studies. Most of them are conducted in academic referral centers, whereas the present study examined unselected nationwide data. A multinational European study lasting 5 years until the year

2005 reported first-year anti-rheumatic medication in 200 SLE patients. AMs were less (46%) and oral glucocorticoids more (83%) commonly used than in the present study, and 60% of the patients received immunosuppressive agents. The most common immunosuppressant was azathioprine (25%), followed by cyclophosphamide (24.5%), including both oral and intravenous dosing (284). An UK study based on prescription data in the General Practice Research Database in 1990-1999 found that AMs were prescribed for 38%, azathioprine for 14%, methotrexate for 5% and glucocorticoids for 51% of the incident SLE patients. The proportions of other immunosuppressive agents were minor and the method used identified only outpatient drugs (43), as did the present study. A study retrieving data from the national database of the German Collaborative Arthritis Centres showed in a subanalysis of outpatient drug therapy in incident SLE patients over the years 1993 - 2012, that the initiation with glucocorticoid therapy diminished and the use of non-steroidal anti-inflammatory drugs (NSAIDs) expanded. The same study on established SLE in years between 1994 and 2012, found that AMs and MMF became more common and glucocorticoids less common over time. In a cross-sectional evaluation in the year 2012 the German SLE patients used anti-rheumatic drugs as follows: glucocorticoids in 69%, AMs in 56%, azathioprine in 22%, MMF in 15% and NSAIDs in 23% of the patients (354).

The rest of the studies reported medication only for established SLE patients with longer disease duration (184,187,355). A cross-sectional RELESSER-T study performed in Spain in 2011-2012 reported that 89% of the patients were on glucocorticoids, 83% on AMs, 33% on azathioprine, 23% on cyclophosphamide, 17% on methotrexate and 15% on MMF (187). The earlier EURO-Lupus cohort study from years 1990-2000 documented that 48% of 1000 SLE patients were prescribed AMs, 73% oral glucocorticoids, 16% azathioprine, 9% oral cyclophosphamide and 6% methotrexate (184). In the observational, community-based study from the years 2002-2006 in San Francisco, 55% of the 881 patients reported using HCQ annually, and 69% of them received at least one immunosuppressive drug (355). None of the studies reported a combination of two or more DMARDs (184,187,355). In comparison to the previous studies, the Finnish initiation regimen seems to be active and follows more closely the proposed international guidelines (9,12).

6.3.2 Comorbid medication in incident SLE patients

The present study found that incident SLE patients had overall more abundant purchases of drugs for preselected concomitant diseases compared with the general population. The excess medication could be explained by the regular frequent visits to a specialist, which may help recognize and treat comorbidities in earlier stage. Nonetheless, the literature shows that SLE patients are predisposed to certain co-morbidities due to therapy and the

disease itself. Known concomitant conditions in SLE are infections, metabolic syndrome (including dyslipidemia, hypertension, cardiovascular diseases and hyperglycemia), thrombosis, malignancies and osteoporosis (12,305,356).

Despite the importance of traditional cardiovascular risk factors, they do not completely explain the increased risk for cardiovascular events in SLE patients (278,357,358). Increased atherosclerosis has been hypothesized to develop mainly due to a continuous, longstanding inflammatory process and side-effects of anti-inflammatory drugs. Available data demonstrates that the disease itself with multiple defects in immune system like increased production of interferon I, C1q deficiency and increased endothelial apoptosis, is tightly bound to the unique pathogenesis of accelerated early atherosclerosis in SLE (180). In addition, renal damage, glucocorticoids and positive anti-phospholipids have been shown to be partly responsible for the excess CVD (188,278,358). The guidelines for the management of hypercholesterolemia, hypertension and diabetes rely on the data from the general population (358), and no SLE-specific recommendations are available.

Treatment results from the population cannot be generalized to patients with SLE. The randomized two-year Lupus Atherosclerosis Prevention Study (LAPS) did not meet the primary outcomes in decreasing subclinical atherosclerosis measures and disease activity in lupus patients (359). Also the study concentrating on clinically stable SLE patients showed no superiority of rosuvastatin compared with placebo in terms of carotid intima-media thickness in two years or in disease activity in 12 months, although there was a significant difference in low-density lipoprotein (LDL) cholesterol level and in high-sensitivity CRP after one year of treatment with rosuvastatin 10mg/day treatment (360). Yet, as the atherosclerosis has a crucial role in SLE and the benefits of statins in the general high-risk population are clear, statins are recommended as the first-line drug in lowering high lipid levels (12,217,358). In the present study, the early SLE patients (14%) received lipid-lowering therapy consisting mostly of statins, 3.5 times more frequently than the age- and sex-adjusted control population. In Spain, a quarter of established SLE patients received statins in 2011-2012 (187).

Glucocorticoids have a dual role in CVDs. On the other hand they work directly to reduce inflammation, but at the same time at least with higher doses they may promote hyperglycemia and hypertension (180,221,223). The incident SLE patients in the present study received glucose-lowering therapy slightly more frequently than the general population, but the evaluation of concomitant medication was made shortly after diagnosis and the exposure to the glucocorticoids was not long. The results of the present study are in line with the guidelines to treat hypertension in SLE, which recommend angiotensin-converting enzyme (ACE) inhibitors as primary drugs, followed by thiazide

diuretics, calcium-channel blockers and beta-blockers (217,358). Especially renal involvement highlights the importance of blood pressure control (217,361). The overall usage of antihypertensives in the SLE cohort was at higher level than in the population.

A Puerto Rican comorbidity study on 877 established SLE patients found hypothyroidism to be more prevalent (19%) than diabetes (12%) among SLE patients, but the results were not compared to the general population (119). A Brazilian study instead reported significantly more subclinical hypothyroidism and thyroid autoantibodies in established SLE patients than in controls (362). A retrospective study on 300 SLE patients from the UK showed that the prevalence of hypothyroidism was almost six times higher in the SLE population than in the background population (363). In line, a recent Israeli retrospective case-control study confirmed a significantly higher prevalence of hypothyroidism in 5018 SLE patients than in age- and gender-adjusted 25 090 controls (364). In the present study the SLE patients received medication for hypothyroidism almost five times more often than the controls.

The data concerning SLE and obstructive pulmonary diseases is almost non-existent. The role of asthma in SLE is controversial. Few earlier studies have analyzed the association between SLE and allergic disorders, including asthma. One study showed no elevated risk for IgE-associated allergic disorders, and another study reported fewer allergic disorders compared with non- SLE controls (365,366). The opposite result has been subsequently published. The Taiwanese study relying data on national insurance claims of dataset of 1673 incident SLE patients and 6692 randomly selected age- and gender-adjusted controls found that asthma in patients was a little more common than in controls with odds ratio of 1.43 (142). In the present study the use of medication for obstructive pulmonary diseases was at a higher level than in the general population.

Since SLE is predominant in females, the role of sex hormones in SLE is interesting. The complex mechanism is still under research (367). The disease occurs frequently in females at child-bearing age (184,284), and due to aggressive treatment and improved prognosis patients may experience menopausal symptoms more often than patients in earlier decades. Safety data of exogenous estrogens in SLE are limited, but in selected patients oral contraceptives did not increase the amount of severe disease exacerbations (280). In parallel, a randomized study found no difference in disease activity and flares between hormone replacement therapy (HRT) and control groups in mild and moderate SLE. However, the risk for thrombosis seemed to be elevated with the use of HRT (281), and HRT is not recommended for SLE patients with anti-phospholipid antibodies, ongoing disease activity, an earlier history of thrombosis, or atherosclerotic heart disease (217). In the present study females with SLE used reimbursed sex hormones more often than those

without the disease. This may be partly explained by the need of birth control and earlier postmenopausal age due to immunosuppressive treatment and disease stage. It must be acknowledged, though, that not all sex hormones are included in the reimbursed drugs, and the total picture of sex hormone usage is therefore incomplete in the present results.

The present study shows similarities in the overrepresented comorbidities in SLE patients with the above- mentioned studies. However, the results drawn from the drug purchase register as such cannot be generalized as comorbidities of the patients.

6.4 WORK DISABILITY AND MORTALITY AS OUTCOME MEASURES

6.4.1 Work disability

The present study clearly showed that even early SLE has a significant impact on patients' ability to work. Compared to the general population the incident SLE patients had a five times higher risk for permanent WD and the disease itself was the main reason. It is generally assumed that SLE and conditions related to disease may cause incapacity to work, although earlier reports have not specified the causes of WD (10,290,302).

The comparison of studies on WD is hampered by different study settings, identification of WD and patients, definition of sick leaves, social security systems and work-associated factors (10,291,295,296). SLE occurs often in females at reproductive age (26). WD statistics do not account lower functional capacity of those females who are not gainfully employed but are instead homemakers. Studies are sparse, small and only a few of them concentrate on early SLE (10,286,289,290,294,295,297,299-304). There are no data on the impact of therapeutic procedures on WD in SLE, possibly due to multidimensional disease and hetegeneous and individual treatment policy.

The present study method detected the long-term, over 10 weekdays lasting WD periods and found that all SLE patients had on an average 32 annual WD days per year. The amount of them increased over the follow-up time. In an earlier Finnish hospital-based cohort study, working SLE females had lost 2.5 times more workdays in the preceding 12 months in contrast to those with no disease (295). In a Dutch study, the long periods of WD days were more common in SLE patients than in patients with granulomatous polyangiitis (297). Also in a cross-sectional study on the database of the German Collaborative Arthritis, the mean loss of working time in the past year was long, 9.9 weeks in a cohort of 1248 SLE patients with a mean disease duration over 10 years (296). Moreover, the study on early SLE demonstrated that WD periods lasting over 14 days in the past year were more common among patients in the Carolina Lupus Cohort (21%) than in controls (11%) (10).

The data on patient-related factors and WD in SLE has widely shown association with African-American race and higher age at diagnosis into higher rates of total work cessation (286,290). In Finland, the population is almost entirely Caucasian (345), and the mean age at disease onset was 42 years in the present study. The earlier studies on WD detected rates of 13-43 % of permanent WD after 3-18 years (10,286,289,290,294,295,297,299-304). There are only a few reports on WD in early SLE patients (299,302,304). In the present study, 6% of SLE patients were retired due to health reasons for any cause 5 years after diagnosis. In Canada the WD rate in 216 incident SLE patients raised progressively over time since diagnosis and was 13% at 2 years, 19% at 5 years and 21% at 10 years (304). The rate of the present study at 5 years is three times less than in the Canadian study, possibly partly explained by the nationwide study setting and strict and reliable pension-based definition of WD. A cross-sectional, multi-center US study demonstrated that after the average of 3.4 years of diagnosis, 40% of 152 early SLE patients reported WD due to SLE (299). A Chinese cross-sectional study, advancing patient self-reports on WD found that 37% of 105 SLE patients were not working due to SLE after 10 years of disease duration. Interestingly, half of those WD patients had stopped working already two years after disease onset, indicating an early impact of SLE on work disability (302). As a summary of previous data and the results of the present study, SLE is a threat for work ability (10,286,289,290,294,295,297,299-304).

6.4.2 Mortality

The survival of the incident SLE patients was lower than in the background population in Finland. The leading causes of death were cardiovascular diseases (37%). The shorter life expectancy in SLE patients is well-documented in previous studies. European studies, mostly in established SLE, have reported SMR of 1.3-4.6 (49,53,312,318,323,324,326,328). A Greek study collected an inception SLE cohort from the records of hospital and private clinics in the years 1982-2001 and found a SMR of 1.3 (50). The figure is consistent with the present study. The other study on incident SLE cohort reported a higher SMR of 2.7 in Rochester in the USA, but the collection of the 48 SLE patients was done from medical records dating back to years 1980-92 (316).

Survival studies on SLE commonly have small numbers of patients (17,32,51,61). Looking at the five-year survival rates of SLE patients before the millennium and omitting the location of the study, the rates range from 60% to 97% (48,312). The 5-year survival rates in the studies made since the millennium have reported rates between 80 and 99.5% (40,325). The results of the present study were similar to most of the recent European studies (32,55,184). The general trend in the survival is a clear improvement during the decades, at least in the short term. Still, there is an apparent discrepancy on survival rates from the

western world compared to studies from the other parts of the world (40,184,307,321). The possible explanations for the distinct rates could be the unbalanced distribution of welfare and the differences in the features and severity of the disease between various ethnicities. It has also been suggested that recognition of milder disease forms and earlier identification of SLE and concomitant diseases may account for better survival rates in the recent studies (323).

Most of the reports on causes of death in SLE are cohort studies, but there are a few researches that identified patients entirely from death certificate registries (339,341). The disadvantage of those studies based only on death registers is that they do not necessarily identify all SLE patients if SLE is not involved in the process of death. The strengths of the present study are the inception cohort, reliable death certificate register and multiple cause of death analysis. Underlying causes of death in the present cohort were in line with most European recent studies (326,331,333). Renal involvement leading to death in the early course of disease was rare (3%). This finding is most likely due to short follow-up of the present study, as the incidence of lupus nephritis increases along with longer disease duration (181,368).The result may also be attribute to better therapeutic interventions on lupus nephritis (330). Moreover, the prevalence of lupus nephritis is lower in Caucasians than in the other races (369). Yet, in the only previous nationwide Finnish investigation from years 1972-78, SLE itself was responsible for over half of the deaths of 142 SLE patients and 27% of the patients died due to renal causes. Infections, cerebrovascular accidents and central nervous system involvement due to active SLE were accountable for 17%, 12% and 7% of the deaths, respectively (116).

As the overall survival in SLE has become better, cardiovascular causes have taken precedence over the traditional SLE-related causes of death (330,331). Already in the 1970s Urowitz et al represented a bimodal mortality in SLE, in which patients with early-stage SLE died because of active lupus with multiple infection and the patients with longstanding disease died mostly due to atherosclerotic heart disease (317). Based on the multinational European cohort in 2000-2004, the bimodal mortality is currently changed and infections and cardiovascular events are equally represented in the early and late deaths related to SLE (331). The results of the present study suggest that cardiovascular disease is exacerbated in the early stages of SLE, although it is possible that the high mean age at diagnosis may have impact on the results.

The limitation of the present study is the lack of comparison of the causes of death with the general population. A Swedish hospital register-based study from years 1964-1994 on 4737 SLE patients found that in the age -group of 20-39-year-old patients the risk of death due to atherosclerotic cardiovascular disease was 16 times higher compared to the general

population (326). Moreover, a US study from the University of Pittsburgh Medical Center identified 498 SLE females in the years 1980-1993 and found that in comparison with 2208 age-adjusted control females with 35-44 years of age females, the probability of myocardial infarction was 52 times higher in SLE patients (370). A retrospective US study compared an inception cohort of 70 SLE patients to 2565 age- and sex-stratified controls years 1991-2008 and discovered that SLE patients had almost two times higher risk for death and cardiovascular disease already two years before the diagnosis. When the previous cardiovascular disease was adjusted, after 540 patient-years of follow-up SLE patients were almost two times more likely to die or have a new cardiovascular incident than the reference population. The authors speculated that late diagnosis or an accelerated atherosclerotic process prior to diagnosis may explain the observation (17). In future studies it would be worthwhile to concentrate on preclinical or early stages of SLE in terms of atherosclerosis.

The format of the Finnish death certificates categorized all infections under the immediate or the contributing cause of death, not under the class of underlying cause of death. This complicates the comparison between the studies, but describes the process of death more precisely. In the present study infections were responsible for most of the deaths when SLE was an underlying cause of death. Infections were involved in one fifth of the deaths. This finding is in line with some earlier studies from developed countries (55,318) and differs from studies performed in developing countries reporting higher percentages up to 60 % (308,309,314). Some studies have supported the belief that immunosuppressive medication used for active SLE predisposes to severe, life-threatening infections (19,71,154). The Danish study showed that lethal infections occurred most likely in the early stage of SLE and were most often pneumonias (318). In the present study pneumonia and septicemia precipitated most of the infection-related deaths in incident SLE patients.

A large multisite international SLE cohort study in the years 1970-2001 showed that mortality due to overall cancer was not increased (SMR 0.8), but for certain specific malignancies like in lung cancer and NHL mortality was notably increased (18). The prospective European multinational study reported malignancy in 8% of the 91 deaths. There was no association between previous use of immunosuppressive drugs and cancer (331). In the present study malignancy was the cause in 17% of the deaths.

In summary, the risk of death is increased soon after the diagnosis in SLE patients. Elimination of excess cardiovascular risk in SLE needs more attention. Further studies on long-term survival in incident SLE are needed.

6.5 THE CLINICAL RELEVANCE OF EPIDEMIOLOGICAL APPROACH TO DISEASE

Due to heterogeneous disease profile and low annual incident SLE numbers especially in the Scandinavian countries, clinical studies on SLE are difficult to carry out. As the incidence, age at diagnosis, disease spectrum and severity and mortality differ greatly between races and societies, the results from other countries should not to be generalized as such in Finland (21,27). In order to attain accurate knowledge of SLE in Finland, the study must be local. An epidemiologic approach like in the present study is often descriptive and offers information of the nature, comorbidity and prognosis of the disease for the health care management at the society level and for the diagnostics and therapy at the health care specialist level.

The approach to the incidence of SLE was performed by a retrospective and longitudinal nationwide register study, and the perspective was supplemented by a prospective population-based study in a defined area in Northern Savo. In the present study, it was found that in Finland the incidence of adult SLE is not increasing, the disease is more infrequent in males, and male SLE patients die younger and at an earlier stage of the disease than females. Although males died earlier in SLE, in the comparison to the general population the risk of death in SLE females was higher than in males. Also the occurrence of SLE was the highest in perimenopausal Finnish female patients, not in the childbearing aged as in many studies from Asia and the United States (27,37,63). This character may partly protect the society from the possible SLE-induced problems during pregnancies. Still also young females and children can get this long-term disease. Incidence of pediatric SLE in the present study was at the same level as two decades ago and equal to incidence studies worldwide (41,61,105-114). The gender difference was already present in children, although not as robust as in adults. In the present study the majority of pediatric SLE patients got their disease at teenage, known to be at a vulnerable stage in their life (371,372). The children's age at diagnosis and also female disease onset predominantly at the time of menopause in the present study suggest the role of sexual hormones in the disease process (155,159). The results concerning age at diagnosis and gender in pediatric SLE are in line with previous literature (29,106).

One of the original purposes of the study was to assess the burden of SLE to the society. The selected study material enabled study of the burden to society by work disability, drug purchases, comorbidity medication and mortality risk in SLE patients. From the economic point of view, earlier studies have shown, in the cluster of rheumatic diseases, SLE is responsible for the greatest indirect costs (287). As the indirect costs are comprised of the loss of productivity, the present study concentrated on WD in SLE incident patients.

Although the present study did not clarify the comorbidities of SLE directly or at the individual level, some information on the excess risk for comorbidities can be seen through the evaluations of purchased medications for the preselected disease categories as the purchases were compared to the background population. Most probably the excess purchases of certain medicines excluding anti-rheumatics are not to be explained plainly by the overtreatment of other diseases while frequently visiting a specialist because of SLE. In the present study, the distribution of total medical costs from the diagnosis until death in the cohort of deceased patients revealed that the highest costs during the disease course resulted from cardiovascular diseases, infections and the disease itself. All of the same disease categories were also major causes of death in incident SLE patients.

6.6 FUTURE IMPLICATIONS

Based on the results of the present study SLE patients should be recognized as a high-risk population for cardiovascular diseases, and regular monitoring of risk factors is needed. Cardiovascular safety must be considered while prescribing drug treatment. Anti-rheumatic medication is preferred to glucocorticoids, and high-dose glucocorticoids should be used only for critical disease flares and as short periods as possible. Therapy of the most severe cases with SLE could be coordinated by one consultation center in Finland as the incidence of severe diseases is rather low. E-consultations would enable such an arrangement.

In future studies the pathogenesis of early stages of atherosclerosis in SLE should be explored more precisely. It would also be interesting to compare the use of medicines for cardiovascular diseases between the patients in the present register study cohort before SLE diagnosis and the general population. Studies on longer-term survival and WD are needed. The present cohort of incident SLE patients is now updated until 2014, and three population controls have been identified for each patient.

Our register material lacks clinical data. A clinical register, including all SLE patients in Finland, is urgently needed to raise SLE research and care to a higher level. The register system enables collection of structured data and makes the classification of SLE and measuring of disease activity easier. Such a register would allow gathering larger patient groups and nationwide evaluation. The Finnish register data could be combined with data from other countries in international research collaboration.

7 Conclusions

1. In a register-based longitudinal study, the nationwide incidence of SLE in Finland for adults was 1.7 and for children 0.4 per 100 000 in the years 2000-2007. The highest peaks of incidence were seen in females close to menopausal age.

2. Survival of SLE patients is inferior to the general population already soon after diagnosis. The results emphasize the role of cardiovascular diseases over traditional disease-related causes in early deaths of SLE patients.

3. The initial treatment strategy of SLE is active in Finland and consists mostly of DMARDs in 90% and antimalarial agents in three -quarters of the patients. SLE patients more commonly receive medication for various preselected concomitant comorbidities than the background population.

4. Incident SLE patients have over five times increased risk for permanent disability pensions compared with the population. The main cause leading to preterm retirement is the disease itself.

5. In a population-based prospective study on incidence and distribution of connective tissue diseases, the greatest number of patients with a CTD was classified into the category of undefined disease. In the year 2010 in the Northern Savo hospital district the incidences of various CTDs were similar to the rates before the millennium. Incidence of SLE was 3.4 per 100 000.

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Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease. This thesis updated the incidence of SLE by two different methods. The initial therapy of SLE in Finland was shown to reflect international treatment recommendations. In SLE, survival was lower, work disability higher and drugs for preselected comorbidities more commonly used already in early disease compared to the general population. Cardiovascular disease was the main cause of death.

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