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## Complications of Systemic Lupus Erythematosus

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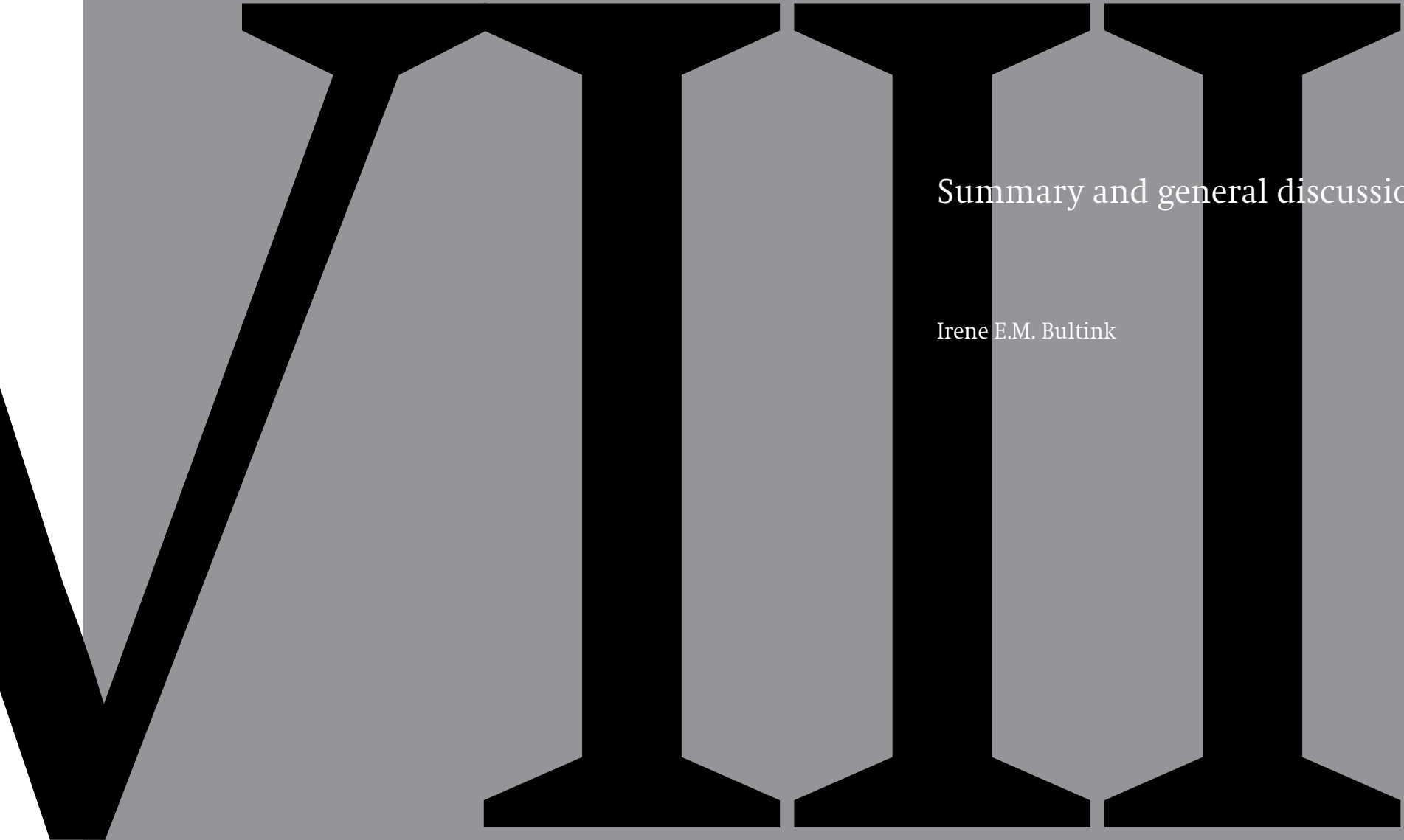
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Summary and general discussion

Irene E.M. Bultink

## BACKGROUND OF THE THESIS

The purpose of this thesis was to investigate the prevalence of, and risk factors for three important complications in patients with systemic lupus erythematosus (SLE): osteoporosis, cardiovascular disease, and infections. In addition, the employment status in patients with SLE was investigated in relationship to organ damage and quality of life.

### Systemic lupus erythematosus

SLE is a systemic inflammatory autoimmune disease with a variable disease course and outcome. The disease is characterized by the involvement of multiple organ systems, which may subsequently lead to the destruction and failure of organ functions. As a consequence of better diagnostic methods as well as improvement in immunosuppressive treatment strategies, the survival of patients with SLE has improved dramatically over the last decades. However, the prolonged survival of patients with SLE is also associated with considerable morbidity due to complications, which may be due to the disease itself (organ damage caused by disease activity), drug side effects, or comorbidities, and are associated with functional limitations and a reduced quality of life. These findings underline the importance of the assessment of complications in patients with SLE and to unravel their aetiology in order to develop strategies to prevent their occurrence.

### The SLE Cohort Amsterdam

The studies described in this thesis were performed in 153 outpatients with SLE of the VU University Medical Center, the Jan van Breemen Institute, the Slotervaart Hospital and the Academic Medical Center in Amsterdam, The Netherlands. All patients fulfilled the revised criteria for the classification of SLE and were included in the SLE Cohort Amsterdam between 2001 and 2005. The formation of the SLE Cohort Amsterdam gave the opportunity to study the disease course, complications and health-related quality of life in a large group of patients with SLE.

## SUMMARY

**Chapter 2** presents a review of the results of recent studies (including the results of the studies described in **Chapters 3, 4, 5 and 6**) on three important disease complications in patients with SLE. First osteoporosis and vertebral fractures, which contribute to damage in the most frequently involved organ system in patients with SLE: the musculoskeletal system. Secondly, atherosclerotic cardiovascular disease, which is the major cause of cardiovascular, neuropsychiatric and peripheral vascular organ damage in SLE. The third part highlights the results of recent studies on infectious complications, which are still a major cause of death in patients with SLE.

### Osteoporosis and vertebral fractures

The aetiology of the high prevalence of low bone mineral density (BMD) in patients with SLE is supposed to be multifactorial, involving both non-disease related and disease related factors. The incidence of symptomatic vertebral and peripheral fractures has been demonstrated to be 5 times higher in female SLE patients as compared to age-matched healthy controls, but the importance of identifying prevalent vertebral fractures in patients with SLE had not been recognized. In **Chapter 3**, we describe the results of our cross-sectional study in 107 patients with SLE on the prevalence of and risk factors for osteoporosis and vertebral fractures. BMD was measured using dual x-ray absorptiometry (DXA) and vertebral fractures were scored using the method of Genant. While osteoporosis, defined as a T score less than -2.5 SD in the lumbar spine and/or the hip, was found in only 4% of the patients, osteopenia was present in 39% of the patient group, despite a relatively young mean age (41.1 years). In multiple regression analyses, low body mass index and postmenopausal status were significantly associated with a low BMD in both the spine and the hip. Moreover, deficiency of 25 hydroxyvitamin D (25[OH]D), defined as a serum level < 25 nmoles/liter, was associated with low BMD in the spine. At least 1 vertebral fracture was detected in 20% of the patients and the prevalence of vertebral fractures was associated with ever use of intravenous methylprednisolone and male sex. In conclusion, we found a high prevalence of low BMD and vertebral fractures in patients with SLE, which emphasizes that osteoporosis is a common feature in SLE. Furthermore, our study demonstrated undertreatment of SLE patients who were diagnosed with osteoporosis or were at high risk for the development of osteoporosis.

### Cardiovascular disease

Multiple, both traditional and non-traditional risk factors for the premature cardiovascular disease have been identified in patients with SLE. We explored the role of asymmetric dimethylarginine (**Chapter 3**) and we investigated the prevalence of the metabolic syndrome (**Chapter 4**) in relationship to cardiovascular events and disease characteristics in our cohort of SLE patients.

### The role of asymmetric dimethylarginine

Previous studies have demonstrated increased oxidative stress in patients with SLE. Studies in the general population have demonstrated that the nitric oxide pathway and its endogenous inhibitor asymmetric dimethylarginine (ADMA) play a role in the pathogenesis of cardiovascular disease. In the general population, high plasma ADMA levels are associated with endothelial dysfunction, and high ADMA levels are a predictor of acute coronary events. Moreover, in vitro studies have demonstrated up-regulation of methylation of arginine residues in proteins, in the presence of anti-dsDNA antibodies, which are highly specific for SLE. As ADMA is released upon proteolysis of methylated proteins, anti-dsDNA antibodies may be a trigger for enhanced ADMA production in SLE. Based on these data, we performed a study on the relationship between plasma ADMA levels and cardiovascular events, disease characteristics and titre of anti-dsDNA antibodies in patients with SLE, as described in Chapter 4. Cardiovascular disease, defined as  $\geq 1$  previous arterial cardiovascular event, was recorded in 16/107 (15%) patients and increased significantly across tertiles of ADMA levels (see chapter 4, figure 1). In addition, mean plasma ADMA levels were significantly higher in patients with SLE with a history of cardiovascular events than in patients without a cardiovascular event history. Moreover, high ADMA levels were associated with a high SLEDAI disease activity score, high titre of anti-dsDNA antibodies and low serum HDL levels. These findings suggest, that anti-dsDNA antibodies might play a role in the development of CVD in SLE by enhancing ADMA production. However, a prospective study in a larger study group is required to answer definitively the question of whether raised plasma ADMA levels are an independent risk factor for future cardiovascular events in patients with SLE.

### Metabolic syndrome

The metabolic syndrome is a condition characterized by the clustering of cardiovascular risk factors, including hypertension, obesity, insulin resistance and

dyslipidaemia, and is associated with an increased risk of diabetes mellitus and cardiovascular mortality in the general population, especially in women. In patients with SLE, an increased prevalence of insulin resistance has been demonstrated.

In **Chapter 5** we describe the results of our study in 141 female patients with SLE with mean age 39 years, on the prevalence of the metabolic syndrome, as defined by a modified National Cholesterol Education Program (NCEP/ATP III) definition, using body mass index  $\geq 30$  kg/m<sup>2</sup> instead of waist circumference as a measure for obesity. Moreover, the relationship between metabolic syndrome score (MetS score) and disease characteristics and cardiovascular events was evaluated. We found a high prevalence (16%) of the metabolic syndrome, defined as MetS score  $\geq 3$ , in our group of young women with SLE in comparison to the 3.2% frequency found in healthy young women in the Amsterdam Growth and Health Longitudinal Study in The Netherlands. The mean MetS score was significantly higher in patients with SLE and a history of cardiovascular events than in those without a previous cardiovascular event. A high MetS score was significantly associated with previous treatment with intravenous methylprednisolone, renal insufficiency, older age, higher erythrocyte sedimentation rate and higher C3 levels.

We concluded that the associations found between the metabolic syndrome and high levels of inflammation in the present study suggest that the metabolic syndrome might provide a link between inflammation and the increased vascular risk in SLE. In addition, the assessment of the metabolic syndrome in patients with SLE might be important to identify subgroups of patients that are at disproportional high risk of developing cardiovascular disease and diabetes mellitus. Further studies are necessary to investigate whether the metabolic syndrome is a predictor of cardiovascular events and diabetes mellitus in patients with SLE.

### Infections

The increased infection rate in patients with SLE has been attributed in part to defects in the complement system, which has an important role in host defence against microorganisms. SLE patients homozygous for mannose-binding lectin (MBL) variant alleles have been demonstrated to be at an increased risk of acquiring serious infections in comparison with patients who are heterozygous or homozygous for the normal allele. This association suggests a correlation between functional MBL activity and the occurrence of infections in SLE patients. Therefore, we investigated the relationship between the functional biological activity of MBL and

its relationship with the occurrence of infections (major and minor) in 103 patients with SLE. The results of this study are described in **Chapter 6**. Fifty percent of the SLE patients had suffered at least one infectious episode since lupus onset and 37% of these infectious episodes were major infections, defined as infections requiring hospital admission and intravenous administration of antibiotics. The spectrum of infections was broad. The most common infection was Herpes zoster skin infection, which had occurred in 16% of the patients. In multiple regression analysis, disease duration was significantly positively associated and hydroxychloroquine use (within the last three months before the first major infection) was significantly negatively associated with the occurrence of the first major infection. Functional activity of MBL was measured by three different assays: functional MBL serum levels, MBL-induced C4 deposition and complete MBL pathway activity in serum. The prevalence of severely decreased MBL serum levels (<0.05 µg/ml) in SLE patients was similar to that of healthy laboratory workers (13% and 14%, respectively). Reduced complement C4 deposition (<10% of the activity of the standard) was present in 21% of the SLE patients versus 16% in healthy controls. Functional activity of the MBL pathway (<10% of the activity of the standard) was found in 43% of the patients with SLE versus 28% in healthy controls. Although the prevalence of reduced complement C4 deposition and the prevalence of reduced MBL pathway activity were higher in patients with SLE in comparison to healthy controls, neither functional MBL serum levels nor MBL pathway activity was associated with infections or major infections in regression analyses. Based on these findings, we concluded that patients with SLE frequently suffer from (major) infections, but a deficiency in the functional MBL activity does not play a role in the susceptibility to infections or major infections.

### **Employment status in relationship to organ damage and quality of life**

As a consequence of disease complications and fatigue, many patients with SLE experience functional limitations, which may lead to work loss. Withdrawal from the workforce may lead to lowered self-esteem, reduced income and social isolation. Moreover, work loss has been recognized as the most important factor for disease-related costs in patients with rheumatic diseases. The objective of the study described in **Chapter 7** was to evaluate working status in relationship to organ damage and health-related quality of life in patients with SLE. For this purpose, patients with SLE, aged 18 to 64 years, were assessed for demographic factors, disease characteristics, and self-reported working status, as defined by paid

employment. Examination of health-related quality of life was performed using the Short Form (SF)-36. In 147 patients with SLE (mean age 38 years, mean disease duration about 6 years), a high rate of unemployment (59%) was found, though 93% of the patients had previously worked. The frequency of unemployment in patients with SLE was much higher than the 36% unemployment rate (26% in men and 46% in women) in the general Dutch population, aged 15 to 64 years. In the patients who had stopped or reduced working, SLE itself was mentioned as the only reason for this decision in 55% of the patients, other reasons only in 25% of the patients, and both SLE and other reasons were reported by 20% of the patients. Unemployed patients had a significantly higher median age at disease onset, a higher frequency of neuropsychiatric organ damage and diabetes than employed patients. Moreover, patients without paid employment had a significantly lower health-related quality of life, as ascertained by 8 out of 9 of the SF-36 summary measures.

We concluded, that unemployment is high in our Dutch patients with SLE, despite mild organ damage and access to primarily publicly funded health care and educational systems. Drop-out from work was in the majority of patients attributed (at least partially) to disease related factors. Higher age at disease onset, neuropsychiatric organ damage, diabetes mellitus and a reduced quality of life were associated with unemployment in our patient group.

### **GENERAL DISCUSSION AND FUTURE PERSPECTIVE**

This thesis underscores the importance of osteoporosis, cardiovascular disease and infections as frequent disease complications in patients with SLE. The aetiology of these complications in SLE is multifactorial, including risk factors that also apply to the general population, disease-related and treatment-related risk factors. The identification of new factors associated with disease complications in SLE is important, not only to develop more insight into their pathogenesis, but also to develop management strategies to prevent their occurrence.

We found a high prevalence of low bone mineral density and vertebral fractures in patients with SLE and this finding has recently been confirmed in Brazilian patients with SLE.<sup>1</sup> Moreover, our study demonstrated undertreatment of osteoporosis in patients with SLE. Based on these findings, we recommend spinal radiographs as well as BMD measurement by DXA in SLE patients treated with corticosteroids and/or in postmenopausal patients with SLE, in the assessment of osteoporosis

and future fracture risk. In addition, life style advice should be given and, when indicated, treatment with appropriate anti-osteoporosis medication. In view of the conflicting results of studies, the role of corticosteroids in the development of osteoporosis and fractures in patients with SLE is still under debate. A longitudinal follow-up study of patients in the SLE Cohort Amsterdam will give us the opportunity to study this subject further.

In the search for risk factors for cardiovascular disease, we demonstrated an association between high plasma ADMA levels, a history of cardiovascular events and high titres of anti-dsDNA antibodies. Our findings are supported by the recent study of Petri et al which demonstrated an association between high plasma ADMA levels, coronary calcification and high titres of anti-dsDNA antibodies in SLE.<sup>2</sup> Since the results of both studies are founded on cross-sectional data, a prospective study is required to elucidate further the role of high plasma ADMA levels in the development of cardiovascular disease and to unravel the relationship between high titres of anti-dsDNA antibodies and high ADMA levels in SLE.

The relative influence of the multiple risk factors associated with cardiovascular disease in SLE is still under debate and will be subject of further research. In the meantime, screening for and the management of modifiable risk factors for atherosclerosis in patients with SLE is advocated. A high prevalence of multiple risk factors has been demonstrated in patients with SLE and the majority of these risk factors may be relatively easily recognized and managed in clinical practice by lifestyle advice or medication. Inadequate management of hypertension and hypercholesterolaemia in patients with SLE has been demonstrated,<sup>3</sup> but the preliminary results of a current, large-scale, prospective study evaluating the effect of different intervention strategies to reduce cardiovascular risk in SLE are promising.<sup>4</sup>

We have demonstrated in the present thesis, that a deficiency in the functional activity of the MBL pathway of complement activation does not play a role in the susceptibility to (major) infections in patients with SLE. However, this does not exclude an influence of defects in the complement system on the occurrence of infections in SLE. MBL-induced complement activity was reduced in patients with SLE as compared to healthy controls and therefore, the presence of complement inhibitors or dysfunction of C4 might play a role. Furthermore, additional consumption of complement factors other than C4 might be important in patients with SLE, because deficiency in MBL pathway activity was more prevalent than

deficiency in the C4 deposition assay. Further research is needed to investigate the role of complement dysfunction and genetic and functional deficiencies, consumption of complement factors and inhibitors of complement factors in relationship to infections in SLE.

The high prevalence of unemployment and the association with specific types of organ damage and a reduced health-related quality of life found in our cross-sectional and retrospective study, underlines the need for a longitudinal study on working status in relationship to demographic factors, education, work related factors, disease characteristics and quality of life in patients with SLE.

The SLE Cohort Amsterdam was initially formed in 2001 to perform the studies described in this thesis. We have recently initiated a longitudinal follow-up study in this growing cohort of patients with SLE, which will give us the opportunity to investigate which risk factors and biomarkers are associated with disease progression and the development of complications in patients with SLE. In addition, this prospective study will also focus on the individual and socio-economic impact of the disease, in order to identify modifiable risk factors for the reduced health-related quality of life and work loss in this patient group.

The ultimate goal of the performed and ongoing studies in the SLE Cohort Amsterdam is the development of strategies to prevent the occurrence of disease complications in patients with SLE and the implementation of these prevention strategies in routine clinical practice. Our approach is in line with the recently published EULAR recommendations for the management of SLE, addressing the major issues in the management of the disease.<sup>5</sup>

## COMPLICATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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