

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



How to Avoid Delay in SLE Diagnosis and Management

Hani Almoallim^{1,2}, Esraa Bukhari², Waleed Amasaib² and Rania Zaini¹

¹*Umm Alqura University, Makkah*

²*King Faisal Specialist Hospital, Jeddah
Saudi Arabia*

1. Introduction

Systemic lupus erythematosus (SLE) is a wide spectrum disease with many clinical manifestations. Lack of awareness of the disease itself, with its common and rare presentations results in significant delay in diagnosis and consequently serious compromise of patients' care.

Physical examination will always retain its importance as the most common diagnostic test used by doctors and as an essential tool for modern practice (Joshua, Celermajer et al. 2005). Findings from proper musculoskeletal (MSK) examination is extremely useful in diagnosing rheumatologic disorders especially where gold standard diagnostic tests are lacking. From this perspective there should be much emphasis on basic bedside skills among clinicians searching for arthritis. Asking about morning stiffness and joint swelling are simple enough to pick up early arthritis (Paget 2007). Performing an active range of motion testing of joints as a screening method would pick up limitations in joints mobility from active arthritis. In real practice, the picture is not simple as such. Despite the impact of MSK disorders on health care, rheumatological diseases are often overlooked or inadequately assessed by doctors (Jones, Maddison et al. 1992). This chapter will explore some of the issues around this complex clinical and educational problem.

SLE (the disease of thousand faces) is not only affecting the joints. Major organ involvement can be the first presenting symptom(s) and/or sign(s). Knowledge of some of the common presenting features of SLE apart from arthritis would help greatly in early recognition of this multisystem disease. Renal, central nervous system (CNS), and cardiovascular system (CVS) are commonly affected in SLE patients. Knowing the risk factors, early detection and close follow up will have positive impact on patient's outcome. This chapter will discuss some of the clinical issues arising while managing SLE patients that are commonly overlooked by clinicians. Late onset SLE and other rare associations like Kikuchi Fujimoto disease will be discussed in this chapter as well.

2. Deficiencies in musculoskeletal examination skills

MSK symptoms are the most common health complications that require medical attention, accounting to 20% of both primary care and emergency-room visits (Rasker 1995). In a health survey, MSK disorders were ranked first in prevalence as the cause of chronic health

problems, long term disabilities, and consultations with a health professional (Badley, Rasooly et al. 1994). In Saudi Arabia, MSK disorders is the second major cause of outpatients visit in primary care centers and private clinics (MOH 2009). A number of different medical specialties are involved in treating patients with musculoskeletal complaints, including general practitioners, family physicians, internists, orthopedic and surgeons, working in teams with other health professionals, but often without a multispecialty focus. In order to truly improve the outcome of treatment for musculoskeletal conditions, it is important that experts in the various specialties work more closely together and look for commonality of approach, as they often treat the same patients but from different angles.

Despite the high prevalence of musculoskeletal disorders in all fields of clinical practice, studies show a lower level of competence and confidence in MSK cognitive and clinical skills (including physical examinations) across clinicians (Akesson, Dreinhofer et al. 2003; Almoallim, Khojah et al. 2007; Beattie, Bobba et al. 2008). Also, a continuous neglect of musculoskeletal examination skills in clinical practice is observed. We reported a case of SLE with active arthritis where the diagnosis was delayed for seven days after hospital admission due to the lack of basic skills in MSK examination (Almoallim, Khojah et al. 2007). The patient in the report presented to the emergency room with fever and pancytopenia and apparently the focus of the treating medical team was mainly on these presenting findings. This might have restricted the clerking done on admission to "hematology and infectious diseases" while what should have been done was a complete history and thorough physical examination regardless of initial impression. Musculoskeletal assessment should be a part of routine clerking (Lillicrap, Byrne et al. 2003). Assuring such attitude among clinicians will prevent unnecessary delay in diagnosis. If a simple musculoskeletal screening examination focused mainly on range of motion testing to assess function was done, this patient's active arthritis would have been picked up on admission. This would have initiated early search for a rheumatological disease and start treatment without a delay.

Despite this impact of MSK disorders on health care, rheumatological diseases are often overlooked or inadequately assessed by doctors (Jones, Maddison et al. 1992). Thus, patients with complaints about bones and joints are often ignored and their problems underestimated by doctors. In a study among 200 general medical inpatients in a teaching hospital, it was found out that the signs and symptoms of MSK disorder which were recorded in the hospital notes was only 5.5% and 14% respectively. This compared poorly with recorded examinations of other systems and regions for example, cardiovascular symptoms were recorded in 100% of the cases; respiratory and abdominal symptoms were recorded in 99%, the nervous system, skin and female breasts symptoms were recorded in 77% and 13% respectively (Doherty, Abawi et al. 1990). In another report, only 40% of patients admitted to general medicine ward had the history of their MSK symptoms recorded and only 14.5% of these patients received comprehensive MSK examination (Ahern, Soden et al. 1991). Furthermore, 80% of symptomatic patients received either no treatment for their rheumatic disorders, or treatment that was regarded as suboptimal or inappropriate (Ahern, Soden et al. 1991). Another report showed even a higher percentage of patients – 63% of all patient admitted to general medicine ward- had MSK symptoms or its signs, but relevant MSK history was missed in 49% of the patients records, while signs were missed in 78%; 42% of those with MSK conditions would have benefitted from additional treatment (Lillicrap, Byrne et al. 2003). A more recent report reviewed 150 patient notes in three different hospitals from the acute admission wards for medicine and surgery and the medical assessment unit. Factors considered included whether GALS screenings

had taken place, documentation of MSK examinations and assessment of confidence of junior doctors in assessing MSK conditions. GALS screenings were performed in 4% of patients on the medical assessment unit, 7% in acute medical and 0% in acute surgical patients on admission. Examination of the MSK system yielded better results with 16%, 22% and 10% on each of the respective wards. Interviews with junior doctors found 10% routinely screening for MSK conditions, despite 87% feeling confident in taking MSK histories (Sirisena, Begum et al.).

Matzkin et al. (2005) indicated that the majority (79%) of the study respondents including medical students, residents, and staff physicians failed the basic MSK cognitive examination. This suggests that training in MSK medicine is inadequate in both medical school and in most residency training programs. Worldwide, undergraduate and postgraduate medical teaching of MSK disorders is currently brief and not directly relevant to the knowledge and skills commonly required for the management of these conditions in an outpatient setting.

In undergraduate education, inadequate MSK education has been reported. Medical students spend very few hours on the MSK system, both in basic science and in clinical training. It is quite common for students to leave medical schools without being able to make a general assessment of the musculoskeletal system. On the other hand, it would be considered a total neglect if a medical graduate is incompetent at adequately assessing the heart or lungs. Harvard medical students have reported general dissatisfaction of their confidences in examining MSK system as compared to their skills in examining pulmonary system (Day, Yeh et al. 2007). They suggested more time to be devoted to MSK medicine and more integration between pre-medical and clinical courses.

The American Association of Medical Colleges claims that most medical schools do not effectively educate future physicians on MSK medicine in spite of the increasing prevalence of MSK conduction across medical practice ((AAMC) 2005). The obvious discrepancy between the magnitude of MSK conditions and physicians competences, which mostly stemmed from the educational deficiencies at the medical schools, is maintained across years ((AAMC) 2005; Day, Yeh et al. 2007; Clark, Hutchison et al. 2010). Akesson and colleagues (2003) argued that teaching at the undergraduate and graduate programmes is not adequate and the resulting competence does not reflect the impact of these conditions on individuals and society. A comprehensive study reviewing the curricula of all Canadian medical schools indicated that directors of undergraduate MSK programmes felt dissatisfied with the curricular time devoted to MSK education (Pinney and Regan 2001). In a comprehensive study based on a national survey in Saudi Arabia using the Delphi technique, internal medicine knowledge and skills competencies including rheumatology were determined and prioritized (Almoallim 2010). Table 1 represents only rheumatological skills competencies that were identified. Note that the score of 3: indicates must know the topic, 2: should know the topic, 1: interesting to know the topic. It was decided in this research that any competency with a score ≥ 2.2 should be considered a core competency. Table 2 represents overall disease ratings with the number of competencies identified for each disease. Such findings would help greatly in designing educational programmes and assessment methods based on priorities and it will help in determining what skills for rheumatological diseases should be taught. It is a common recommendation among experts to give proper attention to training in MSK conditions for both undergraduate and postgraduate training programmes.

In the postgraduate programme the same limitation was highlighted since the 1980s: Goldenberg et al (1985) reported that the majority of directors of residency programs

thought that many basic skills and techniques were not taught adequately and that the training of their rheumatology residents was not equal to that of residents in cardiology or gastroenterology. General dissatisfactions of MSK training was reported among the internal medicine residents and family practice. United States residents expressed their dissatisfaction of their competence in performing MSK examinations at various parts of the body and revealed that to the inadequate or poor training (Clawson, Jackson et al. 2001).

2.1 Possible obstacles toward an appropriate MSK medical practice

Previous studies suggested many reasons related to MSK poor clinical skills and physical examinations in particular (Clawson, Jackson et al. 2001; Akesson, Dreinhofer et al. 2003; (AAMC) 2005; Matzkin, Smith et al. 2005; Day, YEh et al. 2007; Dequeker, Esselens et al. 2007; Thompson 2008; MOH 2009; Clark, Hutchison et al. 2010):

- Vague training of MSK in undergraduate programmes;
- Underestimate the prevalence of MSK conditions and its impact on individuals and society
- MSK is not considered as main competence among medical graduates because it is not a life threatening condition.
- Number of different specialties involved in treating patients with MSK conditions do not share common approach regardless of specialties interventions,
- Lack of a proper teaching in MSK is essential in the low competence in MSK generally and physical examinations
- Lack of summative evaluation of MSK physical examination contributes to medical graduate low level of competencies
- The lack of holistic approach and the focus of specialties
- The lack of standardize approach to the clinical assessment of MSK problems whether presenting to primary care, rheumatology or orthopedics that give a benchmark for this competency.
- The disparity in the approach to examination between rheumatologists and orthopaedic surgeons mostly leads to poor performances in MSK physical examinations
- The lack of appropriate teaching and evaluation of MSK because the physical examination teachers are not skilled in MSK examinations and thus bone and joint diseases are not screened.

2.2 Global initiative toward MSK medicine

The global initiative to disseminate awareness to MSK wellbeing had made the World Health Organization (WHO) designate the years 2000 to 2010 as Bone and Joint Decade (Lidren 2003). In the light of the worldwide commitment, the focus increases on the responsibility of medical education and training programmes in providing adequate musculoskeletal education. Therefore, global consensus among international experts from different specialties and organizations developed a recommendation for MSK teaching in undergraduate medical education (Woolf, Walsh et al. 2004).

A standardized approach to the clinical assessment of a musculoskeletal problem is suggested by Wolf and Akesson (2008): such a standardized approach will be conducted whether the patient is presenting to primary care, rheumatology or orthopedics. It also will provide a benchmark for this competency and can also be used as a teaching aid (Woolf and Akesson 2008). The issue is whether this kind of standardization would be widely accepted by different disciplines or not.

SN	RHEUMATOLOGICAL DISEASES (SKILLS COMPITENCIES)	EXPERT RATING
1	To demonstrate competency skills in obtaining comprehensive history from patient with rheumatological disorders	2.60
2	To demonstrate competency skills in applying general principle of joint examination (screening exam, inspection, palpation, range of motion, & special tests) in musculoskeletal examination	2.50
3	To demonstrate competency skills in performing comprehensive musculoskeletal examination including (the hands & wrists, elbows, shoulders, TMJ, the neck, spine & sacroiliac joints, knees, hips, ankles & feet).	2.20
4	To interpret the ANAs results	1.80
5	To interpret synovial fluid analysis results including polarized light microscopy	1.70
6	To demonstrate competency skills in obtaining comprehensive history from patient with back pain.	2.30
7	To identify on plain x-ray of joints findings consistent with RA.	1.90
8	To demonstrate competency skills in examining patient with RA.	2.30
9	To identify on plain x-ray findings consistent with spondyloarthropathies.	1.70
10	To identify on plain x-ray findings consistent with crystal related joint disease.	1.70
11	To identify on plain x-ray findings consistent with JRA.	1.30
12	To demonstrate competency skills in examining patient with crystal-related joint disease.	1.60
13	To demonstrate competency skills in examining patient with SLE.	2.30
14	To demonstrate competency skills in examining patient with scleroderma.	1.80
15	To demonstrate competency skills in examining patient with rheumatic fever.	2.30
16	To demonstrate competency skills in examining patient with soft tissue rheumatism.	1.50
17	To demonstrate competency skills in obtaining comprehensive history from patients suspected to have vasculitis.	2.00
18	To demonstrate competency skills in examining patient with nerve entrapment syndrome.	1.70
19	To demonstrate competency skills in eliciting physical signs consistent with spondyloarthropathies.	1.60
20	To demonstrate competency skills in performing joint aspiration.	1.00

Table 1. Rheumatological diseases (skills compitencies)

GALS (Gait, Arms, Legs and Spine) a locomotor screening was developed and validated as a rapid screening protocol / system for MSK with the aim for a quick identification of significant abnormalities (Doherty, Dacer et al. 1992). Various spectrums of health specialties could utilize this screening routine before specific examination and teach it to trainees and medical students. Tab 3 represents a quick screening tool for MSK disorders adopted from (Woolf and Akesson 2008).

KNOWLEDGE COMPETENCIES BREAKDOWN	MEAN WEIGHTED RESPONSE	NO.OF IDENTIFIED COMPETENCIES
Approach To The Patient With Joint Pain	1.91	13
Approach To The Patient With Low Back Pain	2.00	6
Rheumatoid Arthritis	2.12	14
Spondyloarthropathies(SpA)	1.89	17
Crystal Related Joint Disease	1.95	16
Osteoarthritis	2.36	7
Bacterial Septic Arthritis	2.32	6
Systemic Lupus Erythematosus	2.13	9
Scleroderma	1.65	6
Inflammatory Myopathies(Polymyositis &Dermatomyositis)	1.69	7
Sjogren’s Syndrome	1.65	4
Vasculitis	1.78	8
Juvenile Rheumatoid Arthritis (Juvenile Idiopathic arthritis)	1.74	5
Miscellaneous Syndromes	0.90	1
TOTAL		119

Table 2. Disease Specific Ratings For Rheumatological Diseases

3. Late onset SLE

It is true that most SLE patients are in the child bearing age but SLE can occur in elderly. SLE has always been considered a disease of the young. Little attention has been given to late onset disease. In contrast with childhood disease, studies on elderly SLE patients are scarce (Boddaert, Huong et al. 2004). Late onset disease is the type of SLE whose manifestations begin after the age of 50 in majority of the studies (Boddaert, Huong et al. 2004; Karoubi Nordon, Hayem et al. 2007; Rovensky and Tuchynova 2008) or after the age of 65 (Pu, Luo et al. 2000). SLE should be considered in the differential diagnosis while dealing with certain clinical settings in elderly population. Clinicians recognizing this clinical entity will help greatly to assure early diagnosis of SLE and avoid unnecessary delay in diagnosis and management.

Screening questions	
1	"Do you suffer from any pain or stiffness in your arms, legs, neck or back?"
2	"Do you have any swelling of your joints?"
3	"Do you have any difficulty with washing and dressing?"
4	"Do you have any difficulty with going up or down stairs or steps?"
Screening examination	
Gait	Observe the patient walking forwards for a few meters, turning and walking back again. Recognize abnormalities of the different phases – heel strike, stance phase, toe-off and swing phases. Look for abnormalities of the movement of arms, pelvis, hips, knees, ankles and feet.
Inspection of standing patient	View the patient from the front, side and back, looking for any abnormalities, particularly of posture and symmetry. Apply pressure in the midpoint of each supraspinatus and roll an overlying skin fold to examine for tenderness.
Spine	Ask the patient to flex the neck laterally to each side. Place several fingers on the lumbar spinous processes and ask the patient to bend forward and attempt to touch their toes whilst standing with legs fully extended, observing for normal movement and feeling for expansion of space between spinous processes.
Arms	ask the patient to place both hands behind their head and then move elbows right back, then straighten the arms down the side of the body and bend elbows to 90° with palms down and fingers straight. Turn hands palms up and make a tight fist with each hand, then place, in turn, the tip of each finger onto the tip of the thumb. Squeeze the metacarpals from second to fifth cautiously for tenderness.
Legs	get the patient to recline on a couch, then flex, in turn, each hip and knee while holding and feeling the knee. Passively rotate the hip internally. With the leg extended and resting on the couch, press down on the patella while cupping it proximally to examine for tenderness or swelling of the knee. Squeeze all metatarsals and then inspect the soles of the feet for callosities.

Table 3. Quick screening tool for msk disorder

Overall, the incidence of late-onset SLE is low, but there are variable numbers reported in the literature, ranging from as low as 3.7% (Costallat and Coimbra 1994) and to as high as 20.1% (Jacobsen, Petersen et al. 1998). This may be related to the different ethnic backgrounds included in the studies and the variable definitions of late-onset SLE. Most of the literature indicated that the sex ratio declines with age in SLE. In a pooled analysis of 714 cases of late-onset SLE reported in the literature and 4700 young SLE patients, the female to male ratio observed with age in SLE was 4.4:1 vs. 10.6:1 respectively (Boddaert, Huong et al. 2004). This probably reflects the relationship between SLE and estrogen status which decline in the elderly.

Late onset SLE is not a well studied disease and it has distinct clinical features. Although the disease activity and major organ involvement is less than in the early onset disease, it can cause more morbidity and mortality. In one study, there were significant number of patients with late onset SLE who died during the research period which may be related to the comorbidities and the use of medication which are age related rather than the disease itself (Bertoli, Alarcon et al. 2006). Skin manifestations, photosensitivity, Raynaud phenomenon, arthritis, nephritis and neuropsychiatric manifestations were less frequent in comparison with young SLE patients. In late-onset SLE, a higher occurrence of pulmonary involvement, serositis, and Sjögren's syndrome were observed (Boddaert, Huong et al. 2004; Rovensky and Tuchynova 2008).

There are variable findings in the literature about the occurrence of anti ds DNA antibodies in late-onset SLE (Padovan, Govoni et al. 2007; Rovensky and Tuchynova 2008). These antibodies did not correlate with organ complications of late-onset disease in one study (Padovan, Govoni et al. 2007). A higher prevalence of rheumatoid factor, anti-Ro and anti-La antibodies were observed in late-onset SLE. However, lower prevalence of anti-RNP antibodies and hypocomplementemia were observed as well (Maddison 1987; Belostocki and Paget 2002; Boddaert, Huong et al. 2004; Padovan, Govoni et al. 2007).

In general, late onset SLE is characterized by a lower disease activity (Costallat and Coimbra 1994; Boddaert, Huong et al. 2004). This fact does not exclude significant morbidity associated with it. The seriousness of some clinical presentations may preclude clinicians from considering autoimmune diseases as an etiology in their work up. This may result in unnecessary delay in diagnosing late onset SLE. We reported a case of late onset SLE in a 65 year old female patient, previously healthy, who presented with progressive paraplegia and sensory level at T4 (Almoallim, Bukhari et al. 2009). MRI showed extensive transverse myelitis (TM) involving the thoracic spine. Antinuclear antibodies (ANA), anti-double stranded DNA antibodies (Anti ds DNA) and lupus anticoagulant were all positive. The diagnosis was delayed for a month after hospital admission due to lack of awareness of basic work up to diagnose SLE. Obviously, SLE was not considered in the basic differential diagnosis of this patient. What had been required was simply considering SLE as a possible etiology then ordering ANA as a screening tool for SLE.

4. Neuropsychiatric manifestations of SLE (NPSLE)

NPSLE may still present a very difficult diagnostic challenge for clinicians (Joseph, Lammie et al. 2007). Neurologic features at the onset of SLE is regarded rare, occurring only in approximately 3% in some studies and up to 24% in others (Joseph, Lammie et al. 2007). NPSLE affects more than half of SLE patients. It ranges in severity from mild symptoms like headache to severe neurological dysfunction. Clinicians particularly general internists and neurologists who are dealing primarily with patients presenting with complex neurological presentations should consider autoimmune diseases and particularly SLE in their differential diagnosis. Awareness of the 19 neuropsychiatric syndromes defined by ACR as an associated feature with NPSLE is essential. (See corresponding chapters for further details).

The most prevalent symptoms are headache, seizures, mood disorders and cerebrovascular disease. Regarding headaches, data showed that there was no significant difference in the prevalence of tension type headache and migraine between the SLE patient and the general population (Mitsikostas, Sfikakis & Goadsby, 2004).

Simple or complex attention, memory, reasoning, executive skills, language, visual-spatial processing and psychomotor speed are normal cognitive functions, and any significant deficit in one or all of these functions is defined as cognitive dysfunction by ACR. These dysfunctions are usually underestimated and require careful testing to avoid unnecessary delay in diagnosis.

Guillain-Barre syndrome (GBS), myasthenia gravis (MG), plexus injury, TM, aseptic meningitis and autonomic dysfunctions are less frequent and rare neurological manifestation associated with SLE. GBS is an acute, rapidly progressive, autoimmune demyelinating polyneuropathy resulting in symmetric, ascending paralysis that can be severe involving the respiratory muscles and require mechanical ventilation. This disease is relatively rare among SLE patients as it is only associated in 7 out of 1100 GBS cases in an early study (Leneman 1966). MG is another autoimmune disorder affecting the proximal, bulbar and extraocular muscles due to antibodies directed against the post synaptic acetylcholine receptors resulting in weakness of the muscles. Among 78 patients with this disease, 6 patients (7.7%) had SLE (Sthoeger, Neiman et al. 2006). It was concluded in this study that MG patients should be evaluated for the coexistence of SLE, and assessment for MG is suggested in lupus patients with unexplained muscular weakness. Various case reports showed the association between them (Vaiopoulos, Sfrikakis et al. 1994; Bhinder, Majithia et al. 2006). The prevalence of TM in SLE patients is 1-2% (Kovacs, Lafferty et al. 2000). It can occur as the initial manifestation of SLE in up to 39% or within the first five years of a diagnosis of SLE in 42% of the total patient population analyzed in one study (Kovacs, Lafferty et al. 2000). The predominant presentation of TM in SLE is a sensory level commonly in the thoracic region, spastic paraparesis and sphincter disturbance (Kovacs, Lafferty et al. 2000; D'Cruz, Mellor-Pita et al. 2004). TM as a presenting feature of late onset SLE is rare. Few cases were reported; one patient out of 15 in a report of TM as a presenting feature for SLE (D'Cruz, Mellor-Pita et al. 2004), two patients out of 14 in an older series about TM in SLE (Kovacs, Lafferty et al. 2000) and two case reports (Chen, Lai et al. 2004; Almoallim, Bukhari et al. 2009).

5. How to avoid delay in diagnosis and management of renal involvement in SLE?

Lupus nephritis (LN) is one of the most worrisome and potentially serious complication of SLE and a delay in recognition and treatment of LN lead to significant morbidity and mortality. LN occurs in 40 to 70% of SLE patients (Cameron, 1999a; Seligman et al, 2002) especially in the first year after diagnosis during the first three months (Eilertsen et al, 2011). Early searching for renal involvement in SLE is crucial to prevent it from progression. The goal of clinicians taking care of lupus patients is to identify individuals with signs of early renal disease who are at risk for renal damage. Appropriate treatment can be initiated early to prevent inflammatory lesions from progression to sclerotic ones (end stage LN).

There are simple parameters that should be followed in each clinical visit to pick up early disease. Clinicians should monitor blood pressure, urine analysis and possibly renal function test and anti ds DNA antibodies in each clinical visit. The following are abnormal parameters that suggest renal involvement and mandate biopsy: elevated anti ds DNA antibodies and decreased C4 were more commonly seen in proliferative lupus nephritis compared with non proliferative lupus nephritis (Wen, 2011), hematuria (>5 red blood cells per high power field on urine microscopy), nephrotic (>3.5 g protein/24hrs) or

subnephrotic range proteinuria ($>0.5\text{g protein}/24\text{hrs}$), or protein/creatinine ratio (>1.0), casts (>5 haemogranular or red blood cast), elevated urea and creatinine and elevated blood pressure ($\text{BP} > 140/90 \text{ mmHg}$).

There is a clear need to consider kidney biopsy early on in the course of the disease to help guide therapy and suggest long term prognosis. Kidney biopsy can determine the degree and severity of renal involvement through established histopathological guidelines. Determining the stage of kidney disease have a significant impact on determining response to therapy. Most nephrologists agree that kidney biopsy is worthwhile in SLE patients with abnormal urine analysis and/or reduced renal function. They suggest that kidney biopsy should be performed as soon as clinical signs of renal involvement are evident in order to accelerate treatment decisions and minimize risk of inflammation induced irreversible renal damage (Contreras et al, 2002). Delaying kidney biopsy is unfortunately a practice that is still observed among some rheumatologists and nephrologists. Lack of adequately trained nephrologists/radiologists who can perform kidney biopsy safely might be a factor that explains this delay. Less frequent follow up visits for lupus patients due to overwhelmed rheumatology practices in some parts of the world is another possible factor. Poor monitoring, inadequate control of lupus disease activity, and lack of awareness of the need to consider kidney biopsy are all other possible factors.

It was demonstrated early on in the literature in a cohort of 87 patients with LN that delay between the detection of the onset of renal disease and renal biopsy was a significant predictor at the time of a first renal biopsy for subsequent renal insufficiency (relative risk 4.9; 95% confidence interval 1.7 to 14.5; $p < 0.001$) and death due to lupus renal involvement (relative risk 6.7; 95% confidence interval 2.1 to 21.2; $p < 0.001$) (Esdaile, Joseph et al. 1994). Delaying therapy, because of presumably mild disease, is often associated with increased glomerular injury and fibrosis and therefore a lesser response to immunosuppressive drugs (Esdaile, Joseph et al. 1994). Several other recent studies reported that a delay in renal biopsy (and therapy) is a strong independent predictor of poor outcome in LN (Faurscho et al, 2006; Fiehn et al, 2003). Sometimes significant renal disease (stage 3, 4 and 5) can be found in renal biopsy even in the absence of impaired renal function or even in the presence of low level of proteinuria (urine:protein/creatinine ratio < 1.0) (Christopher-Stine et al, 2006). A full discussion on issues related to kidney biopsy in SLE is presented in another chapter in this book.

5.1 Control of risk factors in lupus nephritis

An important goal for proper medical care for lupus patient, particularly from a renal perspective is the control of risk factors such as proteinuria, hypertension, dyslipidemia and diet control.

5.1.1 Proteinuria and hypertension

Heavy proteinuria is a common feature of patients with proliferative LN and progressive renal impairment (Dubois et al, 1987). Serial studies by the Stanford group demonstrated that heavy proteinuria is a predictor of progressive renal impairment (Buckheit et al, 1997). Therefore, reduction of proteinuria independent of reduction in blood pressure is associated with subsequent beneficial effect on the progression of renal disease (Lewis et al, 1993; Maschio et al, 1996; Petersen et al, 1995; The Gisen Group 1997). Early intervention on proteinuria has a major impact in preventing the progression of kidney disease in SLE.

Aggressive reduction of proteinuria should be a goal for any clinician taking care of LN patients.

A number of reports indicated that aggressive treatment of hypertension inhibits progressive renal injury (Petersen et al, 1995; Brazy et al, 1990; Rosansky et al, 1990). Few mmHg reduction in blood pressure value does matter on the long term. The hypertension detection and follow-up programs showed that patients whose BP was 129/86 mmHg versus 130/90 mmHg had greater preservation of renal function (Shulman et al, 1989). It should be recognized that hypertension is also a strong risk factor for developing atherosclerosis which lead to increased risk of heart attacks and strokes. This is to add to the extreme importance of controlling hypertension in lupus patients.

5.1.2 Dyslipidemia

Dyslipidemia is a common feature of lupus patients treated with steroids and also with progressive renal injury and nephrotic syndrome. There is a strong relation in LN patients between cholesterol concentration and proteinuria. There are several reports in non-diabetic renal disease with proteinuria that relate increase cholesterol and triglyceride to an increase in loss of renal function (Apperloo, de Zeeuw & de Jong, 1994; Maschio et al, 1989; Samuelsson et al, 1993). Hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors (statins) are beneficial in lowering low density lipoprotein (LDL) cholesterol. Fish oils and fibric acid analogs are helpful in lowering triglyceride and raising high density lipoprotein (HDL) cholesterol and should be considered in patients with dyslipidemia. Again, it is hoped that this issue should not be neglected by clinicians taking care of lupus patients.

5.2 The role of angiotensin converting enzyme inhibitors in patients with lupus nephritis

Angiotensin converting enzyme inhibitors (ACEI) represent a class of drugs used to treat many common diseases like hypertension, heart failure, post myocardial infarction, and microalbuminuria in diabetic patients and nowadays is also used in SLE for many purposes. They work by inhibiting the angiotensin converting enzyme that is responsible for converting angiotensin 1 to angiotensin 2. ACEI have an anti-inflammatory property as angiotensin 2 has pro-inflammatory effect on the cells of different organ system. ACE has been found to be high in synovial fluid (Veal et al, 1992) and rheumatoid nodule in rheumatoid arthritis patients (Goto et al, 1992) which suggest its role in the inflammation. In SLE patients, ACEI have an end organ protection effect by its multiple effects on hypertension and proteinuria. ACEI delay the occurrence of renal involvement and are associated with decreased risk of disease activity in patients with SLE (Duran-Barragan et al, 2008). This is an impressive and important finding that should alert all clinicians taking care of lupus patients to be aware of this valuable effect on patients outcome. Every effort should be spent to assure that LN patients are maintained on these drugs. Lupus patients are chronic steroid users which make them liable for hypertension, diabetes mellitus (DM), and coronary artery disease (CAD). Numerous studies have shown beneficial effects of using ACEI in the management and prevention of these conditions. Unfortunately, many clinicians including rheumatologists tend not to use ACEI/ARBs (angiotensin receptors blockers) commonly in SLE patients or they delay introducing them early in the course of the disease. One possible reason for this delay is that physicians tend to focus more on acute and dramatic presentations of SLE rather than monitoring risk factors that would show

beneficial effects on the long term. Therefore, a comprehensive approach to care for lupus patients should be followed.

6. Cardiovascular involvement in SLE

SLE is associated with a variety of cardiovascular manifestations; some are life threatening (including myocardial infarction) and others are much less serious. There are several risk factors for heart related conditions, many of which can be avoided. Cardiovascular disease is a major cause of morbidity and mortality in SLE.

Pericarditis remains the most common cardiovascular disease in SLE and occur in 12- 48% (Moder, Miller & Tazelaar, 1999). It should be included in the differential diagnosis of SLE patients presenting with shortness of breath, low grade fever, pleuritic chest pain and/or dry cough. ANA test should be ordered for any young lady in childbearing age with pleuritic chest pain. This is to avoid delaying the diagnosis of SLE as pericarditis can be a presenting feature. Other less frequent cardiac manifestations of SLE are myocrditis (which is usually silent), endocarditis with one characteristic but rare presentation as Libman-Sack endocarditis known as verrucous non bacterial thrombotic endocarditis, valvular disease, arrhythmias, pulmonary hypertension, and systemic hypertension.

6.1 SLE and accelarated atherosclerosis

Today with SLE patients living longer due to more effective drug therapies, CAD has become a leading cause of late mortality in SLE. Women with aged 35-44 were found to have 50 times more risk of myocardial infarctions than aged matched controls (Mazni et al, 1997). Several case-control studies, both autopsy studies and myocardial perfusion studies have consistently shown a 30-40% prevelance of sub-clinical CAD in SLE patient (Korkmaz, Cansu & Kasifoqlu, 2007). Despite an increasing appreciation of the importance of cardiovascular disease in SLE, recognition of traditional risk factors have been noted to be suboptimal. As an example, in one academic rheumatology practice, deficits in knowledge and management of cardiac risk factors were observed among both SLE patients and their physicians (Costenbader et al, 2004). This is again to emphasize the point of increase awareness of this serious issue in lupus patients. Lack of comprehensive approach to care for SLE patients may lead to significant delay in diagnosing a reversible cardiac risk factor. Obviously, this will result in delay in management and increase in cardiac morbidity and mortality.

Many cases with SLE have evidence of subclinical accelerated atherosclerosis (figure 1). It is related to both traditional and non traditional risk factors for CAD. The traditional risk factors are demographics, family history, smoking, hypertension, DM, and dyslipidemia, while the non traditional risk factors include chronic inflammation, presence of autoantibodies, prolonged vascular inflamation, corticosteroid use (10 mg change in prednisolone lead to change in mean arterial pressure of 1.1 mmHg after adjustment for age, weight and antihypertensive drug use, and 10 mg increase in prednisolone was associated with a mean weight change of 5.50 ± 1.23 (Petri, 2000)), renal disease and antiphospholipid antibodies. One factor that has repeatedly been shown to affect the prevelance of CAD in SLE is active disease. Appropriate management of active SLE is one of the best preventive measures. Due to the high prevelance of CAD in SLE patient, SLE itself should be viewed as a CAD risk factor in the same way as DM is (Bradley, 2009; Shah, Shah & Krishnan, 2009).

SLE patients should have an annual fasting blood glucose and a urinalysis at every clinic visit to assess for protienuria, glucosuria and hematuria. Patients with evidence of impaired glucose tolerance should undergo dietary changes to prevent frank diabetes from developing. Blood pressure(BP) should be followed at every clinical visit with a goal BP of less than 130/80 mmHg. For prehypertensive patients, the physician first should try therapeutic lifestyle changes (exercise and diet modification) and assess renal function. If blood pressure is consistently above 140/90 mmHg, despite therapeutic lifestyle changes, then antihypertensive medications should be started with preferable drugs such as ACEI. The cholesterol recommandation for lupus patients are more stringent than those for the average patients. Lupus patients should have an annual fasting lipid profile with a goal LDL <100 mg/dl (<2.6 mmol/L) (Wajed et al, 2004). Statin therapy is indicated for LDL>130 mg/dl (> 3.4 mmol/L) even in those without traditional CAD risk factors. Statins have been shown to directly improve endothelial function even in patient with normal lipid profile (Vaughan et al, 2000; Laufs et al, 1998). Also, these patients should be counseled on smoking cessation and weight reduction if their BMI >25. Low dose aspirin should be considered for those patients with traditional risk factors and those that are antiphospholipid antibody positive (Erkan et al, 2002; Bertias et al, 2008; Wahl et al, 2000). Screening patients at higher risk by non invasive techniques like carotid Duplex or Single Photon Emission Computed Tomography-Dual Isotope Myocardial Perfusion Imaging (SPECT-DIMPI) can help in early detection of subclinical atherosclerosis (Sella et al, 2003). To prevent long-term cardiovascular consequences, these patients should be treated aggressively, both to control their primary lupus disease activity and to minimize modifiable CAD risk factors. Life style modification, weight reduction, statins for hyperlipidemia, controlling blood pressure, controlling DM and minimizing the glucocorticoids use all these can minimize the CAD in SLE patients.

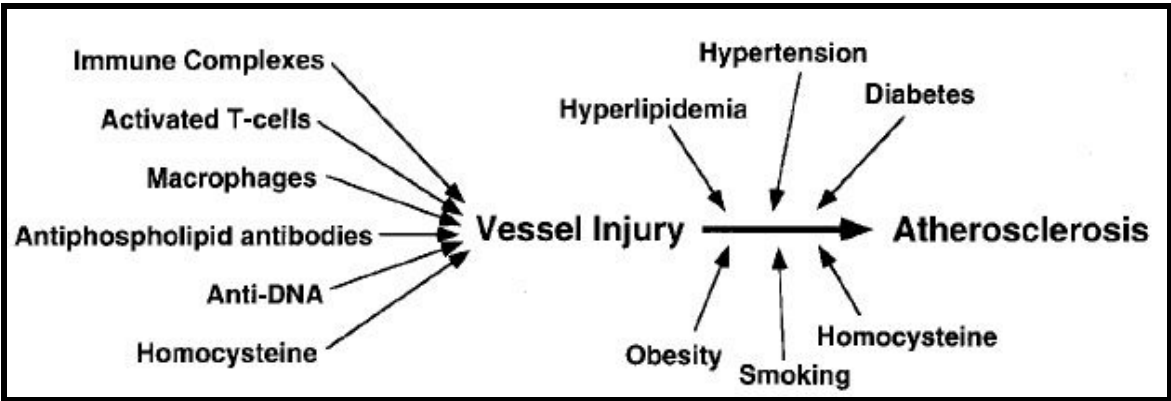


Fig. 1. Two-stage model of accelerated atherosclerosis in SLE (Petri, 2000)

7. The role of antimalarial drugs in SLE

Currently, there is over-emphasis from many international authorities in SLE on the need to maintain all lupus patients on antimalarial drugs (AMD). This is based on the abundance of data that confirm their huge beneficial effects in SLE. They are one of the most widely tolerated medications used in the treatment of SLE since 1955 (Scherbel, Schuchter & Harrison, 1957; Tye et al, 1959). They are safe even during pregnancy. Like any other medication, they have their side effects. However, an antimalarial drug like

hydroxychloroquine (HCQ) on a daily low dose has no or mild side effects and serious complications are rare. Ocular toxicity is the most important toxicity of HCQ, so regular ophthalmological check up is important. Chloroquine is found to have more side effects than hydroxychloroquine. Nowadays, AMD are not only used for patients with organ damage or patients with active disease but they are essential and key treatment for all patients with SLE. They should be started alone or with other medications once the diagnosis is made. A recent data showed the beneficial effects not only on the disease itself but on many other factors. For this reason, AMD should never be stopped in patients with SLE. Over the last decades many studies were done on AMD (especially HCQ) and it showed that HCQ has an effect in lowering fasting glucose and calculated insulin resistance (Penn et al, 2010) and reducing insulin degradation (Smith et al, 1987). There is significant reduction in total cholesterol, triglyceride (TG), LDL and very low density lipoprotein(VLDL) and significant increase in high density lipoprotein (HDL) level among patients using AMD and prednisolone than those with prednisolone alone (Borba & Bonfa, 2001; Rahman, 1999; Tam et al, 2000). As the HCQ showed its effect on glycemic control and lipid profile, it might decrease the risk for atherosclerosis. In addition, HCQ inhibits platelet aggregation and adhesion (Petri, 1996) so it is a mild anticoagulant and can decrease the risk of thrombosis (both arterial and venous) in patients with SLE (Kaiser, Cleveland & Criswell, 2009; Wallace, 1987) but this effect is still under trials. Data showed protective effect of HCQ on the BMD especially on the spine (Mok, Mak & Ma, 2005). Lupus activity was significantly reduced among patients who were using HCQ, and can reach up to 50% in some studies (Ruiz-Irastorza et al, 2010). It has positive impact on the survival and can protect against irreversible organ damage. As SLE and other rheumatological diseases affect female in child bearing age and they will have concerns regarding taking medications during pregnancy. HCQ does not appear to have effect on the fetus and it is not associated with any congenital anomalies. In addition data showed that its use during pregnancy decreases lupus activity. Other non-rheumatological specialities like nephrology and obstetrics and gynaecology may underestimate the clinical value of continuing AMD in all SLE patients. LN patients who are followed exclusively by nephrologists are not maintained on HCQ as observed in some centres unfortunately. This is probably because some believe that HCQ is not considered as one of the standard therapies for LN. However, AMD are standard therapies for SLE.

8. Rare manifestations of SLE

One of the approaches to avoid delay in SLE diagnosis and management is to recognize rare presentations of SLE. Fever of unknown origin is an example of this. Fever by itself is very common in SLE. It may affect up to 50% of SLE patients as a sign of active disease (Petri, 2002). Patients with SLE frequently develop abnormalities in one or more of the three blood cell lines. Awareness of different hematological abnormalities affecting SLE patients is essential. The association between idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP) and SLE should be noted. Rare entities like Kikuchi-Fujimoto's disease (KFD) or histiocytic necrotizing lymphadenitis (a benign, self-limited disease of unknown etiology which affects mainly young women, characterized by localized lymphadenopathy, predominantly in the cervical region, fever and leukopenia) has been reported in association with SLE. It can present before, at the same time, or after the clinical appearance of KFD (Boddaert, Huong et al. 2004).

8.1 Kikuchi-Fujimoto disease

Kikuchi-Fujimoto disease (KFD) or Necrotizing Lymphadenitis is a rare, benign, self-limited disease that was first reported in Japan in 1972. It affects the female predominantly with female to male ratio 4:1 (Al Salloum, 1998; Dorfman, 1987; Lopez et al, 2000). It usually resolves spontaneously between one and four months (Santana et al, 2005) and up to six months in another study (Kucukardali et al, 2007). Although it is benign, there are reported cases of disease progression and mortality rate can reach up to 2.1% (Kucukardali et al, 2007). KFD is found to be associated with many comorbid diseases; SLE was the most frequently associated with it. Among 224 cases with KFD, 32 of them had SLE. Of these, eighteen (56%) had both diseases together, six (19%) developed SLE later, four (12%) already had SLE previously and four (12%) had incomplete SLE as they did not meet the ACR criteria for SLE (Kucukardali, Solmazgul et al. 2007).

8.2 Thrombotic Thrombocytopenia Purpura (TTP)

TTP is a life threatening condition in which there is platelet aggregation that result in microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. It presents with the pentad of MAHA, thrombocytopenia, fever, acute renal failure and neurological manifestations. SLE is one of its secondary causes and it correlates with disease activity (Cheung, 2006) but rarely occurs as a first manifestation although there was a reported case in which a patient was diagnosed to have TTP and SLE simultaneously (Vasoo, Thumboo & Fong, 2002). Making the diagnosis of TTP in SLE patient is difficult as classical TTP symptoms may be due to SLE disease activity. The diagnosis of TTP can be established by the presence of thrombocytopenia, fragmented red blood cells (schistocytes) in blood film, increase bilirubin and lactate dehydrogenase, high urea and creatinine, normal coagulation profile and negative Coomb's test. It is important to rule out other serious conditions like disseminated intravascular coagulation (DIC) and intracranial haemorrhage (thrombocytopenia and neurological manifestation) by ordering coagulation profile and CT head respectively. The hallmark of TTP is detection fragmented RBC's in blood film. It is mandatory to have a peripheral smear conducted in any SLE patient presenting with new onset of anemia and thrombocytopenia. It is obvious that early diagnosis and aggressive treatment can make a huge difference in outcome.

8.3 Immune Thrombocytopenic Purpura (ITP)

ITP is a disease characterized by the presence of antibodies against platelets. This results in early clearance of platelets particularly by the spleen, and decreases their life span from 7-10 days to few hours. It presents by symptoms related to decrease platelet count as petechial haemorrhage, easy bruising, gum bleeding or epistaxis and menorrhagia in women. Intracranial bleeding is rare. ITP is a diagnosis of exclusion as more serious conditions like haematological malignancies must be ruled out first especially in people more than 60 years of age. It is characterized by presence of low platelet and normal haemoglobin and white blood cells count (WBC) except if there is concomitant iron deficiency anaemia or anaemia of chronic disease, normal PT and PTT, decrease platelet or presence of giant platelet in peripheral blood film and increase the number of megakaryocyte in bone marrow. An association between ITP and SLE has been recognized for decades and it can be the first manifestation in some patients with SLE (Jun, et al, 2008; Mestanza-Peralta et al, 1997). It has been estimated that 3-15% of patients with apparently isolated ITP go on to develop SLE (Karpatkin, 1980).

8.4 Fever of Unknown Origin (FUO)

FUO is a documented fever of >38°C on several occasions, for> 3 weeks without reaching the diagnosis after the initial diagnostic workup (Abdelbaky et al., 2011). FUO remains an important health problem that requires demanding efforts in order to reach the diagnosis despite the presence of advanced technology. Infections, connective tissue diseases, neoplasms are major causes that should be first ruled out before thinking about other causes. It was shown that among 100 patients with FUO, 50% were found to have infections, 24% were found to have connective tissue diseases (33.3% of them diagnosed as SLE, 20.8% familial Mediterranean fever, 16.6% rheumatoid arthritis, 12.5% Still’s disease & rheumatic fever and 4.3% Behcet’s disease/ Chron’s disease), no cause was identified in 11%, while the remaining 8% and 7% were found to have miscellaneous causes and neoplasia respectively (Abdelbaky et al, 2011).

How to avoid delay in SLE diagnosis and management?	Action plan
1. Consider SLE in the differential diagnosis of multisystemic presentations.	<ul style="list-style-type: none">• Order screening ANA.
2. Assure screening for MSK abnormalities in all acutely ill patients.	<ul style="list-style-type: none">• Ask about joint pain, swelling and morning stiffness.• Perform simple active range of motion test as a screening tool for MSK abnormalities.
3. Be aware of neurological manifestations of SLE (seizure, stroke, TM, MG, GBM, etc).	<ul style="list-style-type: none">• Include in your work-up screening ANA.• Educate clinicians taking care of neurological diseases about this.
4. Be aware of CAD risk factors in SLE patients	<ul style="list-style-type: none">• Life style modifications, weight reduction, check BP in every clinic visit, annual fasting blood glucose, statins for LDL>130mg/dl,
5. to decrease disease activity and possibly to decrease the risk of atherosclerosis.	<ul style="list-style-type: none">• Maintain all patients on HCQ
6. Fever is common in SLE and it might be a presenting feature.	<ul style="list-style-type: none">• Order screening ANA.
7. Be aware of different hematological abnormalities related to SLE (cytopenias, ITP, KFD, TTP).	<ul style="list-style-type: none">• Order screening ANA.• Order peripheral smear for any SLE patient with new onset anemia and thrombocytopenia.
8. SLE can still affect elderly population.	<ul style="list-style-type: none">• Order screening ANA as appropriate to the clinical presentation.• Educate clinicians taking care of elderly patients about this.

Table 4. Some recommended steps to avoid delay in SLE diagnosis and management

9. Conclusion

We discussed in this chapter several issues that can face clinicians in their daily work with SLE patients. Our aim was to focus on how to prevent delay in SLE diagnosis and management. Table 4 represents some recommended steps that might help in this regard. Enhancing MSK examination skills among clinicians in general is an international concern. This clearly will result in early detection of patients with clinical evidence of arthritis including SLE. There are several clinical settings and presentations where SLE should be considered. Late-onset SLE can affect elderly patients with few differences than classical SLE patients. NPSLE represents a diagnostic challenge to clinicians. There are 19 neuropsychiatric syndromes defined by ACR as an associated feature with NPSLE. Delay in considering kidney biopsy in SLE patients once indicated results in poor renal outcomes. Adjusting risk factors for renal disease like proteinuria, hypertension and dyslipidemia is vaguely considered by some clinicians. The leading cause of mortality in SLE is cardiac. Clinicians taking care of SLE patients should put prevention of cardiac morbidities and mortalities an important goal in their management agenda. With new modalities of treatment and the wide use of AMD since 1955 there is significant improvement in survival and quality of life in patients with SLE. Therefore, all lupus patients should be maintained on AMD like HCQ. SLE can present initially with a variety of hematological manifestations like ITP, TTP and KFD. SLE should be in the differential diagnosis of FUO.

10. Acknowledgments

The work to produce this chapter was supported by Alzaidi's Chair of research in rheumatic diseases- Umm Alqura University.

11. References

- Association of American Medical Colleges (2005) *Contemporary issues in medicine*. Washington, DC: Musculoskeletal Medicine Education.
- Abdelbaky, M.S. et al (2011) Prevalence of connective tissue diseases in Egyptian patients presenting with Fever of unknown origin. *Clinical Medicine Insights. Arthritis & Musculoskeletal Disorders*, 4, pp.33-41.
- Ahern, M.J. et al (1991) The musculo-skeletal examination: a neglected clinical skill. *Australian New Zealand Journal of Medicine*, 21(3), pp.303-306.
- Akesson, K., Dreinhofer, K.E., & Woolf, A.D. (2003) Improved education in musculoskeletal conditions is necessary for all doctors, *Bulletin of the World Health Organization*, 81(9), pp.677-683.
- Almoallim, H. (2010) Knowledge and Skills Competencies for the Undergraduate Internal Medicine Curriculum in Saudi Arabia. [Internet] Available from : <http://services.aamc.org/30/mededportal/servlet/s/segment/mededportal/?subid=8177>.
- Almoallim, H. et al (2009) Transverse myelitis as a presenting feature of late onset systemic lupus erythematosus. *Annals of Saudi Medicine*, 29 (2), pp.156-167.

- Almoallim, H. et al (2007) Delayed diagnosis of systemic lupus erythematosus due to lack of competency skills in musculoskeletal examination. *Clinical Rheumatology*, 26 (1), pp.131-133.
- Al Salloum, A.A. (1998) Kikuchi's disease and systemic lupus erythematoisus in a Saudi child. *Annals of Saudi Medicine*, 18(1), pp.51-53.
- Apperloo, A.J., de Zeeuw, D. & de Jong, P.E. (1994) Discordant effects of enalapril and lisinopril on systemic and renal hemodynamics. *Clinical Pharmacology and Therapeutics*, 56 (6 Pt.1), pp.647-658.
- Badley, E.M., Rasooly, I. & Webster, G.K. (1994) Relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilization: findings from the 1990 Ontario Health Survey. *Journal of Rheumatology*, 21(3), pp.505-514.
- Beattie, K.A. et al (2008) Validation of the GALS musculoskeletal screening exam for use in primary care: a pilot study. *BMC Musculoskeletal Disorders*, 9, pp.115.
- Belostocki, K.B. & Paget, S.A. (2002) Inflammatory rheumatologic disorders in the elderly. Unusual presentations, altered outlooks. *Postgraduate Medicine*, 111 (4), pp.72-74.
- Bertoli, A.M. et al (2006) Systemic lupus erythematosus in a multiethnic US cohort. XXXIII. Clinical [corrected] features, course, and outcome in patients with late-onset disease. *Arthritis and Rheumatism*, 54(5), pp.1580-1587.
- Bertsias, G. et al (2008) EULAR recommendations for the management of systemic lupus erythematosus. Reprot of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Annals of the Rheumatic Diseases*, 67(2), pp.195-205.
- Bhinder, S., Majithia, V. & Harisdangkul, V. (2006) Myasthenia gravic and systemic lupus erythematosus: truly associated or coincidental – two case reports and review of the literature. *Clinical Rheumatology*, 25(4), pp.555-556.
- Boddaert, J. et al. (2004) Late-onset systemic lupus erythematosus: a personal series of 47 patients and pooled analysis of 714 cases in the literature. *Medicine (Baltimore)*, 83(6), pp.348-359.
- Borba, E.F. & Bonfa, E. (2001) Longterm beneficial effect of chloroquine diphosphate on lipoprotein profile in lupus patients with and without steroid therapy. *Journal of Rheumatology*, 28(4), pp.780-785.
- Bradley, I. (2009) Systematic lupus erythematosus and premature coronary artery disease. [Online] Available from: <http://www.clinicalcorrelations.org/?p=4593> [Accessed 9 August 2011]
- Brazy, P.C. & Fitzwilliam, J.F. (1990) Progressive renal disease: role of race and antihypertensive medications. *Kidney International*, 37(4), pp.1113-1119.
- Buckheit, J.B. et al (1997) Modeling of progressive glomerular injury in humans with lupus nephritis. *American Journal of Rheumatology*, 273 (1 Pt.2), pp.F158-F169.
- Bulkley, B.H. & Roberts, W.C. (1975) The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. A study of 36 necropsy patients. *American Journal of Medicine*, 58(2), pp.243-264.
- Cameron, J.S. (1999a) Lupus nephritis. *Journal of the American Society of Nephrology*, 10(2), pp.413-424.

- Cameron, J.S. (1999b) Lupus nephritis: an historical perspective 1968-1998. *Journal of Nephrology*, 12(Suppl 2), pp.S29-S41.
- Chen, H.C. et al (2004) Longitudinal myelitis as an initial manifestation of systemic lupus erythematosus. *American Journal of the Medical Sciences*, 327(2), pp.105-108.
- Cheung, W.Y. (2006) Thrombotic thrombocytopenic purpura and systemic lupus erythematosus-distinct entities or overlapping syndromes? *Transfusion & Apheresis Science*, 34(3), pp.263-266.
- Christopher-Stine, L, et al (2007) Renal biopsy in lupus patients with low levels of proteinuria. *Journal of Rheumatology*, 34(2), pp.332-335.
- Clark, M.L., Hutchison, C.R. & Lockyer, J.M. (2010) Musculoskeletal education: a curriculum evaluation at one univeristy. *BMC Medical Education*, 10, p.93.
- Clawson, D.K., Jackson, D.W. & Ostergaard, D.J. (2001) It's past time to reform the musculoskeletal curriculum. *Academic Medicine*, 76(7), pp.709-710.
- Colpan, A. et al (2007) Fever of unknown origin: analysis of 71 consecutive cases. *American Journal of the Medical Sciences*, 334(2), pp.92-96.
- Contreras, G. et al. (2002) Lupus nephritis: a clinical review for practicing nephrologists. *Clinical Nephrology*, 57(2), pp.95-107.
- Costallat, L.T. & Coimbra, A.M. (1994) Systemic lupus erythematosus: clinical and laboratory aspects related to age at disease onset. *Clinical and Experimental Rheumatology*, 12(6), pp.603-607.
- Costenbader, K.H. et al (2004) Cardiac risk factor awareness and management in patients with systemic lupus erythematosus. *Arthritis & Rheumatism*, 51(6), pp.983-988.
- Day, C.S. et al (2007) Musculoskeletal medicine: an assessment of the attitudes and knowledge of medical students at Harvard Medical School. *Academic Medicine*, 82(5), pp.452-457
- D'Cruz, D.P. et al (2004) Transverse myelitis as the first manifestation of systemic lupus erythematosus or lupus-like disease: good functional outcome and relevance of antiphospholipid antibodies. *Journal of Rheumatology*, 31(2), pp.280-2285.
- Dequeker, J., Esselens, G. & Westhovens, R. (2007) Educational issues in rheumatology. The musculoskeletal examination: a neglected skill. *Clinical Rheumatology*, 26(1), pp.5-7.
- Doherty, M., Abawi, J. & Pattrick, M. (1990) Audit of medical inpatient examination: a cry from the joint. *Journal of the Royal College of Physicians of London*, 24(2), pp.115-118.
- Doherty, M. et al (1992) The "GALS" locomotor screen. *Annals of the Rheumatic Diseases*, 51(10), pp.1165-1169.
- Dorfman, R.F. (1987) Histiocytic necrotizing lymphadenitis of Kikuchi and Fujimoto. *Archives of Pathology & Laboratory Medicine*, 111(11), pp.1026-1029.
- Dubois, E.L. & Wallace, D.J. Clinical and laboratory manifestations of systemic lupus erythematosus. In Wallace, D.J. & Dubois, E.L. eds. *Dubois lupus erythomatosus*. 3rd ed. Philadelphia: Lea & Febiger. pp. 317-449.
- Duran-Barragan, S. et al (2008) Angiotensin-converting enzyme inhibitors delay the occurrence of renal involvement and are associated with a decreased risk of disease activity in patients with systemic lupus erythematosus—results from

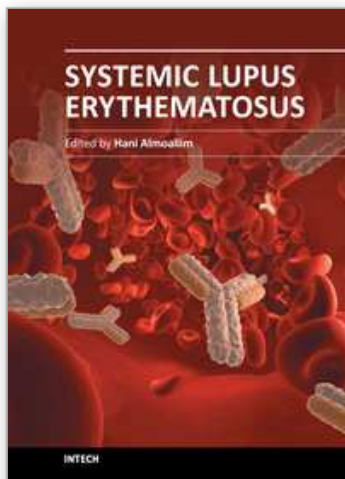
- LUMINA (LIX): a multiethnic US cohort. *Rheumatology (Oxford)*, 47(7), pp.1093-1096.
- Eilertsen, G.O. et al (2011) Decreased incidence of lupus nephritis in northern Norway is linked to increased use of antihypertensive and anticoagulant therapy. *Nephrology, Dialysis, Transplantation*, 26(2), pp.520-627.
- Erkan, D. et al (2002) A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)*, 41(8), pp.924-929.
- Esdaile, J.M. et al (1994) The benefit of early treatment with immunosuppressive agents in lupus nephritis. *Journal of Rheumatology*, 21(11), pp.2046-2051.
- Faurschou, M. et al (2006) Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *Journal of Rheumatology*, 33(8), pp.1563-1569.
- Fiehn, C. et al (2005) Lack of evidence for inhibition of angiogenesis as a central mechanism of the antiarthritic effect of methotrexate. *Rheumatology International*, 25(2), pp.108-113.
- The GISEN Group (1997) Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*, 349 (9069), pp.1857-1863.
- Goldenberg, D.L. et al (1985) Rheumatology training at internal medicine and family practice residency programs. *Arthritis & Rheumatism*, 28(4), pp.471-476.
- Goto, M. et al., (1992) Constitutive production of angiotensin converting enzyme from rheumatoid nodule cells under serum free conditions. *Annals of the Rheumatic Diseases*, 51(6), pp.741-742.
- Haider, Y.S. & Roberts, W.C. (1981) Coronary arterial disease in systemic lupus erythematosus; quantification of degrees of narrowing in 22 necropsy patients (21 women) aged 16 to 37 years. *American Journal of Medicine*, 70(4), pp.775-781.
- Hochberg, M.C. et al (1985) Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. *Medicine (Baltimore)*, 64(5), pp.285-285.
- Jacobsen, S. et al (1998) A multicentre study of 513 Danish patients with systemic lupus erythematosus.I. Disease manifestations and analyses of clinical subsets. *Clinical Rheumatology*, 17(6), pp.568-477.
- Jones, A., Maddison, P. & Doherty, M. (1992) Teaching rheumatology to medical students: current practice and future aims. *Journal of the Royal College of Physicians of London*, 26(1), pp.41-43.
- Joseph, F.G., Lammie, G.A. & Scolding, N.J. (2007) CNS lupus: a study of 41 patients. *Neurology*, 69 (7), pp.644-654.
- Joshua, A.M., Celermajer, D.S. & Stockler, M.R. (2005) Beauty is in the eye of the examiner: reaching agreement about physical signs and their value. *Internal Medicine Journal*, 35(3), pp.178-187.
- Jun, S.E., Park, S.S. & Lim, Y.T. (2008) Prevalence and clinical significance of the positive antinuclear antibody in children with idiopathic thrombocytopenic purpura. *Korean Journal of Pediatrics*, 51(11), pp.1217-1221.

- Kaiser, R., Cleveland, C.M. & Criswell, L.A. (2009) Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. *Annals of the Rheumatic Diseases*, 68(2), pp.238-241.
- Karoubi Nordon, E. et al (2007) Late onset systemic lupus erythematosus: a new approach. *Lupus*, 16(12), pp. 1011-1014.
- Karparkin, S. (1980) Autoimmune thrombocytopenic purpura. *Blood*, 56(3), pp.329-343.
- Korkmaz, C., Cansu, D.U. & Kasifoğlu, T. (2007) Myocardial infarction in young patients (< or =35 years of age) with systemic lupus erythematosus: a case report and clinical analysis of the literature. *Lupus*, 16(4), pp.289-297.
- Kovacs, B. et al (2000) Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. *Annals of the Rheumatic Diseases*, 59(2), pp.120-124.
- Kucukardali, Y. et al (2007) Kikuchi-Fujimoto disease: analysis of 244 cases. *Clinical Rheumatology*, 26(1), pp. 50-54.
- Laufs, U. et al (1998) Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation*, 97(12), pp.1129-1135.
- Leneman, F. (1966) The Guillain-Barre syndrome. Definition, etiology, and review of 1,100 cases. *Archives of Internal Medicine*, 118(2), pp.139-144.
- Lewis, E.J. et al (1993) The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *New England Journal of Medicine*, 329(20), pp.1456-1462.
- Lidgren, L. (2003) The bone and joint decade 2000-2010. *Bulletin of the World Health Organization*, 81(9), p.629.
- Lillicrap, M.S., Bryne, E. & Speed, C.A. (2003) Musculoskeletal assessment of general medical in-patients—joints still crying out for attention. *Rheumatology (Oxford)*, 42(8), pp.951-954.
- Lopez, C. et al (2000) Kikuchi-Fujimoto necrotizing lymphadenitis associated with cutaneous lupus erythematosus: a case report. *American Journal of Dermatopathology*, 22(4), pp.328-333.
- Maddison, P.J. (1987) Systemic lupus erythematosus in the elderly. *Journal of Rheumatology Supplements*, 14 (Suppl 13), pp.182-187.
- Manzi, S. et al (1997) Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *American Journal of Epidemiology*, 145(5), pp.408-415.
- Maschio, G. et al (1996) Effect of the angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *New England Journal of Medicine*, 334(15), pp.939-945.
- Maschio, G. et al (1989) Serum lipids in patients with chronic renal failure on long-term, protein-restricted diets. *American Journal of Medicine*, 87(5N), pp.51N-54N.
- Matzkin, E. et al (2005) Adequacy of education in musculoskeletal medicine. *Journal of Bone & Joint Surgery (American)*, 87(2), pp.310-314.
- Mestanza-Peralta, M. et al (1997) Thrombocytopenic purpura as initial manifestation of systemic lupus erythematosus. *Journal of Rheumatology*, 24(5), pp.867-870.
- Ministry of Health (2009) *The Annual Health Report – 1430H*. Riyadh: Ministry of Health.
- Mitsikostas, D.D., Sfikakis, P.P. & Goadsby, P.J. (2004) A meta-analysis for headache in systemic lupus erythematosus: the evidence and the myth. *Brain*, 127(Pt.5), pp.1200-1209.

- Moder, K.G., Miller, T.D. & Tazelaar, H.D. (1999) Cardiac involvement in systemic lupus erythematosus. *Mayo Clinic Proceedings*, 74(3), pp.275-284.
- Mok, C.C., Mak, A. & Ma, K.M. (2005) Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. *Lupus*, 14(2), pp.106-112.
- Padovan, M. et al (2007) Late onset systemic lupus erythematosus: no substantial differences using different cut-off ages. *Rheumatology International*, 27(8), pp.735-741.
- Paget, S. (2007) The European League Against Rheumatism guidelines for early arthritis. *Nature Clinical Practice Rheumatology*, 3(7), pp.374-375.
- Penn, S.K. et al (2010) Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. *Journal of Rheumatology*, 37(6), pp.1136-1142.
- Peterson, J.C. et al (1995) Blood pressure control, proteinuria, and the progression of renal disease. *Annals of Internal Medicine*, 123(10), pp.754-762.
- Petri, M. (1996) Hydroxychloroquine use in the Baltimore Lupus Cohort: effects on lipids, glucose and thrombosis. *Lupus*, 5 (Suppl 1), pp.S16-S22.
- Petri, M. (2000) Detection of coronary artery disease and the role of traditional risk factors in the Hopkins Lupus Cohort. *Lupus*, 9(3), pp.170-175.
- Petri, M. (2002) Epidemiology of systemic lupus erythematosus. *Best Practice & Research Clinical Rheumatology*, 16(5), pp.847-858.
- Pinney, S.J. & Regan, W.D. (2001) Educating medical students about musculoskeletal problems. Are community needs reflected in the curricula of Canadian medical schools? *Journal of Bone & Joint Surgery (American)*, 83-A(9), pp.1317-1320.
- Pu, S.J. et al (2000) The clinical features and prognosis of lupus with disease onset at age 65 and older. *Lupus*, 9(2), pp.96-100.
- Rahman, P. (1999) The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. *Journal of Rheumatology*, 26(2), pp.325-330.
- Rasker, J.J. (1995) Rheumatology in general practice. *British Journal of Rheumatology*, 34(6), pp.494-497.
- Rosansky, S.J. et al (1990) The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. *Archives of Internal Medicine*, 150(10), pp.2073-2076.
- Rovensky, J. & Tuchynova, A. (2008) Systemic lupus erythematosus in the elderly. *Autoimmunity Reviews*, 7(3), pp.235-239.
- Ruiz-Irastorza, G. et al (2010) Clinical efficacy and side effects of antimalarials in systemic erythematosus: a systematic review. *Annals of the Rheumatic Diseases*, 69(1), pp.20-28.
- Samuelsson, O. et al (1993). Apolipoprotein-B-containing lipoproteins and the progression of renal insufficiency. *Nephron*, 63(3), pp.279-285.
- Santana, A. et al (2005). Kikuchi-Fujimoto's disease associated with systemic lupus erythematosus: case report and review of the literature. *Clinical Rheumatology*, 24(1), pp.60-63.
- Scherbel, A.L., Schuchter, S.L. & Harrison, J.W. Comparison of effects of two antimalarial agents, hydroxychloroquine sulfate and chloroquine phosphate, in patients with rheumatoid arthritis. *Cleveland Clinic Quarterly*, 24(2), pp.98-104.

- Seligman, V.A. et al (2002) Demographic differences in the development of lupus nephritis: a retrospective analysis. *American Journal of Medicine*, 112(9), pp.726-729.
- Sella, E.M. et al (2003) Myocardial perfusion scintigraphy and coronary disease risk factors in systemic lupus erythematosus. *Annals of the Rheumatic Diseases*, 62(11), pp.1066-1070.
- Shah, M.A., Shah, A.M. & Krishnan, E. (2009) Poor outcomes after acute myocardial infarction in systemic lupus erythematosus. *Journal of Rheumatology*, 36(3), pp.570-575.
- Shulman, N.B. et al (1989) Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. *Hypertension*, 13 (Suppl 5), pp.I80-I90.
- Sirisena, D. et al (2011) Musculoskeletal examination—an ignored aspect. Why are we still failing the patients? *Clinical Rheumatology*, 30(3), pp.403-407.
- Smith, G.D. et al (1987) Effect of chloroquine on insulin and glucose homoeostasis in normal subjects and patients with non-insulin dependent diabetes mellitus. *British Medical Journal (Clinical Research Edition)*, 294(6570), pp.465-467.
- Sthoeger, Z. et al (2006) High prevalence of systemic lupus erythematosus in 78 myasthenia gravis patients: a clinical and serologic study. *American Journal of Medical Sciences*, 33(1), pp.4-9.
- Tam, L.S. et al (2000) Effect of antimalarial agents on the fasting lipid profile in systemic lupus erythematosus. *Journal of Rheumatology*, 27(9), pp.142-145.
- Thompson, A.E. (2008) Improving undergraduate musculoskeletal education: a continuing challenge. *Journal of Rheumatology*, 35(12), pp.2298-2299.
- Tye, M.J. et al (1959) Lupus erythematosus treated with a combination of quinacrine, hydroxychloroquine and chloroquine. *New England Journal of Medicine*, 260(2), pp.63-66.
- Vaiopoulos, G. et al (1994) The association of systemic lupus erythematosus and myasthenia gravis. *Postgraduate Medicine Journal*, 70(828), pp.741-745.
- Vasoo, S., Thumboo, J. & Fong, K.Y. (2002) Thrombotic thrombocytopenic purpura in systemic lupus erythematosus: disease activity and the use of cytotoxic drugs. *Lupus*, 11(7), pp. 443-450.
- Vaughan, C.J., Gott, A.M. & Basson, C.T. (2000) The evolving role of statins in the management of atherosclerosis. *Journal of the American College of Cardiology*, 35(1), pp.1-10.
- Veale, D. et al (1992) Production of angiotensin converting enzyme by rheumatoid synovial membrane. *Annals of the Rheumatic Diseases*, 51(4), pp.476-480.
- Wahl, D.G. et al (2000) Prophylactic antithrombotic therapy for patients with systemic erythematosus with or without antiphospholipid antibodies: do the benefits outweigh the risks? A decision analysis. *Archives of Internal Medicine*, 160 (13), pp.2042-2048.
- Wajed, J. et al (2004) Prevention of cardiovascular disease in systemic lupus erythematosus—proposed guidelines for risk factor management. *Rheumatology*, 43(1), pp.7-12.
- Wallace, D.J. (1987) Does hydroxychloroquine sulfate prevent clot formation in systemic lupus erythematosus? *Arthritis & Rheumatism*, 30(12), pp.1435-1436.

- Wen, Y.K. (2011) Renal biopsy findings in new-onset systemic lupus erythematosus with clinical renal disease. *International Urology & Nephrology* 00: 1-6 (accessed 8 August 2011)
- Woolf, A.D., & Akesson, K. (2008) Primer: history and examination in the assessment of musculoskeletal problems. *Nature Clinical Practice Rheumatology*, 5 (1), pp.26-33.
- Woolf, A.D., Walsh N.E. & Akesson, K. (2004) Global core recommendations for a musculoskeletal undergraduate curriculum. *Annals of the Rheumatic Diseases*, 63(5), pp.517-524.



Systemic Lupus Erythematosus

Edited by Dr Hani Almoallim

ISBN 978-953-51-0266-3

Hard cover, 554 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Hani Almoallim, Esraa Bukhari, Waleed Amasaib and Rania Zaini (2012). How to Avoid Delay in SLE Diagnosis and Management, Systemic Lupus Erythematosus, Dr Hani Almoallim (Ed.), ISBN: 978-953-51-0266-3, InTech, Available from: <http://www.intechopen.com/books/systemic-lupus-erythematosus/how-to-avoid-delay-in-sle-diagnosis->

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen