Research Article

Frequency of subclinical Coronary Artery Disease in Patients with systemic lupus erythematosus using ^{99m}Technetium Tetrofosmin Myocardial Perfusion Scintigraphy: relation to disease activity and low grade inflammation

Hala Lotfy Fayed[*]MD, Khalil FA[**]MD, Sayyed S[***]MSc and Saleh AH[****]MSc

[*] Department of Rheumatology & Rehabilitation, Faculty of Medicine - Cairo University

[**] Department of Nuclear Medicine - KFSH-B

[***] Department of Cardiology Specialist at PSCC-Q

[****] Department of Clinical and chemical pathology specialist - KFSH-B

Abstract

Introduction: Systemic Lupus Erythematous (SLE) is an autoimmune systemic chronic inflammatory disease with known cardiovascular manifestations. Premature coronary heart disease has emerged as a major cause of morbidity and mortality in SLE. Subclinical coronary artery disease (CAD) is a potential challenge in patients with SLE. The increased cardiovascular risk can be explained only partially by an increased prevalence of classic risk factors for cardiovascular disease; more important it also appears to be related to chronic inflammation. A persistent low level of inflammation plays a major role in atherosclerosis and CAD. The high-sensitivity CRP (hsCRP) accurately measures low levels of C-reactive protein to identify low but persistent levels of inflammation and thus helps predict the risk of developing CVD. ^{99m}Tc-labelled Tetrofosmin is a sensitive noninvasive tool for screening and early detection of myocardial ischemia in patients with SLE. **Aim of this study:** The aim of the present study was to determine the frequency of subclinical premature myocardial ischemia in SLE patients in view of the traditional as well as non-traditional risk factors for the development coronary artery disease (CAD), and highlight its relation to disease activity and low-grade systemic inflammation. **Patients and methods**: A case-control study that comprised ٦٠ SLE patients (Group I – Patients) with no past or present clinical symptoms or signs suggestive of coronary artery disease , and ٣٠ age and sex-matched subjects (Group –II Control subjects) who were attending the rheumatology outpatient clinic of a tertiary hospital in Saudi Arabia. They were subjected to thorough history taking and clinical examination as well as laboratory investigations including hsCRP. Both patients and controls have then undergone resting ECG, followed by ^{99m}Tc-Tetrofosmin Gated Single Photon Emission Computed Tomography (SPECT) pharmacological Stress and Rest myocardial perfusion scintigraphy. **Results:** Group I included ٥٤ (٩٠٪) females and ٦ (١٠٪) males, with mean age ٢٩±١١ years; age range was ١٨-٤٠ years, with disease duration ranging from ٢-١٥ years. Group-II comprised ٢٧ (٩٠٪) female subjects and ٣ (١٠٪) male subjects with mean age ٣١±١٣ years; age range was ١٨-٤٤ years. Twenty patients (٣٣.٣٣٪) had quiescent disease with SLEDAI score=٠; thirteen patients (٢١.٦٦٪) had mild disease activity with SLEDAI score ranging between ١-٥; seventeen (٢٨.٣٣٪) patients had moderate disease activity with SLEDAI score ranging between ٦-١٠; seven patients (١١.٦٦٪) had high disease activity with SLEDAI score ranging between ١١-١٩; and ٣ patients (٥٪) had very high disease activity with SLEDAI score ٢٠ or more. On stress SPECT study, ٢٣ (٣٨.٣٣٪) SLE patients showed reversible myocardial perfusion defects, compared to ٢ subjects (٦.٦٦٪) in the control group who showed stress-induced hypoperfused segments. (p =٠.٠٠١*). There was significant statistical difference in the number of patients with positive Tetrofosmin stress-induced myocardial perfusion defects between SLE patients with longer disease duration >٧ years than those with disease duration ≤٧ years with (p <٠.٠٠١*). There was a significant statistical difference in the scan results with more positive cases among patients with higher disease

activity (p <٠.٠٠١*). The number of patients with positive Tetrofosmin stress-induced myocardial perfusion defects was significantly higher in patients with high-risk hsCRP (>٣mg/L) than in patients with low-intermediate risk hsCRP (≤٣mg/L) with p value < ٠.٠٠١* There was significant statistical difference between HCQ users SLE patients when compared to non-HCQ users SLE patients with p<٠.٠٠١* suggesting a protective role for antimalarial therapy against CAD. **Conclusion and Recommendations:** Low-grade chronic inflammation is an important predictor for development of premature CAD in SLE. Adequate control of the disease activity, proper monitoring of inflammatory markers like hsCRP, screening of SLE patients especially, those with severe disease course, or uncontrolled disease as well as those with longer disease duration using non-invasive diagnostic tool like ^{٩٩m}Tc-Tetrofosmin Gated Single Photon Emission Computed Tomography (SPECT), and adding medications like hydroxychloroquine and statins with protective effects

Keywords: ^{٩٩m}Tc-Tetrofosmin Myocardial Perfusion Scintigraphy, systemic lupus erythematosus, myocardial ischemia, coronary artery disease (CAD).

Introduction

Systemic Lupus erythematosus (SLE) is a chronic multifaceted autoimmune inflammatory disease characterized by acute and chronic inflammation that can affect any part of the body. It primarily affects young women (more than ٩٠٪ of new patients presenting with SLE are women in the childbearing years) (Cojocaru et al., ٢٠١١).

Cardiac involvement in patients with SLE can involve all components of the heart, including the pericardium, conduction system, myocardium, endocardium and valves, and coronary arteries although the latter was described much later than the other cardiovascular manifestations (D'Cruz et al., ٢٠٠٧).

Premature /accelerated coronary heart disease has emerged as a major cause of morbidity and mortality in SLE: it has been increasingly recognized that patients with SLE have a high cardiovascular mortality; fatal myocardial infarction has been reported to be ٣ times higher in patients with SLE than in age- and gender -matched control subjects (Willerson & Ridker, ٢٠٠٤).

In addition to mortality, cardiovascular morbidity is also markedly increased in these patients, compared with the general population, with the striking clinical characteristic of young female patients with SLE presenting with cardiovascular events (Zeller and Appenzeller , ٢٠٠٨).

The hospital admission rate for cardiovascular morbidity was found to be ٢.٣ times more likely in young women with SLE compared to young women without SLE because of acute myocardial infarction (Ward, ١٩٩٩).

The overall prevalence of clinical coronary artery disease in SLE patients is increased in various cohorts compared with the general population: fivefold in the early Toronto cohort (Urowitz et al., ١٩٧٦) that first recognized the increased risk of cardiovascular disease in SLE; ninefold in a Swedish lupus population described in ١٩٨٩ (Jonsson et al., ١٩٨٩); at least sevenfold in a Canadian cohort (Esdaile et al., ٢٠٠١); ranged between ٦٪ and ١٦٪ in various studies (Gladman & Urowitz, ١٩٨٧; Petri et al.,١٩٩٢; Manzi et al., ١٩٩٧; Borchers et al., ٢٠٠٤). Various case-control series have confirmed that the risk of myocardial infarction in patients with SLE is increased between ٩- and ٥٠-fold over that in the general population (Ross, ١٩٩٩; Haque & Bruce, ٢٠٠٥).

Furthermore, studies showed that the myocardial infarction (MI) occurred at an average age of ٤٩ years in SLE patients compared with ٦٥–٧٤ years in the general population (Urowitz et al., ١٩٧٦); Young female patients in the ٣٥–٤٤-year age group with SLE have a ٥٠-fold increased risk of MI compared to women without lupus (Manzi et al., ١٩٩٧).

Subclinical coronary artery disease (CAD) may occur in up to ٤٠٪ of lupus patients

(Bruce et al., ٢٠٠٣B). The incidence of subclinical atherosclerosis is also increased in SLE: In studies by Roman and his colleagues, carotid plaque was found in ٣٧٪ of SLE patients compared with ١٥٪ of controls (Roman et al., ٢٠٠٣; Roman et al., ٢٠٠٧). Subclinical carotid atherosclerosis was found in ٤٠٪ of another cohort (Manzi et al., ١٩٩٩). Asanuma and coworkers also found an increased prevalence of subclinical atherosclerosis in ٣١٪ of SLE patients compared with ٩٪ of controls (Asanuma et al., ٢٠٠٣); ٥٥٪ of SLE patients had impaired flow-mediated dilation, compared with ٢٦.٣٪ of control subjects when endothelial dysfunction was used as a marker of atherosclerosis (El-Magadmi et al., ٢٠٠٤).

Clinical epidemiological observations strongly suggest that, together with classical traditional/ conventional risk factors (age, obesity, hypertension, diabetes mellitus, dyslipidemia, previous vascular event, menopause and smoking), other non-conventional/disease-specific factors (disease duration, presence of inflam-mation, renal disease, antiphonspholipid antibodies, anti-oxLDL antibodies, corticosteroid use and cumulative dose of glucocorticoids) promote accelerated atherosclerosis in autoimmune diseases like SLE (McMahon et al., ٢٠١١).

Lupus is now considered to be an independent risk factor for the development of atherosclerosis. Viewing atherosclerosis as an inflammatory disease may be the clue for understanding this association (Zeller & Appenzeller, ٢٠٠٨).

Epidemiological observations have linked inflammation with the cardiovascular events. Inflammation is increasingly being considered central to the pathogenesis of atherosclerosis and an important risk factor for vascular disease. Evidence strongly suggests that atherosclerotic plaque is largely driven by inflammation and an active immunological response, in contrast to the long-held belief that plaque is a passive accumulation of lipids in the arterial wall (Sinicato et al., ٢٠١٣).

The chronic inflammatory state per se has been linked to acceleration of the atherosclerotic process which is underlined by an increased incidence of cardiovascular disease (CVD) in SLE, as well as other autoimmune disorders (Zeller & Appenzeller, ٢٠٠٨).

Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future cardiovascular events. High-sensitivity C-reactive protein (hsCRP) is considered the most reliable and accessible marker for clinical detection of systemic inflammation in current use (Willerson & Ridker, ٢٠٠٤).

Abou-Raya & Abou-Raya, in ٢٠٠٦ stated that the excess risk of CAD observed in autoimmune disease appears to be driven by systemic inflammation, directly or indirectly through its damaging effects on the vasculature; and thus the concept of inflammation as a cardiovascular risk factor, and that among various markers of inflammation, the CRP level was a particularly powerful predictor of cardiovascular disease independently of serum lipid levels.

Del Rincon and colleagues (٢٠٠٣) suggested that CRP can be causally involved in the pathophysiology of atherosclerosis and its complications through its localization in the atheromatous plaques and stimulation of macrophages to produce Tissue Factor (TF) antigen, an important procoagulant found in atheromatous plaques that initiate the thrombotic complications secondary to atherosclerosis.

Chronically raised levels of inflammatory mediators may drive the inflammation that subsequently contributes to endothelial damage (Bacon, ٢٠٠٥). Chronic endothelial damage and vascular inflammation may be induced both by conventional risk factors and systemic inflammation, and represent important mechanisms in atherogenesis (Agewall, ٢٠٠٣; Bacon, ٢٠٠٥). Endothelial dysfunction is a key event in atherogenesis

and appears before the histopatholical evidence of atherosclerotic lesion (Agewall, ٢٠٠٣).

Inflammation and atherosclerosis have been linked for decades, although the underlying mechanism and the antigens causing immune activation are not totally elucidated. Activated monocytes, macrophages and T cells and cytokines have an important role in atherogenesis. C reactive protein (CRP) is considered an independent risk factor for CVD. In addition, autoantigens and autoantibodies have also important role in atherogenesis in general population (Abusamieh & Ash, ٢٠٠٤).

Studies have suggested that a persistent low level of inflammation plays a major role in atherosclerosis and CVD. The hsCRP accurately measures low levels of CRP to identify low but persistent levels of inflammation and thus helps predict the risk of developing CVD (Yousuf et. al., ٢٠١٣); Ridker and his colleagues in ٢٠٠٠ showed that of ١٢ markers measured, hs-CRP was the strongest univariate predictor of the risk of cardiovascular events.

Although earlier studies have suggested that active SLE patients do not have elevated CRP levels, recent studies using a sensitive method have revealed that most SLE patients have elevated CRP levels during the evolution of the disease process, irrespective of concomitant active infection (Williams et al., ٢٠٠٥; Al-Mekaimi et al., ١٩٩٧).

Similarly, earlier investigators found no association between CRP levels and the patterns of organ involvement in SLE. However, investigators have recently described an association between CRP and various organ involvements (Lee et al., ٢٠٠٨): musculoskeletal (Mok et al., ٢٠١٣), pulmonary (Mochizuki et al., ١٩٩٩), and renal involvement in SLE (Zuniga et al., ٢٠٠٣).

Nikpour and coworkers, in ٢٠١١ found that despite marked variability over time among patients with SLE, hsCRP level is significantly predictive of CAD, independently of the Framingham risk score and SLE disease activity score, which highlights the pivotal role of inflammation in the development of CAD in SLE, and makes a case for measuring hsCRP in routine CAD risk assessment of patients with SLE. They also suggested that SLE patients with an hsCRP level of ١.٦ mg/L or greater was associated with significantly increased CAD risk and represent a group in whom measures to prevent CAD events must be implied.

Patients with lupus are now living a great deal longer than they did earlier before the use of corticosteroids. Thus, while corticosteroids may well control the disease by suppressing inflammation and overreactive immune response, it can causally be related to premature coronary artery disease by increasing the traditional Framingham risk factors of dyslipidemia, hyperglycemia, hypertension, and obesity, as well as increasing patient life expectancy with longer time of chronic inflammation.

Hydroxychloroquine (HCQ) therapy is thought to be cardioprotective and is associated with lower serum cholesterol thus may ameliorate risk for CAD to some extent (Stojan & Petri, ٢٠١٣). Studies noted that non-use of hydroxychloroquine was associated with higher aortic stiffness in SLE patients measured by ultrasound (Selzer et al., ٢٠٠١), more carotid artery plaque (Roman et al., ٢٠٠٣). In addition, antimalarials have been shown to lower total cholesterol in patients receiving steroids, and may minimize steroid induced hypercholesterolemia (Rahman et al., ١٩٩٩), lower fasting blood glucose conentrations (Petri, ١٩٩٦), prolongs the half-life of the active insulin-receptor complex thus augmenting insulin-stimulated responses (Bevan et al., ١٩٩٧), and show beneficial effects on thrombosis formation (Edwards et al., ١٩٩٧) and reversal of platelet aggregation (Espinola et al., ٢٠٠٢). Multiple retrospective cohort studies have shown a reduced incidence of thrombotic events (Jung et al., ٢٠١٠; Kaiser et al., ٢٠٠٩; Ruiz-Irastorza et al., ٢٠٠٦).

Notably, all-cause mortality rates in patients with SLE have decreased in recent decades, except for CVD-related mortality

(Bjornadal et al., ٢٠٠٤). Thus, understanding, screening and early diagnosing as well as treating the risk factors for CVD in SLE are important.

Patients and Methods

The study included two groups; Group I (Patients) comprised sixty patients with SLE who fulfilled the ٢٠١٢ Systemic Lupus International Collaborating Clinics (SLICC) diagnostic criteria (Petri et al., ٢٠١٢) who were attending the rheumatology outpatient clinic of a tertiary hospital in Saudi Arabia, and Group II (Control subjects) included thirty age- and sex-matched subjects. All participants had no history or present clinical symptom or sign suggestive of coronary artery disease (CAD). All included patients were taking glucocorticoid preparations for >١ year.

The study was carried in accordance to the code of ethics of the world medical association (Declaration of Helsinki). Written informed consents were taken from the patients as well as control subjects after explaining the whole procedures to them. Thorough history taking and clinical examination as well as laboratory investigations including: complete blood count (CBC) with differential counts, fasting blood glucose, complete lipid profile (serum total cholesterol, LDL-cholesterol, HDL-cholesterol, and serum total triglycerides), urinalysis with microscopy, ٢٤ hours urinary proteins, high sensitivity C-reactive protein (hs-CRP), Complement ٣ (C٣), Complement ٤ (C٤), as well as autoantibodies profile including antinuclear antibodies (ANA), anti-double stranded DNA antibodies (AdsDNA).

As regards thr hsCRP: the American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups as follows; Low risk less than ١.٠ mg/L; Aaverage/intermediate risk: ١.٠ to ٣.٠ mg/L; High risk: above ٣.٠ mg/L (Yousuf et al., ٢٠١٣).

Disease activity of SLE patients was evaluated by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Activity categories have been defined on the basis of SLEDAI scores as follows; No activity (SLEDAI = ٠); Mild activity (SLEDAI = ١-٥); Moderate activity (SLEDAI = ٦-١٠); High activity (SLEDAI = ١١-١٩); Very high activity (SLEDAI ٢٠) (Bombardier et al., ١٩٩٢).

Patients has then undergone resting ECG, followed by ^{٩٩m}Tc-Tetrofosmin Gated SPECT Pharmacological Stress and Rest myocardial perfusion scintigraphy for detection of underlying myocardial ischemia regardless the presence or absence of any symptoms suggestive for myocardial ischemia,

Patients on Beta-blockers or nitrates compounds were instructed to stop Beta-blockers drugs for at least two days and nitrates compounds for at least ٢٤ hours. Patients were asked to be fasting for ٦-٨ hours before the test. Patients with any contraindication for adenosine injection were excluded from the screening program. Pharmacological Stress ECG was done by using IV Adenosine injection at a dose of ١٤٠ µg/kg/min over a period of ٦ minutes, with sequential ECG recording, frequent arterial blood pressure and pulse measurements. Three minutes after adenosine injection, ٢٠ mCi of ^{٩٩m}Tc-Tetrofosmin was injected intravenously, and imaging study was done ٣٠-٤٥ minutes post-injection of radiotracer (stress study). A cardiologist was in attendance to supervise the pharmacologic stress test. The test was terminated immediately if any of the following occurred: grade ٢ or ٣ atrioventricular blockade, systolic hypotension of ≤٨٠ mm Hg, a ≥٢-mm decrease in the ST segment, angina, headache, hyperventilation, and/or gastrointestinal symptoms.

In cases with positive stress study (definite stress-induced hypoperfused myocardial segments), another study on another separate day was done after injection of a similar dose ٢٠ mCi ^{٩٩m}Tc-Tetrofosmin, during resting condition (rest study). Images were acquired ٤٥-٦٠ minutes post-injection of radiotracer.

Isotopic scanning of the heart was done as follows:

١- Stress cardiac Gated SPECT study was done ٣٠-٤٥ minutes after injection of ٢٠ mCi (٧٤٠ MBq) at the end of adenosine injection or on occurrence of ECG significant changes: Patients and control subjects were centered and positioned properly to enable the camera to get as close as possible to the body, and also to achieve a comfortable position during the study which decreased the incidence of patients' movements during the study. Metallic objects were avoided as much as possible to minimize risk of artifact. Tomographic images were then acquired by the use of a state of art rotating gamma camera fitted with low energy high-resolution collimator (LEGP). The energy peak for the gamma camera was adjusted at ٢٠% energy window centered on the ١٤٠ KeV. Data were collected over a ١٨٠° rotational arc in a step and shot mode starting from ٤٥° right anterior oblique to ٤٥° left posterior oblique; ٣٢ projections were obtained with ٢٠-sec/ projection. All data were corrected for dead time and reconstructed in ٦٤X٦٤ matrices. This set of images is called stress images.

٢- Rest study was done in cases with positive stress study (presence of hypoperfused myocardial segments) as follows:

On another day, another set of images were taken under the same circumstances mentioned before, ٤٥-٦٠ minutes after injection of a second dose ٢٠ mCi (٧٤٠ MBq) of ^{٩٩m}Tc-tetrofosmin (rest study).

Following acquisition, projection images were combined mathematically to create cross sectional pictures of the radionuclide distribution through the chest.

Once reconstruction of the projection images has been achieved, a three-dimensional block of data indicating the distribution of radionuclide throughout the chest is available. So we can get three slices groups, namely Short axis slices, Vertical long axis slices, and Horizontal long axis slices. Serial short axis slices are displayed from the apex to the base. Left ventricular myocardial segmentation scheme is used for tomogram analysis. Myocardial images were divided into ١٨ segments in short axis (apical, midventricular and basal slices) plus two segments in the vertical long axis for apical perfusion (Fig. ١).

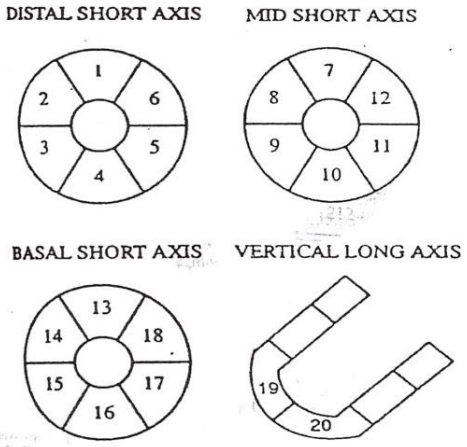

Fig. ١: Left ventricular wall segmental evaluation.

Images were assessed blindly (without any ECG information or any other clinical data about patients) by visual inspection. By the aid of the computer system, left ventricular functional parameters could be achieved; this include for example left ventricle ejection fraction percentage (EF %), as well as any wall motion abnormalities.

Statistical Analysis

Data were summarized using means and standard deviation (SD) or medians with

ranges as applicable, whereas categorical variables were presented as percentages and counts. Differences between groups were tested using independent t-test or Mann–Whitey Test as appropriate. Analysis of Variance (ANOVA) or its non-parametric equivalent; the Kruskal–Wallis test were used. Categorical variables were also compared using Chi-square test. Linear regression models were established to study the correlation between myocardial perfusion defects and various parameters of the study. The data were analyzed using SPSS (Statistical Package for the Social Sciences), version ١٥.٠, Chicago, Illinois. P values <٠.٠٥ were considered significant.

Results

Among SLE patients group (Group I): ٢ male patients (٣.٣٣٪) were heavy smokers, ١٧ patients (٢٨.٣٣٪) had positive family history of CAD, ٢٨ patients (٤٦.٦٦٪) had controlled hypertension and under regular treatment, ٢٣ patients (٣٨.٣٣٪) had type II diabetes mellitus (D.M.) and receiving anti-hyperglycemic agents, ٣٥ patients (٥٨.٣٣٪) had dyslipidemia, ٤٢ patients (٨٤٪) gave history of a sedentary lifestyle; Among the control group (Group II): ١ subjects (٣.٣٣٪) was heavy smoker; ٨ subjects (٢٦.٦٦٪) had positive family history for CAD; ٤ control subjects (١٣.٣٣٪) had hypertension and under regular treatment, ٣ subjects (١٠٪) had type II D.M., ١٦ (٥٣.٣٣٪) had dyslipidemia, ٢٠ subjects (٦٦.٦٦٪) had sedentary life style.

Two groups were included in this study; (Group I) sixty patients with SLE and (Group II) thirty age and sex-matc

subjects and ٣ (١٠٪) male subjects with mean age ٣١±١٣ years; age range was ١٨-٤٤ years.

Data of both groups regarding the risk factors for coronary artery disease (CAD) is shown in table (١), as follows:

Table (١): Demographic data for CAD risk factors among the two groups

Risk factor	Group I	Group II	P
Smoking	٢ (٣.٣٣٪)	١ (٣.٣٣٪)	١.٠٠
Family history	١٧ (٢٨.٣٣٪)	٨ (٢٦.٦٦٪)	٠.٨٦
Hypertension	٢٨ (٤٦.٦٦٪)	٤ (١٣.٣٣٪)	٠.٠٠١*
Type II D.M.	٢٣ (٣٨.٣٣٪)	٣ (١٠٪)	٠.٠٠٥*
Dyslipidemia	٣٥ (٥٨.٣٣٪)	١٦ (٥٣.٣٣٪)	٠.٦٥
Sedentary lifestyle	٤٢ (٧٠٪)	٢٠ (٦٦.٦٦٪)	٠.٧٤

(*): means significant P value < ٠.٠٥.

Within group I: mean BMI was ٢٧.٩±٣.٢, mean fasting blood glucose (FBG) was ٨.٧±١.٣ mmol/L, mean serum total cholesterol was ٦.٢±٠.٨ mmol/L, mean serum LDL-cholesterol was ٤.٥±٠.٤ mmol/L, mean serum HDL-cholesterol was ١.٥±٠.٧ mmol/L, and mean serum triglycerides (TGs) was ٤.١±١.٥ mmol/L. Among group II: mean BMI was ٢٦.٧±٤.٦, mean fasting blood glucose was ٧.٩±١.٦ mmol/L, mean serum total cholesterol was ٧.٣±١.٥ mmol/L, mean serum LDL-cholesterol was ٤.٨±٠.٧ mmol/L, mean serum HDL-cholesterol was ١.٢±٠.٣ mmol/L, and mean serum triglycerides was ٥.٩±٢.١ mmol/L. Comparison between the two groups as regards CAD risk factors as well as hsCRP is shown in table ٢.

Table (٢): Comparison between the two groups as regards CAD risk factors as well as hsCRP

Variable	Group I	Group II	P
BMI	٢٧.٩±٣.٢	٢٦.٧±٤.٦	٠.١٥
FBG	٨.٧±١.٣	٧.٩±١.٦	٠.٠١٢*
Total Ch	٦.٢±٠.٨	٧.٣±١.٥	<٠.٠٠١*
LDL-Ch	٤.٥±٠.٤	٤.٨±٠.٧	٠.٠١١*
HDL-Ch	١.٥±٠.٧	١.٢±٠.٣	٠.٠٢*
S. TGs	٤.١±١.٥	٥.٩±٢.١	<٠.٠٠١*
hsCRP	٥.٣±٤.٧	٠.٧±٠.٤	<٠.٠٠١*

(*): means significant P value < ٠.٠٥.
BMI: body mass index, FBG: fasting blood glucose, BP: Blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein, hsCRP: high-sensitivity C-reactive protein.

Within group I, and according to SLEDAI score, ٢٠ patients (٣٣.٣٣%) had quiescent disease (SLEDAI score=٠); ١٣ patients (٢١.٦٦%) had mild disease activity (SLEDAI score=١-٥); ١٧ patients (٢٨.٣٣%) had moderate disease activity (SLEDAI score=٦-١٠); ٧ patients (١١.٦٦%) had high disease activity (SLEDAI score=١١-١٩); and ٣ patients (٥%) had very high disease activity (SLEDAI score=٢٠).

Mean serum level of high sensitivity C-reactive protein (hsCRP) among group I was ٥.٣±٤.٧ mg/L, compared to ٠.٧±٠.٤ mg/L among group II. Within group I: twenty six patients (٤٣.٣٣%) had high risk serum high sensitivity CRP (hsCRP) >٣mg/L with mean value of ٥.٨±٤.٢ mg/L, while ٣٤ (٥٦.٦٦%) were low-intermediate risk ≤٣mg/L, with mean value of ١.٣±١.٧ mg/L.

As regards medications received by the studied group of SLE patients: ٣٩ patients (٦٥%) patients were taking hydroxyl-chloroquine (HCQ), while ٢١ patients (٣٥%) patients were not taking HCQ due to previous retinal toxicity or fear of skin pigmentation.

During the procedure, all participants of both groups showed negative resting ECG study for any signs of myocardial ischemic changes, however, ٥ patients (٨.٣٣%) showed positive pharmacological stress-induced ECG changes in the form of more than ٠.٣ mm ST segment depression, ١٧ patients (٢٨.٣٣%) developed headache, and /or dyspnea with no significant ECG changes, which improved spontaneously after stoppage of adenosine injection, in comparison to subjects of group II, only one patient (٣.٣٣%) developed positive pharmacological stress-induced ECG changes in the form of more than ٠.٣ mm ST segment depression, ٤ subjects (١٣.٣٣%) developed headache, and /or dyspnea with no significant ECG changes, which improved spontaneously after stoppage of adenosine injection.

On stress SPECT study, ٢٣(٣٨.٣٣%) patients showed significant stress-induced hypoperfused segments, which showed significant improvement in the subsequent rest study i.e. reversible perfusion defects. They showed the following statistical criteria: ١٠(١٦.٦٦%) patients had single hypoperfused segment, whereas, ١٣ (٢١.٦٦%) patients showed multiple hypo-perfused segments. Only one patient had stress-induced LV dilatation with impaired left ventricle EF= ٣٨%, and anterior wall hypokinesia, whereas, all other patients showed normal LV wall motions as well as normal EF% with mean value ٥٤±٣.٦٪. The sequence of the left ventricular walls affection between our patients was in the following manner: the anterior wall was the commonly affected, then the septum, inferior wall and lastly the lateral wall.

As regards group II, two subjects (٦.٦٦٪) showed single significant, mild stress-induced hypoperfused segments. These hypoperfused segments were seen at the

anterior wall which showed significant improvement in the subsequent rest study. All subjects had normal left ventricular EF%, with mean value ٥٩±٣.٢٪, as well as normal wall motions.

The comparison between both groups as regards Stress-Rest myocardial perfusion study the imaging results are shown in table (٣) and figure (٢).

Table (٣): Comparison between both groups as regards the results of the Stress-Rest myocardial perfusion scintigraphy

Imaging results	Group I N=٦٠	Group II N=٣٠	P value
No. of positive cases of myocardial ischemia	٢٣/٦٠ (٣٨.٣٣٪)	٢/٣٠ (٦.٦٧٪)	٠.٠٠١*
No. of negative cases of myocardial ischemia	٣٧/٦٠ (٦١.٦٧٪)	٢٨/٣٠ (٩٣.٣٣٪)	

(*): means significant P value < ٠.٠٥.

With regards the disease duration among SLE patients, the number of patients with positive Tetrofosmin stress-induced myocardial ischemic segments: ١٨ (٧٨.٢٦٪) patients of the total positive cases had disease duration >٧ years compared to ٥ positive cases who had disease duration ≤٧ years, showing a significant statistical difference in favor of patients with longer disease duration (p <٠.٠٠١), as shown in table (٤) and figure (٣).

Table (٤): Comparison of positive cases for myocardial ischemia among SLE patients according to disease duration

Variable	Disease duration >٧ years	Disease duration ≤٧ years	P value
No. of SLE patients with positive scan results	١٨/٢٣ (٧٨.٢٦٪)	٥/٢٣ (٢١.٧٤٪)	<٠.٠٠١*
No. of SLE patients with negative scan results	٩/٣٧ (٢٤.٣٢٪)	٢٨/٣٧ (٧٥.٦٨٪)	

(*): means significant P value < ٠.٠٥.

With regards to the comparison of the scan results with various grades of disease activity scores according to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scoring system, there was a significant statistical difference in the scan results with more positive cases among patients with higher disease activity

Comparison of the scan results with various grades of disease activity scores according to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scoring system is illustrated in table (٥) and figure (٤)

Table (٥): Comparison of the scan results with and SLEDAI scores

Disease activity index (SLEADI)	SLE patients with positive myocardial scintigraphy for ischemia N=٢٣	SLE patients with negative myocardial scintigraphy for ischemia N=٣٧	P value
No activity (Score ٠) N=٢٠	٠ (٠٪)	٢٠ (٥٤.٠٥٪)	<٠.٠٠١*
Mild activity (Score ١-٥) N=١٣	٢ (٨.٦٩٪)	١١ (٢٩.٧٣٪)	<٠.٠٠١*
Moderate activity (Score ٦-١٠) N=١٧	١٣(٥٦.٥٢٪)	٤ (١٠.٨١٪)	<٠.٠٠١*
High activity (Score ١١-١٩) N=٧	٥ (٢١.٧٤٪)	٢ (٥.٤٠٪)	<٠.٠٠١*
Very High (Score ٢٠) N=٣	٣ (١٣.٠٤٪)	٠ (٠٪)	<٠.٠٠١*

(*): means significant P value < ٠.٠٥.

The number of patients with positive Tetrofosmin stress-induced myocardial ischemia / myocardial perfusion defects was significantly higher in patients with high-risk hsCRP (>٣mg/L) than in patients with low-intermediate risk hsCRP (≤٣mg/L). (p value < ٠.٠٠١) (Table ٦, and figure ٥).

Table (٦): Comparison of cases with positive myocardial perfusion defects according to serum hsCRP levels among SLE patients

Variable	Serum hsCRP >٣mg/dL (high risk)	Serum hsCRP ≤ ٣ mg/dL (low-intermediate risk)	P value
No. of positive cases for myocardial perfusion defects	٢١/٢٣ (٩١.٣٪)	٢/٢٣ (٨.٧٪)	<٠.٠٠١*
No. of negative cases for myocardial perfusion defects	٥/٣٧ (١٣.٥١٪)	٣٢/٣٧ (٨٦.٤٩٪)	

(*): means significant p value < ٠.٠٥.

Comparing the number of patients with positive Tetrofosmin stress-induced myocardial ischemia among SLE patients as regards the medications used in their management revealed that only ٤/٢٣ (١٧.٤٠٪) of SLE patients with positive results for myocardial ischemia were on antimalarial therapy as part of their treatment compared to ١٩(٨٢.٦٠٪) of SLE patients with myocardial perfusion defects were not on antimalarial therapy as part of their therapeutic regimen, this difference was stastistically significant (p<٠.٠٠١) (Table ٧, and figure ٦).

Table (٧): Comparison of the imaging results between HCQ users and Non-HCQ users SLE patients.

Medications	HCQ users SLE patients N= ٣٩/٦٠	Non-HCQ users SLE patients N=٢١/٦٠	P value
No. of cases with positive myocardial scintigraphy for ischemia	٤/٢٣ (١٧.٤٠٪)	١٩/٢٣(٨٢.٦٠٪)	<٠.٠٠١*
No. of cases with negative myocardial scintigraphy for ischemia	٣٥/٣٧ (٩٤.٥٩٪)	٢/٣٧ (٥.٤١٪)	

(*): means significant P value < ٠.٠٥.

Our results showed a positive correlation with BMI, FBG, total cholesterol, LDL-cholesterol, triglycerides (TGs), disease duration, disease activity according to SLEDAI scores, and hsCRP as well as a negative correlation with HDL-cholesterol as illustrated in table ٨

Table (٨): Correlations between the numbers of affected segments of myocardial ischemia and various variables

Variable	Myocardial ischemia	
	R	P
BMI	٠.٦٧١**	٠.٠٠١*
FBG	٠.٤١٥**	٠.٠٠١*
High BP	٠.٠٧٣	٠.٥٧٨
Total cholesterol (Ch)	٠.٤٠٦**	٠.٠٠١*
LDL-Ch	٠.٣٨٦**	٠.٠٠٢*
HDL-Chl	-٠.٣٤٨**	٠.٠٠٦*
S. TGs	٠.٥٢٣**	<٠.٠٠١*
Disease Duration	٠.٦٥٤**	<٠.٠٠١*
Disease Activity	٠.٥٠٩**	<٠.٠٠١*
hsCRP	٠.٤٧٠**	<٠.٠٠١*

(*): means significant P value < ٠.٠٥.

BMI: body mass index, FBG: fasting blood glucose, BP: Blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein, hsCRP: high-sensitivity C-reactive protein

Multivariate logistic regression was done and showed that hsCRP was the main predictor for the presence of myocardial ischemia independent of other risk factors for CAD. (ß =٠.٦٢٩, ٩٥٪ CI ٠.٣٦٣-٠.٧٨٣ p <٠.٠٠١).

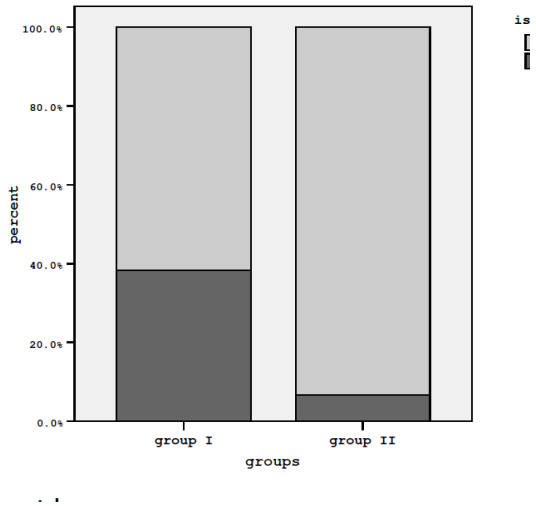

Figure ٢: Comparison between both groups as regards the positive results of the Stress-Rest myocardial perfusion scintigraphy.

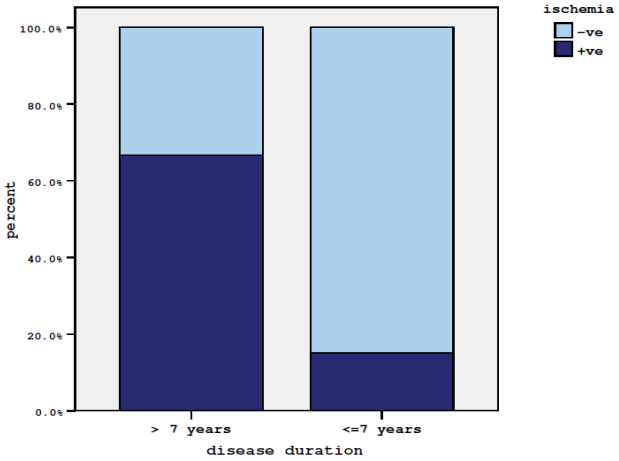

Figure ٣: Comparison of positive cases for myocardial ischemia among SLE patients according to disease duration:

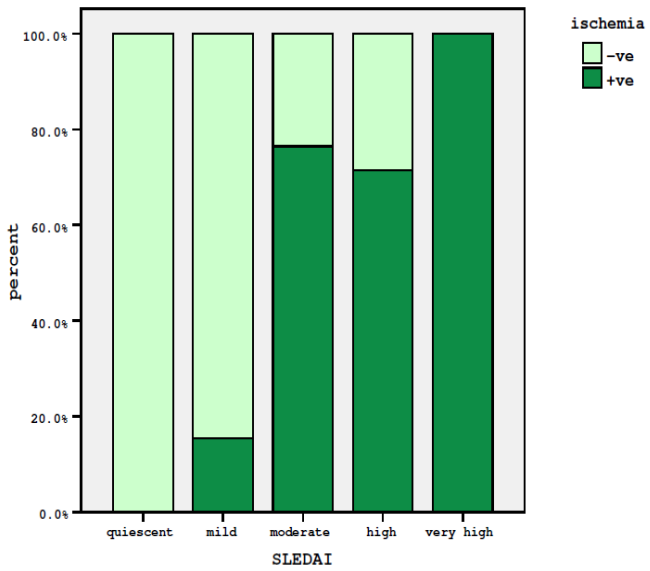

Figure ٤: Comparison of the scan results with and SLEDAI scores

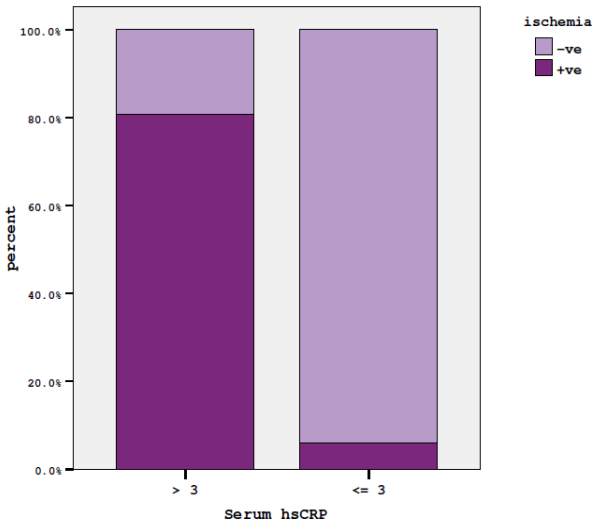

Figure ٥: Comparison of cases with positive myocardial perfusion defects according to serum hsCRP levels among SLE patients

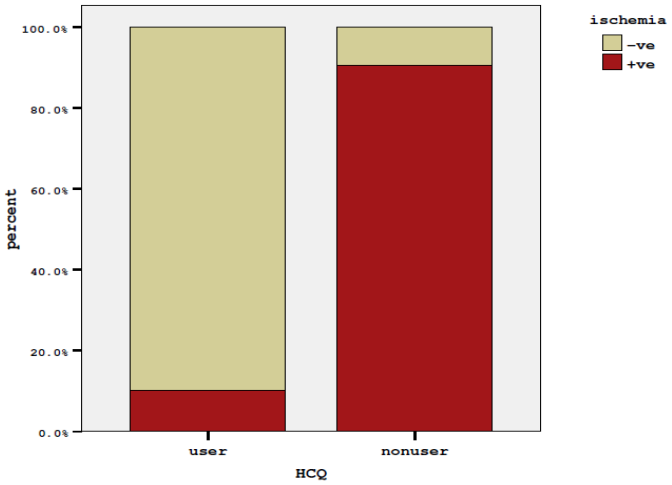

Figure ٦: Comparison of the imaging results between HCQ users and Non-HCQ users SLE patients

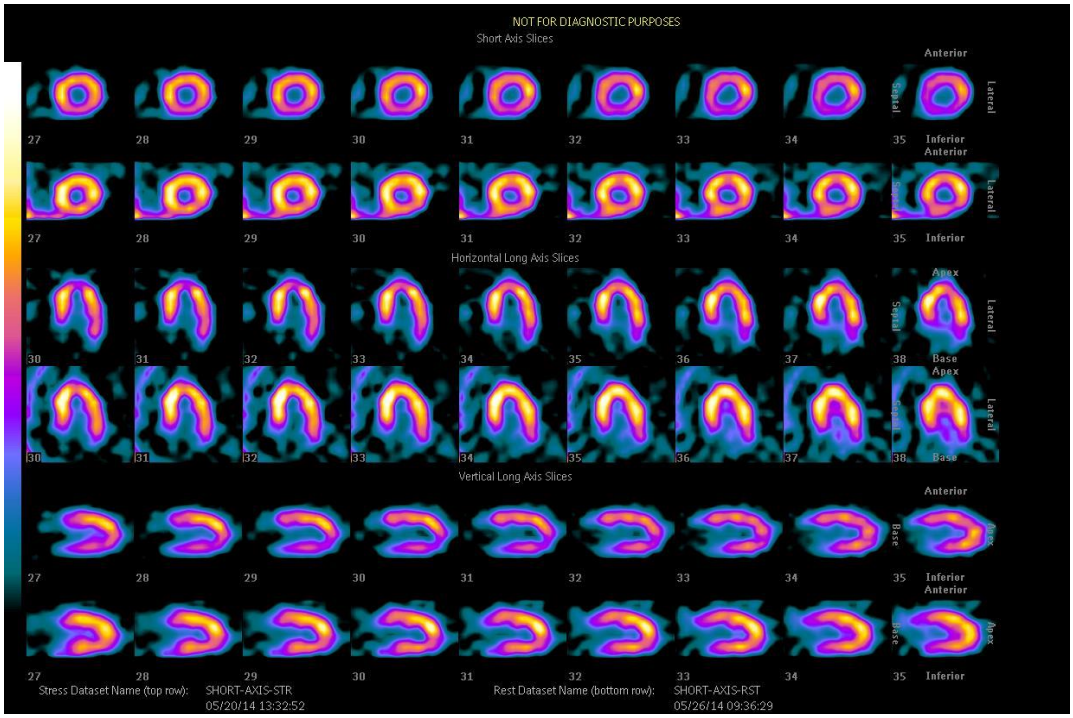

Figure ٧: ٢٧ years old female patient with SLE for ٥ years, SLEDAI score at the time of the study was ١٥. She was under combined high dose prednisone, and cyclophosphamide therapy. Scan image showed average LV cavity size, EF% = ٥٦٪. Images showed single small sized reversible moderate hypoperfused segment at the inferior segments of the apex. Total defect score = ٣.

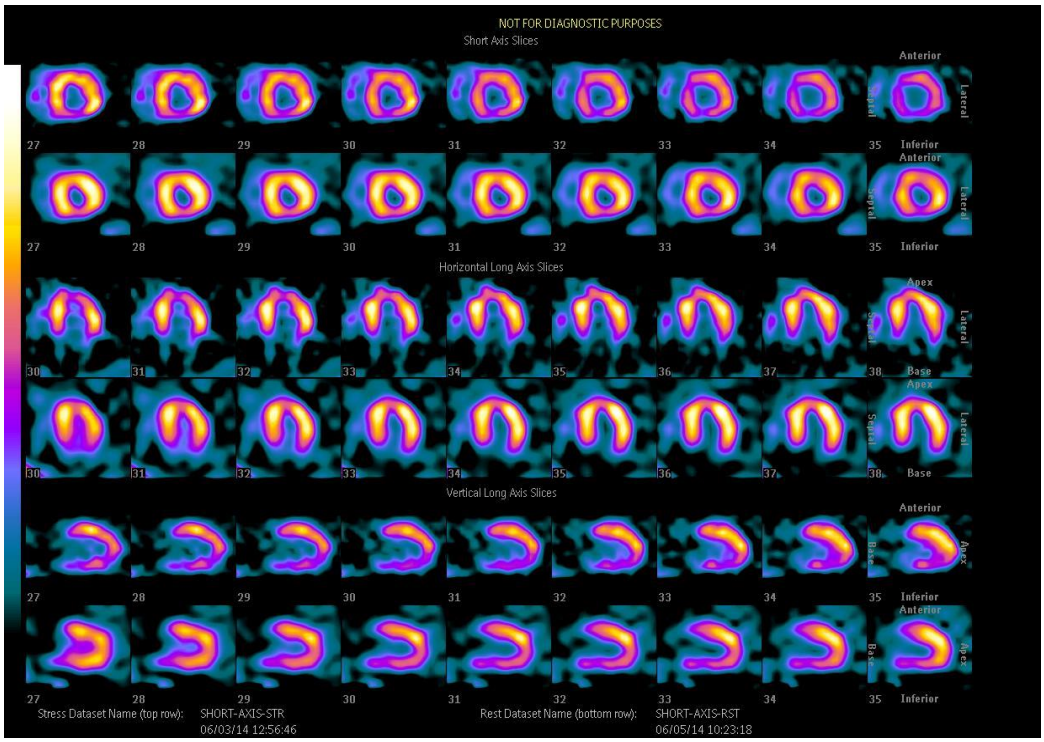

Figure ٨: ٣٤ years old female patient with SLE for ٧ years, SLEDAI score at the time of the study was ١٢, she was under combined moderate dose prednisone, and mycophenolate mofetil therapy, scan image showed stress- induced mild transient ischemic dilatation of the left ventricle, EF% = ٤١٪. Images showed two small sized reversible moderate hypoperfused segments at the apex as well as the inferior wall. Total defect score = ٤.

Discussion

Systemic lupus erythematosus represents the classic model of a chronic immune complex-mediated inflammatory disease of blood vessels with certain inflammatory features of the disease as well as markers of chronic inflammation that lead to the development of atherosclerosis in SLE (Bruce, ٢٠٠٥).

Subclinical coronary artery disease (CAD) may be prevalent in patients with systemic lupus erythematosus (SLE) especially young patients and represents a potential challenge. These patients are at a greater risk for developing myocardial infarction (Zakavi et al., ٢٠٠٩).

The mechanisms of CAD in SLE patients are probably multifactorial. Several possible mechanisms for ischemia, such as vasculitis, vasospasm, microvascular disease, and thrombosis with or without atherosclerosis, are potential causes of coronary events. Other identified risk factors for cardiovascular disease that may contribute to the coronary disease in SLE patients include circulating immune complexes, activated T cells, antiphospholipid antibodies, and hyper-homocysteinemia (Petri, ٢٠٠٠, Bruce et al., ٢٠٠٠A; Manzi et al., ٢٠٠٠).

Myocardial damage in SLE can occur secondary to hypoperfusion and inflammation and, even though silent for a period of time, it often results in heart failure (Lin et al., ٢٠٠٣; Panchal et al., ٢٠٠٦). Lin and his colleagues have shown myocardial impairment early in SLE, long before symptom onset (Lin et al., ٢٠٠٣).
Accelerated coronary artery disease (CAD) and myocardial infarction (MI) in young patients with SLE is well documented; however, the prevalence of coronary involvement is unknown (Zeller & Appenzeller, ٢٠٠٨).

Published reports show that coronary disease (angina pectoris or acute MI) is more common in women with SLE than in the general population. Moreover, the mean age of patients with SLE who had coronary disease was younger than seen in the general population (Urowitz & Gladman, ١٩٩٩).

According to published studies, ١٦-٨٢٪ of systemic lupus erythematosus (SLE) patients have myocardial perfusion abnormalities. (Hosenpud et al., ١٩٨٤, Bruce et al., ٢٠٠٠A. Schillaci et al., ١٩٩٩, Sun et al., ٢٠٠١)

Patients with systemic lupus erythematosus have up to a ٥٠-fold increased risk of developing atherosclerotic cardiovascular disease (Kahlenberg and Kaplan, ٢٠١١).

To investigate subclinical coronary artery disease in young adult SLE patients, we investigated sixty SLE patients:٥٤ (٩٠٪) females and ٦ (١٠٪) males with mean age ٢٩±١١ years; age range was ١٨-٤٠ years, with disease duration ranging from ٢-١٥ years (mean± SD ٧±٥ years). asymptomatic for CVD symptoms, as well as thirty sex- and age- matched controls. All included patients were taking glucocorticoid preparations for >١ year.

The frequency of myocardial perfusion abnormalities on stress SPECT study in the studied SLE patients was ٢٣/٦٠ (٣٨.٣٣٪) which was significantly higher than perfusion abnormalities in the studied control subjects ٢/٣٠ (٦.٦٦٪). All of the perfusion defects in our study were reversible and showed improvement in the subsequent rest study. We studied SLE patients with disease duration (٢-١٥ years), in attempt to evaluate risk for CAD in younger patients with SLE.

Early investigation for CAD in the preclinical stage in young women with SLE is justified because cardiovascular events are an important cause of morbidity and mortality in this population (Kuller et al., ١٩٩٥). Accordingly, the American Guidelines for the Prevention of Cardiovascular Disease in Women include SLE patients in the high risk group for cardiovascular disease (Mosca et al., ٢٠١١).

The frequency of abnormal findings on myocardial scintigraphy in our study is consistent with those from other studies of

SLE patients: Our results came in agreement with Baharfard and his colleagues in ٢٠١١ who evaluated ٢١ patients with SLE (mean age ٣٦.٩±١٢.٨), low-risk category for CAD pretest , and no suspected or documented CAD using Tc-٩٩m single photon emission tomography (SPECT) myocardial perfusion imaging (MPI) and its association with some clinical and laboratory parameters in an asymptomatic SLE population, and found abnormal myocardial perfusion results in ٨ (٣٨٪) patients, together with a significant association between the presence of dyslipidemia and myocardial perfusion abnormalities, but no significant association between other traditional and SLE-specific risk factors; they suggested that asymptomatic CAD is common in SLE patients, even in those thought to be low risk for CAD and in the absence of cardiac symptoms.

Also, Zakavi and his colleagues in ٢٠٠٩ investigated subclinical CAD in young adult patients (mean age of ٢٨.٢ ± ١٢.٠٥ years) with SLE, and studied ١٨ female and two male patients with proven diagnosis of SLE and no history of CAD were studied. Six patients (٣٣.٣٣٪) had mild reversible perfusion defects on myocardial perfusion scan, and hypokinesia was noted in three patients on gated images, and concluded that myocardial perfusion abnormalities are fairly frequent in SLE patients

Our results were also consistent with the study performed by Bruce and colleagues (٢٠٠٠B) who evaluated ١٣٠ female patients independent of CAD risk factors or coronary disease history, included older patients using SPECT dual isotope myocardial perfusion imaging (DIMPI), and recorded segmental perfusion abnormalities, severity and reversibility of any abnormality, and number of vessel territories involved. They found that ٥٢ (٤٠٪) patients had an abnormality of myocardial perfusion; the perfusion defects were reversible in ٤٧ (٩٠٪), suggesting a high prevalence of early CAD among SLE patients and that the early detection of disease can be targeted for a focused program of risk factor management. Bruce and colleagues (٢٠٠٣A) also investigated ١٢٩ women with SLE without history of coronary artery disease and found that ٤٩ (٣٨٪) had myocardial perfusion defects (MPI) highlighting that myocardial perfusion abnormalities are common in women with SLE without known coronary artery disease (CAD), suggesting a high burden of subclinical CAD.

Earlier, Hosenpud and his colleagues in ١٩٨٤ investigated ٢٦ patients with SLE younger than ٥٠ years, irrespective of previous cardiac history using exercise thallium-٢٠١ cardiac scintigraphy, and showed segmental myocardial perfusion abnormalities in ١٠ of the ٢٦ studied (٣٨.٤٦٪): Five (١٩.٢٣٪) patients had reversible defects suggesting ischemia, four (١٥.٣٨٪) patients had persistent defects consistent with scar, and one patient (٣.٨٤٪) had both reversible and persistent defects in two areas; however, they found no correlation between positive thallium results and duration of disease, amount of corticosteroid treatment, major organ system involvement or age, and they concluded that segmental myocardial perfusion abnormalities are common in patients with SLE, and questioned whether this reflects large-vessel coronary disease or small-vessel abnormalities.

On the other hand, in ٥٠ consecutive SLE patients (٣٩.٢±١٢.٩ years old, ٩٠٪ females), Plazak and coworkers.in ٢٠١١ demonstrated the presence of myocardial ischemia (perfusion defects) in ٢٥ (٥٠٪) patients (a higher percentage than our study); persistent defects in ١٨ (٣٦٪) and exercise-induced defects in ٧ (١٤٪) subjects, using SPECT. Also, Schillaci and coworkers in١٩٩٩ evaluated myocardial perfusion in lupus patients with no CAD risk factors and asymptomatic for CAD symptoms using rest/dipyridamole stress technetium-٩٩m sestamibi single-photon emission computed tomography (SPECT), and revealed a higher prevalence: ١٨/٢٨ patients (٦٤.٢٨٪) of myocardial perfusion abnormalities in asymptomatic lupus patients.

Our results showed that positive scan results were correlated with longer disease duration, higher disease activity, higher

BMI, higher fasting blood glucose (FBG), higher total cholesterol, higher LDL-cholesterol, higher triglycerides, lower HDL-cholesterol as well as higher hs CRP.

Multivariate logistic regression was done and showed that hsCRP was the main predictor for the presence of myocardial ischemia independent of other risk factors for CAD. (ß =٠.٦٢٩, ٩٥٪ CI ٠.٣٦٣-٠.٧٨٣ p <٠.٠٠١)

Our results came in agreement with Sella and colleagues in ٢٠٠٣ who investigated ٨٢ female patients with SLE and no angina pectoris [disease duration >٥ years, age ١٨–٥٥ years (٣٧± ١٠ years), disease duration ١٢٧± ٥٧ months, SLEDAI score ٦±٥, who had used steroids for at least one year] using myocardial perfusion scintigraphy by SPECT with Tc ٩٩m-sestamibi at rest and after dipyridamole induced stress.
They showed myocardial perfusion abnormalities in ٢٣ (٢٨٪) patients: fifty six per cent of the total myocardial defects were reversible, ٢٠٪ were fixed, and ٢٤٪ were reversible and fixed defects. Logistic regression analysis showed that low HDL-cholesterol level and diabetes mellitus were correlated with abnormalities in myocardial perfusion in these patients, and that current vasculitis was also associated with abnormal scintigraphy, suggesting that perfusion defects may represent an early stage of subclinical atherosclerosis (Sella et al., ٢٠٠٣A).

Another study by Sella and coworkers in ٢٠٠٣, ninety female SLE patients (ages ٢٠-٥٥ years, disease duration >٥ years, and current or previous steroid treatment for ≥١ year) showed myocardial perfusion defects in ٣٠ patients (٣٣٪) on dipyridamole-induced stress myocardial perfusion scintigraphy with SPECT using ٩٩m Tc-sestamibi, then patients proceeded to coronary angiography to find that only ٣٨٪ of patients with myocardial perfusion abnormalities had atherosclerotic plaques suggesting the multifactorial etiology of CAD in SLE

Sella and colleagues studied patients of more than five years of SLE, who had used steroids for at least one year. They found that positive scan results were correlated with longer steroid use, higher steroid dose, longer steroid treatment and greater cumulative prednisone dose. Moreover, the duration of prednisone treatment may be related to the duration of SLE and higher prednisone use may be related to a more severe disease However, they did not find significant difference in prednisone use, duration or cumulative steroid dosage between patients with SLE with normal or abnormal myocardial scintigraphy. (Sella et al., ٢٠٠٣B)

Rahman and coworkers in ٢٠٠٠ reported that the incidence of premature CAD in patients with SLE independent of steroid use was (٤.٥/١٠٠٠) which was greater than that observed in the Framingham Heart Study (٢.٨/١٠٠٠ women).

Petri and colleagues in ١٩٩٢ found at least one CAD risk factor in ٩٧٪ of ٢٢٥ patients evaluated, the most prevalent of which was a sedentary life style (٧٠٪), followed by hypercholesterolaemia found in ٥٦٪, arterial hypertension in ٤١٪, family history of premature CAD in ٤١٪, and obesity in ٣٨٪; ٥٣٪ of patients had at least three of these traditional risk factors.

Our results showed that within the SLE patients who showed evidence of myocardial ischemia, only ١٧.٤٠٪ were on hydroxychloroquine therapy compared to ٨٢.٦٠٪ were not on hydroxychloroquine as part of their therapy regimen suggesting a protective role for hydroxychloroquine against possible CAD

There is emerging evidence regarding the protean beneficial effects of hydroxyl-chloroquine in SLE, including control of mild disease activity, prevention of flares, and reduction of CHD-related mortality. Possible mechanisms for the cardio-protective effect of hydroxychloroquine include reduction in lipid levels and blood glucose. At present, hydroxychloroquine is recommended as staple therapy in all patients with SLE, including during pregnancy. In large population studies, hsCRP has been shown to predict CHD events, independently of traditional risk factors. In SLE, hsCRP levels fluctuate

greatly over time due to the relapsing remitting nature of the disease, and its therapies. However, despite this variability over time, mean hsCRP level appears to be predictive of CHD events in SLE, even after adjusting for the Framingham risk score and cumulative disease activity score. Ammirati and coworkers in ٢٠١٤ studied ٥٠ SLE patients (٨٦٪ female): mean age ٤٤±١٠ years, and showed that SLE patients had a higher prevalence of subclinical atherosclerosis than sex- and age-matched control subjects. They also showed that patients under HCQ therapy presented a modified metabolic profile, a reduced T-cell activation associated with decreased subclinical atherosclerosis.

Moreover, Romero-Diaz and colleagues in ٢٠١٢ studied a cohort of ١٣٩ SLE patients (٩٣٪females), and demonstrated that disease duration, age at enrolment and SLE disease activity mean area under the curve in SLE patients after ٥.١ years of follow-up were main predictors of CAD. They also found that the use of antimalarials was protective

Furthermore, in a longitudinal study, hs-CRP level was negatively correlated with hydroxychloroquine use, supporting a role for these drugs in prevention of CAD in SLE (Nikpour et al., ٢٠٠٩).

Inflammation is thought to be the pivotal link between SLE and atherosclerotic vascular disease, with immune mechanisms thought to play a key role in plaque formation and rupture (Hansson, ٢٠٠٩). Inflammatory mechanisms are important in the pathogenesis of atherosclerosis. These concurrent developments have led to the concept that inflammatory mediators operative in SLE might be causal in the accelerated atherosclerosis observed, a concept supported by clinical studies showing that this acceleration is not fully explained by traditional vascular risk factors (Ayoub et al., ٢٠٠٨).

Detection of low-grade elevation of serum concentration of hs-CRP helps to predict a healthy person's risk of CAD, heart attack, independently of traditional risk factors; people with high normal values, have ١.٥-٤ times risk of having heart attack when compared to those with low normal values (Mok et al., ٢٠١٣).

In SLE, hsCRP levels fluctuate greatly over time due to the relapsing remitting nature of the disease, and its therapies However, despite this variability over time, mean hs-CRP level appears to be predictive of CAD events in SLE (Nikpour et al., ٢٠٠٩A). Studies several decades ago have reported that CRP level was not elevated in active SLE except for the presence of serositis, polyarthritis and nephritis (Suh et al., ٢٠٠١; Moutsopoulos et al., ١٩٨٣).

This is consistent with our results which demonstrated that ٢٦/٦٠ SLE patients (٤٣.٣٣٪) had high risk serum high sensitivity CRP (hsCRP) >٣mg/L which significantly correlated with disease activity according to SLEDAI, and that ٢١/٢٣ (٩١.٣٪) of SLE patients with myocardial perfusion abnormalities on SPECT had high risk serum hsCRP >٣mg/dL

These results came in agreement with Mok and his colleagues (٢٠١٣) who studied the level of hsCRP in ٢٨٩ patients (٩٤٪ women); age mean ± SD ٣٩.٠ ± ١٣.١ years, and SLE duration mean ± SD ٧.٨ ± ٦.٧ years), and its relationship with disease activity, damage, and cardiovascular risk factors in patients with SLE. They found that hsCRP was detectable in ٧٧% of SLE patients with clinically active disease and showed a significant correlation with clinical SLEDAI score. High-risk hsCRP level >٣ mg/liter was significantly associated with certain cardiovascular risk factors: male sex, long-term smoking, diabetes mellitus, a higher atherogenic index, and a history of arterial thromboembolism.

Besides, Barnes and his colleagues (٢٠٠٥) also reported that hsCRP levels were significantly higher in SLE patients than controls. However, hsCRP level did not correlate with SLE disease activity scores. Two more studies also demonstrated that hsCRP levels correlated significantly with SLE activity (Lee et al., ٢٠٠٨; Bertoli et al., ٢٠٠٨).

Although hsCRP level has been demonstrated to be an independent risk factor of cardiovascular disease in the general population, there is paucity of data regarding hsCRP level and cardiovascular risk in SLE (Kaptoge et al., ٢٠١٠) Also, hsCRP is one of the components of the Reynolds cardiovascular risk score (Ridker et al., ٢٠٠٧); a cohort study by Toloza and colleagues in ٢٠٠٤ also showed a significant relationship between higher CRP levels at baseline and vascular events

Scintigraphy is useful in identifying myocardial inflammatory disease that, in the case of SLE patients, can occur in ٣-١٥٪ of patients at some point in the evolution of the disease (Zakavi et al., ٢٠٠٩). Myocardial perfusion imaging (MPI) single photon emission computed tomography (SPECT) executed in phases of rest and stress is a sensitive method to detect early myocardial perfusion abnormalities as well as defining regional wall thickening and assessing ventricular function (Cheng et al., ٢٠١٠; Zakavi et al., ٢٠٠٩).

Single photon emission computed tomography of Tc-٩٩m tetrofosmin (Tc-٩٩m TF) myocardial perfusion imaging in patients with SLE is a useful noninvasive imaging modality to detect cardiac involvement in SLE patients with or without cardiac symptoms and signs (Lin et al., ٢٠٠٣A). Electrocardiogram (ECG)-gated myocardial perfusion single photon emission computed tomography (SPECT) can be used to assess myocardial perfusion and left ventricular function simultaneously (Kumita et al., ٢٠٠٦).

Sun and coworkers in ٢٠٠١ investigated ٣٣ SLE female patients (age ٢٢-٤٥ years) with non-specific complaints such as chest discomfort and/or dyspnea and/or occasional palpitation, as well as ٢٨ SLE patients without any cardiovascular symptoms/signs using a rest/stress dipyridamole Tc-٩٩m myocardial perfusion SPECT scan. Perfusion abnormalities were detected in ٢٧/٣٣ (٨٤.٣٧٪) symptomatic cases, and ١٢/٢٨ (٤٢.٨٥٪) cases in the group of asymptomatic SLE patients. They concluded that Tc-٩٩m myocardial perfusion SPECT is a useful non-invasive imaging modality to detect cardiovascular involvement in asymptomatic SLE patients as well as with non-specific clinical complaints of heart disease.

Plazak and colleagues in ٢٠١١ showed myocardial perfusion defects in ٢٥/٥٠ (٥٠٪) of relatively young, mostly female, SLE patients using Tc-٩٩m sestamibi SPECT, and concluded that SPECT is a sensitive useful tool to detect myocardial ischemia in these asymptomatic patients when compared to other tools.

Also, Zakavi and colleagues (٢٠٠٩) investigated ٢٠ SLE patients (١٨ females and ٢ male patients) with mean age of ٢٨.٢±١٢.٠٥ years using SPECT, and found reversible myocardial perfusion abnormalities in ٦/٢٠ (٣٠٪),as well as hypokinesia in ٣ patients on gated images.

Scintigraphic myocardial perfusion defects have been shown to detect subclinical CAD and can be predictive of subsequent coronary events, independent of traditional Framingham risk factors (Nikapour et al., ٢٠٠٩B): In a study that compared stress radionuclide myocardial perfusion scintigraphy (MPS) testing, coronary artery calcium scanning, and noninvasive coronary angiography for diagnostic and prognostic cardiac assessment, Berman and coworkers showed evidence supporting the diagnostic accuracy and risk stratification data for MPS for symptomatic patients with known or suspected coronary artery disease (Berman et al., ٢٠٠٧)

In addition, Ammann and coworkers (٢٠٠٣) evaluated ٢٧٠ patients using SPECT studies: ٤١ patients (١٥٪) showed stress-induced reversible uptake defects although coronary angiography showed no significant CAD. While the sensitivity of SPECT for detecting CAD has been reported to exceed ٩٠٪, the specificity ranges between ٥٣-١٠٠٪ making it an excellent tool for screening for CAD.

In another study by Lin and colleagues (٢٠٠٣) to evaluate the utility of myocardial perfusion single-photon emission computed tomography (SPECT) in detection of

cardiac involvement in SLE, they investigated fifty SLE patients without any cardiac symptom/sign and showed myocardial perfusion abnormalities in ١٩/٥٠ (٣٨٪) asymptomatic SLE patients thus concluding that SPECT is a useful noninvasive imaging modality to detect cardiac involvement in symptomatic or asymptomatic SLE patients.

Data suggest that myocardial scintigraphy can be used to screen SLE patients. Screening tests for coronary artery disease (CAD) are useful in high-risk patients. (Hallegua & Wallace, ٢٠٠٠) Detection of atherosclerosis in an early preclinical stage could avoid future cardiovascular events, since preventive interventions could be initiated in these patients (Bruce et al., ٢٠٠٠).

Previous studies have demonstrated the prognostic value of myocardial perfusion scintigraphy with pharmacologically induced stress (dipyridamole infusion) performed with SPECT images using ^{99m}Tc-sestamibi in patients with CAD risk factors (Stratmann et al., ١٩٩٤; Heller et al., ١٩٩٥; Stratmann et al., ١٩٩٦). This non-invasive tool shows high sensitivity (٩٥–١٠٠٪) and variable specificity (٧٥–١٠٠٪) (Follansbee et al., ١٩٩٦). Hypoperfusion observed on myocardial scintigraphy suggests the presence of ischemia in the case of reversible perfusion defects and fibrosis in the case of fixed defects (Sella et al., ٢٠٠٣B).

Conclusion

Pramature/accelerated coronary artery disease (CAD) is common among systemic lupus erythematosus patients. Low-grade chronic inflammation is an important predictor for development of premature CAD in SLE. Subclinical CAD warrants screening in young patients with SLE, especially those with longer disease duration, higher disease activity and those with chronically elevated hs CRP. Gated myocardial perfusion scintigraphy using ^{99m}Tc-Tetrofosmin Gated Single Photon Emission Computed Tomography (SPECT) is a sensitive non-invasive screening modality suitable for early detection of subclinical myocardial perfusion abnormalities in these patients.

Recommendation

Hereby, we recommend screening of SLE patients especially those with longer disease duration, continuously active disease, higher serum levels of hsCRP, particularly when they have multiple CAD risk factors using a sensitive, simple, accurate, non-invasive diagnostic modality. ^{99m}Tc-Tetrofosmin Gated SPECT myocardial perfusion imaging study can be the ideal diagnostic imaging modality.

Adequate control of the disease activity, proper monitoring of inflammatory markers like hsCRP, screening of SLE patients especially, those with severe disease course, or uncontrolled disease as well as those with longer disease duration

Minimizing the use of medications like corticosteroids that multiplies risk of CAD through increasing traditional risk factors**,** and adding medications like hydroxyl-chloroquine with protective effects**.**

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