

Atherosclerosis in Rheumatic Diseases

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Introduction

As association between accelerated atherosclerosis and systemic lupus erythematosus (SLE), typical by the occurrence of a myocardial infarction in a 30 year old woman who had had the disease for more than 10 years was suggested in 1976.¹ The same author reported bimodal pattern of mortality in SLE, with early death from active disease and late deaths from cardiovascular disorders. Several subsequent reports have supported an increased cardiovascular risk among SLE patients. This opened up the interest in the new understanding of atherosclerosis and systemic rheumatic diseases.

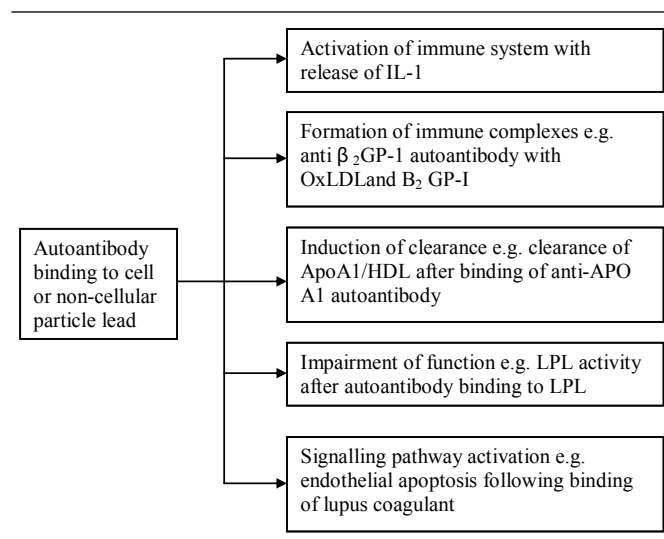
Though there is a wide spectrum of systemic rheumatic diseases but SLE, Rheumatoid arthritis, antiphospholipid antibody syndrome and systemic sclerosis are the common ones wherein studies on atherosclerotic cardiovascular and cerebrovascular disease are increasingly available. Traditional cardiovascular risk factors, such as hypertension and dyslipidemia are more prevalent in SLE patients and certainly contribute to an increased incidence of cardiovascular disease (CVD)². However, cohort studies have shown that the increased cardiovascular risk in SLE cannot be explained by traditional risk factors only but disease specific factors contribute significantly as well.^{3,4,5}

The most studied disease in this direction is SLE which is a complex autoimmune prototype multisystem disease characterized by chronic inflammation of virtually every organ including blood vessels. The atherogenic cascade of events and chronic immunoinflammation with autoantibodies are interlinked in systemic rheumatic diseases to contribute premature atherosclerosis.

Evidence for increased incidence of atherosclerotic CVD in SLE

In 2 prospective follow-up studies CVD end points in SLE patients were compared with those in a reference population without SLE. Manji et al⁶ observed in 498 patients with 6.7 years follow-up that incidence of myocardial infarction (MI) in all age groups of women with SLE with a 7-fold higher incidence in all age groups combined and a particularly increased risk more than 50 fold in women aged 35-44 years. Jonsson et al⁷ observed myocardial infarction occurred 9 times more frequently in 86 adult patients on a follow-up of 6 years.

In two large hospitalized retrospective studies CVD incidence is 2-4 times more common in SLE patients compared with those of non-SLE patients.^{9,10} A case control study comparing 8,688 patients with AMI with 33,923 controls from the General Practice Research Database (GPRD) in UK found

Table I : Mechanism of atherogenic autoantibody interference

that 41 SLE patients in the database to be 2.67 times more likely to have an AMI than their controls after correction for the presence of traditional risk factors.⁵ These studies show that in SLE patients CVD risk estimation based on the Framingham Heart Study data underestimates the actual CVD risk and thereby provide further evidence for the presence of disease-specific mechanisms involved in the increased incidence of CVD in SLE. The current evidence indicates that atherosclerosis plays an important role in SLE-related CVD, even in young patients. Histopathologic studies from postmortem SLE patients showed more extensive and severe atherosclerotic lesions at various points of vasculature when compared with non-SLE controls.^{10,11} In addition, endothelial dysfunction and the presence of subclinical atherosclerosis as assessed by US study of carotid arteries¹², flow-mediated dilatation¹³ (FMD) method and electron beam tomography images¹⁴ are demonstrated in heterogeneous SLE patient groups.

Mechanisms of atherosclerosis

Endothelial dysfunction and chronic inflammation initiate and propagate atherosclerosis. The endothelial dysfunction is both structural and functional with impaired capacity to release the vasodilatory, anti-inflammatory and antioxidative

nitric oxide. This increases vascular permeability and induces vasoconstriction. In addition, various pathologic stimuli activate the immune system and initiate the release of proinflammatory cytokines. Together with an impaired anti-inflammatory defense of dysfunctional endothelium, this leads to activation and influx of inflammatory cells into the vessel wall.

Atherosclerosis lesions are characterized by presence of large number of inflammatory cells including monocyte/macrophages, mast cells, dendritic cells and T-cells. Infiltrated macrophages form foam cells by engulfing oxidized LDL and constitutes early fatty streak. This leads to plaque development which influences intraplaque inflammation, thrombocyte aggregation, smooth muscle cell and fibroblast proliferation and matrix production. The remodeling of plaque and extent of inflammatory infiltrate determine the plaque stability. Plaque rupture initiates thrombus formation and vessel occlusion.

Role of autoantibody formation

Large number of autoantibody production and binding to proteins or cells can induce the following changes in the immune system. (Table 1)¹⁵

This has led to unabated proatherogenic pathophysiological changes including dyslipidemia, activation of immune system, with release of mediators, activation of immune complexes, induction of clearance endothelial cell apoptosis, oxidative stress and possibly a reduction of endothelial progenitor cells. The consequences of combination of traditional risk factors and autoantibody binding results in chronic low-grade inflammatory state and endothelial dysfunction. Ultimately these will potentiate atherosclerotic CVD events in SLE. (Figure 1)¹⁵

Role of traditional and non-traditional risk factors

Traditional and non-traditional CVD risk factors are known to be more prevalent in SLE patients than in controls.² These include the following as

Figure 1 : Overview of potential mechanisms underlying the pathophysiology of accelerated cardiovascular disease in systemic lupus erythematosus

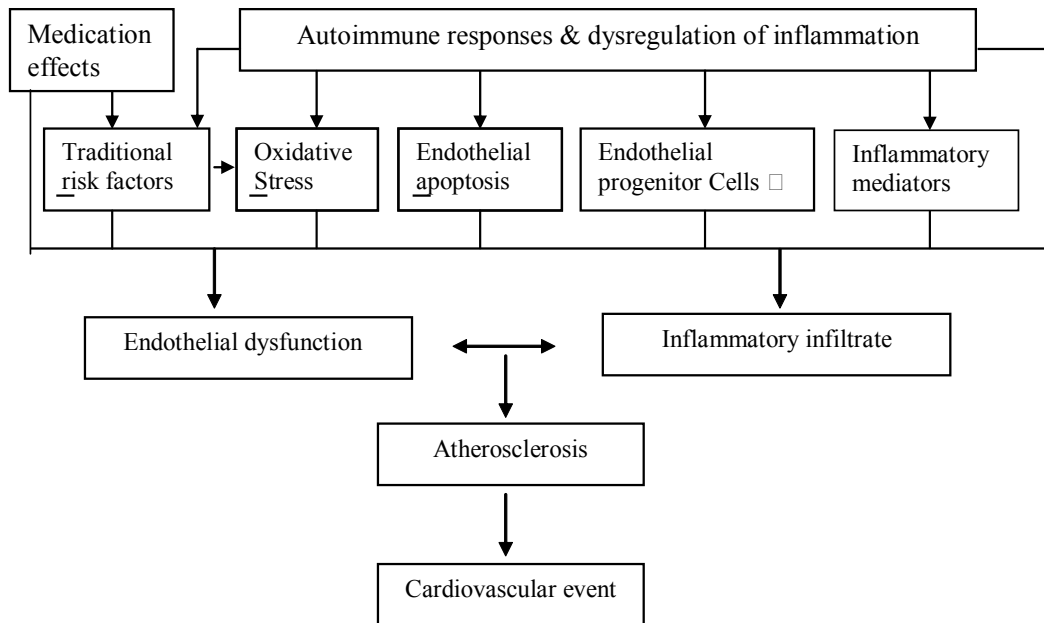


Table 2 : Risk factors for risk factors in SLE-CVD

Traditional risk factors	Non-traditional risk factors
Hypertension	Steroid therapy
Hyper cholesterolemia	Proinflammatory HDL
Hyper homocysteinemia	Endothelial apoptosis
Low HDL	Anti HSP antibodies
Diabetes mellitus	Increased Ox-LDL
Renal impairment	Increased CIC
Elevated CRP	Elevated inflammatory cytokines
Insulin resistance	Dendritic cell overexpression
Smoking	Decreased endothelial progenitor cells

in Table 2.^{2,3,16,17,18,19} Several studies in SLE patients that prolonged use of prednisone is associated with atherosclerotic changes¹⁶ although there are some contradictory observations.²⁰ Roman et al found that more aggressive immunosuppression, including higher doses of prednisone and use of cyclophosphamide or hydroxychloroquin was associated with the absence of plaque.²¹

Traditional risk factors may be influenced by SLE-specific factors. Antiphospholipid antibodies in 30-

50% SLE patients adversely affect the lipid profile and induce lipid peroxidation. Autoantibodies are produced against other lipid components like HDL, Apo-A1 and lipoprotein lipase (LPL). All these increase lipid peroxidation and make these lipid components dysfunctional.^{22,23} Hence, HDL is proatherogenic and proinflammatory because of autoantibody binding to HDL/APO-I; anti-LPL antibody correlates with triglyceride levels, disease activity and markers of inflammation.

Endothelial cell apoptosis

Autoantibodies in SLE bind to endothelium to target 60Kd heat shock protein (HSP) and cause endothelial cell apoptosis upon binding of anti HSP 60 antibodies.¹⁹ Similarly lupus anticoagulant and anti-DNA antibodies induce endothelial cell apoptosis. Endothelial apoptosis contributes to the loss of endothelial integrity and thereby to the initiation of atherosclerosis.²⁴ Apoptotic endothelium is also prothrombotic in SLE²⁵ which is further aggravated by circulating annexin V and plasma tissue factor.²⁶ Increased endothelial cell apoptosis may represent an important mechanism for the development of both atherosclerosis and thrombosis.

Increased Oxidative stress and impaired oxidant defense

Oxidative stress is increased in SLE because of lipid peroxidation. Plasma levels of Ox-LDL are elevated and correlate with the presence of CVD.²⁷ In addition, Ox-LDL and minimally modified LDL are found immunogenic.²⁸ Autoantibodies against Ox-LDL are elevated in SLE patients and facilitate Ox-LDL uptake by macrophages²⁹ to produce foam cells.

Several antioxidant defenses are impaired in SLE. Diminished HDL levels due to anti-HDL antibodies in SLE is unable to exert antioxidant properties and LDL oxidation and uptake by monocytes remain unabated. High levels of asymmetric dimethyl arginine (ADMA) in SLE patients inhibit nitric oxide production from endothelium to cause endothelial dysfunction and potentiate acute coronary events.³⁰ These high levels of ADMA correlated well with anti-ds DNA.³¹

Dysregulation of inflammation

In SLE, the major proatherosclerotic pathogenic derangements are proinflammatory state and endothelial dysfunction. The proinflammatory state is characterized by an activated immune system with elevated levels of proinflammatory cytokines and dysregulation of inflammatory cell response.

Levels of inflammatory cytokines are elevated in active and inactive periods of SLE,³² indicating there is chronic low grade inflammation that increases during relapse of disease. Several of these cytokines like IL-6, IK-1, IL-12, IL-18, MCP1, TNF- α are proinflammatory and proatherogenic. But IL-10, IL-1 RA are atheroprotective. Patients with SLE have higher plasma levels of adhesion molecule and E-selectin³³ which are associated with CVD.³⁴

In atherosclerotic plaque macrophage, dendritic cells, Ox-LDL and HSPs activate T-cells and subsequently stimulate B-cells to produce antibodies. However T-cell activation is inhibited by the HDL component APO A-1 and APO-A1 levels are reduced in SLE patients.³⁵ After T-cell

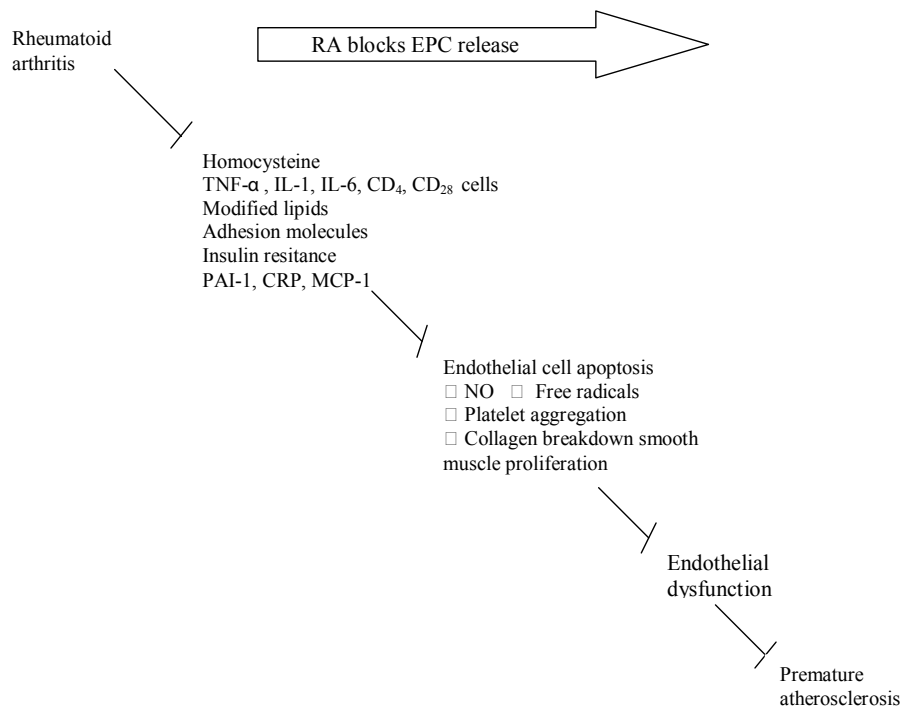
activation, CD 40L remains upregulated and interact with CD40 to facilitate atherogenesis via T-cell independent mechanisms.

Defective endothelial regeneration by endothelial progenitor cells

Endothelial apoptosis is compensated by endothelial repair which is mostly done by endothelial progenitor cells (EPC) from bone marrow. In SLE circulating EPCs are reduced reflecting an impaired capacity for endothelium regeneration which may contribute to accelerated atherosclerosis.³⁶

Increased annexin V binding to the circulating progenitor cells suggested increased apoptosis as the underlying mechanisms of EPC deficiency.³⁶ Consequently with this, SLE serum was found to induce haematopoietic stem cell apoptosis.^{37,38} Therefore in SLE patients EPC level is chronically low and endothelial cell loss is hardly regenerated with resultant apoptosis.

In rheumatoid arthritis chronic inflammation can promote endothelial cell activation and vascular dysfunction. Predisposition to vascular damage in RA is probably mediated by multiple pathways including inflammatory cytokines,³⁹ acute phase reactants,⁴⁰ chemokines,⁴¹ prothrombotic and adhesion molecules,²² cytotoxic responses,²³ insulin resistance,⁴² Ox-LDL⁴³ and homocysteine.⁴⁴ This leads to blood vessel damage, endothelial cell apoptosis, decreased nitric oxide, increased platelet aggregation and smooth muscle proliferation, all of which can promote endothelial dysfunction and premature atherosclerosis. Bone marrow response to vascular damage is impaired in RA in which decreased EPC number and abnormal EPC function are found.⁴⁵ Reduced EPC numbers and abnormal EPC function clearly correlate with increased atherosclerosis, impaired vasculogenesis after ischaemia and predict future cardiovascular events.^{47,27} The pathogenic mechanisms involved in premature CVD in rheumatoid arthritis are illustrated in Figure 2.^{47,48}

Figure 2 : Predisposition to vascular damage in RA through multiple pathways

The observed risk factors in RA for premature CVD are age, duration of disease (usually more than 10 years), co-existent hypertension, persistent chronic inflammation and disease severity; these are associated with carotid atherosclerotic plaque formation even before the clinical CVD events.⁴⁹

Clinical implications

There is substantial evidence that SLE and rheumatoid arthritis patients have a markedly increased risk of atherosclerotic cardiovascular disease by both traditional and non-traditional proatherosclerotic factors. Although several lines of evidence support the idea that auto-antibody formation plays a role in the pathogenesis of the accelerated atherosclerosis, the mechanisms through which this induces a chronic low-grade inflammatory state and endothelial dysfunction are complex and have not been fully elucidated.

SLE and RA patients should be regarded as a population at high risk for the development of CVD, similar for example to patients with diabetes, in whom prompt identification and stringent treatment

of CVD risk factors is recommended.⁵⁰ Guidelines for CVD risk management in SLE patients were recently proposed, targeting mainly the traditional CVD risk factors and centering around life style modifications and the use of traditional drugs such as statins, angiotensin-converting enzyme inhibitors and aspirin.⁵⁰ Similar preventive strategies for traditional and non-traditional risk factors operate in RA.^{51,52} Additional emphasis is given to control disease activity with DMARDs and biologicals and to improve endothelial function.⁵³ In the future, selective intervention that target the chronic inflammation, immune dysregulation, endothelial dysfunction and metabolic derangement in the pathophysiology of atherosclerosis will hopefully provide further benefit.

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Abridged Index

Cardiology

- AMI in elderly 728
- Antiplatelet drug resistance 105
- Bare metal stents 53
- Broad QRS tachycardia 783
- CAD & Sleep disorders 182
- CAD in women 645
- Chronic heart failure- diagnosis 590
- Drug eluting stents 57
- Early metabolic intervention 421
- Heart failure 192
- Hypertension and obesity 548
- Hypertension- changing guidelines 426
- Hypertension- Combination therapy 434
- Hypertension- endothelial cell dysfunction 32
- Hypertension in Type 2 diabetes 439
- Newer thrombolytics Vs primary angioplasty 14
- Pre-operative cardio-pulmonary assessment 725
- Refractory heart failure- devices and surgery 596
- Safety of stents 70
- STEMI- newer drugs 112
- Thrombolysis in AMI 535
- Valvular heart disease in pregnancy 653
- Young hypertensive- investigation 570

Clinical Pharmacology

- Chirality of drugs 178
- Drug interactions- mechanisms 674
- Probiotics and Prebiotics 258

Critical Care & Emergency Medicine

- Bio-terrorism 406
- DIC 230
- Febrile emergencies 217
- Heat stroke 817
- Metabolic abnormalities in critically ill 500
- Resuscitation- trauma in pregnancy 42

- Snake bite- update on management 691
- Statins in critical care 491
- Wavelet analysis of heart rate variability 142

Endocrinology

- Diabetes- mega trials 664
- Diabetes prevention 849
- Glucagon analogs 459
- Incretin hormones 1
- Insulin in Type 2 Diabetes 453
- Maternal Hypothyroidism & Pregnancy 342
- Multinodular thyroid disease 615
- Neuropathy in diabetes- management 810
- Obesity- experience with sibutramine 540
- Obesity- SCOUT trial 544
- Oral hypoglycemics- current status 441
- Prediabetes- interventions 633
- Thyroid disease in India 334
- Type II diabetes-profile 94

Gastroenterology

- IBD in India 250
- IBD-recent advances 264
- Hepato-pulmonary syndrome 748
- Non-variceal bleed- management 833

Geriatrics

- Abdominal pain in elderly 239
- Improving longevity 779
- Preventive strategies 731

Haematology

- Polycythemia- Investigation 358
- DVT- Investigation 368

Infections & Tropical Medicine

- Enteric fever 201
- Antileishmanial resistance 486
- Antimalarial drug resistance 477
- Chikungunya 205

Colonization Vs infection 330
Dengue- resurging infection 739
Leptospirosis in India 799
Nosocomial Pneumonia 290
Post-exposure prophylaxis in HIV 752
Tropical chronic pancreatitis 323
Tropical pyomyositis 697

Lipidology

Aggressive lipid lowering 298
HDL-therapy 313
Isolated Triglyceridemia 302
Mixed dyslipidemias 764
Postprandial lipids- role in atherosclerosis 857

Nephrology

Acute renal failure- management 603
Anemia in CKD 163
Glomerulonephritis- management 82
Nephrotoxicity- herbal drugs 150
Proteinuria- complications 156
Renal replacement therapy 610

Neurology

Acute ischaemic stroke 117
First seizure- management 246
Migraine prophylaxis 378
Parkinson's Disease- Non motor symptom complex 9
Refractory Epilepsy- Investigation 578
Stroke Unit 131
Thrombolysis in ischemic stroke 519
TIAs 347

Oncology

Infection & cancers 168
Non Hodgekin's lymphoma- treatment 789
Solid tumours- targeted therapy 508

Psychiatry

Depression- new horizons 404

Pulmonology

Bronchial asthma- management 283
COPD- long term management 271
COPD- Non invasive ventilation 383
Hemoptysis with normal X-Ray chest 587
Lung cancer- recent advances 717
Pulmonary embolism- thrombolysis 529
Solitary pulmonary nodule- investigation 824

Rheumatology

Ankylosing spondylitis- management 472
Atherosclerosis 882
Monoarthritis- Investigation 374
Osteoporosis-recent advances 628
Rheumatoid arthritis- disease control 466
Vasculitis 76

Miscellaneous

Amyloidosis- recent advances 391
Communication skills 557
Communication with angry patient 845
Diagnostic reasoning- Baye's theorem 563
Digital Gangrene 863
Evidence based medicine- Update 21
Global warming- health hazards 703
Medical Errors 873
Meditation- clinical application 712
Stem cell plasticity 770