Atherosclerosis in Systemic Lupus

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Disclosures

- Relevant financial disclosures
  - None
Objectives

- Understand the significance of atherosclerotic burden in systemic lupus and its impact on mortality in this population
- Discuss the role of traditional and lupus-specific factors in development of atherosclerosis
- Discuss prevention strategies from a primary care perspective
Cardiovascular risk in Lupus

- Accelerated atherosclerosis is a major cause of morbidity and mortality in SLE
- Vascular functional abnormalities in lupus are present even shortly after disease diagnosis (1)
- Patients with SLE have a 2.66 times higher risk of cardiovascular events compared to the general population (2)
- Traditional cardiovascular risk factors do not account for the entire risk (3)
## Risk factors

### Nonmodifiable

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Family history</td>
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<tr>
<td>Male Gender</td>
<td>Genetic predisposition</td>
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### Modifiable

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>Diabetes</td>
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<tr>
<td>Hyperlipidemia</td>
<td>Obesity</td>
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<tr>
<td>Cigarette smoking</td>
<td>Homocysteine</td>
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### SLE specific risk factors

<table>
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<th>Risk Factor</th>
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<td>Disease activity and duration</td>
<td>Renal disease</td>
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<td>Glucocorticoids</td>
<td>NSAIDs</td>
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<td>Antiphospholipid antibodies</td>
<td>Vitamin D deficiency</td>
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Smoking

- Leading preventable cause of death in the United States- 400,000 deaths annually.
- 8% of deaths attributable to second-hand smoke exposure
- Smoking one to four cigarettes daily still increases coronary artery disease risk
- Directly related to increased rates of: myocardial infarction, sudden death, aortic aneurysm formation, peripheral vascular disease, and stroke (4)
Smoking

- Smoking among patients with SLE increases the risk of having a cardiovascular event three fold compared to nonsmokers with SLE (5)
- Smokers had significantly higher disease activity compared with ex-smokers and never smokers in a multivariate analysis (6)
- Smoking also interferes with the efficacy of antimalarial therapies (7)
- Nicotine has been shown to strongly inhibit the uptake of chloroquine in cultured cells, but whether this effect occurs in vivo is unknown (8)
Hypertension

- Hypertension is a major problem in SLE patients.
- Seventy-five percent of patients in the Hopkins Lupus cohort are hypertensive.
- The presence of hypertension in SLE increases the risk of cardiovascular events 2.66-fold (2),
- increases the progression of carotid plaque (9),
- increases the risk of coronary artery disease, stroke, and poor renal outcomes (10, 11)
- Only 9% of hypertensive lupus patients reach a goal blood pressure of less than 120mmHg with antihypertensive therapy (12)
Hyperlipidemia

- Lowering LDL cholesterol levels with statins reduces coronary events by up to one third over a 5-year period in the general population.
- Within 3 years of diagnosis, 40.3% of patients in the Toronto cohort developed sustained elevated total cholesterol which was a good predictor of future cardiovascular events (13).
- Patients who developed hypercholesterolemia tended to have a higher cumulative dose of steroids, were not on antimalarial therapy, and had an age of onset of SLE > 35 years old.
- Triglyceride (non-fasting and fasting) levels are also predictive of coronary artery disease in lupus patients (14).
Diabetes mellitus

- Presence of diabetes confers an equivalent risk to aging 15 years, an impact higher than that of smoking (15).
- Two- to eightfold higher rates of future cardiovascular events compared to nondiabetic individuals.
- 75% of all deaths in diabetic patients result from CHD.
- Paucity of data in regards to the association of diabetes with SLE.
- Isenberg et al. found a prevalence of only 1.9% of an overlap SLE/DM in their cohort (16).
- In the Hopkins Lupus Cohort, presence of diabetes doubled the risk of cardiovascular events compared to the baseline SLE risk (2).
Obesity

- Obesity is associated with more morbidity than smoking, alcoholism, and poverty (17).
- It may soon overtake cigarette abuse as the leading cause of preventable death in the U.S. (18).
- Increases risk of developing type 2 diabetes mellitus, hypertension, dyslipidemia, heart failure, coronary heart disease, atrial fibrillation, obstructive sleep apnea/sleep-disordered breathing, proteinuria, and osteoarthritis (19)
Homocysteine

- Amino acid derived from the demethylation of dietary methionine
- Elevated homocysteine may result due to dietary or genetic factors
- Is an independent risk factor for stroke and thrombotic events in patients with SLE (20)
- It may also be a risk factor for the later development of coronary artery disease in SLE (21)
SLE-specific risk factors
Disease activity and duration

- Incidence of cardiovascular events is significantly higher in patients with high SLE disease activity (2)
- Inverse relationship between SLE activity and plaque size (22)
- Disease duration is significantly associated with coronary calcium scores (23)
- Longer disease duration and higher SLICC damage index are independent predictors of carotid plaque (24)
Renal disease

- Patients with proteinuria have an increased risk of thrombosis (25)
- Elevated serum creatinine is associated with early atherosclerosis in patients with SLE (26)
- History of lupus nephritis is associated with subclinical atherosclerosis (27)
Glucocorticoid therapy

- Glucocorticoid use has been associated with atherosclerosis in SLE (28).
- A dose of prednisone of 7.5mg or more was associated with a 2.56-fold increased risk of cardiovascular events (29).
- In SLE patients, a change in prednisone dose of 10 mg was associated with a change in cholesterol of 7.5±1.46 (SE) mg%, a change in mean arterial blood pressure of 1.1 mmHg, and a mean weight change of 5.50±1.23 (SE) lb (30).
- In the Hopkins Lupus Cohort, the effect of corticosteroids is independent of disease activity and traditional cardiovascular risk factors (2).
- Taking prednisone at a dose of 10mg/day or more leads to significantly higher rates of CVE (2).
- A cumulative dose equivalent to >10 mg/day for 10 years is associated with a higher risk of atherosclerosis (30).
Nonsteroidal antiinflammatory drugs

- NSAID treatment predisposes to non-fatal and fatal cardiovascular events (31)
- Rofecoxib is associated with the highest risk of myocardial infarction, Ibuprofen with the highest risk of stroke, and Diclofenac with the highest risk of cardiovascular death. Naproxen seems least harmful (32)
- Hill et al found NSAIDs to increase cardiovascular events in SLE (33).
- Besides the cardiovascular risk, NSAID use in SLE patients increases the risk of worsening glomerular filtration (34).
Antiphospholipid antibodies

- A high anticardiolipin antibody level is an independent risk factor for myocardial infarction and cardiac death (35).
- The presence of antiphospholipid antibodies was associated with a greater than 4-fold increased risk of myocardial infarction, stroke, or peripheral vascular disease in a study of 182 SLE patients who were followed for a mean of 8.3 years (36).
Vitamin D

- Low serum levels of 25-hydroxyvitamin D have been associated with stroke (37), myocardial infarction (38), hypertension (39), diabetes mellitus (40), hypertriglyceridemia, obesity, and the metabolic syndrome (43).
- In SLE, low vitamin D levels are associated with increased atherosclerotic burden (44), high disease activity and dyslipidemia (45), higher BMI and insulin resistance (46).
C-reactive protein

- In SLE patients, hsCRP had no association with cardiovascular damage in the Hopkins Lupus cohort (47), but it was associated with damage to various organs, particularly those of the pulmonary and musculoskeletal systems.
Prevention and treatment
General

- Recommendations for therapy are based on prevention guidelines for the general population.
- SLE should be considered a coronary heart disease equivalent (48)
STOP SMOKING!

- THE single most important intervention in preventive cardiology
- Reduces CHD mortality by 36% as compared with mortality in subjects who continue smoking
- Low-yield cigarettes do not appear to reduce the risks of myocardial infarction.
- The first-line evidence-based pharmacological options include: bupropion, nicotine replacement therapy (gum, inhaler, lozenge, nasal spray, or patch), and varenicline.
- There is no concern with the use of any of these pharmacotherapies in SLE patients.
Hypertension therapy

- Treatment of hypertension in SLE is based on the Seventh Report of the Joint National Committee (49).
- In the Hopkins Lupus Cohort, the risk of cardiovascular events increased with any elevation above 120mmHg (2) so a more aggressive approach may be warranted.
- Thiazide diuretics- potential metabolic side effects including hypercholesterolemia, hypertriglyceridemia, and hyperglycemia (50).
- ACE inhibitors- preferred first line agents in SLE. Long track record of safety and efficacy and have been studied in patients with lupus nephritis and severe hypertension, where they were shown to improve renal function in 64% of patients while also improving BP control (51).
- β-blockers may precipitate or worsen Raynaud's phenomenon (52), and can rarely cause drug-induced lupus (53, 54) so they are used as second-line agents.
Aspirin

- There are no randomized, controlled trials of aspirin use as primary or secondary prevention of CVD in SLE patients.
- In a study that examined mortality reduction in SLE, aspirin was associated with a 70% reduction of all-cause mortality, and antiphospholipid antibodies were not associated with increased mortality (55).
- In the absence of contraindication, the use of aspirin is recommended in any patient with SLE who has a history of CVD, positive antiphospholipid antibodies or lupus anticoagulant, history of hypertension, diabetes mellitus, hypercholesterolemia and a history of smoking (56).
Hydroxychloroquine

- Hydroxychloroquine is cardioprotective (57)
- Lowers total cholesterol in patients receiving steroids (58)
- Lowers fasting blood glucose concentration (59)
- Reduces incidence of thrombotic events (60)
- Improves overall survival in patients with SLE (61)
Hyperlipidemia treatment

- Goal LDL in SLE is <100
- Lifestyle changes: reduce total and saturated fat in the diet, lose weight (if overweight or obese), perform aerobic exercise, and eat a diet rich in fruits and vegetables
- Statins are the most effective drug for prevention of coronary heart disease, heart attack, stroke, and death
  BUT
- LAPS trial- NO benefit in the primary (coronary artery calcium) and secondary (carotid IMT, carotid plaque) atherosclerosis outcomes of SLE patients (62).
Omega-3 fatty acids

- Omega-3 fatty acids have no conclusive evidence of benefit in primary or secondary prevention of coronary vascular events (63).
- Furthermore, they have been shown to increase LDL levels up to 45% (64, 65) so we recommend against their use in SLE patients.
Niacin

- The AIM-HIGH trial (66) showed no clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels. There was also an unexpected rate of ischemic stroke among patients in the niacin group.
- Niacin use is avoided in the Hopkins Lupus cohort.
Hyperhomocysteinemia

- Combination therapy of folic acid, vitamin B6 and B12
- Lack of evidence that homocysteine reduction lowers risk of atherosclerosis in general population
- Treatment in specific patient populations may be appropriate, including in SLE
Vitamin D Deficiency

- Whether vitamin D supplementation modifies the risks linked to its deficiency is currently not known.
- Until further data are available, treatment of vitamin D deficiency with a goal 25-hydroxyvitamin D level of 40 ng/mL or more (67) is recommended.
Immunosuppressives

- MMF reduces coronary allograft vasculopathy (68) and decreases cardiovascular mortality by 20% in renal transplant recipients compared to azathioprine (69).
- A 2 year prospective study of 25 patients with SLE treated with MMF showed no evidence of a decrease in the progression of atherosclerosis as measured by carotid intima media thickness or coronary artery calcium compared to patients with SLE who were not treated with MMF (70).
- Data from the Hopkins cohort showed that methotrexate use was highly associated with noncalcified plaque in SLE in a multivariate analysis (71). The homocysteine levels did not differ compared to the patients who were not on methotrexate.
Ongoing research

- CANTOS trial- canakinumab, an IL-1 β inhibitor, in stable postmyocardial infarction patients with persistent hsCRP elevation (73).
- The cardiovascular inflammation reduction trial (CIRT) (73) is a phase 3 clinical trial of low dose methotrexate (10mg/week) in stable coronary artery disease patients with persistent elevations of hsCRP.
- B cell–depletion strategies primarily with antibodies targeting CD20 are being investigated and their impact on B-2 and B-1 cells and on CVD needs to be determined (74).
- Belimumab is a humanized monoclonal antibody that inhibits the binding of BAFF and could potentially find application in the context of atherosclerosis (75).
- Experimental treatment options: maraviroc, blocking the CD40-TRAF6 interaction, blocking the macrophage migration inhibitory factor (MIF) receptor binding, inhibition of CCL5-CXCL4, and blocking CCR2 (76), but none of these approaches have been tested in lupus models.
Conclusions

- Accelerated atherosclerosis and its long term sequelae are the major causes of late mortality in SLE.
- Treatment strategies include an aggressive approach in therapy of traditional cardiovascular risk factors with targets equivalent to the ones used for established CVD.
- Smoking inhibits the effect the antimalarials and should be immediately addressed.
- In the absence of contraindications, hydroxychloroquine should be used in EVERY patient.
- Despite the negative results of the LAPS trial, statins remain the mainstay of treatment of hyperlipidemia, while fish oil and niacin use are discouraged.
- ACE inhibitors should be used as first line agents for treatment of hypertension to a goal of less than 120mmHg systolic.
Conclusions

- Aspirin should be used in any patient with SLE who has a history of CVD, positive antiphospholipid antibodies or lupus anticoagulant, history of hypertension, diabetes mellitus, hypercholesterolemia and a history of smoking.
- Despite the lack of conclusive benefit, the treatment of vitamin D deficiency and hyperhomocysteinemia is encouraged.
References

References