THE CARDIOVASCULAR INFLAMMATORY CONTINUUM

DR AB MAHARAJ
Disclosures:

On National Advisory Boards of:
  (1) Pfizer Pharmaceuticals
  (2) MSD
  (3) Roche Pharmaceuticals
  (4) Abbott

International:
AfME Rheumatology Board of Pfizer

Educational Grant: Servier Laboratories
Atherosclerosis in Inflammatory disorders

Atherosclerosis is a chronic inflammatory disease that leads to the development of plaques in the arterial walls, which can cause narrowing of the blood vessels and increase the risk of heart disease and stroke. The process involves the accumulation of lipids, particularly cholesterol, in the arterial walls, leading to the formation of atherosclerotic plaques.

The diagram illustrates the mechanisms involved in the development of atherosclerosis. Monocytes, which are a type of immune cell, migrate into the arterial wall and differentiate into macrophages. These macrophages engulf LDL (low-density lipoprotein) cholesterol, forming foam cells. The process is further complicated by the presence of oxidized LDL (oxLDL) and reactive oxygen species (ROS), which promote inflammation and plaque formation.

Key factors in the development of atherosclerosis include:
- Oxidized LDL (oxLDL)
- Low-density lipoprotein (LDL)
- Reactive oxygen species (ROS)
- High-density lipoprotein (HDL)
- TNF (tumor necrosis factor)
- IL-6 (interleukin-6)
- Homocysteine

These factors contribute to the formation of atherosclerotic plaques, which can lead to cardiovascular disease. Understanding the mechanisms involved in atherosclerosis is crucial for developing effective prevention and treatment strategies.

References:
Figure 1. In RA, primary site of inflammation is synovial tissue, from which cytokines can be released into systemic circulation.
Atherosclerotic plaque

Coronary artery

Interferon-γ, Interleukin-1, TNF

Adipose tissue

Interleukin-1

TNF

Interleukin-6

Liver

Acute-phase reactants

Serum amyloid A

CRP
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Study size (patients/controls)</th>
<th>Study</th>
<th>Study type</th>
<th>Study size (patients/controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallberg-Jonsson (1997)</td>
<td>Epidemiological</td>
<td>606/NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic lupus erythematosus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rajagopalan (2004)</td>
<td>Observational</td>
<td>43/43 (plus 43 with CAD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roman (2003)</td>
<td>Prospective</td>
<td>197/197</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lima (2002)</td>
<td>Observational</td>
<td>65/69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiphospholipid syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sherer (2007)</td>
<td>Observational</td>
<td>16/16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psoriasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ankylosing spondylitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathieu (2008)</td>
<td>Observational</td>
<td>60/60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sjögren’s syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaudo (2005)</td>
<td>Observational</td>
<td>37/35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progressive systemic sclerosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timar (2008)</td>
<td>Observational</td>
<td>40/35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; NA, not applicable.
Rheumatoid Arthritis

- Prevalence: 1 %
- Increased mortality from CVD
- MI 2x commoner in ♀ with RA as compared to controls
- Traditional risk factors do not influence CVS mortality in RA pts.
- RA pts have a higher prevalence of diastolic dysfunction
- Increased mortality in RA pts with MI as compared to controls
• High incidence of silent ischaemia
• RA specific factors play a role
• Extent of atherosclerosis proportional to disease activity
• Male and advanced age of onset – poor prognosis
SLE

- Autoimmune disease affecting predominantly women of child-bearing age
- High rate of premature CVD
- CVD – most common cause of death in pts with SLE
- Framingham risk factors are less important predictors of CVS events in pts with active SLE
- > 40% of pts with SLE have asymptomatic myocardial perfusion abnormalities
- High incidence of increased LV mass
Risk Factors for Atherosclerosis and Risk Factors Related to Systemic Lupus Erythematosus (SLE).

Figure 2 Continuum of SLE-specific and traditional risk factors for CVD

Skaggs, B. J. et al. (2012) Accelerated atherosclerosis in patients with SLE—mechanisms and management

Antiphospholipid Syndrome

- Poor correlation between APLS and premature atherosclerosis
- SLE with anti $\beta_2$G1 antibodies have increased incidence of MI
Psoriasis and PsA

- Chronic inflammatory conditions
- Increased prevalence and severity of CVS in these pts
Systemic Sclerosis

- Myocardial perfusion injury - well documented in PSS
- Patent epicardial vessels and normal intramural coronary vessels
- Oral nifedipine associated with improvement in myocardial perfusion
Ankylosing Spondylitis

- Mortality 1.6-1.9 fold greater in pts with AS as compared to general population
Sjögren’s Syndrome

• Endothelial dysfunction well documented in Sjogren’s Syndrome
• Immune dysregulation
• Higher incidence in pts with Anti-Ro antibodies and leucopenia
• Unclear if Sjogren’s Syndrome is an independent risk factor for premature CVD
Mechanisms of premature CVD

TRADITIONAL AS WELL AS NON TRADITIONAL RISK FACTORS
Non-traditional risk factors

• Striking similarities noted in the inflammatory and immunologic reactions of Atherosclerosis and RA
- Reasons for the development of CVD in RA complex
- Several mechanisms
Premature CVD

↑ proinfl cytokines

Abn vasc repair

genes

Premature CVD
Premature CVD

- Steroid use
- Cytotoxic T cells
- Antibodies to endothelial cells
Increased levels of Pro-inflammatory cytokines

- TNF α
- IL-6
- IL-17
- CRP
Abnormal Vascular Repair

- ↓ circulating EPC’s
- Quantitative and qualitative defect in EPC’s in RA/SLE/PSS
- Imbalance between vascular damage and repair
- Leads to endothelial dysfunction
- SLE- increased apoptosis of endothelial cells
Atherosclerosis in Inflammatory disorders

(2012) Accelerated atherosclerosis in patients with SLE — mechanisms and management
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2012.14
Genetic Polymorphism

Genetic polymorphism of

- TNF receptor Type II
- PAI I
- Coagulation factor XIII subunit A
Cytotoxic T cells

- $\uparrow$ levels of CD4$^+$CD28$^-$ in pts with RA
- These cells cause endothelial cell cytotoxicity
Autoantibodies

- To endothelial cells components
- Their precise role as yet unclear
Corticosteroids

- Inconsistent results from clinical trials

Steroids induce:
- Hypertension
- Insulin resistance
- Lipid abnormalities
- Obesity

CVD
Steroids in Chronic Inflammatory Diseases

- Exact role of steroids in the development of CVD in chronic inflammatory conditions is yet to be defined
Traditional risk factors

- Smoking
- Systemic Hypertension
- Dyslipidaemias
- Microalbuminuria
- Insulin resistance
- Hyperhomocysteinaemia
Risk Assessment and Prevention

• Preventive strategies to start soon after diagnosis
• Awareness
• Guidelines lacking
• Unanswered questions???
## Decreasing Traditional Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Recommended modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Counseling; nicotine patches or gum; bupropion</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure monitoring and antihypertensive therapy; salt and weight control; exercise</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Counseling, diet/exercise, statins when indicated, control of disease activity; target LDL cholesterol level to &lt;3.37 mmol/l and HDL cholesterol level to &gt;1.04 mmol/l</td>
</tr>
<tr>
<td>Increased BMI</td>
<td>Counseling; diet; exercise</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Vitamin supplementation and monitoring</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Weight control; treatment of underlying inflammatory condition</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>Counseling; monitoring and treating risk factors</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Proper control of underlying disease and prompt treatment of symptoms</td>
</tr>
<tr>
<td>Additional prethrombotic risk</td>
<td>Low-dose aspirin; consider anticoagulation in selected cases</td>
</tr>
<tr>
<td>Abnormal vascular repair</td>
<td>Statins and proper control of disease activity could improve this abnormality</td>
</tr>
</tbody>
</table>

Abbreviation: CVD, cardiovascular disease.

Decreasing Disease specific risk Factors

- Paracetamol
- NSAIDS: COX II vs NS NSAIDS
- Aggressive treatment of underlying condition
- Hydroxychloroquine in SLE
- Corticosteroids
- Methotrexate
- Biologics
Summary:

- Patients with systemic inflammatory diseases are at significantly increased risk of cardiovascular events, which contribute to the high morbidity and mortality associated with these diseases.
• Evidence suggests that rheumatoid arthritis and systemic lupus erythematosus are independent risk factors for the development of premature cardiovascular disease (CVD)
• As factors promoting premature CVD-associated mortality might be present early in the natural history of inflammatory disease, preventive strategies to decrease cardiovascular risk should start shortly after diagnosis.
Specific guidelines need to be developed that address the management of cardiovascular risk factors in rheumatoid arthritis, systemic lupus erythematosus and potentially other inflammatory conditions.
• Recent evidence suggests that optimal treatment of inflammatory disorders could result in improvements in vascular function and lead to decreases in the risk of CVD
NOTICE-PUBLIC BAR

OUR PUBLIC BAR IS PRESENTLY
NOT OPEN BECAUSE IT IS
CLOSED. MANAGER
Northampton General Hospital NHS

Family planning advice
Use rear entrance
References:


Thank You!