CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS: CAUSES, CONSEQUENCES AND OPEN QUESTIONS
Conflict of interest statement

• Clinical trials
  • Global Chief Investigator: Astra-Zeneca
  • Chief Investigator: TRACE RA (partly funded by Pfizer)
  • Principal Investigator: Roche, Pfizer, Abbvie, UCB, BMS, Novartis

• Unrestricted Grants
  • Pfizer, (Wyeth), Abbott (Abbvie)

• Honoraria for lectures / advisory boards
  • Roche, Abbvie, Pfizer, Novartis, UCB, BMS, Lilly, GSK, MSD, Genesis

• Congress organisation
  • Abbvie, BMS, Genesis, MSD, Novartis, Pfizer, Roche, UCB

• Hospitality
  • Roche, Abbvie, UCB, Novartis

• Co-Investigator:  BSRBR (partly funded by the industry)

• Expert:  NICE (National Institute of Research & Clinical Excellence)
Outline

– What is the problem?
  • CVD morbidity and mortality in RA
– What is the nature of this problem?
– Atherosclerosis / Atherothrombosis and CVD in RA
  • Is it highly prevalent?
  • Is it accelerated?
    – Why?
– Are processes other than atherosclerosis of relevance?
– Genes and CVD in RA
– Summary
Outline

– What is the problem?
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RA - symptoms/signs

• Joint symptoms
  – Pain
  – Swelling
  – Stiffness

• Constitutional upset
  – Fatigue
  – Weight loss
  – Pyrexia
RA - Joint destruction/deformity
RA - Multi-system involvement
Bio-Psycho-Social impact integration

Physical

Psychological

Social

OUTCOME
RA: overall mortality

Gloucester: “oh let me kiss these hands”

Lear: “let me wipe them first, they smell of mortality”

King Lear
The problem: CVD mortality in RA
Ischaemic heart disease

<table>
<thead>
<tr>
<th>Event/Disease</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>1.2</td>
<td>1.0 - 1.5</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>1.5</td>
<td>0.9 - 2.5</td>
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</tbody>
</table>

Congestive heart failure

<table>
<thead>
<tr>
<th>Event/Disease</th>
<th>RR</th>
<th>CI</th>
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<tbody>
<tr>
<td>CHF</td>
<td>1.5</td>
<td>0.9 - 2.5</td>
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Peripheral vascular disease

<table>
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<tr>
<th>Event/Disease</th>
<th>RR</th>
<th>CI</th>
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<tbody>
<tr>
<td>PVD</td>
<td>1.8</td>
<td>1.2 - 2.6</td>
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Cerebrovascular disease

<table>
<thead>
<tr>
<th>Event/Disease</th>
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<th>CI</th>
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<tbody>
<tr>
<td>CVD</td>
<td>1.7</td>
<td>1.3 - 2.3</td>
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Type 2 diabetes

<table>
<thead>
<tr>
<th>Event/Disease</th>
<th>RR</th>
<th>CI</th>
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</thead>
<tbody>
<tr>
<td>RA</td>
<td>1.2</td>
<td>1.0 - 1.4</td>
</tr>
</tbody>
</table>

Hyperlipidemia

<table>
<thead>
<tr>
<th>Event/Disease</th>
<th>RR</th>
<th>CI</th>
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<tbody>
<tr>
<td>RA</td>
<td>1.2</td>
<td>1.1 - 1.3</td>
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</table>

Hypertension

<table>
<thead>
<tr>
<th>Event/Disease</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
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<td>1.1 - 1.4</td>
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“Causes”
Classical risk factors
- Hypertension
- Dyslipidaemia
- Obesity
- IR/Metabolic Syndrome
- Inflammation
- Other

Processes
- Atherothrombosis
- Arteriosclerosis
- Vasculitis
- Microvascular dysfunction
- Myocarditis and Others

Outcomes
- Normal
- Disability
- Death

Pathophysiologic effect
- Myocardial Ischaemia
- Diastol./Syst. dysfunction

Clinical expression
- Normal
- Symptoms (e.g. angina)
- Acute Coronary Syndromes
- Heart Failure
- Arrhythmias…..
Cardiovascular “pathology” in RA

Rheumatoid heart disease (classical inflammation):

Ischaemic Heart Disease:

Most cardiovascular deaths in RA are due to ischaemic pathologies (i.e. MI, CHF, sudden death)

Bacon & Kitas, ARD, 1994

Kitas et al: Clin Med 2001
The reason: “INFLAMMATION” et al.

Atherosclerosis is a chronic inflammatory disorder...

...similar to RA...
### Effect of “inflammation”

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Area under the ROC Curve (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>0.61 (0.59–0.62)</td>
</tr>
<tr>
<td>Current cigarette smoking (vs. nonsmoking)</td>
<td>0.63 (0.61–0.64)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.64 (0.63–0.65)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.65 (0.64–0.67)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>0.65 (0.64–0.67)</td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td>0.66 (0.64–0.67)</td>
</tr>
</tbody>
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**Figure 1.** Odds Ratios for Coronary Heart Disease among 2459 Patients with Coronary Heart Disease and 3969 Controls.
Accelerated atherosclerosis

Non-RA

RA

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What is the evidence for (accelerated) atherosclerosis in RA?

• Theory: the role of inflammation
Accelerated atherosclerosis

Non-RA

RA

Effect of inflammation

Inflammation → “classical” CVD risk factors → Vasculature

Inflammation

Diagram:
- Chronic inflammatory disease
- Hypertension
- Smoking
- Heart shock proteins
- Inflammation
- Endothelial dysfunction
- Atherogenesis
- Coronary heart disease/ischaemic heart disease

Graph:
- Increasing cardiovascular risk
- SLE
- RA
- DM + metabolic syndrome
- Classical risk factors
- General population

What is the evidence for (accelerated) atherosclerosis in RA?

- Theory: the role of inflammation
- Evidence for sub-clinical atherosclerosis (Dr. A. Protogerou)
What is the evidence for (accelerated) atherosclerosis in RA?

• Theory: the role of inflammation
• Evidence for sub-clinical atherosclerosis
• Vascular work + Epidemiology: RA = Type 2 DM
CVD morbidity in RA = DM

Nurmohamed & Kitas: ARD 2011; 70: 881
Stamatelopoulos et al, ATVB 2009; 29: 1702
Linhardsen et al, ARD 2011; 70: 929
What is the evidence for (accelerated) atherosclerosis in RA?

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- An abundance of Classical and novel risk factors
Obesity in RA
PHYSICAL INACTIVITY IN RHEUMATOID ARTHRITIS

• Highly prevalent
• Very low levels of activity
• Various reasons
• Associates with:
  – vascular dysfunction
  – multiple CVD risk factors
  – basal metabolic rate
  – Abnormal CV response to stress

Stavropoulos-Kalinoglou et al / Metsios et al / Sandoo et al / van Zanten et al
Body composition - Rheumatoid cachexia

Potential causes:
- Systemic inflammation
  - ↑ Pro-inflammatory cytokines
  - Pain and fatigue
  - ↓ Physical activity
- Low testosterone levels
- Smoking
- Corticosteroids

Manifestations:
- ?↑ CVD-related risk
- ?↑ Visceral fat
- ↑ Total fat mass
- ↓ Muscle mass

Insulin Resistance in RA

Excessive insulin: increased testosterone, increased cholesterol. Excessive glucose stored as fat. We end up with reduced energy, most of the food stored as fat, with increased risk for diabetes, reduced burning of fat.

Pancreas secretes insulin

Food becomes glucose in the blood

Cells are insulin resistant, the efficiency is VERY low. So glucose not absorbed.

Insulin Resistant Cell

Cells still don't have energy, so you feel hungry

Eat More Food

Produce even more insulin

Excessive blood glucose as they are not absorbed by the cell

Excessive blood glucose

Glucose in blood

Eat Food

Stavropoulos-Kalinoglou et al, ART 2012, in press
Hypertension in RA

- Of the total RA population in care, 70% are hypertensive...

- Of those with hypertension, 40% remain undiagnosed...

- Of those diagnosed, ~80% are sub-optimally controlled....

Panoulas et al: Rheumatology 2007; 46: 1477
Dyslipidaemia in RA

Age (Years)

% Dyslipidaemic

20-30 | 30-40 | 40-50 | 50-60 | 60-70 | 70-80 | >80

Toms et al, ARD 2010
Dyslipidaemia in RA (Dr. Anne-Grete Semb)

Inflammation

↓ LDL
↑ Small dense particles
↑ PAF-AH activity
↑ sPLA2
↑ sphingolipid content

↓ HDL
↑ ceruloplasmin & SAA
↑ sPLA2
↑ PAF-AH activity
↓ enzyme activity (HL, LCAT, PLTP, CETP)

↑ VLDL
↓ enzyme activity (HL, LPL)
↑ sphingolipid content

Toms T et al: Curr Vasc Pharmacol 2010; 8: 301
Toms T et al: RA susceptibility genes associate with dyslipidaemia in RA. ARD 2011
# RA treatment effects on CVD risk factors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs / Coxibs</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Lipids, DM</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Met. Syndrome, Homocysteine</td>
</tr>
<tr>
<td>Steroids</td>
<td>Hypertension, Dyslipidaemia, Insulin resistance</td>
</tr>
<tr>
<td>Biologics</td>
<td>Lipids, BP, Body composition</td>
</tr>
</tbody>
</table>

Gasparyan et al: Curr Vasc Pharmacol 2011  
Toms et al: Curr Vasc Pharmacology 2010
What is the evidence for (accelerated) atherosclerosis in RA?

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BUT

• Is it accelerated atherosclerosis or plaque instability?
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**BUT**

- Is it accelerated atherosclerosis or plaque instability?
- Higher re-infarction rate
Increased case fatality / reinfarction in RA

RA: N=40
Case-matched controls for Age, sex, risk factors, ACS

RA:
20% no chest pain (***)
Delayed thrombolysis
Less cardiac Ix
Less cardiac rehabilitation

Douglas et al, ARD 2006; 65(3): 348-53
Rantapaa-Dahlqvist et al, ARD 2007
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• Higher re-infarction rate
• Evidence of plaque instability by 64 slice CT angiography
Figure 1  Per patient (panels A and B) and per segment (panel C) analysis of differences in coronary plaque presence and composition in RA and controls. A. Proportions of subjects with one, 2, or ≥3-vessel disease, both non-obstructive (<50%) and obstructive (≥50%); B. Number of patients with any, NCP, MP, or CP in RA and controls. C. Fraction of coronary segments harbouring any plaque, NCP, MP, or CP in RA and controls. Results in mean (95% CI). *p<0.05, **p<0.01, ***p<0.001 for all comparisons between RA and controls. RA, rheumatoid arthritis; NCP, non-calcified plaque; MP, mixed plaque; CP, calcified plaque.
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• Unstable (carotid) plaque composition “phenotype” in gene microarrays
SAM Statistical Analysis of Microarray Data By Bootstrapping to account for Multiplicity

Expression Data Analysis

Hierarchial Clustering of Expression Data using Li&Wong dChip method

RA+IHD RA-IHD OA+IHD OA-IHD

Genes up-regulated 2 Fold or Greater only in RA+IHD vs RA-IHD

T cell receptor gamma locus
Granzyme 2
Cathepsin W (lymphopain)
Jagged 1 (Alagille syndrome)
mitogen-activated protein kinase kinase 2
natural killer cell group 7 sequence
p53 regulated PA26 nuclear protein

Halligan E et al, Rheumatology 2004
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- Evidence of plaque instability by 64 slice CT angiography
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- Necropsy evidence

• ...there was less histologic evidence of atherosclerosis but greater evidence of inflammation and instability in RA patients (n=41) compared to controls (n=82, matched for age, sex, CVD history and autopsy date)...

• “...these differences suggest that the mechanisms responsible for CVD morbidity and mortality may be different in patients with RA”
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Microvascular disease in RA (Dr. Sophie Mavrogeni)

- Disease phenotype: rheumatoid vasculitis
- Positive stress thallium scans – Normal coronary angiography
- Positive stress contrast echo - Normal coronary angiography
- Cardiac MRI
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Genes, Inflammation and Hypertension in RA

- GNB3 825TT
- ET-1 5665TT
- TGF 869T
- IL6 174 C

Enhanced Na/H exchanger activity → Reduced NO/ET1 → Arterial stiffness
Enhanced signalling → Reduced NO/ET1 → Arterial stiffness

- Enhanced signalling
- Arteriolar radius
- Peripheral resistance
- Stroke volume
- Heart rate
- Cardiac output
- BP

Sandoo et al, J. Human Hypertension 2011
Panoulas et al (several)
RA susceptibility/severity genes

Lipid metabolism genes

Toms T et al: RA susceptibility genes associate with dyslipidaemia in RA. ARD 2011
The Impact of Inflammation on Metabolomic Profiles in Patients With Arthritis

Stephen P. Young,1 Sabrina R. Kapoor,2 Mark R. Viant,1 Jonathan J. Byrne,1 Andrew Filer,3 Christopher D. Buckley,2 George D. Kitas,4 and Karim Raza2

Objective. Inflammatory arthritis is associated with systemic manifestations including alterations in metabolism. We used nuclear magnetic resonance (NMR) spectroscopy-based metabolomics to assess metabolic fingerprints in serum from patients with established rheumatoid arthritis (RA) and those with early arthritis.

Methods. Serum samples were collected from newly presenting patients with established RA who were naïve for disease-modifying antirheumatic drugs, matched healthy controls, and 2 groups of patients with synovitis of ≤3 months’ duration whose outcomes were determined at clinical followup. Serum metabolomic profiles were assessed using 1-dimensional 1H-NMR spectroscopy. Discriminating metabolites were identified, and the relationships between metabolomic profiles and clinical variables including outcomes were examined.

Results. The serum metabolic fingerprint in established RA was clearly distinct from that of healthy controls. In early arthritis, we were able to stratify the patients according to the level of current inflammation, with C-reactive protein correlating with metabolic differences in 2 separate groups (P < 0.001). Lactate and lipids were important discriminators of inflammatory burden in both early arthritis patient groups. The sensitivities and specificities of models to predict the development of either RA or persistent arthritis in patients with early arthritis were low.

Conclusion. The metabolic fingerprint reflects inflammatory disease activity in patients with synovitis, demonstrating that underlying inflammatory processes drive significant changes in metabolism that can be measured in the peripheral blood. The identification of metabolic alterations may provide insights into disease mechanisms operating in patients with inflammatory arthritis.

The etiology of rheumatoid arthritis (RA) is not fully understood but involves both genetic and environmental factors. In addition to synovitis, there are widespread systemic effects mediated by proinflammatory cytokines that impact on metabolism. Tumor necrosis factor α, interleukin-1 (IL-1), and IL-6 all promote...
There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance.
— Hippocrates

Summary

• CVD is an important comorbidity in RA and responsible for most of the increased mortality of this disease.

• There is evidence for atherosclerotic processes being at play, possibly accelerated. Plaque instability however, may be a more important determinant of outcome.

• The causes of accelerated atherosclerosis and plaque instability, and the interplay between “classical” and “novel” risk factors / mechanisms require further elucidation.

• The importance of processes other than atherosclerosis is re-emerging and needs a lot of investigation in terms of pathogenesis, clinical importance and relevance to outcome.

• There are several ways in which specific genetic polymorphisms may be involved in the processes linked to CVD in RA: these merit further investigation.

• Interventions to improve outcome – a lot of work needed
Thanks to:

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- Dudley R&D
- UK CRN

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- Abbott UK
- Amgen UK
- Elli-Lilly Norway
ATACC-RA consortium

www.atacc-ra.com