Getting To The Heart (And Other Co-Morbidities) Of Psoriasis

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Skin disease as an experimental model

“These [opportunities] are to utilize the skin, its diseases, and its reactions to discover fundamental phenomena and laws that have wide applicability throughout medicine, biology, and science”

Psoriasis and co-morbidities experimental model

Mediating factors

- Pathophysiology
  - Th1/17 inflammation (atherosclerosis, thrombosis, lipid metabolism)
  - Epidermal proliferation (↑uric acid, oxidative stress)
  - Angiogenesis (endothelial dysfunction)

- Treatment
  - Increase CV risk (e.g. cyclosporine, acitretin)?
  - Decrease CV risk (e.g. methotrexate, TNF inhibitors)?

- Psychosocial impact
  - Depression, alcohol and smoking, lower socioeconomic status

Genes and loci associated with psoriasis, diabetes and CV diseases

- PSORS2/3/4
- CDKAL1
- ApoE4
- TNFAIP3

Environmental risk factors
- Smoking
- Obesity

Psoriasis, inflammation, and CV risk

1. Immune abnormalities are profound and psoriasis is frequently not treated or adequately controlled

2. Psoriasis severity is associated with greater levels of systemic inflammation (e.g. CRP, ICAM-1, serum amyloid A, Th-1 and Th-17 cytokines)

3. UNIFYING THEORY: Inflammation may be a common pathway to a variety of diseases including atherosclerosis, obesity, and insulin resistance
Risk of Myocardial Infarction in Patients With Psoriasis

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Psoriasis is a common, chronic, immune-mediated disease that affects about 2% to 3% of the adult population.1,2 Approximately 6% to 11% of patients with psoriasis also have an associated inflammatory arthropathy (psoriatic arthritis).3-4 The extent of body surface area affected by psoriasis is variable, ranging from limited disease (<2% body surface area) in approximately 80% of patients to more extensive skin involvement in approximately 20% of patients.5 Psoriasis has serious impacts on health-related quality of life, even in patients with limited body surface area involvement.6

The pathophysiology of psoriasis is characterized by an increase in antigen presentation, T-cell activation, and T-helper cell type 1 (Th1) cytokines, resulting in thick, scaly red plaques and in some patients, arthritis.7,8 Psoriasis

Context Psoriasis is the most common Th1 helper cell type 1 (Th1) immunological disease. Evidence has linked Th1 diseases to myocardial infarction (MI). Psoriasis has been associated with cardiovascular diseases, but has only been investigated in hospital-based studies that did not control for major cardiovascular risk factors.

Objective To determine if within a population-based cohort psoriasis is an independent risk factor for MI when controlling for major cardiovascular risk factors.

Design, Setting, and Patients A prospective, population-based cohort study in the United Kingdom of patients with psoriasis aged 20 to 90 years, comparing outcomes among patients with and without a diagnosis of psoriasis. Data were collected by general practitioners as part of the patient’s medical record and stored in the General Practice Research Database between 1987 and 2002, with a mean follow-up of 5.4 years. Adjustments were made for hypertension, diabetes, history of myocardial infarction, hyperlipidemia, age, sex, smoking, and body mass index. Patients with psoriasis were classified as severe if they ever received a systemic therapy. Up to 5 controls without psoriasis were randomly selected from the same practices and start dates as the patients with psoriasis. A total of 55,695 control patients and patients with mild (n = 127,139) and severe psoriasis (n = 3,837) were identified.

Main Outcome Measure Incident MI.

Results There were 11,194 MIs (2.0%) within the control population and 2,319 (1.8%) and 112 (2.9%) MIs within the mild and severe psoriasis groups, respectively. The incidence per 1,000 person-years for control patients and patients with mild and severe psoriasis were 3.58 (95% confidence interval [CI], 3.52-3.65), 4.04 (95% CI, 3.88-4.21), and 5.13 (95% CI, 4.22-6.17), respectively. Patients with psoriasis had an increased adjusted relative risk (RR) for MI that varied by age. For example, for a 30-year-old patient with mild or severe psoriasis, the adjusted RR of having an MI is 1.29 (95% CI, 1.14-1.46) and 3.10 (95% CI, 1.98-4.86), respectively. For a 60-year-old patient with mild or severe psoriasis, the adjusted RR of having an MI is 1.08 (95% CI, 1.03-1.13) and 1.36 (95% CI, 1.13-1.64), respectively.

Conclusions Psoriasis may confer an independent risk of MI. The RR was greatest in young patients with severe psoriasis.
Psoriasis – a risk factor for CAD and MI?

Psoriasis → Smoking → Hypertension → Diabetes → Obesity → Lipids → CVD

CVD: Cardiovascular disease.

PET/MRI courtesy of NN Mehta
Medical Informatics: UK Medical Record Databases

- Established in 1987 by UK government
- >12 million patients, 67+ million person years of follow up
- GP’s coordinate all of the patient’s care
- Measures important confounders (BMI, smoking, alcohol use)
- Widely used scientifically (1500 + publications)
- Psoriasis
  - Accurately captured with algorithms that allow confirmation of diagnosis by dermatologist
  - Severity captured indirectly by treatment patterns

https://www.cprd.com/intro.asp
https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database
Clinical Significance:

1. Increased risk of MI, stroke, cardiovascular death, diabetes
2. 5 years of life lost
3. Risk of cardiovascular disease in patients with severe psoriasis similar to risk conferred by diabetes
4. Patients treated for severe psoriasis are 30X more likely to experience MACE (attributable to psoriasis) than to develop a melanoma

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adj. RR Mild</th>
<th>Adj. RR Severe</th>
</tr>
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<tbody>
<tr>
<td>MI(^1)</td>
<td>1.05</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke(^2)</td>
<td>1.06</td>
<td>1.4</td>
</tr>
<tr>
<td>CV Death(^3)</td>
<td>Not done</td>
<td>1.6</td>
</tr>
<tr>
<td>MACE(^4)</td>
<td>Not done</td>
<td>1.5</td>
</tr>
<tr>
<td>Diabetes(^5)</td>
<td>1.11</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Psoriasis and CV risk knowledge is rapidly expanding

- 9 meta-analyses covering 500,000+ psoriasis patients and 29+ million controls
- An estimated 11,500 extra MACE events attributable to psoriasis in the US per year

Comparison of cardiometabolic outcomes: Psoriasis vs. RA


<table>
<thead>
<tr>
<th></th>
<th>Psoriasis</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (all patients)</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>CV Death (DMARD)</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>All cause mortality (DMARD)</td>
<td>1.8</td>
<td>1.6</td>
</tr>
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</table>

Prevalence of CVD increases with increasing body surface area affected by psoriasis (iHOPE N= 9000)

Odds Ratio

<table>
<thead>
<tr>
<th>BSA</th>
<th>Mild (N=4523)</th>
<th>Moderate (N=3122)</th>
<th>Severe (N=1081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-10%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;10%</td>
<td></td>
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</table>

Psoriasis and CVD: Mechanistic insights

Metabolic and CV gene expression > cycle and inflammatory disease categories in lesional vs non lesional psoriasis biopsies

KC-Tie2 psoriasis skin specific inflammation mouse


18-FDG PET/CT – A Novel Imaging Biomarker of Inflammation

- Biomarker for CD68+ macrophages in fatty plaques
- Elevated vascular inflammation is predictive of future cardiovascular events
- Increased vascular inflammation improves with treatments known to lower CV risk (statins) within 4-12 weeks
- Increasingly used as a surrogate for cardiovascular trials

Naik HB et al Arterioscler Thromb Vasc Biol. 2015 Dec;35(12):2667-76
New Findings 2016-2017

1. Psoriasis is associated with increased arterial and subcutaneous fat inflammation based on FDG-PET/CT
2. Adipose under psoriasis plaques express miRNA’s that modulate lipid metabolism
3. IL-6 mediates psoriasiform associated thrombosis
4. HLA-C*06:02 is associated with a higher burden of atherosclerosis
5. Psoriasis is more strongly associated with metabolic syndrome and mortality than atopic dermatitis

Should psoriasis be aggressively treated to lower the risk of CV disease?

1970: Silent Killer
2004: Secret Killer
2017: Visible Killer?
TNF inhibitors and methotrexate are cardioprotective in RA meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TNF (RR)</th>
<th>MTX (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV all</td>
<td>0.70</td>
<td>0.72</td>
</tr>
<tr>
<td>MI</td>
<td>0.59</td>
<td>0.81</td>
</tr>
<tr>
<td>CHF</td>
<td>0.75 (NS)</td>
<td>0.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.52</td>
<td>0.78 (NS)</td>
</tr>
<tr>
<td>MACE</td>
<td>0.30</td>
<td>0.38 (NS)</td>
</tr>
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</table>

Q: Should psoriasis be aggressively treated to lower the risk of CV disease?
A: We don’t know (for certain)

- Observational data suggest methotrexate and TNF inhibitors lower the risk of CV events
- Data do not yet exist to demonstrate a protective effect of phototherapy, apremilast, ustekinumab, secukinumab, and ixekizumab on CV events

RCTs evaluating impact of psoriasis treatment on CV risk

• **Vascular Inflammation in Psoriasis Trials (VIP)**
  – Does treatment with adalimumab or phototherapy lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis? (NCT01553058)
  – Does treatment with ustekinumab lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis (NCT02187172)
  – Does treatment with secukinumab lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis (NCT02690701)

• **Cardiovascular Inflammation Reduction Trial (CIRT)**
  – Does methotrexate lower the risk of major vascular events in patients with a history of MI and diabetes or metabolic syndrome? (NCT01594333)
Clinical Implications: Well established comorbidities of psoriasis

- Heart Attack, Stroke, CV death
- Metabolic syndrome (obesity, insulin resistance, cholesterol abnormalities, hypertension)
- Diabetes
- Psoriatic arthritis
- Mood Disorders (anxiety, depression, suicide)
- Crohn’s Disease
- T cell lymphoma (rare)
Clinical Implications: Emerging co-morbidities

• Sleep apnea
• Nonalcoholic steatohepatitis (NASH)
• Chronic obstructive pulmonary disease (COPD)
• Adverse infectious disease outcomes
• Chronic and end stage renal disease
• Peptic ulcer disease
• Sexual dysfunction
Clinical Implications: Psoriasis Comorbidity

• Screen for PsA and determine impact on physical and emotional health
• Educate about CV risk; screen or refer for known risk factors
• When using immune modulating treatment
  – Refer for age appropriate cancer screening (lung, colon, breast, cervical)
  – Age appropriate vaccination

### Biologic Selection Depends on Many Factors

<table>
<thead>
<tr>
<th>Scenario</th>
<th>TNF</th>
<th>IL12/23</th>
<th>IL-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term data</td>
<td>Emerging</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>FDA approved</td>
<td>FDA approved</td>
<td>FDA approved*</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>FDA approved</td>
<td>FDA approved</td>
<td>Warning!</td>
</tr>
<tr>
<td>Associated with decreased MI and stroke</td>
<td>Yes</td>
<td>TBD</td>
<td>TBD</td>
</tr>
<tr>
<td>CHF</td>
<td>No warning</td>
<td>No warning</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Warning!</td>
<td>No benefit or harm phase II</td>
<td>Promising phase II</td>
</tr>
<tr>
<td>Ease of administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient is obese</td>
<td>Infliximab preferred</td>
<td>Weight-based dosing</td>
<td>Flexible dosing**</td>
</tr>
<tr>
<td>Rapid onset and highest efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term persistence</td>
<td></td>
<td></td>
<td>TBD</td>
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Psoriasis and comorbid diseases

Epidemiology

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Philadelphia, Pennsylvania; London, United Kingdom; Bethesda, Maryland; and Norfolk, Virginia

Psoriasis and comorbid diseases

Implications for management

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Psoriasis: Look beyond the skin

“. . . For the secret of the care of the patient is in caring for the patient.”

– Francis W. Peabody October 21 1925

To refer patients for the VIP trials:

215-662-SKIN or SkinVIP@upenn.edu
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\text{American Skin Association}
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