Psoriasis and the metabolic syndrome

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Inflammation as a foundation of metabolic dysregulation and cardiovascular disease risk

• Diseases of systemic immune activation and inflammation, e.g. systemic lupus, rheumatoid arthritis, psoriasis and atopic dermatitis have excess cardiovascular disease risk.

• Cardiologists have long suspected a critical link between high levels of circulating immune cytokines and CVD risk.

• A critical link in humans was made in the last year through study of canakinumab (an IL-1β antibody) in patients with established cardiovascular disease.

• Biology: TNF → IL-1β → IL-6 → CRP

• Biology: TNF & IL-1β induce immune adhesion molecules (ICAM-1, VCAM-1) on endothelial cells that would promote monocyte/macrophage migration to vascular intima and may also promote platelet activation in thrombus formation.
CANTOS Canakinumab Study

- Patients with prior MI and thus at high risk for another event randomized to canakinumab (anti-IL-1β) vs. placebo.

- Overall study showed significant reduction in MI or other major cardiovascular events with canakinumab.

- A subset analysis was conducted on those patients who achieved a CRP target of 2 or less (PD measure of successful inhibition of IL-6 mediated by blockade of IL-1β). The canakinumab effect was a 25% reduction in MI or major cardiac events.

- This is an impressive reduction considering the complexity of cytokine and inflammatory pathways associated with CVD.
What is relationship of psoriasis with Metabolic Syndrome (MS)?

- Many studies have found MS is increased in psoriasis patients [systematic review and meta-analysis: April Armstrong et al, JAAD 68:654-62 (2013)]. Except for one study, odds ratio (OR) 1.4 to >6. Meta-analysis with co-variate adjustments has OR 1.22 for mild, OR 1.56 for moderate, OR 1.98 for severe psoriasis.

- Gelfand study in UK [Langan et al., JID 132:556-562 (2012)] finds essentially same adjusted odds ratios for mild to severe psoriasis.

- These data lead to the question of how psoriasis contributes to either increased MS components and also downstream cardiovascular disease/diabetes which also have increased OR in psoriasis.
Elements of risk for psoriasis patients

- Obesity is common and is a defining or contributing factor to MS
- Vascular inflammation is a common feature of moderate-to-severe psoriasis
- Psoriasis skin disease likely contributes factors that drive vascular inflammation, hypertension, and glucose-intolerance.
- Inflammatory cytokines and cardiovascular risk proteins are elevated in blood circulation over and above non-psoriatic disease controls
- Obesity/metabolism may be modified by psoriatic disease process and potentially cutaneous psoriasis extends to third layer of skin – subcutaneous adipose tissue
A Proposed Model for the Relationship Between Skin Inflammation and CVD Risk

Skin inflammation

1. Endothelial cell adhesion molecule induction by TNF
2. Chemokines promote inward-trafficking of T-Cells and DCs/macrophages
3. Wide range of inflammatory molecules made by inflammatory cells and some fraction released into systemic circulation

Cardiovascular risk

A. Liver
- IL-4
- C-Reactive Protein
- Serum Amyloid A

B. Vessels
- Endothelial cell effect
- ICAM/adhesion molecules
- Metabolic effects (lipoprotein lipase)
- Structure/stiffness endothelial function

Soluble/circulating cytokines, chemokines, hormones, and mediators

Bad
- TNF
- Leukin IL-4
- etc.

Good
- adiponectin
- IL-10

Do not know interdependence of inflammation in different organs and tissues.
Serum Proteomics

- Increased expression of inflammatory and cardiovascular risk proteins is common in moderate-to-severe psoriasis patients
- Increased expression of a few proteins is likely due only to high BMI and no disease contribution
- Increased expression many proteins is not due to high BMI, but is due to presence of psoriasis as a disease and some of these are clearly correlated with the extent of skin involvement as measured by the PASI.
- To extent these findings reflect features of MS, psoriasis as a disease adds to conventional risk factor of obesity.
Conclusions – Metabolic Syndrome or Not, Psoriasis is Bad for Cardiovascular Health

• Psoriasis is more than skin deep. It extends into the third skin layer (adipose tissue) and it is a driver of systemic inflammation and cardiovascular risk

• The metabolic syndrome (MS) is more common in psoriasis patients and, when present, likely influences cardiovascular risk

• Psoriasis, independent of the MS, further increases cardiovascular risk through cytokines, hormones (renin), CVD "risk proteins", circulating leukocyte activation, and overt vascular inflammation.