Biomarkers of inflammation

Maureen L. McGary, DNP, NP-C
Assistant Professor
Georgetown University
I will not discuss off label use or investigational use in my presentation.

I don’t have financial relationships to disclose related to the topic I will present.
Rheumatologic inflammatory and disease-specific biomarkers: An update for primary care.

Learning Goals:

Upon completion of this presentation the participant will be able to:

✧ Discuss the appropriate biomarker testing for specified major rheumatologic disorders.
✧ Describe role of presented cytokines in inflammation for specified major rheumatologic disorders.
✧ Apply the results of biomarker testing to improve the referral process for patients to rheumatology specialists.
✧ Apply the results of biomarker testing to improve the initial treatment for patients while awaiting evaluation by a rheumatology specialist.
Epidemiology of Rheumatic Disorders in the United States

- For the period 2010-2012, an estimated 52.5 million (22.7%) adults reported doctor diagnosed arthritis or other form of RA, gout, lupus, or fibromyalgia (CDC, 2013a).

- Total direct costs attributable to arthritis and other rheumatologic causes were $80.8 billion ($115 billion in 2013 dollars; CDC, 2007).

- The most common cause of disability in the US is rheumatologic conditions, including arthritis (CDC, 2014a).
Epidemiology of Rheumatic Disorders in the United States

• Approximately 294,000 American children under the age of 18 have arthritis or other rheumatologic disorders. (Sacks, Helmick, Luo, Ilowite, & Bowyer, 2006).

• Arthritis and rheumatologic disorders affect women more often than men, those of African decent and whites more than those of Hispanic or Asian decent (CDC, 2013a).

• 67 million adults in the U.S. will have arthritis per CDC estimates by 2030 (CDC, 2014a).
Autoimmune diseases occur when something triggers the immune system to fail to recognize self. The regulatory T cells no longer function to maintain the immune system’s recognition of self, an attack on self begins, and this begins the hallmark inflammatory process.

There are a number of causes of this error. These include stress, viral and bacterial infections, sunlight, solvents, among others. Research on exactly which trigger is the culprit for certain diseases continues.
Review of the autoimmune process as applicable to inflammatory diseases

(Nature Reviews, 2015)
Inflammation

(University of Utah, 2015)
Review of the autoimmune process as applicable to inflammatory diseases

(VASODILATION)

(ALBUMIN)

(ENDOTHELIAL CONTRACTION)

(VM)
Review of the autoimmune process as applicable to inflammatory diseases

(University of Utah, 2015)
Review of the autoimmune process as applicable to inflammatory diseases
THE ROLE OF COMPLEMENTS
Biomarkers of Inflammation

Types and roles

...measurable substances, processes, or structures that are found in the body or in body products used to predict or influence the occurrence of a disease process or the outcomes of the disease.
Acute Phase Reactants

- C-Reactive Proteins (CRP)
- Erythrocyte Sedimentation Rate (ESR)
- Serum Complement Proteins
- Platelets
C-Reactive Protein

Information from the American Association for Clinical Chemistry (AACC) on hs-CRP used for cardiac risk screening

http://labtestsonline.org/understanding/analytes/hscrp/tab/test/

and CRP used for generalized inflammation such as infection or autoimmune diseases

http://labtestsonline.org/understanding/analytes/crp/tab/test/

Be sure to order the appropriate test based on which diagnosis you are exploring.
Pentraxins

Acute phase proteins (APP)

Two of significance in humans:

**C Reactive Protein** is expressed during acute phase response to tissue injury or inflammation

**Serum amyloid P component** may have a role in atherosclerosis and amyloidosis
Erythrocyte Sedimentation Rate

The distance that erythrocytes fall (in mm) during one hour in a venous sample.

Normal values: 0-15 mm/hr
Newer test allow for 30 minute turnaround
Platelets

✧ Process of increased platelet count
✧ Significance of Increased platelet count
✧ Low to low normal platelet count
Serum Complement Proteins

✧ C3
✧ C4
✧ CH50
Antinuclear Antibodies (ANA)

✧ Anti-double stranded DNA (anti-ds-DNA)

✧ Anti-Smith (anti-Sm) and anti-RNP

✧ Anti-SSA (Ro) and Anti-SSB (La)

✧ Many other disease specific antibodies
Anti - Carbamylated Protein (Anti - CarP) Antibodies

✧ Recently identified antibodies that may be present years before RA onset

✧ Associated with erosive RA

✧ Test done by Rheumatology
Rheumatoid Arthritis: anti-CCP (ACPA)

✧ As sensitive as, and more specific than, IgM rheumatoid factors (RF) in early and fully established disease
✧ May predict the eventual development into RA when found in undifferentiated arthritis
✧ A marker of erosive disease in RA
✧ May be detected in healthy individuals years before onset of clinical RA
✧ Normal range: 0-5 U/mL
IgM Rheumatoid Factor (RF)

✧ Is found in 60-80% of persons with established RA but only 50-60% of persons with early RA

✧ Is present in many other disorders

✧ While it does not correlate with disease activity, higher levels do suggest the likelihood of more severe disease and extra-articular manifestations of RA.

✧ Test is for IgM class but around 15% have IgG RF

✧ Normal range < 20, but check normals for your lab.

✧ High lipid levels may affect this test, elderly may have higher results
The Identification of and Role of Biomarkers in Specific Disease States

- Inflammatory Arthropathies
  - Rheumatoid Arthritis
  - Juvenile Idiopathic Arthritis
  - Psoriatic Arthritis
  - Ankylosing Spondylitis
Rheumatoid Arthritis: Physical Assessment

(ACR, 2015)
Looking for RA: Lab assessment

- Complete blood count (CBC)
- Comprehensive metabolic panel (CMP)
- Rheumatoid Factor (RF)
- Antibodies to citrullinated peptides including anti-CCP (also called ACPA)
- Erythrocyte Sedimentation Rate (ESR)
- C-reactive protein (CRP)

(ACR, 2015)
# 2010 ACR/EULAR Classification Criteria for RA

## Joint Distribution (0-5)

<table>
<thead>
<tr>
<th>Joint Distribution</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

≥6 = definite RA

## Serology (0-3)

- Negative RF AND negative ACPA: 0
- Low positive RF OR low positive ACPA: 2
- High positive RF OR high positive ACPA: 3

## Symptom Duration (0-1)

- <6 weeks: 0
- ≥6 weeks: 1

## Acute Phase Reactants (0-1)

- Normal CRP AND normal ESR: 0
- Abnormal CRP OR abnormal ESR: 1

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What if the score is <6?

- Patient might fulfill the criteria...
  - **Prospectively** over time (cumulatively)
  - **Retrospectively** if data on all four domains have been adequately recorded in the past

[http://www.rheumatology.org/Portals/0/Files/ra_class_slides.pdf](http://www.rheumatology.org/Portals/0/Files/ra_class_slides.pdf)
Algorithm to Classification of RA Including Radiographs

1. ≥1 swollen joint, which is not best explained by another disease?
   - Yes
     - ≥6/10 on the scoring system?
       - Yes
         - RA
       - No
         - Document result of the scoring system
   - No
     - Longstanding inactive disease suspected?
       - Yes
         - Perform radiographic assessment
       - No
         - Radiographs already available
           - Yes
             - Erosions typical for RA present?
               - Yes
               - RA
               - No
               - Not RA
           - No
             - Not RA
Juvenile Idiopathic Arthritis

(http://adolescenthippain.weebly.com/juvenile-idiopathic-arthritis.html)
Juvenile Idiopathic Arthritis

✧ Primarily diagnosed based on clinical presentation

✧ Markers of inflammation
  ✧ ESR
  ✧ CRP

✧ CBC: anemia of chronic disease

✧ RF & anti-CCP are not diagnostic but high titers of anti-CCP *may indicate* more erosive disease

(Kim & Dong, 2010)
Juvenile Idiopathic Arthritis
Psoriatic Arthritis

Table. The CASPAR classification criteria for PsA

To be classified as having PsA, a patient must have inflammatory articular disease (joint, spine, enthesal) with ≥ 3 of the following 5 points:

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of psoriasis (one of a, b, c):</td>
<td></td>
</tr>
<tr>
<td>(a) Current psoriasis*</td>
<td>Psoriatic skin or scalp disease currently present, as judged by a rheumatologist or a dermatologist</td>
</tr>
<tr>
<td>(b) Personal history of psoriasis</td>
<td>A history of psoriasis obtained from patient or family physician, dermatologist, rheumatologist, or other qualified health care professional</td>
</tr>
<tr>
<td>(c) Family history of psoriasis</td>
<td>A history of psoriasis in a first- or second-degree relative by patient report</td>
</tr>
<tr>
<td>2. Psoriatic nail dystrophy</td>
<td>Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis observed on current physical examination</td>
</tr>
<tr>
<td>3. Negative test result for RF</td>
<td>By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range</td>
</tr>
<tr>
<td>4. Dactylitis (one of a, b):</td>
<td></td>
</tr>
<tr>
<td>(a) Current</td>
<td>Swelling of an entire digit</td>
</tr>
<tr>
<td>(b) History</td>
<td>A history of dactylitis recorded by a rheumatologist</td>
</tr>
<tr>
<td>5. Radiological evidence of juxta-articular new bone formation</td>
<td>Ill-defined ossification near joint margins (excluding osteophyte formation) on plain x-ray films of hand or foot</td>
</tr>
</tbody>
</table>

CASPAR, CIAssification criteria for Psoriatic ARthritis; PsA, psoriatic arthritis; RF, rheumatoid factor; ELISA, enzyme-linked immunosorbent assay.

* Current psoriasis scores 2; all other items score 1.
SPONDYLOARTHRITIS

Ankylosing Spondylitis
SPONDYLOARTHRITIS

Ankylosing Spondylitis

✧ Teens to 40’s
✧ Men 3 times more than women
✧ Presence of Human leukocyte antigen B27 (HLA-B27) increases chances of SA and is more likely to have bowel involvement. Positive HLA-B27 is not definitive for dx of AS
Vasculitides

- Polymyalgia Rheumatica
- Giant Cell Arteritis
- Behçet's Disease
Polymyalgia Rheumatica
Polymyalgia Rheumatica

ESR: elevated > 30 but may be over 100 (90-94% have elevated ESR)

✧ Negative RF and ANA the prevalence of positive assays for antinuclear antibody and rheumatoid factor rise with age.

✧ Normocytic anemia may be present

✧ Many will have CRP > 5 (99%)
## Polymyalgia Rheumatica

<table>
<thead>
<tr>
<th>Symptom/finding</th>
<th>Points without ultrasound (0-6)</th>
<th>Points with ultrasound (0-8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness &gt;45 minutes</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hip pain/limited range of motion</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Negative rheumatoid factor or anticyclic citrullinated peptide antibody</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No other joint involvement</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ultrasound 1: at least one shoulder with subdeltoid bursitis, biceps tenosynovitis, and/or glenohumeral synovitis, and at least one hip with synovitis or trochanteric bursitis</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Ultrasound 2: bilateral subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis</td>
<td>NA</td>
<td>1</td>
</tr>
</tbody>
</table>

A score of ≥4 without ultrasound or a score of ≥5 with ultrasound is classified as PMR.

Polymyalgia Rheumatica

Patient fulfilling PMR case definition (primary or secondary care)
1. Assess comorbidities¹, other relevant medications and other risk factors for steroid related side effects²
2. Assess possible risk factors for relapse/prolonged therapy³
3. Consider specialist referral (experience or risk of side-effects, relapse/prolonged therapy and/or atypical presentation)
4. Document minimal clinical and laboratory dataset

Start oral prednisone equivalent 12.5–25mg/day⁴:

- Consider MTX if at high risk for side effects/relapse and/or prolonged therapy⁴

Clinical improvement at 2–4 wk?⁷
- yes
  - Gradual tapering of glucocorticoids⁶
  - Remission³
  - yes → Taper prednisone until discontinuation¹⁰,¹¹,¹²

- no → Confirmation of PMR
  - yes → Diagnosis in question
  - no → Increase steroid dose¹³

- Re-assess

Remission³

Relapse⁹

yes → Taper prednisone until discontinuation¹⁰,¹¹,¹²

no → Taper prednisone until discontinuation¹⁰,¹¹,¹²

¹Consider i.m. methylprednisolone as an alternative to oral prednisone⁵
Giant Cell Arteritis (Temporal Arteritis)
Giant Cell Arteritis (Temporal Arteritis)

♟ Occurs in about 10% of patients with PMR
♟ Is associated with PMR
♟ Elevated CRP & ESR
♟ Normocytic anemia
♟ Thrombocytosis
Patient with clinical features of GCA (age >50 years)

Assess GCA probability
1. Evidence of anterior extracranial circulation ischemia (AION, PION, ophthalmic artery occlusion, CRAO, cilioretinal artery occlusion, amaurosis fugax)
2. New onset headache or neck pain
3. Abnormal laboratory results (ESR, platelets or CRP)
4. Jaw claudication
5. Abnormal superficial temporal artery (beading, nodularity, absence of pulse, local tenderness)
6. Constitutional symptoms (fatigue, malaise, fever, weight loss)
7. Polymyalgia rheumatica

Take out one point for each of above findings if it can be explained by a chronic preexisting condition

Very low clinical suspicion: (No more than 1 positive finding)
- Evaluate for alternative diagnosis

Moderate clinical suspicion: (2 positive findings)
- Oral prednisone (1 mg/kg/day)
- Continue steroids
- TAB

High clinical suspicion: (More than 2 positive findings)
- Intravenous solumedrol (1 gm/day)
- Oral prednisone (1 mg/kg/day)
- TAB

Consider contralateral biopsy if clinical suspicion remains high for GCA ± continue steroids
Behçet's Disease/Syndrome
Behçet's Disease/Syndrome

✧ No specific tests

✧ Vessel biopsy showing vasculitis

✧ Pathergy Test: however only small percent will be positive but a positive test is informative
Behçet's Disease/Syndrome

For diagnosis: must have one required criteria and 2 minor criteria

Required Criteria
Recurrent oral ulcerations: minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period

Minor Criteria
• Recurrent genital ulceration: aphthous ulceration or scarring observed by physician or patient
• Eye lesion: anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination or retinal vasculitis observed by ophthalmologist
• Skin lesions: erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions, or acneform nodules observed by physician in post-adolescent patients not on corticosteroid treatment
• Positive pathergy test (Behcetine test) read by physician 24-48 hours.
Systemic Lupus Erythematosus

For primary care screening in the presence of symptoms:

✧ Positive ANA
✧ Positive Anti dsDNA
✧ Positive Anti-phospholipid antibody
✧ Low Complements C3, C4, CH50
✧ U/A: check for proteinuria
<table>
<thead>
<tr>
<th>System</th>
<th>ACR criteria*</th>
<th>SLICC criteria†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac/ pulmonary</td>
<td>Pleuritis (pleuritic pain or rub, or pleural effusion), or pericarditis (documented by electrocardiography, rub, or pericardial effusion)</td>
<td>Serositis (pleurisy for more than one day, pleural effusion, or pleural rub; pericardial pain more than one day, pericardial effusion, pericardial rub, or pericarditis)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hemolytic anemia, or leukopenia (&lt; 4,000 cells per mm³), or lymphopenia (&lt; 1,500 cells per mm³), or thrombocytopenia (&lt; 100,000 cells per mm³)</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Positive ANA result, Elevated anti-dsDNA, anti-Sm, or antiphospholipid antibodies, Discoid rash, Photosensitivity, Oral ulcers or nasal ulcers</td>
<td>Positive ANA result, Elevated anti-dsDNA, anti-Sm, or antiphospholipid antibodies, low complement (C3, C4, CH 50), or direct Coombs test (in the absence of hemolytic anemia), Chronic cutaneous lupus, Nonscarring alopecia, Oral ulcers or nasal ulcers</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Nonerosive arthritis involving two or more joints</td>
<td>Synovitis involving two or more joints and at least 30 minutes of stiffness in the morning</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Seizure or psychosis</td>
<td>Seizures, psychosis, mononeuritis complex, myelitis, or peripheral or cranial neuropathy</td>
</tr>
<tr>
<td>Renal</td>
<td>Persistent proteinuria &gt; 0.5 g per day or &gt; 3+ on urine dipstick testing, or cellular casts</td>
<td>Urinary creatinine (or 24-hour urinary protein) &gt; 500 mg, or red blood cell casts</td>
</tr>
<tr>
<td>Skin/mucosal</td>
<td>Malar rash</td>
<td>Acute cutaneous lupus or subacute cutaneous lupus</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; ANA = antinuclear antibodies; anti-dsDNA = anti–double-stranded DNA antibodies; anti-Sm = anti-Smith antibodies; SLICC = Systemic Lupus International Collaborating Clinics.

*—At least four of 11 ACR criteria required for diagnosis.
†—At least four of 13 SLICC criteria, including at least one clinical criterion and one immunologic criterion, required for diagnosis, or patient must have had biopsy-confirmed lupus nephritis in the presence of a positive ANA or anti-dsDNA result.

Information from references 8 and 13.

(Lam, Ghetu, & Bieniek, 2016)
Sjögren's Syndrome

drnadiakidermandentist.wordpress.com

Patients with Sjögren’s syndrome often exhibit inflammatory dry eye, as seen here.

www.reviewofoptometry.com
Sjögren's Syndrome

American-European Consensus Criteria for Sjögren’s Syndrome

In order to make a diagnosis of Sjögren’s syndrome, the following criteria must be met:

I. Ocular Symptoms (at least one)
Symptoms of dry eyes for at least 3 months
A foreign body sensation in the eyes
Use of artificial tears 3 or more times per day

II. Oral Symptoms (at least one)
Symptoms of dry mouth for at least 3 months
Recurrent or persistently swollen salivary glands
Need for liquids to swallow dry foods
Sjögren's Syndrome

III. Ocular Signs (at least one)
Abnormal Schirmer’s test, (without anesthesia; ≤5 mm/5 minutes)
Positive vital dye staining of the eye surface

IV. Histopathology
Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥1 per 4 mm²)

V. Oral Signs (at least one)
Unstimulated whole salivary flow (≤1.5 mL in 15 minutes)
Abnormal parotid sialography
Abnormal salivary scintigraphy

VI. For a primary Sjögren’s syndrome diagnosis:
Any 4 of the 6 criteria, must include either item IV (Histopathology) or VI (Autoantibodies)
Any 3 of the 4 objective criteria (III, IV, V, VI)
Sjögren's Syndrome

VI. Autoantibodies (at least one)

✧ Anti-SSA (Ro) or

✧ Anti-SSB (La)

✧ or both
Sjögren's Syndrome

Anti-SSA (Ro)
- Primarily associated with Sjögren’s
- Detected in 76% of patients with primary Sjögren’s
- Detected in only 10-15% of patients with secondary Sjögren’s
- Detected in 50% of patients with subacute cutaneous lupus
- Associated with other conditions, for example: neonatal lupus syndrome and congenital heart block

Anti-SSB (La)
- Detected in 40-60% of patients with Sjögren’s
- Rarely detected without SSA
- Associated with ANA-negative SLE and Scleroderma

Tran.V.K. (n.d.).
Utilization of laboratory values in improving the referral process
Research into triggers of RA such as the possible role of oral bacteria, most likely *Porphyromonas gingivalis*. (Bingham, 2015)

Elevated plasma levels of Citrullinated Proteins and hydroxyproline may be a useful biomarkers for early osteoarthritis. When used in an algorithm that includes anti-CCP, early OA can be distinguished. (Ahmend et al. 2015).

Osteoarthritis was thought to be related to increase weight bearing load in obese patients. Newer research indicates that there is a connection between negative effects on joint tissues from Ø

http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-pathophysiology-2/


References


References


