Rheumatologic Diseases in Women

Rosalind Ramsey-Goldman, MD, DrPH
Solovy Arthritis Research Society
Professor of Medicine
February 18, 2014
Objectives

• Describe the spectrum and burden of rheumatologic diseases in women
• Identify features of the most common rheumatic disease, osteoarthritis (OA)
• Distinguish features of the most challenging rheumatic disease, lupus (SLE)
• Characterize features of the most misunderstood “rheumatic disease”, fibromyalgia (FM)
• Recognize the most progress in treating rheumatic disease, rheumatoid arthritis (RA)
Rheumatic Diseases, Arthritis, and other Diseases of the Muscles, Joints, and Bone

• Over 100 different forms of rheumatic diseases, arthritis and other diseases of muscles, joints and bones impacting health and well-being of 50 million Americans.

• Rheumatic diseases can cause joint and organ destruction, severe pain, disability and even death.

• Latest figures regarding arthritis and other rheumatic diseases show that they led to $127.8 billion in medical costs in U.S., more than $124 billion in costs for cancer care.
Burden of Rheumatic Diseases in Women

- One in 12 women will develop a rheumatic disease in her lifetime.
- One in 20 men will develop a rheumatic disease in his lifetime.
- 75% of 1.3 million American adults who develop rheumatoid arthritis are female.
- Women are two to three times more likely to develop rheumatoid arthritis and 10 times more likely to develop lupus than men.
- Rheumatoid arthritis often strikes between the ages of 35-50, while lupus often develops between the ages of 15-44.
- Minority populations are also preferentially affected.
TABLE. Unadjusted and age-adjusted* annualized prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation (AAAL)† among adults aged ≥18 years, and prevalence of AAAL among those with doctor-diagnosed arthritis, by selected characteristics — National Health Interview Survey, United States, 2010–2012

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prevalence in the adult population</th>
<th>Prevalence of AAAL among adults with doctor-diagnosed arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doctor-diagnosed arthritis</td>
<td>AAAL</td>
</tr>
<tr>
<td></td>
<td>Unadjusted % (95% CI)</td>
<td>Adjusted % (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unadjusted % (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted % (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.7 (22.3–23.0)</td>
<td>21.4 (21.1–21.7)</td>
</tr>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–44</td>
<td>47.8</td>
<td>7.3 (7.0–7.6)</td>
</tr>
<tr>
<td></td>
<td>2.7 (2.6–2.9)</td>
<td>9.8 (9.5–10.1)</td>
</tr>
<tr>
<td></td>
<td>37.5 (35.4–39.7)</td>
<td>43.2 (42.4–44.1)</td>
</tr>
<tr>
<td>45–64</td>
<td>34.9</td>
<td>30.3 (29.8–30.9)</td>
</tr>
<tr>
<td></td>
<td>13.4 (12.9–13.9)</td>
<td>18.6 (18.2–19.0)</td>
</tr>
<tr>
<td></td>
<td>4.4 (43.2–45.6)</td>
<td>34.2 (43.2–45.2)</td>
</tr>
<tr>
<td>≥65</td>
<td>17.3</td>
<td>49.7 (48.7–50.6)</td>
</tr>
<tr>
<td></td>
<td>22.0 (21.3–22.8)</td>
<td>24.9 (23.5–24.3)</td>
</tr>
<tr>
<td></td>
<td>44.4 (43.2–45.6)</td>
<td>44.2 (43.2–45.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>48.3</td>
<td>19.1 (18.6–19.7)</td>
</tr>
<tr>
<td></td>
<td>18.6 (18.2–19.0)</td>
<td>8.0 (7.7–8.4)</td>
</tr>
<tr>
<td></td>
<td>41.9 (40.5–43.3)</td>
<td>44.2 (43.2–45.2)</td>
</tr>
<tr>
<td>Women</td>
<td>51.7</td>
<td>26.0 (25.5–26.5)</td>
</tr>
<tr>
<td></td>
<td>23.9 (23.5–24.3)</td>
<td>11.5 (11.1–11.8)</td>
</tr>
<tr>
<td></td>
<td>44.2 (43.2–45.2)</td>
<td>41.7 (40.2–43.2)</td>
</tr>
</tbody>
</table>
Overview: Osteoarthritis

– OA is the **most common** form of arthritis
  • Nearly 27 million Americans have OA (2008 estimate)
– More than just “wear and tear”
  • Articular cartilage, subchondral bone, synovial membrane, genetic factors all implicated
– Disease-modifying drugs do not exist
  • Treatment is based on symptom control
Worldwide Prevalence of Osteoarthritis in Men and Women

Fig. 1. Prevalence of osteoarthritis of the knee, by age group, sex, and region, 2000 (16). A regions = developed countries in North America, Western Europe, Japan, Australia, and New Zealand. AF = countries in sub-Saharan Africa. AM BD = developing countries in the Americas. EM = countries in the Eastern Mediterranean and North African regions. EU BC = developing countries in Europe. SEA = countries in South-east Asia. WP B = countries in the Western Pacific region.
### Risk Factors for Osteoarthritis

**Table 1. Risk factors for incidence and progression of osteoarthritis of the knees, hips, and hands**

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th></th>
<th>Hand</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>Vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td>Smoking (protective)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td>Alignment</td>
<td></td>
<td>Intensive sport activities</td>
</tr>
<tr>
<td>High bone mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone density</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy (protective)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hip</strong></td>
<td></td>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>High bone mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hand</strong></td>
<td></td>
<td>Grip strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>High bone mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td></td>
<td></td>
<td></td>
<td>Intensive sport activities</td>
</tr>
<tr>
<td>Knee</td>
<td>Age</td>
<td>Vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hormone replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alignment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>Age</td>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High bone mass index</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Degree of evidence for association is categorized as strong, intermediate, or suggested.*

*Bull World Health Organ. 2003;81(9):648.*
OA: Non-Pharmacologic Treatment

- Mild or intermittent symptoms: may need only reassurance or non-pharm treatment
- Patient education
  - self-management programs (education, self-efficacy enhancement, coping strategies)
  - social support
- Physical and occupational therapy
  - exercise to preserve range of motion, strength, aerobic capacity
  - assistive devices
  - improve ambulation and ADLs
- Weight loss (if overweight)
OA Pharmacologic Treatment

• Systemic
  o non-narcotic analgesic (e.g., acetaminophen)
  o anti-inflammatory (NSAIDS, selective cyclooxygenase-2 inhibitors)
  o narcotic analgesics (for advanced OA)

• Local
  o intra-articular
    • corticosteroid
    • *hyaluronic acid* – no evidence to support its use
Overview of Lupus

• Chronic autoimmune inflammatory disease
• Multisystem disease
• Exacerbations and remissions
• Immune dysregulation
  – Loss of tolerance to self antigens
  – Production of autoantibodies
  – Impaired clearance of apoptotic bodies
  – Immune complex mediated tissue damage
LUPUS

......a disease of self sabotage
US Epidemiologic Studies in SLE


Misdiagnosis of SLE

263 referred for SLE

- 134 (51%) SLE
- 4 (1.5%) Scleroderma
- 7 (2.6%) Sjogrens
- 1 (<1%) Poly/Dermatomyositis
- 14 (5%) Fibromyalgia
- 76 (29%) Antinuclear Antibody (ANA) (+)
- 27 (10%) Non-rheumatic disease
Prevalence and Sociodemographic Correlates of Antinuclear Antibodies in the United States

Minoru Satoh,1 Edward K. L. Chan,2 Lindsey A. Ho,3 Kathryn M. Rose,3 Christine G. Parks,4 Richard D. Cohn,3 Todd A. Jusko,4 Nigel J. Walker,4 Dori R. Germoire,4 Irene Z. Whitt,5 Patrick W. Crockett,6 Brad A. Pauley,2 Jason Y. F. Chan,1 Steven J. Ross,2 Linda S. Birnbaum,6 Darryl C. Zeldin,4 and Frederick W. Miller5

Objective. To estimate the prevalence, types, and sociodemographic and biobehavioral correlates of antinuclear antibodies (ANAs) in the US.

Methods. We conducted a cross-sectional analysis of 4,754 individuals from the National Health and Nutrition Examination Survey 1999-2004. ANAs were assessed by indirect immunofluorescence. In ANA-positive individuals, cellular staining patterns were determined, and specific autoantibody reactivities were assessed by immunoprecipitation.

Results. The ANA prevalence in the US population of individuals ages 12 years and older was 13.8% (95% confidence interval [95% CI] 12.2–15.5%). ANA prevalence increased with age (P = 0.01), and ANAs were more prevalent among females than males (17.8% versus 9.6%; P < 0.001), with the female-to-male ratio peaking at 40–49 years of age. ANA prevalence was modestly higher in African Americans compared with whites (age-adjusted prevalence odds ratio [POR] 1.30, 95% CI 1.00–1.70). Remarkably, ANAs were less common in overweight and obese individuals (age-adjusted POR 0.74) than in persons of normal weight. No significant associations of ANA with education, family income, alcohol use, smoking history, serum levels of cotinine, or C-reactive protein were observed. In ANA-positive individuals, nuclear patterns were seen in 84.6%, cytoplasmic patterns were seen in 21.8%, and nucleolar patterns were seen in 6.1%; the most common specific autoantibodies were anti-Ro (3.9%) and anti-Su (2.4%).

Conclusion. These findings suggest that more than 32 million persons in the US have ANAs, and that the prevalence is higher among females, older individuals, African Americans, and those with a normal body weight. These data will serve as a useful baseline for future investigations of predictors and changes in ANA prevalence over time.
Estimated Prevalence of Autoantibodies in Healthy People or Patients with ILE/SLE

<table>
<thead>
<tr>
<th>Population</th>
<th>ANA positivity by IFA at titre of 1:160 (%)</th>
<th>Predominant ANA staining patterns (% of samples demonstrating pattern)</th>
<th>Anti-SSA/Ro antibody positivity (%)</th>
<th>Anti-dsDNA or anti-Sm antibody positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy individuals</td>
<td>5(^{15})</td>
<td>Speckled (50%)(^{17})</td>
<td>3.9(^{20})</td>
<td>&lt;1(^{+})(^{50})</td>
</tr>
<tr>
<td>ILE</td>
<td>83(^{16})</td>
<td>Speckled (76%)(^{16}) or homogeneous (53%)(^{29})</td>
<td>7.5–9(^{29,31})</td>
<td>4–13.6(^{29,31})</td>
</tr>
<tr>
<td>SLE</td>
<td>95(^{16})</td>
<td>Homogeneous (40%)(^{16}) or speckled (46%)(^{29})</td>
<td>24–60(^{51})</td>
<td>Up to 70(^{51})</td>
</tr>
</tbody>
</table>

*Data are from representative studies only, and are not exhaustive. \(^{+}\)No healthy controls in this study were anti-dsDNA antibody positive and anti-Sm antibodies were present in only one of 93 individuals. Abbreviations: ANA, antinuclear antibody; dsDNA, double-stranded DNA; IFA, immunofluorescence assay; ILE, incomplete lupus erythematosus; SLE, systemic lupus erythematosus; Sm, Smith antigen.

What is not Lupus?

ANA+  \(\pm\)  SLE
Organ Damage Increases Over Time Even in the Setting of Decreasing Disease Activity

Disease Activity Over 5 Years

Organ Damage Over 5 Years

Time to Renal Involvement in Multi-Center SLE Cohort

SLE Patients Have Impaired Function in Multiple Activities of Daily Life

Impact of Increased Disease Activity on Work Loss in SLE

Unadjusted Standardized Mortality Ratio (SMR) Estimates (by Calendar-Year Period) in a Large International Multi-Site SLE Cohort

Improved Outcomes in Lupus

1940-1950s
antimalarials (cutaneous)

1950-1954
corticosteroids, nitrogen mustard
5-year survival, 50%

1960-1970s
cyclophosphamide, azathioprine, chlorambucil, "dialysis"
10-year survival, 65%

1970-1990s
NSAIDs, methotrexate, organ transplantation, plasmapheresis, cyclosporine
10-year survival, 80%

2000s
mycophenylate mofetil biologics

2011
belimumab

Improvement in antibiotic and antihypertensive therapies
Summary

• Diagnostic challenges lead to misdiagnosis
• SLE outcomes have improved over the last 30 yrs
  – Improved mortality, increased morbidity, significant impact on QoL and work loss
• Driven by better control of disease activity and supportive care
• Targeted therapies on the horizon to address unmet need to prevent damage from disease and/or treatment
• Health disparities need to be addressed
Overview of Fibromyalgia

• Prevalence (London, Ontario, Canada):
  – About 5% of females, 1.5% of males
  – Mostly women age 55-64
  – Figures quoted in the USA run closer to 2%
• Sufferers frequently seek medical care
  – 10 office visits, 1 x-ray, 2.5 lab tests yearly
  – One hospitalization Q 3 yrs
  – Average annual cost (1996): $2,274 per pt
• Fibromyalgia is comparable to OA in terms of total cost of claims submitted to private insurers
Diagnosis

• STRICTLY CLINICAL
  – No conventional anatomic findings
• No routine test for diagnosis
• Tests (serologies, imaging, biopsy, EMG/NCV) rule out other causes
• Differential diagnosis is wide, but especially
  – Hypothyroidism (check TSH)
  – Polymyalgia rheumatica (check ESR)
  – Hypercalcemia (check serum Ca)
  – Malignancy - multiple myeloma
New Fibromyalgia Diagnostic Criteria

• 2010 PRELIMINARY DIAGNOSTIC CRITERIA

• A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

• 1. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5.

• 2. Symptoms have been present at a similar level for at least 3 months.

• 3. The patient does not have a disorder that would otherwise explain the pain.
Diagnosis (Other Helpful Clues)

• Key Features (seen 75% of the time):
  – Systemic fatigue
  – Unrefreshing sleep
  – Morning stiffness

• Additional Common Symptoms:
  – Diffuse *joint* pain and pain at other sites
  – Headaches
  – Cognitive / memory complaints ("fibro fog")
  – Many other possibilities ("pan-positive ROS")
Pathophysiology

- “Enhanced pain responses”
- “Central sensitization to pain”
- Physical, emotional, and environmental stressors
- Background of genetic susceptibility?
- Substance P?
  - An 11-amino-acid peptide with multiple roles in nociception
  - Levels of substance P are elevated 3-fold in the CSF of FM pts
  - Amplitude of substance P elevation does not correlate well with level of tenderness
Fibromyalgia Cerebrospinal Fluid Substance P

Substance P (ng/ml)

- Vaeroy
- Russell
- Welin
- Bradley

- Normals
- Fibromyalgia Syndrome

Treatment: what hasn’t worked

- Opioids
  - No well-controlled trials
  - May relieve pain, but are subject to tolerance, side effects, addiction
- Benzodiazepines (may be used for Restless Legs Syndrome or sleep)
- Non-steroidal anti-inflammatory drugs (NSAIDs)
Treatment: what *has* worked

- **Non-Pharmacologic Therapy**
  - Patient education
  - Improved sleep hygiene
  - Gentle aerobic and strengthening exercise
  - Cognitive behavioral therapy
  - Massage therapy?

- **Pharmacologic Therapy**-3 FDA approved drugs
  - Pregabalin
  - Duloxetine
  - Milnacipran
Summary

• Fibromyalgia is a real disease
• Fibromyalgia is NOT a “trash can diagnosis”
• Fibromyalgia can be accompanied by comorbid psychological conditions, but it is NOT in itself a psychological diagnosis
• Fibromyalgia is often treatable
• Successful treatment requires BOTH pharmacologic and non-pharmacologic approaches
• Improved sleep quality and gentle aerobic exercise are key, then try one of the FDA-approved agents
• NO STRONG NARCOTICS
Overview of RA

- Female predominance (F:M=2.5:1)
- RA has a worldwide distribution
  - 0.5-1% disease prevalence in European and North American populations
- Peak incidence 40-60 years of age
- Prevalence of RA increases with age
  - 55-75 years: 4.5%
  - >75 years: 7%
- Increased risk of disability and premature mortality

The Clinical Spectrum of RA (I)

Early PIP swelling

Active with some deformity

Late-stage deformities

The Clinical Spectrum of RA (II)
Risk of RA

- Familial clustering (First degree relative risk=16x)
- Shared Epitope (SE) Hypothesis
  - genetic system conferring risk is through major histocompatibility complex alleles (MHC, or HLA for human leukocyte antigen)
- Presence of SE is associated with increased susceptibility and severity of RA
- Cigarette smoking is best characterized trigger
  - Smoking increases the risk of anti-CCP autoantibody positive RA in patients with the shared epitope

OR for Smoking (pack years (p.y.)) in Combination with Shared Epitope (SE)

Survival of Patients with RA

A. Rheumatoid Arthritis - Activities of Daily Living

- >90%
- 81–90%
- 71–80%
- ≤70%

(Data from Pincus et al, 1987)

B. Rheumatoid Arthritis - Formal Education Level

- >12 Years
- 9–12 Years
- ≤8 Years

(Data from Pincus et al, 1987)

C. Hodgkin’s Disease - Anatomic Stage

- Stage I
- Stage II
- Stage III
- Stage IV
- All Stages, All Causes

(Data from Kaplan, 1972)

D. Coronary Artery Disease - # of Involved Vessels

- 1 Artery
- 2 Arteries
- 3 Arteries
- L Main

(Data from Proudfit et al, 1978)

Courtesy of Ted Pincus, M.D.
The Importance of Early Therapy

Graph: Adapted from Kirwan JR. J Rheumatol. 2001;28:881-886.
Changing Treatment Paradigms

- Biologic therapy
- Combination therapy
- Early intervention
- Aggressive therapy
- Pyramid inversion

Single-drug therapy

Treatment pyramid
Evidence for Improvement in Rheumatoid Arthritis Over Time

Summary

• RA outcomes have improved over the last 30 yrs
  – Improved morbidity and mortality, less surgery, less work loss, less functional loss
• Driven by better control of disease activity
• Targeted biologics can increase control of disease activity, at a reasonable cost (toxicity and $)
• In the current environment, we need to find better ways to manage costs
• Early treatment leads to the best outcomes
Rheumatic Diseases References

- Textbook: Women and Health, Editors: Goldman M, Troisi R, Rexrode K. San Diego, CA: Elsevier. 2nd edition, Chapters 51 (Rheumatoid Arthritis), 53 (Systemic Lupus Erythematosus), 90 (Fibromyalgia) and 96 (Osteoarthritis)
- simpletasks.org
Acknowledgements

- Fibromyalgia: Dr. Calvin Brown, Jr and Dr. Arthur Mandelin
- Osteoarthritis: Dr. Arthur Mandelin and Dr. Leena Sharma
- Rheumatoid Arthritis: Dr. Eric Ruderman and Dr. Darcy Majka
Widespread Pain Index (WPI)

Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

- Shoulder girdle, left
- Shoulder girdle, right
- Upper arm, left
- Upper arm, right
- Lower arm, left
- Lower arm, right
- Jaw, left
- Jaw, right
- Chest
- Abdomen
- Hip (buttock, trochanter), left
- Hip (buttock, trochanter), right
- Upper leg, left
- Upper leg, right
- Lower leg, left
- Lower leg, right
- Upper back
- Lower back
- Neck
Symptom Severity Scale (SS)

- Fatigue
- Waking unrefreshed
- Cognitive symptoms

For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
- 0 = no problem
- 1 = slight or mild problems, generally mild or intermittent
- 2 = moderate, considerable problems, often present and/or at a moderate level
- 3 = severe: pervasive, continuous, life-disturbing problems

- Considering somatic symptoms in general, indicate whether the patient has:
  - 0 = no symptoms
  - 1 = few symptoms
  - 2 = a moderate number of symptoms
  - 3 = a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.