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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Comorbidity in Rheumatoid Arthritis

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Faculty Disclosures

Audrey Gibson, PA-C, MsPAS:

- Speakers Bureau: Abbvie, Sanofi-Genzyme

Objectives

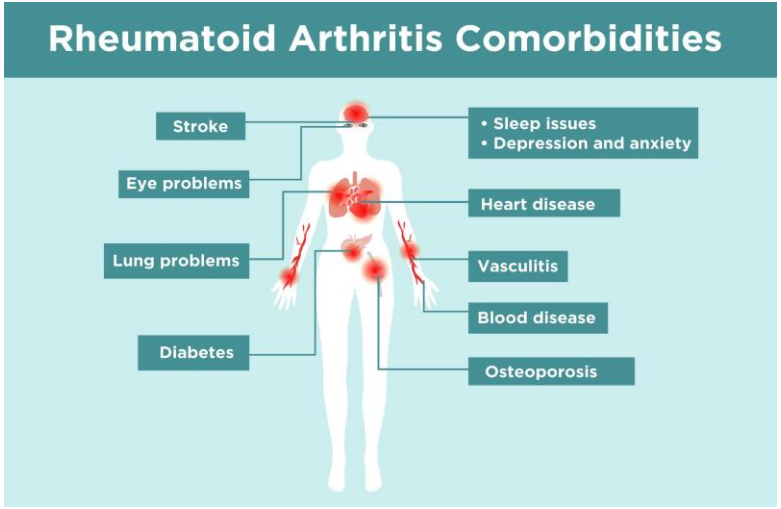
- Identify common comorbidities
- Understand the role of inflammation in these comorbidities
- Discuss possible treatments and/or management

Prevalence of Comorbidities

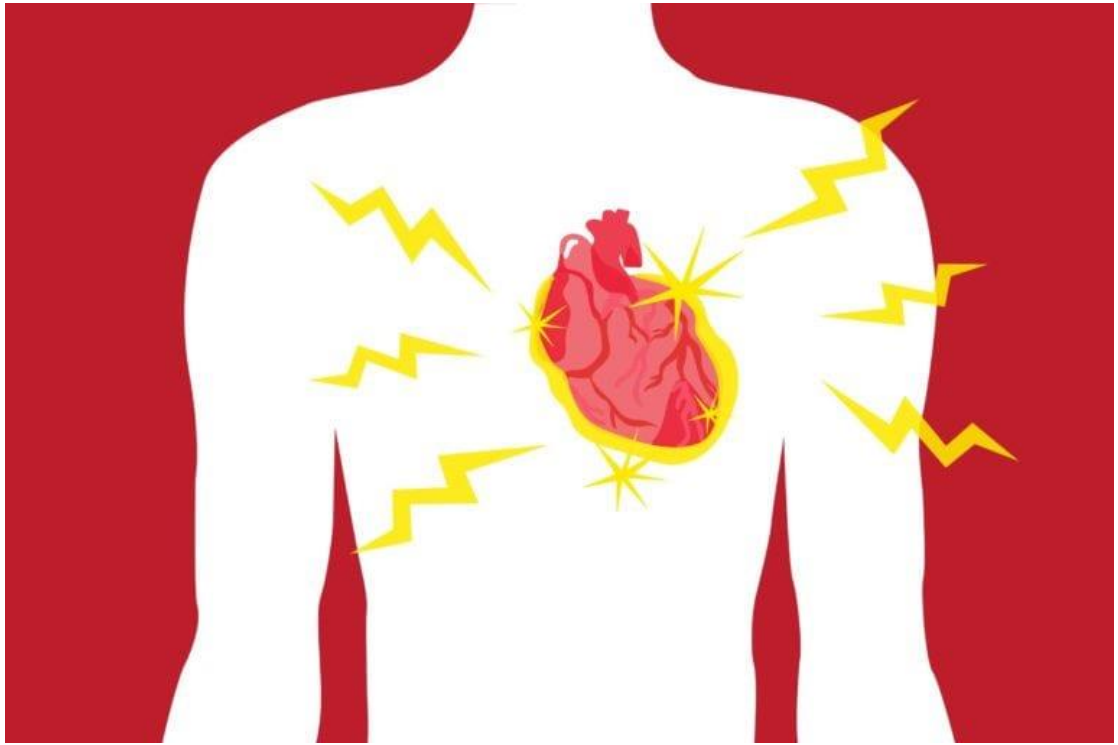
- Occurs in about 40% of patients with rheumatoid arthritis
- Risk factors
  - Presence of rheumatoid factor (RF)
  - Anti-citrullinated peptide antibodies (ACPA)
  - Smoking

Common Comorbidities

- Infections – serious infections, TB, Hepatitis
- Malignancy – nonmelanoma skin cancer, melanoma, solid tumors, History of lymphoproliferative disorder
- Lung Disease
- Cardiovascular Disease
- Neurologic manifestations
- Osteoporosis
- Eye involvement
- Vasculitis
- Diabetes
- Depression and anxiety
- Hematologic
- NASH



Cardiovascular Disease



Not Just Joints

- RA is a systemic disease
- Pts with RA have increased morbidity and mortality
  - 2x more likely to have MI
  - 70% more likely to have stroke
  - 70% more likely to develop infection
- A meta-analysis of 24 observational studies comprising 111,758 patients concluded that the risk of CAD mortality was 59% higher in patients with RA than in the general population

Avina-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. *Arthritis Rheum*. 2008;59:1690-1697.

Cardiovascular Disease

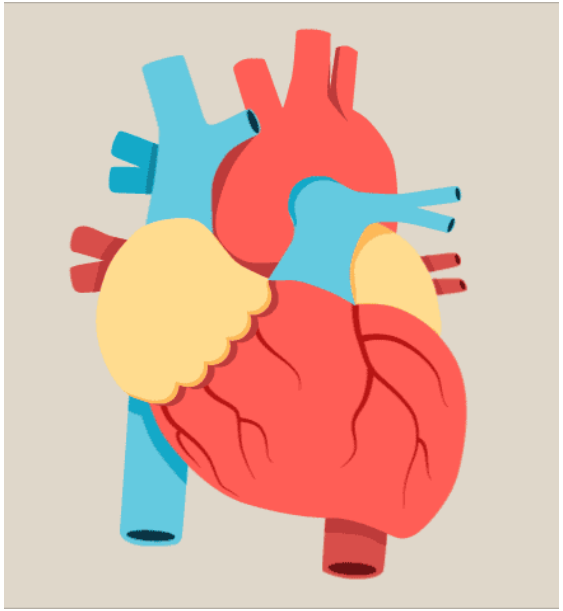
- Pathogenesis
  - Inflammation has a significant role in the development of coronary artery disease (CAD) and that the innate and adaptive immune systems play an important role in the initiation and progression of atherosclerosis.
  - Inflammation – chronic inflammation may accelerate the progression of atherosclerosis, via the effects of cytokines; T-lymphocytes, macrophages, and dendritic cells; immune complexes; coagulation abnormalities; oxidative stress; or a combination of these factors

Cardiovascular Disease

- Markers of increased systemic inflammation are also associated with an increased risk of CAD
- RA appear to have a significantly greater burden of atherosclerotic carotid plaques, suggesting the presence of generalized atherosclerosis
- Coronary artery calcification
- Function of HDL as an antiatherogenic particle is impaired or altered
- Newer medications can change the lipoprotein profile

Cardiovascular Disease

- Increased Risk for CVD
  - Increased prevalence of CV risk factors
  - Increased thrombotic tendency
  - Decreased activity
  - Drugs
  - Endothelial dysfunction
  - Dyslipidemia
  - Insulin resistance
  - CHF
  - HTN
  - Increased inflammation



Managing Traditional Risk Factors

- Dyslipidemia
- HTN
- DM
- Smoking
- Physical activity
- Obesity

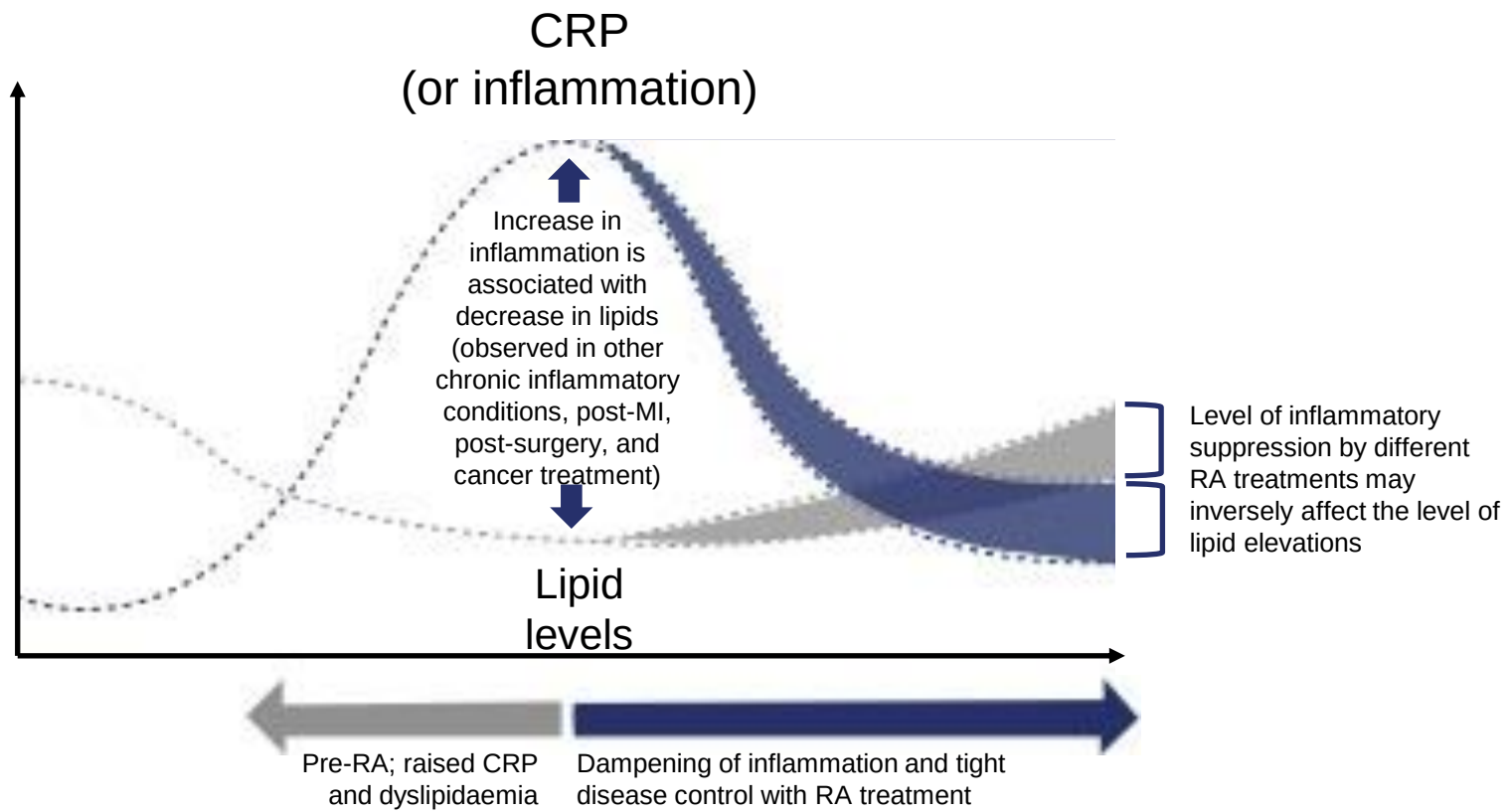
Dyslipidemia

- Interpretation of lipid levels in the context of RA is challenging
- Compared to the general population, patients with RA have lower total cholesterol (TC) and low-density lipoprotein (LDL) levels independent of lipid-lowering therapy. Despite this, RA patients are at increased risk for CVD

Lipid Paradox

- Suppression of total and LDL cholesterol levels during acute or chronic inflammation as well as a proportionately greater suppression of HDL, resulting in a disadvantageous atherogenic index (TC/HDL ratio)
- Inflammation induces qualitative changes to HDL composition

Inverse Relationship Between Changes in Inflammatory and Lipid Parameters



CVD Management

- Screening:
  - Yearly cardiovascular evaluation
  - Focused history and physical examination
  - EKG in patients ≥50 years of age.
  - Low threshold for proceeding to exercise or pharmacologic stress testing in those with symptoms or EKG findings suggestive of CAD
- Risk Estimation: Framingham risk model and AHA CVD risk Calculator

EULAR Recommendations of CVD in RA

- Risk of CVD in pts with RA, IJD, AS and PsA are substantially elevated compared to the general population
- In RA the risk appears comparable to that reported for pts with DM
- Aggressive and targeted CVD risk management
- 2009 EULAR task force formulated 10 recommendations for screening and identifying CVD risk factors.
  Updated 2015

3 Principles:

1. Clinicians should be aware of the higher risk for CVD in pts with RA compared to general population
2. The rheumatologist is responsible for CVD risk management
3. NSAIDs and corticosteroids should be in accordance with treatment specific recommendations

Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Annals of the Rheumatic Diseases*. 2017;76:17-28.

EULAR Recommendations

1. RA should be regarded as a condition associated with higher risk for CV disease. The increased risk appears to be dure to both an increased prevalence of traditional risk factors and the inflammatory burden.
2. Adequate control of disease activity is necessary to lower the CV risk.
3. CV risk assessment using national guidelines is recommended for all patients with RA. Risk assessments should be repeated when anti-rheumatic treatment has been changed.
4. Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria: (i) disease duration >10 years, (ii) RF or anti-CCP positivity and (iii) the presence of certain extra-articular manifestations.
5. TCh/HDL cholesterol ratio should be used when the SCORE module is used.
6. Intervention should be carried out according to national guidelines.
7. Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options.
8. The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors.
9. Corticosteroids: use the lowest dose possible.
10. Recommended smoking cessation.

CV: cardiovascular; coxibs: cyclooxygenase (COX) inhibitors; TCh: total cholesterol; HDL: high-density lipoprotein cholesterol; ACE: angiotensin-converting enzyme.
Adapted from Peters et al. [1].

Statin Use

- Stains still considered mainstay of therapy
- In a study of 3298 Medicare patients with RA, less than half of RA patients with an indication underwent appropriate lipid screening
- Statins are often underutilized for both primary and secondary prevention in RA patients
- Among patients discharged after a first myocardial infarction (MI), the odds of receiving lipid-lowering therapy were 31% lower for RA patients[1]
- Adherence is poor

1. Akkara Veetil BM, Myasoedova E, Matteson EL, et al. Use of lipid-lowering agents in rheumatoid arthritis: A population-based cohort study. *J Rheumatol*. 2013;40:1082-1088.

CVD Prevention Measures

- Smoking cessation
- Lipid lowering
- Healthy diet
- Moderate exercise
- Weight control
- Blood pressure control

Cardiovascular Disease

- Smoking and RA is associated with increased:
  - Risk of disease
  - Risk of CCP+
  - Risk disease severity
  - Extra-articular manifestations
  - Pulmonary disease
  - Cardiovascular complications
  - Death

Hypertension

- May be an increased prevalence of hypertension in RA patients
- Both underdiagnosed and undertreated in RA patients
- Not specific to the RA population; thus, follow American College of Cardiology/American Heart Association guidelines
  - Treating those with in-office blood pressures exceeding 140/90 mm Hg (>130/80 mm Hg if aged >65 years or with concomitant CVD, DM, chronic kidney disease, or 10-year atherosclerotic cardiovascular disease risk >10%)

Managing RA Specific Risk Factors

- Disease activity
  - Associations between the level of RA disease activity and risk of CVD
  - TREAT INFLAMMATION!
  - Treat aggressively to remission or low disease activity to minimize CVD risk

Implication of Drug Selection

- NSAIDs – Chronic use of COX-2 inhibitors and nonselective NSAIDs may increase the risk of myocardial infarction (MI), stroke, and sudden cardiac deaths
- Glucocorticoids – Glucocorticoid use is associated with increased cardiovascular risk in patients with RA
- ASA
- DMARDs

Implication of Drug Selection

- DMARDs
  - **Effective control of disease activity in patients with RA appears to reduce CVD risk**
  - MTX-Both a 2011 and 2015 meta-analysis found that MTX use was associated with a 21 to 28% reduction in all CVD events
  - TNF-A 2015 meta-analysis found that TNF-alpha inhibitors were associated with reduced risk of all CVD events, including myocardial infarction and stroke
    - RA treatment guidelines recommend avoiding TNF inhibitor use in individuals with CHF

Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* 2015; 74:480.

Implication of Drug Selection

- Hydroxychloroquine
  - Prevents DM and has beneficial effects on lipid profiles
- Tocilizumab
  - Increase LDL levels, but it does not appear to increase the risk of CVD
  - Promote more favorable anti-atherogenic lipoprotein function

CVD – Practical Approach

- Who's In Charge?
  - Multidisciplinary Care Team
    - Prevention, screen for and manage all comorbidities associated with RA
      - Problems: TIME, MONEY
      - Not all providers are comfortable with providing
      - PCP tend to underrecognize CV risk in pts with inflammatory arthritis
      - COMMUNICATION is KEY
    - Addressing comorbidity may improve clinical outcomes in early RA[1]

1. Hitchon CA, Biore G, Haraoui B, et al: Self-reported comorbidity s common in early inflammatory arthritis and assoc. with poorer function and worse arthritis disease outcomes: results from Canadian Early Arthritis Cohort. *Rheumatology (Oxford).* 2016;55(10):1751-1762.

Provider Roles

Primary Care

- Perform traditional CVD risk factor screening:
  - Lipids
  - Blood pressure
  - Diabetes mellitus
- Initiation of therapies for traditional CVD risk factors
- Monitoring response to traditional CVD risk factors
- Escalating therapies for traditional CVD risk factors
- Smoking cessation therapies
- Consultations as indicated (cardiology, endocrinology)

Both

- CVD risk assessment using validated risk calculator
- Patient education on CVD risk in RA
- Counseling on healthy lifestyle:
  - Smoking cessation
  - Physical activity
  - Healthy diet and body weight
- Communication with co-managing colleagues

Rheumatologist

- Regular assessment of RA disease activity
- Treatment RA to remission or at least low disease activity
- Utilization of DMARDs that are potentially “cardioprotective”
  - Methotrexate
  - TNFi[a]
  - Hydroxychloroquine
  - Limit use of NSAIDs and glucocorticoids

Figure. Proposed provider roles in cardiovascular disease (CVD) risk reduction for rheumatoid arthritis (RA) patients.
[a]Avoid tumor necrosis factor inhibitor (TNFi) use in patients with congestive heart failure, DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.

Lung Disease

- Interstitial lung disease (ILD) is the most common manifestation of rheumatoid lung disease
- The prevalence of RA-ILD ranged from 3.2 to 6.0 cases per 100,000, and the incidence ranged from 2.7 to 3.8 per 100,000
- Clinically significant RA-ILD occurs in nearly 10% of patients with RA
- Men >women

RA-ILD Risk Factors

- More severe RA
  - +RF and +CCP
- Male sex
- Older age
- Cigarette smoking
- Genetics – MUC5B mutation

Management of RA-ILD

- Optimal treatment for RA-ILD has not been determined
- Guidelines for idiopathic interstitial pneumonias has been to categorize the disease behavior as self-limited, reversible, stable, progressive, or irreversible, with or without the potential for long-term stabilization with therapy

RA-ILD

Rheumatoid arthritis-associated interstitial lung disease: Classification according to disease behavior

Clinical behavior	Treatment and treatment goal	Monitoring strategy
Potentially reversible with risk of irreversible disease (eg, cases of drug-related lung disease in RA)	Remove cause, treat to obtain a response to reverse changes	Short-term (three to six months) observation to confirm disease regression, or occasionally need for palliation
Reversible disease with risk of progression (eg RA-cellular NSIP and some RA-fibrotic NSIP, RA-OP)	Treat to initially achieve response and then rationalize longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (eg, some RA-fibrotic NSIP, some RA-UIP)	No treatment if stable, aiming to maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (eg, some RA-fibrotic NSIP, some RA-UIP)	Consider treatment trial to stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (eg, RA-DAD, most RA-UIP, some RA-fibrotic NSIP)	In absence of contraindications, consider treatment trial in selected patients to slow progression	Short (DAD) or long-term observation to assess disease course, and need for transplant or effective palliation

RA: rheumatoid arthritis; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonitis; OP: organizing pneumonia; DAD: diffuse alveolar damage.

Diabetes

- 10% of the US population has diabetes mellitus (DM)
- Increased prevalence of DM in RA
  - Inactivity
  - Chronic glucocorticoid use
  - Higher level of disease activity → increased insulin resistance

Fatty Liver/NASH

- Nonalcoholic fatty liver disease has become the most common cause of chronic liver disease in the U.S. and worldwide. According to the NIH, an estimated 30 to 40% of adults in the United States have NAFLD, and about 20% of them have NASH
- Certain types of inflammatory arthritis linked with a greater risk of developing nonalcoholic fatty liver disease (NAFLD)
- Nonalcoholic fatty liver disease (NAFLD) occurs when fat accumulates in liver cells and the deposits aren’t the result of alcohol abuse
- NAFLD can progress to nonalcoholic steatohepatitis (NASH), and NASH, in turn, can lead to fibrosis, cirrhosis and liver cancer

Fatty Liver/NASH

- The link between inflammatory arthritis and NAFLD appears to be strongest with PsA
- MTX linked to NAFLD
- Psoriasis and PsA have been linked with obesity, diabetes, and metabolic syndrome – all risk factors for NAFLD
- A study at the University of Pennsylvania Perelman School of Medicine in Philadelphia, found that people with psoriasis and psoriatic arthritis were at increased risk for liver disease, including NAFLD, whether or not they were taking systemic therapy, such as methotrexate. The risk was even higher for those who were
- It's estimated that almost half of patients with psoriasis may have NAFLD

Screening/Management

- No symptoms of NAFL
- Liver testing a routine-labs
- Imaging scans like ultrasounds, CTs, or MRIs can diagnose NAFLD
- A liver biopsy

NASH Prevention

- Weight loss and exercise
- Vitamin E supplements are sometimes recommended
- Lifestyle changes are considered the best
- Mediterranean diet, which involves cutting back on carbs, sugars, and red meat
- Start a low-intensity aerobic exercise program
- Avoid alcohol and NSAID
- No FDA-approved drugs for NASH
- In some cases alter their arthritis medications

Infections

- Patients with rheumatoid arthritis (RA) have an increased prevalence of other serious illnesses
  - Predominant conditions contributing to the comorbidity and mortality of RA are infections, renal impairment, lymphomas, and cardiovascular disease
- Immunosuppression by the disease itself or its treatment
- The presence (often subclinical) of inflammatory lung disease
- An increase in cigarette smoking
- Multiple factors associated with disability and immobility

Infections

- Immunosuppression from corticosteroids and immunosuppressive agents.
  - Increased risk of infection associated with the use of glucocorticoids and immunosuppressives, the use of nonbiologic DMARDs does not appear to be associated with an increased risk of infection.
  - Retrospective study of 27,710 Canadian patients with RA. Among patients who were not taking glucocorticoids, the relative risk (RR) of serious infection for DMARD users was not significantly different from that for nonusers.
  - Mild lymphopenia is very common in RA and may increase the susceptibility to infection.

Vaccines

- Low vaccination rates among pts with rheumatic disease
  - Concerns for efficacy
  - Immunogenicity
  - Safety
- Consider vaccines before starting therapy, thinking ahead to ensure effectiveness

Vaccines

- Flu vaccines are generally safe and effective
  - Contraindication-anaphylaxis
- Pt's may receive live vaccine, except in certain subgroups
  - Ideally given before patients begin immunosuppressive therapy
  - Measle and zoster >4wks before starting immunosuppressive therapy
  - Pts should avoid close contact with family members who have had live vaccines
- Pts should receive repeated pneumococcal vaccines
- PCV13 first then, PPSV23 after >8 weeks

Osteopenia/Osteoporosis

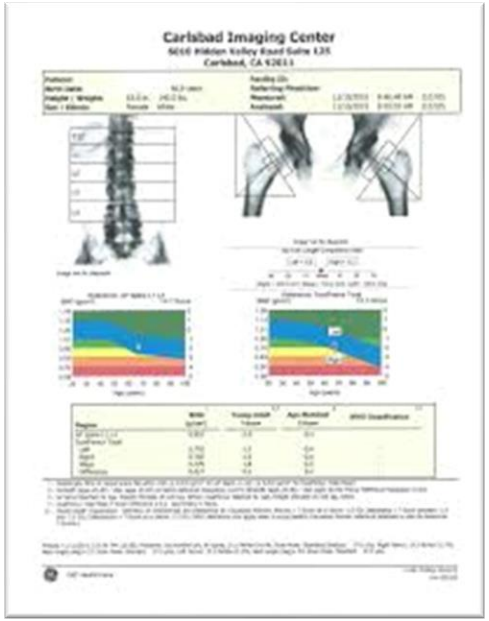
- Prevalence: prevalence of osteoporosis in patients with established RA is about 1.5- to 2-fold higher than in age- and sex-matched comparators without RA
- Increase risk of stress fractures, increased risk of vertebral fractures, height loss
- Glucocorticoids associated

Risk Factors

- Nonmodifiable
  - Advanced age
  - Female gender
  - White/Asian race
  - Low peak bone mass
  - Family history of osteoporosis
  - Personal history of fracture
  - Low body mass index
  - Disability
  - Inadequate physical activity
- Modifiable
  - Cigarette smoking
  - Inadequate calcium intake
  - Inadequate Vit D
  - Low body weight (BMI <21kg/m2)
  - Estrogen def
  - Hypogonadism
  - Chronic glucocorticoid therapy
  - Medications

Screening/Management

- Baseline DEXA
- Low threshold for initiating bisphosphonates
- Labs
- Calcium, Vitamin D, weight bearing exercise, fall prevention



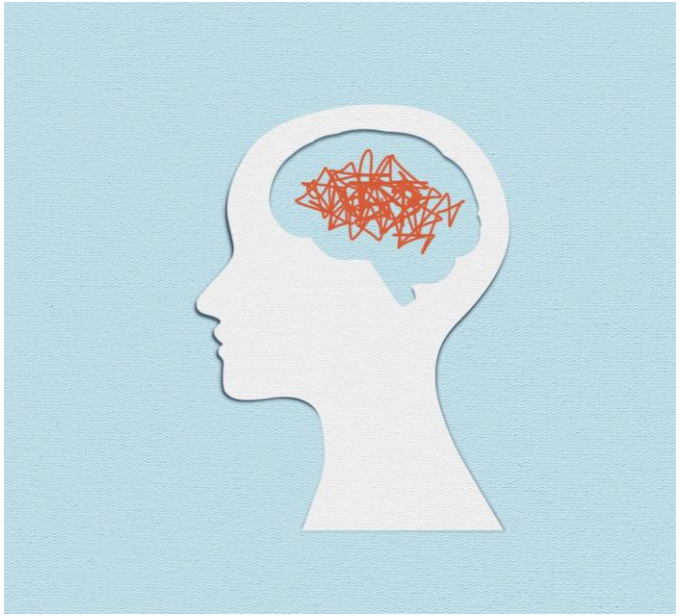
Psychiatric Comorbidities

- Those with RA are disproportionately affected by psychiatric disorders
  - Anxiety
  - Depression
- Associated with poorer odds of achieving remission and increased mortality
- Proinflammatory cytokines such as TNF, IL-6 and IL-1beta are overexpressed in pts with depression compared to healthy controls
  - Effects on neuroendocrine function, neurotransmitter metabolism and brain structures
  - Increased CRP, also present in pts with depression or anxiety

Vallerand IA, Patten SB, Barnabe C. Depression and the risk of rheumatoid arthritis. *Curr Opin Rheumatol.* 2019;31(3):279-284.

Prevalence of Depression

- Depression most common psychiatric comorbidity of RA
- 9.5-41.5% of pts with RA
- 16.8% pts with RA had MDD
- Due to: chronic pain, fatigue, and functional limitations
- Especially at risk during the first year



Nerurkar L, Siebert S, McInnes IB, Cavanagh J. Rheumatoid arthritis and depression: an inflammatory perspective. *Lancet Psychiatry.* 2019:6(2): 164-173.

The Role of Rheumatologist

- One study showed that Rheumatologist rarely brought up the topic of depression
- Screen pts regularly for depression and other disorders and to follow scores
  - Generalized Anxiety Disorder
  - Pt Health Questionnaire
- If scores indicate depression, refer to mental health

Sleath B, Chewning B, de Vellis BM, et al. Communication about depression during rheumatoid arthritis patients visits. *Arthritis Rheum*. 2008;59(2):186-191.

Summary – Be Aggressive

- Aggressively managing RA
- Be Proactive
  - Weight reduction, obesity, exercise
  - HTN
  - COPD, Smoking
  - CVD, Lipids
- Health Maintenance – refer when needed
- PCP Communication