

Men and Lupus

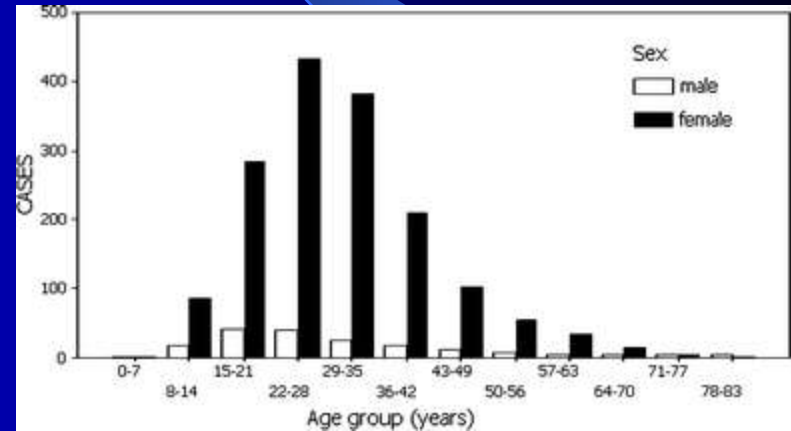
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Men and Lupus

- Epidemiology
- Men's Health Issues
 - Coronary artery disease
 - Osteoporosis
 - Prostate cancer
 - Sexual health
- Question and answer period

Men and lupus: Epidemiology

- Female predominant disease
 - Onset < 30 years of age
 - Female 90%
 - Male 10%
 - Onset > 30 years of age (older-onset)
 - Nearly 50% of cases in each gender
 - Prevalence:
 - African-American men: 1 in 7000-31,000
 - Caucasian men: 1 in >4000
- Drug-induced lupus
 - Same rate in both gender



Feng, et. al. Rheumatol Intl (2010) 30:1017.

Men and Lupus: Epidemiology

More common in men

– Clinical:

- Nephritis
- Rash
 - Malar
 - Discoid
- Serositis
- Thrombocytopenia (low platelets)
- Thrombotic events
- Low lean body mass

– Serology:

- Anti-double-stranded DNA
- Anti-Smith
- Nucleolar ANA patterns

Rheumatology key messages

- . The age of onset is similar in male and female patients with lupus.
- . Men with lupus display **decreased musculoskeletal symptoms, photosensitivity, oral ulcers and Raynaud's phenomenon** than women.
- . There is **no** clear association between gender and mortality or disease activity in SLE.

Murphy & Isenberg. Rheumatology 2013;52:21082115

Men and Lupus: Epidemiology

- Multiplex families:
 - In families with multiple lupus cases, those with affected male relative had increased risk for:
 - Nephritis
 - Hematological manifestations

Men and Lupus: Epidemiology

- African-American men with lupus
 - More likely to have nephritis as 1st clinical symptom
 - Progress from disease onset to nephritis faster than other groups

Men and Lupus: Epidemiology

Feng, et. al. Rheumatol Intl (2010) 30:1017.

- Chinese patients w/ SLE
 - Men had shorter delay in diagnosis owing to more rapid accumulation of ACR classification criteria (clinical manifestations)
- Comparison w/ Chinese women w/ SLE:
 - Adult onset groups:
 - Increased:
 - Pleurisy, discoid LE rash
 - Decreased:
 - Malar LE rash, alopecia, mucosal ulcerations
 - ESR, ANA, Ro (SSA), La (SSB)
 - Pediatric onset groups:
 - No differences

Men and Lupus: Natural history

- LUMINA Multi-ethnic lupus cohort
 - Increased in men with lupus:
 - More rapid accrual of lupus manifestations
 - Higher early damage scores
 - + lupus anti-coagulant
 - Poorer long-term prognosis in men

Men and Lupus: Epidemiology

- Klinefelter's syndrome
 - XXY (extra copy of female X chromosome)
 - Tall, thin, eunuchoid; usually infertile
 - Substantial increase in lupus risk
 - Men with lupus 14 x as likely to be XXY than age-matched controls
 - Suggests female gene (X-linked) genes drive lupus
 - Example: CD40L on X chromosome

Scofield, et. al. Arthritis Rheum (2008) 58:2511.

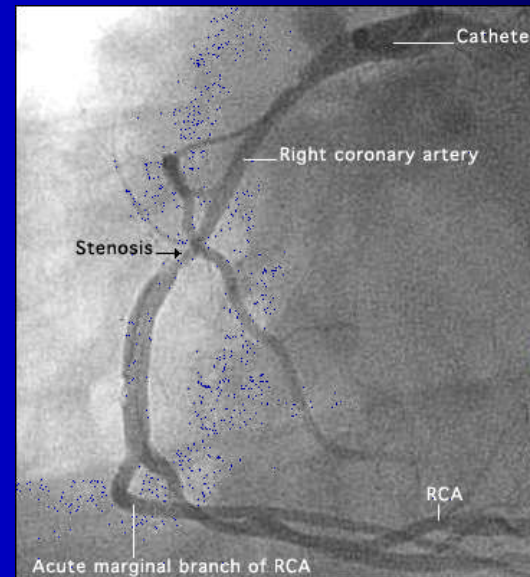
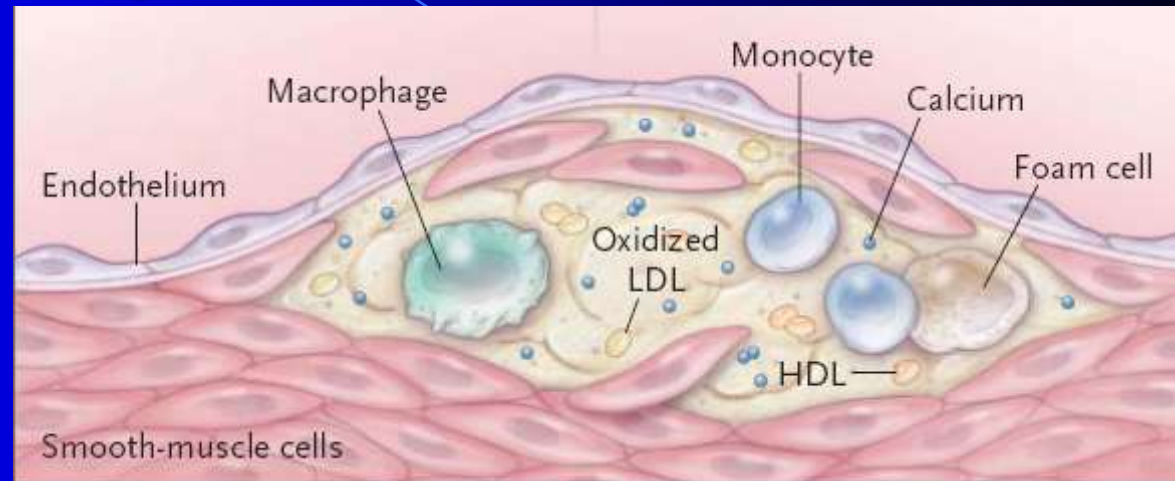
Atherosclerosis/Coronary Artery Disease

● Plaques

- Inflammation
 - Foamy macrophages
- Deposits
 - Oxidized cholesterol
 - Lipids (fat)
 - Calcium
- Fibrous caps

● Plaque rupture

- Exposes tissue factor
- Results in thrombus formation and occlusion of the vessel

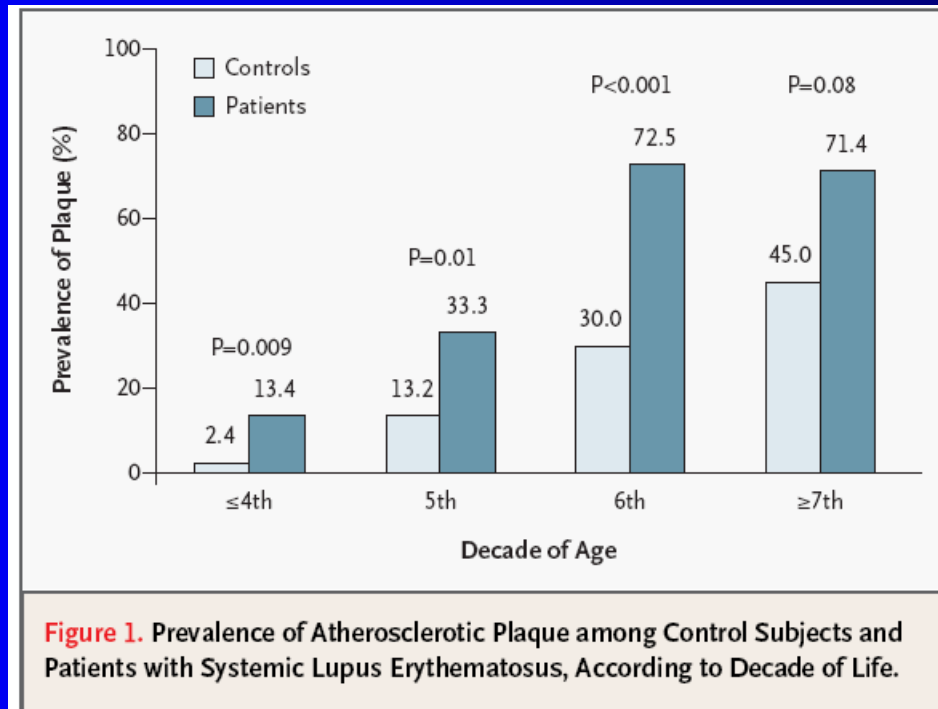


Accelerated Atherosclerosis

- Mortality
 - Leading cause of death in all men is CAD complications
 - The leading cause of death in patients with SLE is complications of atherosclerotic coronary artery disease
- Risk
 - Myocardial infarction:
 - 5%-45% SLE patients
 - Among women with SLE <45 yrs old, risk of MI is 50 times that of age-matched healthy controls
 - Overall 2-52 times higher risk in lupus patients
 - Cerebrovascular disease
 - 2-10 x higher in lupus patients
 - Men have 2x risk of prolonged hospitalization post-stroke
 - Independent of standard risk factors, SLE treatment

Atherosclerosis in SLE

- Estimated prevalence:
 - Odds ratio for atherosclerosis in SLE:
 - 4.9 (Roman, *NEJM*) – 9.8 (Asanuma, *NEJM*)
 - Assessed by carotid ultrasound (IMT) (Roman)
 - Assessed by external beam CT (detects coronary calcium) (Asanuma)



Atherosclerosis in SLE

- Traditional risk factors:

- Gender
 - Male
- Age
 - > 50
- Hypertension
- Family history
 - 1st degree relative with myocardial infarction
- Hyperlipidemia
 - Elevated LDL cholesterol
 - Elevated triglycerides
 - Reduced HDL cholesterol
- Smoking
- Diabetes mellitus
- Overweight

- SLE risk factors

- Younger age at diagnosis of SLE
- Disease duration
- Anti-smith autoantibodies
- Antiphospholipid antibodies
- Dyslipidemia
- Corticosteroid use
- Hyperhomocysteinemia
- SLICC/Damage Index data
 - MI associated with:
 - Male gender
 - hypertension

Atherosclerosis in SLE: Management

- Early, aggressive intervention for risk factors
 - Control hypertension
 - Smoking cessation
 - Treat hyperlipidemia
 - Dietary adjustment
 - “Statins”
 - SLE associated with “atherogenic” lipid profile
 - Increased LDL, lpA, apo A-1 and B, small dense LDL subfractions
 - Weight control
 - Diet
 - Exercise
 - Careful monitoring of blood sugar
 - Particularly if chronic corticosteroids are necessary

Management of blood pressure: When to treat

Blood pressure	Comorbidity	Treatment goal (mmHg)	Medications
>140 and/or >90 for 3-6 visits over 3 months	none	<130/<80	<ul style="list-style-type: none"> •Lifestyle modifications •medication
>130 and/or >80	<ul style="list-style-type: none"> •Diabetes •Proteinuric chronic kidney disease 	<130/<80	
>160 and/or >100	none	<130/<80	<ul style="list-style-type: none"> •Consider 2-drug therapy at outset

Management of blood pressure: JNC VII

Modification	Recommendation	BP reduction (mmHg)
Weight reduction	Maintain normal body weight (BMI, 18.5 to 24.9 kg/m ²)	5-20 per 10 kg weight loss
Adapt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8-14
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 meq/day (2.4 g sodium or 6 g sodium chloride)	2-8
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)	4-9
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks per day in most men and no more than 1 drink per day in women and lighter-weight persons	2-4

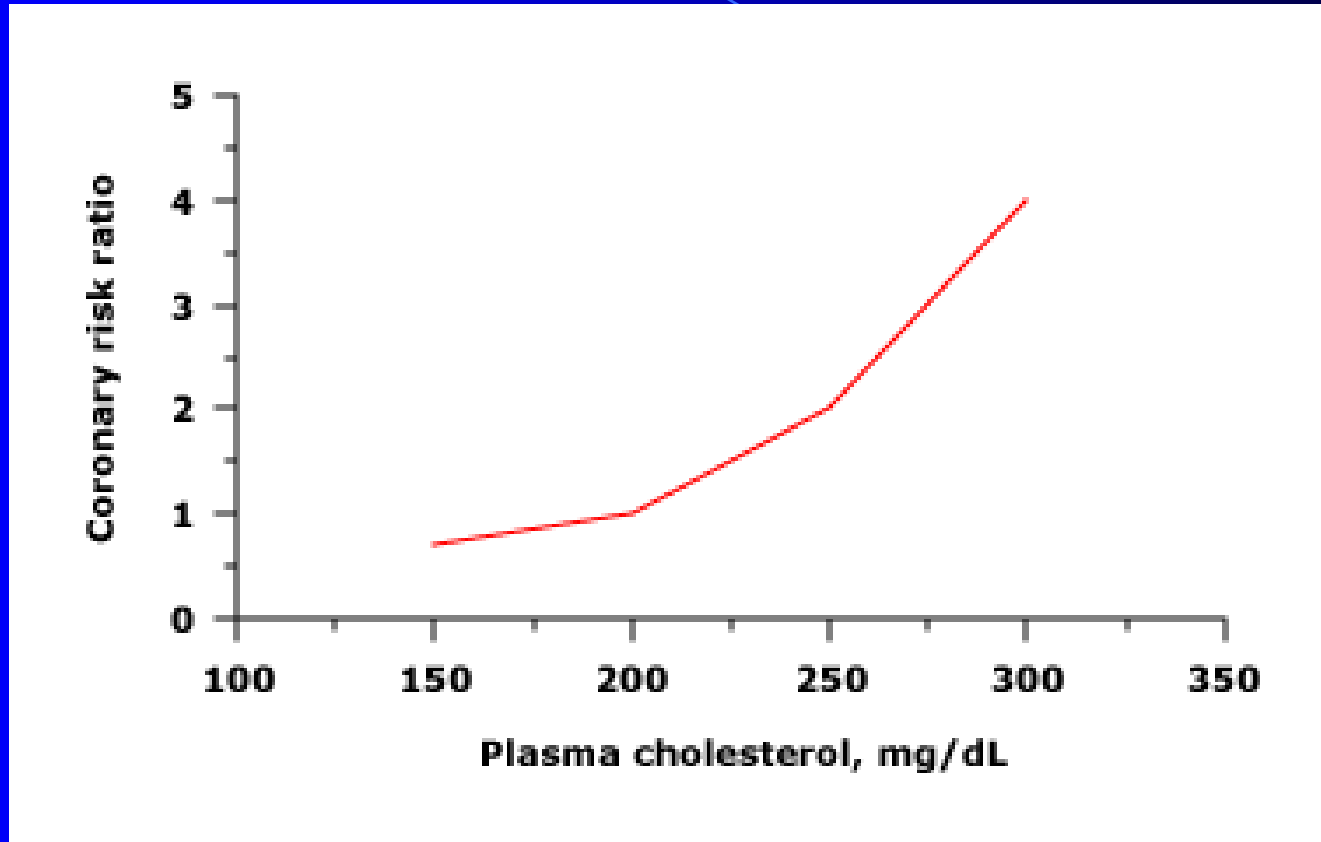
Management of blood pressure: JNC VII

Indication	Antihypertensive drugs
Compelling indications (major improvement in outcome independent of blood pressure)	
Systolic heart failure	ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist*
Post-myocardial infarction	ACE inhibitor, beta blocker, aldosterone antagonist
Proteinuric chronic renal failure	ACE inhibitor and/or ARB
High coronary disease risk	Diuretic (ALLHAT), perhaps ACE inhibitor (HOPE)
Diabetes mellitus (no proteinuria)	Diuretic (ALLHAT), perhaps ACE inhibitor (HOPE)
Angina pectoris	Beta blocker, calcium channel blocker

Adapted from Up-to-Date: FJ Domino & NM Kaplan, "Overview of Hypertension," June 1, 2008

* A survival benefit from an aldosterone antagonist has only been demonstrated in patients with advanced heart failure; in patients with less severe disease, an aldosterone antagonist is primarily given for hypokalemia. Adapted from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, JAMA 2003; 289:2560.

Hyperlipidemia



Relation between plasma cholesterol concentration and six-year coronary heart disease risk in 361,662 men (ages 35 to 57) screened during the MRFIT study. There is a continuous, positive, graded correlation between the plasma cholesterol concentration and coronary risk. To convert plasma cholesterol to mmol/L, divide by 38.5. Data from Stamler, J, Wentworth, D, Neaton, JD, JAMA 1986; 256:2823.

Hyperlipidemia: When to treat

Risk category	LDL goal (mg/dl)	LDL to initiate lifestyle modifications	LDL to initiate drug therapy
CHD or CHD 10-yr risk >20%	< 100	≥ 100	≥ 130
≥ 2 risk factors	≤ 130	≥ 130	<ul style="list-style-type: none"> ● ≥ 130 if 10-yr risk >10% ● ≥ 160 if 10-yr risk <10%
≤1 risk factor	≤ 160	≥ 160	≥ 190

* CHD risk equivalents defined in text. Ten-year risk defined by Framingham risk score (see text). Risk factors that modify LDL goals include cigarette smoking; hypertension (BP 140/90 mmHg or on antihypertensive medication); low HDL-cholesterol (<40 mg/dL [1.03 mmol/L]); family history of premature CHD (CHD in male first degree relative <55 years or CHD in female first degree relative <65 years); age (men 45 years; women 55 years). HDL-cholesterol 60 mg/dL (1.55 mmol/L) counts as a negative risk factor; its presence removes one risk factor from the total count. Almost all people with 0 to 1 risk factor have a 10-year risk <10 percent; thus, 10-year risk assessment in people with 0 to 1 risk factor is not necessary. Adapted from Adult Treatment Panel III at <http://www.nhlbi.nih.gov/>.

Assessing CHD risk

- <http://hp2010.nhlbihin.net/atp/iii/calculator.asp>
 - Age
 - Gender
 - Total and LDL cholesterol
 - Blood pressure and BP treatment (Y/N)
 - Cigarette smoking status

Atherosclerosis in SLE: Management

- Control SLE
 - Hydroxychloroquine (Plaquenil)
 - ACE inhibitors for chronic proteinuria
 - Folic acid for hyperhomocysteinemia
 - Routine rheumatology evaluation and lab assessment
 - Quarterly appointments
 - CBC, chemistries, complement, urinalysis, anti-DNA at each visit
 - Antiphospholipid antibody screen, homocysteine level, fasting lipid panel performed annually
 - Antiphospholipid antibodies
 - Aspirin for asymptomatic patients (?)

Atherosclerosis in SLE: Is there something more?

- Impact of inflammation
 - Uncertain role of inflammation
 - CRP trends do not hold in SLE
- Endothelial cell injury
 - Now four separate studies that confirm widespread endothelial dysfunction in SLE
 - Independent of atherosclerotic disease burden

Men and Lupus: Osteoporosis

- Osteoporosis

- Lupus increases risk (independent of steroid exposure)
 - Lower bone mineral density in men with lupus
 - Risk for lower BMD:
 - Age
 - Alcohol
 - Lower body mass index
 - High-dose steroids
- Early screening
 - 2008 NOF recommendations for men: age 75
 - Consider earlier baseline for men based on risk factors

Men and Lupus: Osteoporosis

- Osteoporosis management
 - Ca⁺⁺: 500 mg/d added to dietary Ca⁺⁺
 - Excess Ca⁺⁺ supplementation may accelerate calcification of atherosclerotic vascular disease
 - Vitamin D: 1000-2000 IU/d
 - 25-OH vitamin D to assess need for replacement
 - Control SLE activity (reduce steroid exposure)
 - Bisphosphonates
 - beneficial in conjunction with initiated high-dose steroids (glucocorticoid-induced osteoporosis)
 - Prolia
 - RANK-ligand antagonist
 - Teriparatide (Forteo)
 - Approved:
 - Male osteoporosis, steroid-induced osteoporosis

Men and Lupus: Sexual health

- Hypogonadism

- Low testosterone levels

- Low baseline levels and decreased response to beta-HCG stimulation
- Independent of co-morbidities

- Testosterone effects

- Deep voice
- Facial hair
- Secondary sexual features
- Higher cholesterol levels
- Higher bone density
- Libido

- Risk for low levels:

- Associated with disease chronicity
- Certain treatments (especially cyclophosphamide)

Men and Lupus: Sexual health

Fertility

- Sperm abnormalities appear to be common
 - Azoospermia, oligospermia, motility abnormalities
- Testicular damage
 - Reduced testicular volume via u/s correlates with sperm abnormalities
 - Likely attributable to lupus damage to the seminiferous tubules
 - Anti-sperm antibodies unlikely to be culprit (present in normals)
- Cytotoxic drug effects
 - Most data in cyclophosphamide, also azathioprine
 - Damage sperm directly
 - Can cause structural injury
 - Testicular atrophy
 - Duct damage
 - Support cell and germ cell destruction
- Lupus nephritis
 - Deterioration of renal function associated with ED and reduced sperm production due to disruption of normal pituitary-hypothalamic axis function

Soares, et. al. Arthritis Rheum (2007) 56:2352

Men and Lupus: Sexual health

- Conception

- Risk for teratogenicity (unknown)
- General recommendations:
 - Avoid conception while taking cytotoxic agents
 - Methotrexate
 - Discontinue x 3 months before starting efforts at conception
 - Hydroxychloroquine
 - Probably no risk
 - Lupus treatments may cause decreased fertility BUT ARE NOT EFFECTIVE CONTRACEPTIVES!

Men and Lupus: Sexual health

- Cyclophosphamide effect
 - $> 6 \text{ g/m}^2$ associated with longterm or permanent azoospermia
 - GnRH is not protective for men
 - Currently only option is sperm banking

Men and Lupus: Sexual health

- Erectile dysfunction
 - Causes:
 - Chronic disease
 - Diabetes
 - Hypertension
 - Obesity
 - Hyperlipidmeia
 - CV disease
 - Smoking
 - Medications (25% of cases)
 - anti-depressants (especially SSRI's)
 - Thiazide diuretics
 - Cimetidine
 - Methotrexate
 - Alcohol
 - Hypogonadism

Men and Lupus: Sexual health

- Erectile dysfunction

- Diagnosis:

- Evaluate for depression and psychogenic factors
 - Review medications
 - Evaluate early AM free and total serum testosterone levels
 - Nocturnal erections
 - Associated with REM sleep, present on awakening
 - Demonstrate intact neural pathways and vascular pathways
 - Nocturnal penile tumescence study
 - Vascular disruption
 - can be measured directly by u/s

Men and Lupus: Sexual health

- Erectile dysfunction
 - Management
 - Testosterone replacement if necessary
 - Phosphodiesterase inhibitors
 - Sildenafil, tadalafil, vardenafil
 - Penile self-injectables
 - Intraurethral alprostadil
 - Vacuum devices
 - Prostheses

Men and Lupus: Sexual health

- Prostate Cancer

- No increase in lupus based on SLICC/ACR data
- Literature review suggests **DECREASED** risk in men w/ SLE

Bernatsky, et. al. Intl J Canc (2011) 129: 2966.

- Screening:

- Age to begin:

- Age 50: white males
- Age 40-45

- Black males
- Men with + family history
- Men known or likely to be BRCA1 mutation +

- Tests

- PSA at 2-4 year intervals
- DRE not always recommended

Summary

- Questions??