Heart Disease Risk Lurks

Seven Common Conditions Where Hidden Heart Disease Risk Lurks

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Disclosures
- No relevant disclosures
- Medical director of molecular diagnostics company
- Development and research of radiation protection, neuroprotective and cardiometabolic micronutrient based therapeutic formulations

Seven Common Conditions Where Hidden Heart Disease Risk Lurks

- Obstructive Sleep Apnea
- Breast Arterial Calcification
- Psoriasis
- Nonalcoholic Fatty Liver Disease
- Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome
Cardiometabolic Risk in Younger Women

ASSOCIATED MEDICAL CONDITIONS
- Increased risk of developing Type 2 Diabetes and Gestational diabetes
- Low HDL and high triglycerides
- Sleep apnea
- Nonalcoholic steatohepatitis
- Metabolic syndrome—43% of PCOS patients (2 fold higher)
- Elevated heart disease prevalence/severity
- Advanced subclinical atherosclerosis

Cardiovascular Risk
- Nurses’ health study: 20-60% increased risk of CAD events
- Studies of pts undergoing coronary angiography: women with h/o hirsutism or PCOS more likely to have CAD and more extensive CAD
Insulin resistance in PCOS

- Norman, et al followed PCOS pts over mean 6 yrs
- If initial nml glu tolerance-- 17% developed glucose intolerance
- If initial impaired glucose tolerance-54% developed type II DM

OBESITY AND INSULIN RESISTANCE

- ½ patients with PCOS are obese (more insulin resistant)
- Obesity is an independent risk factor for glucose intolerance or DM in PCOS
- Hyperinsulinemia contributes to hyperandrogenism through production in the theca cell and through its suppressive effects on sex hormone binding globulin production by the liver

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Atherogenic Dyslipidemia

LDL cholesterol values often underestimate risk when patients have Metabolic Syndrome (Insulin Resistance):

- Elevated Triglycerides
- Small/Dense LDL Particles (Atherogenic Lipid Triad)
- Low HDL Cholesterol

CIMT abnormal in PCOS

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Non-Alcoholic Fatty Liver Disease

Non-Alcoholic Fatty Liver Disease
NAFLD: New and important cardiovascular risk factor
- Independent risk factor
- NAFLD = hepatic manifestation of MS
- Inflammatory state
- Dysfunctional cardiometabolic Phenotype
- CV mortality main risk of NAFLD

Risk factors: Established association
- Obesity
- Type 2 DM: insulin resistance (IR)
- Dyslipidemia
- Metabolic syndrome (MS)

Association of NAFLD w/ CVD
- Studies evaluating coronary artery disease
- Studies evaluating independent CV risk
- Studies evaluating cardiac function
- Studies evaluating endothelial function
- Studies evaluating carotid disease
- Studies evaluating coronary calcium
- Studies evaluating myocardial metabolism

Pathogenesis of CVD in NAFLD
- Insulin resistance
- Visceral fat relation to liver fat
- Epicardial fat (“EAT”)
- Inflammation
- Dyslipidemia
- Intramyocardial fat
- Unique susceptibilities

Insulin resistance and NAFLD
These are ONE
- IR 98%
- NASH
- DM 70%
- MS 85%
- NASH
- DM, MS, CVD

CV risk increases with severity
- Increased CV risk
- Normal Liver
- Steatosis
- NASH
- CVD
- Increased CV risk
NAFLD and increased CVD risk

- Higher prevalence of subclinical atherosclerosis (CIMT, CAC, overt plaque), markers of endothelial dysfunction independent of obesity, MetSyn
- Increased CVD mortality
- Increased myocardial structural/functional abnormalities

NAFLD association with inflammation and CAC in MESA

- NAFLD associated with inflammation and subclinical atherosclerosis independent of obesity, MetSyn
- Association is related to gender and race
- Increasing burden of NAFLD increases prevalence of inflammation, CAC

Epidemiology in RA

- RA patients 2x risk CAD similar to diabetes risk
- Risk often precedes diagnosis
- At time diagnosis, RA patients had 3 times risk of prior MI
- CHF risk doubles
- CHF presentation often atypical with poorer outcomes and less aggressive Rx
Cardiovascular Event Free Probability

Cardiovascular Disease in RA
- Excess cardiovascular risk and mortality in RA
  - Not explained by traditional CV risk factors
- Inflammatory immune mechanisms in atherosclerosis play a role in the pathogenesis of CV disease
  - Provan, Arth Res Ther, 2008
- Elevated inflammatory markers are associated with CV disease
  - Blu-AR 2003
- HDL may NOT be "protective"

CVD risk profile in RA
- Higher frequency of smoking
- Suppression of HDL levels more than other lipid levels during inflammation
- OxHDL…less protective..inflamed
- Apo A1 decreased
- Lower muscle mass compared to fat
- HTN common
- Risk inc with inflammation markers

CVD management/outcome gap
- Less attention to risk factors by MD
- Less exercise by patients
- Less primary and secondary prevention
- Rheumatologists do less lipid Rx
- Angina underdiagnosed. Referrals less
- Lower revascularization and CABG

Therapy for RA affects vascular
- Steroids increase events, BP, insulin resistance, lipids, arterial stiffness, carotid plaque
- Concerns about NSAIDs and CVD (naproxen is best)
- MTX use lower risk for CVD
- TNF inhibitor use lower risk for CVD
Statins and Rheumatoid Arthritis
• Statins are anti-inflammatory
• Slightly lower RA disease activity
• Improved endothelial function and improved central BP/art stiffness
• Statin withdrawal increases event rates. 2% increased risk of MI/month
• Statins impair rituximab therapy

Psoriasis—Inflammatory/immune link with CVD
• Increased risk for heart disease & stroke noted 40 years ago
• Inflammation and immune system
• Higher prevalence of other risk factors
• Key studies and mechanisms linking the disorders
• Effect of Psoriasis therapy on CVD

Link noted in most studies
• Gelfand study (2006): CVD in 130,000 pts vs. 500K w/o psoriasis
• Increased risk with smokers, obese and hyperlipidemic, but not DM or HTN
• Meta-analysis 25% increased risk

Copenhagen study (ACC 2010)
• Track rates of psoriasis in entire adult and pediatric population 1997-2006
• Severe psoriasis: 54% increase stroke, 21% increase MI, 53% incr 10 year death, higher need for angioplasty
• Mild psoriasis—increase stroke and angio Rx
• Worst prognosis—early age severe disease

Psoriasis and Atherosclerosis: Cellular links and mechanisms
• Shared pathogenic feature: inflammation and T-helper 1 cells of adaptive system results in both coronary and skin plaques
• T helper 1 cells and OxLDL
• Release of cytokines
• Other mechanisms that are shared

Mechanisms of athero in psoriasis
Psoriasis, Subclinical Athero and Physiology Changes

- Carotid IMT worsens
- Central BP and arterial stiffness
- Increased aortic stiffness
- Endothelial function declines
- Coronary calcium increases

Psoriasis Therapies Modify CVD Risk

- Cyclosporine worsens HTN, lipids
- Retinoids increase TG, decrease HDL and insulin sensitivity—MetSyn
- Low dose methotrexate and TNF alpha cardioprotective in both psoriasis and RA

CV and Lipid Rx Alter Psoriasis

- Statins are anti-inflammatory
- Theoretic benefit not proven in decreasing severity
- Beta blockers?
- ACE inhibitors?
- Other therapies?

Ed and Cardiovascular Risk

A man with erectile dysfunction and no cardiac symptoms is a cardiac patient until proven otherwise (Jackson, 2006)

It is an independent risk factor for cardiovascular disease, equivalent to a current moderate smoker

- Men presented with ED for 38 months on average before developing acute chest pain

Erectile Dysfunction: Window to CVD Risk in Men

- Risk of future CVD in pts with ED
- Independent CV risk factor—opportunity
- Pathogenesis
- Endothelial function
- Should all men with ED get a workup?
- What should the CVD workup entail?
- Role of risk factor management and the tools for subclinical athero detection

Vasculogenic ED: Early Warning

- Independent risk factor for CVD
- ED precedes CVD symptoms by 2-5 years
- Severity of ED relates to severity of atherosclerosis, PAD, major events
- More predictive in younger (40-49) men
- Men<40 with ED: 7 times risk
Simultaneous Brachial Artery Ultrasound and PAT Protocol

- 10 min
- 5 min
- Baseline Cuff inflation
- 10 min
- Baseline NTG

Breast Arterial Calcification (BAC) (“Cardio-mammography”)

Breast Arterial Calcification: A new marker of CVD risk

- What is BAC?
- What is its significance?
- What is the prognosis?
- What should be the workup?
- How does it compare to other findings?
- Treatment based upon other findings and risk factors
Vascular calcification in BAC

- Intima vs media
- Atherosclerosis vs arterial compliance
- Path study—BAC more localized to tunica media, but some arteries show intimal thickening
- Diabetes and CKD more associated with media thickening

BAC on screening mammograms

- 6-10% incidence—usually not reported by radiologists
- Predictive of future CVD and DM
- Correlates with EBCT
- Should lead to search for underlying disease and risk factors

Positive associations reported

- Age, diabetes, BMI, HTN, albuminuria, TG, homocysteine, hsCRP
- Duration of diabetes and elev BS
- Inverse relationship BAC and smoking
- Spontaneous and artificial menopause
- Multiparity and hx lactation
- Inverse…hormone therapy
- BAC and osteoporosis

MINERVA Kaiser study

- NHLBI prospective 5 year study
- Ethnic differences in BAC presence and gradation
- Value as a tool in refining risk prediction
- N=5400 multiethnic age 60-79
- Traditional and emerging risk factor correlations. Statin use, estrogen, sleep, psychosocial, etc

Questions to be answered

- Race/ethnic differences as in CAC—is it like in MESA Hispanic>white/AA> Asians?
- Quantification of BAC related to severity?
- Does adding BAC gradation or positivity to CV prediction models improve classification of risk in women?
- Relation to other subclinical measures like CAC and CIMT?

Sleep and the Heart

Sleep disorders are relevant to:
- Arrhythmias
- CAD and its progression
- Sympathetic stimulation
- Hypertension
- Cardiomyopathy (CMO)
- Heart failure (CHF)
- Stroke
- Diabetes and Metabolic Syndrome
OSA Definition (AASM)

• Disorder in which people repetitively stop breathing during sleep and have the nighttime consequences of hypoxemia and sleep fragmentation and daytime consequences on sleepiness and cardiovascular morbidity.

• AASM Task Force Sleep 1999

Early signs of atherosclerosis in sleep apnea

• Increased carotid IMT (Drager, 2005)
• Arterial plaque formation (Kaynak, 2003)
• Coronary calcification (Friedlander, 1999)
• Angiographic lesions (Aboyans, 1999)
• Higher pulse wave velocity (Drager 2005)
• Endothelial dysfunction (multiple reports)

OSA Patients Exhibit High Prevalence Of Cardiovascular Disease: Cross sectional studies

- Hypertension
- Ischemic heart disease
- Coronary heart disease
- Bradypnea
- Acute myocardial infarction
- Stroke

Disease Prevalence

Pathophysiology

- Airway obstruction occurs at multiple levels
- Obstruction leads to intermittent HYPOXIA

- Sympathetic activation → vasoconstriction
- Elevated BP and heart rate
- Induces free-radical production
- Activation of inflammatory pathways
- Oxidative stress e.g. lipoproteins
- Platelet activation/increased clotting

Wisconsin Sleep--NEJM

- Correlation of AHI with prevalence of hypertension 4 years later prospectively
- Controlled for confounding variables like body weight
- AHI of 15 in initial study—3 times risk of future HTN

Peppard NEJM 2000

Resistant HTN

- Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension.
- JNC7—no studies systematically evaluating secondary causes of HTN

Pathophysiology
- Decreased nitric oxide/Impaired vasodilation
- Endothelial dysfunction
- Vascular smooth-muscle proliferation (chronic)
- Decreased cerebral blood flow
- Increased CIMT/
- Pulmonary + systemic HTN
- ? Accelerated atherosclerosis?

Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009; 373: 82-93

CLINICAL REVIEW
Obstructive sleep apnoea syndrome – an oxidative stress disorder
Lena Lale

Keywords: Sleep apnoea, oxidative stress, vascular complications, apnoea-hypopnoea index, hypertension, atherosclerosis, mortality

Abstract: Obstructive sleep apnoea syndrome (OSAS) is associated with an increased cardiovascular risk, through impaired endothelial function. The underlying molecular mechanisms are complex, involving oxidative stress, inflammation, and altered cardiovascular function. In addition, OSAS is associated with increased sympathetic activity, which may contribute to the development of hypertension and atherosclerosis. The relationship between OSAS and oxidative stress is complex, and further research is needed to clarify the mechanisms involved.

Nightly oxidative stress
Endothelial dysfunction
Atherogenesis
MI, HTN, Stroke
Mortality

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