

Women, Diabetes and Heart

Health:



New Frontiers for Cardiology

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Objectives

- Compare & contrast incidence of CAD & HF and predictors of CAD in diabetic men and women.
- Discuss possible pathophysiological reasons for the above.
- Define diabetic cardiomyopathy & possible pathophysiologies.
- Describe the role of the inflammatory phenotype in HF and potential interventions to improve outcomes.



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All Cause Cardiovascular Mortality

- * Death rate for men with DM: ↓ over 30 years from 26.4% to 12.8%/1000 persons
- * Nondiabetic men: 4.8%
- * Death rate for women with DM: essentially unchanged from 10%/1000 persons
- * Nondiabetic women: 2.3%



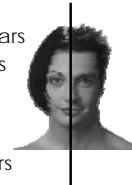
Gregg et al. Ann Intern Med 2007;147:149-155.

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Incidence of CAD and HF in Diabetics

- * Diabetic men
 - * CAD - 24.9% per 1000 person-years
 - * HF - 7.75% per 1000 person-years
- * Diabetic women
 - * CAD - 17% per 1000 person-years
 - * HF - 11.5% per 1000 person-years



Beuters et al. Cardiovascular Diabetology 2003;1:1-16.

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Greater risk for women?



- * CV risk factors more common, more likely to cluster or be more severe in women
- * Some meta-analyses suggest significantly greater risk for CV death for women with diabetes than men.

Gregg et al. Ann Intern Med 2007;147:149-155.

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Why?



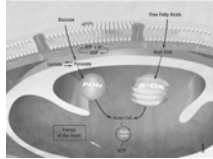
- * For diabetic women, additional independent risk factors for CAD:
 - * High triglycerides/low HDL (diabetic dyslipidemia)
 - * Presence of microvascular complications (microangiopathy)
- * For women, living in Southern Italy (Mediterranean diet) was not associated with risk reduction.

Avogaro et al. Diabetes Care. 2007;30(5):1241-1247

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Diabetic CMP: Mechanisms

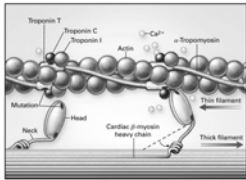
- * Elevated levels of free fatty acids
 - * Increased intracellular FFA associated w/contractile dysfunction
 - * Lipotoxicity → induction of ROS & apoptosis
 - * Vascular & contractile apparatus damage



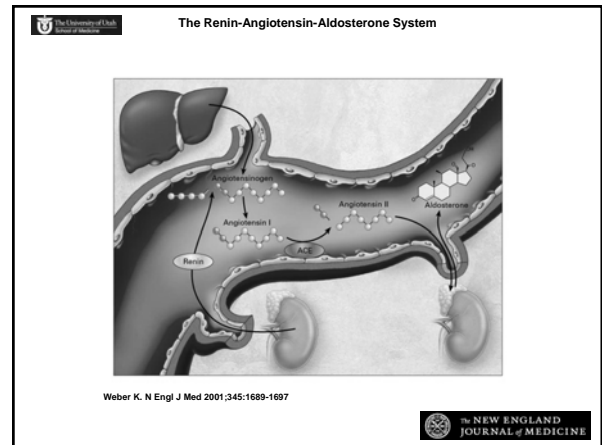
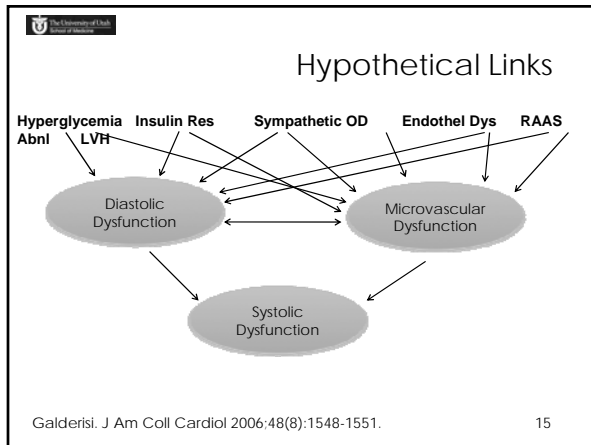
Hayat et al. Clinical Science. 2004;107:539-557.
Matthews. Diabetes. 2007.

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Diabetic CMP: Mechanisms



- * Autonomic dysfunction & gene expression
 - * Activation of RAAS
 - * Expression of fetal genes
 - * Altered contractile proteins β & α myosin heavy chain



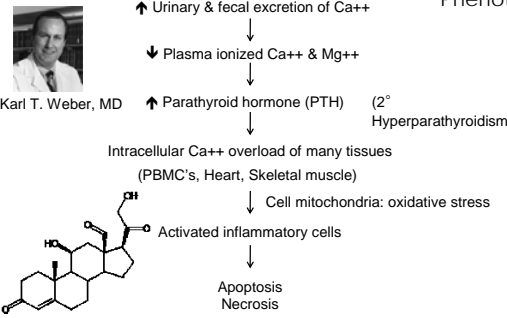
The RAAS in Women & DM

- * [aldosterone] + associated with LV pattern c/w concentric remodeling in women, not men
- * DM: ↑ [renin] ↑ [Ang II] ↑ [aldosterone]
- * Evidence: development of nephrosclerosis, renal and cardiac fibrosis in DM & HTN
- * Promotes effects of angiotensin II (Ang II) & glucose on PAI-1 (promotes thrombosis)

Ramachandran et al. Hypertension. 2004;43:957-962
McFarlane et al. J Clin Endocrinol & Metab 2003;88(2):516-523
Hollenberg et al. Kidney International 2004; 64:1435-1439.

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Aldosterone Heart Failure: An Inflammatory Phenotype



↑ Urinary & fecal excretion of Ca^{++}

↓ Plasma ionized Ca^{++} & Mg^{++}

↑ Parathyroid hormone (PTH) (2° Hyperparathyroidism)

Intracellular Ca^{++} overload of many tissues (PBMC's, Heart, Skeletal muscle)

Cell mitochondria: oxidative stress

Activated inflammatory cells

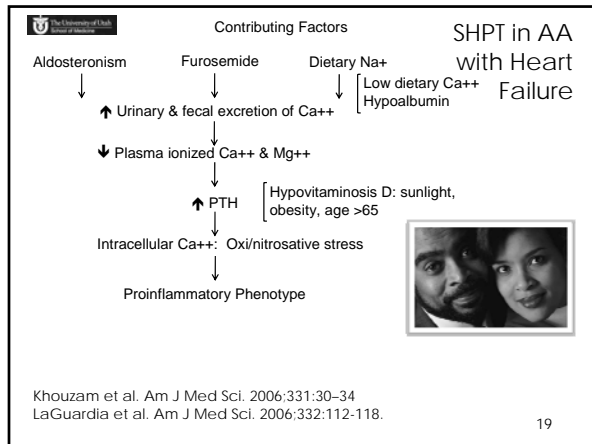
Apoptosis
Necrosis

Chemical structure of Aldosterone: C[C@]12CC[C@@H]3[C@H]([C@@H]1CC[C@@H]2O)CCC4=CC(=O)CC[C@]34C

Karl T. Weber, MD


Chhokar et al. Circ 2005;111:871.

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Hypovitaminosis D: DM

- * Hypovitaminosis D
 - * Associated with insulin resistance and B cell dysfunction
 - * More common in women
 - * More than 50% postmenopausal women taking meds for osteoporosis
 - * 48% preadolescent girls (Maine)
 - * 42% 15-49 y/o AA girls and women
- * Hypovitaminosis D < 30 ng/mL → increased parathyroid hormone secretion




Chiu et al. Am J Clin Nutr 2004; 79:820-825
Holick. N Engl J Med 2007;357:266-281.

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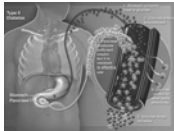

Zinc Deficiency

- * Common in women (DM2), children, adults with HF
 - * Required by more than 100 enzymes
 - * Affects proliferation, maturation of lymphocytes
 - * Impaired macrophage & neutrophil function, natural killer cell & complement function
 - * Protects against oxidative stress (Cu/Zn SOD)
 - * Thought that some immunological features of DM very similar to those of zinc deficiency
 - * Helps stabilize RNA, DNA, ribosomes



HF & DM: Systemic Illnesses


- * Both have some similar features:
 - * RAAS activation
 - * Oxidative stress
 - * Inflammation
- * Related pathophysiologies
 - * Lost minerals: K⁺, Ca⁺⁺, Mg⁺⁺, Zn⁺⁺
 - * Hypovitaminosis D
 - * Secondary hyperparathyroidism

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Possible Interventions

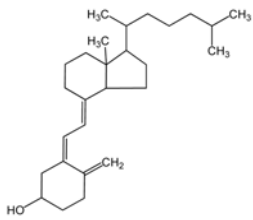
- * Spironolactone: blocks effects of aldosterone
- * HCTZ: blocks urinary excretion of Ca⁺⁺
- * Supplementation: Ca⁺⁺, Mg⁺⁺, D3, K⁺, Zn⁺⁺
- * Parathyroidectomy
- * Cinacalcet: calcimimetic
- * Amlodipine: blocks Ca⁺⁺ L channel
- * Sunlight exposure: hands, face & arms, 5-15 minutes daily, 2-3 times weekly



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Vitamin D Supplementation

- * Cholecalciferol (D3) rec as supplement
- * 25OHD < 20 ng/mL (def): 50,000 IU weekly x 6-8 weeks; then 800 to 1000 IU D3 daily
- * 25OHD 20-30 ng/mL (insuff): 800 to 1000 IU daily for 3 months
- * Malabsorptive states: 10,000 to 50,000 IU daily




Dawson-Hughes. UpToDate. 10/2/2008

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Calcium Supplementation

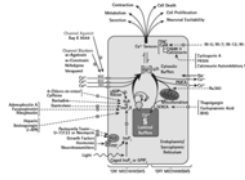
- * Calcium carbonate better with meals
 - * Poorly absorbed with PPI's or H2 blockers (rec citrate)
- * Calcium citrate better in fasting state
- * Divided doses: no more than 500 mg at a time can be absorbed
- * Postmenopausal: 1200 – 1500 mg/daily (plus 800 IU D3)
- * Adults 51 or older: 1200 mg daily (plus 800 IU D3)
- * Adults 19-50: 1000 mg daily (plus 400-800 mg D3)
- * Increase Ca++ intake and maintain vitamin D stores



Rosen. UpToDate. 10/2/2008 25

Ca++: Food


- * 1 cup plain yoghurt (425 mg)
- * 1 Cup skim milk (302 mg)
- * 2% cottage cheese, 1 cup (155 mg)
- * Parmesan cheese, 1 tbsp (69 mg)
- * 1 cup rhubarb (348 mg)
- * ½ cup broccoli (89 mg)
- * 1 cup green beans (58 mg)
- * 3 oz tofu (150 mg)
- * 3-4 oz salmon 225)
- * 3 oysters (100 mg)
- * 3 shrimp (50 mg)



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Zinc Supplementation

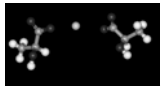
- * Women 19+ years: 8 mg daily
- * Vegetarians require 50% more zinc
- * Foods
 - * 6 oysters (76.7 mg)
 - * King crab (6.5 mg)
 - * Roasted chicken leg (2.7 mg)
 - * 3 ounces cooked lobster (2.5 mg)
 - * 1 ounce cashews (1.6 mg)
- * Large amts iron can decrease Zn absorption (take Fe between meals)
- * Thiazide diuretics deplete zinc (up to 60% increased urinary excretion)



Office of Dietary Supplements, US Gov, Fact Sheet 27

Magnesium Supplementation


- * Difficult to measure (intracellular)
- * Suspect: chronic diarrhea, hypocalcemia, refractory hypokalemia, ventricular arrhythmias
- * Daily excretion of >10-30 mg indicates renal Mg++ wasting (diuretics, cisplatin, aminoglycosides)
- * Slow oral replacement
 - * Slow Mag (Mg(Cl-)2)
 - * Mag-Tab SR (Mg lactate)
 - * 5-7 mEq or 60-84 mg per tablet
 - * 6-8 tablets daily divided for severe
 - * 2-4 tablets for mild
- * Add K+ sparing diuretic to loop diuretic (amiloride) or aldosterone antagonist



Agus. UpToDate. 2/13/2008 28

CV Disease Prevention Guidelines for Women


- * Lifestyle interventions
 - * Smoking cessation
 - * Physical activity
 - * Rehab (post CV events)
 - * Weight: BMI 18.5 to 24.9
 - * Diet rich in fruits, veggies; whole grain, high fiber; oily fish at least twice weekly; limit fat to <10% energy (<7% ideal); cholesterol <300 mg/d; alcohol no > 1 drink/d; sodium to <2.3 g/d (tsp); avoid trans fatty acids
- * BP <120/80
- * LDL <100 (<70)
- * Triglycerides <150
- * HDL >50
- * Non-HDL <130
- * Hgb A1c <7%



Mosca et al. Circulation. 2007;115 29

CV Disease Prevention Guidelines for Women

- * Preventive Drugs
 - * ASA 81 to 325 mg daily in high-risk women
 - * Beta-blockers after MI, ACS, LV dysfxn
 - * ACEI/ARB's post MI, LVEF ≤ 40%, s/s CHF, or DM
 - * Aldosterone antagonism post-MI with ACEI, BB & LVEF ≤40% or s/s CHF
- * Not useful/possibly harmful
 - * Hormone therapy or selective estrogen-receptor modulators
 - * Antioxidants (E, C, beta carotene)
 - * Folic acid
 - * ASA 81 in healthy women <65



Mosca et al. Circulation. 2007;115 30

What Would We Add for Women with DM?

- * Evaluation of [25OHD]
 - * Vitamin D supplementation
 - * Sunlight exposure
- * Calcium supplementation
- * Magnesium supplementation if urinary excretion elevated
- * Zinc supplementation if diuretics or polyuria
- * Use of ACEI + aldosterone antagonists for treatment of HTN, HF, LVH
- * A statin – find an indication (powerful antiinflammatory drugs)



Areas for Further Investigation

- * Characterize the pro-inflammatory phenotype in women with DM 2
- * Investigate the use of aldosterone antagonists and ACEI to prevent diabetic cardiomyopathy in women
- * Aldosterone antagonism in women with DM2 and endothelial dysfunction (NIH study NCT00214825)
- * Development of a dietary supplement containing appropriate amounts of macro and micronutrients specifically for women with DM

