



Sexual dysfunction in diabetes mellitus

Bruce E. Wilson MD

April 20, 2007

WADE Conference

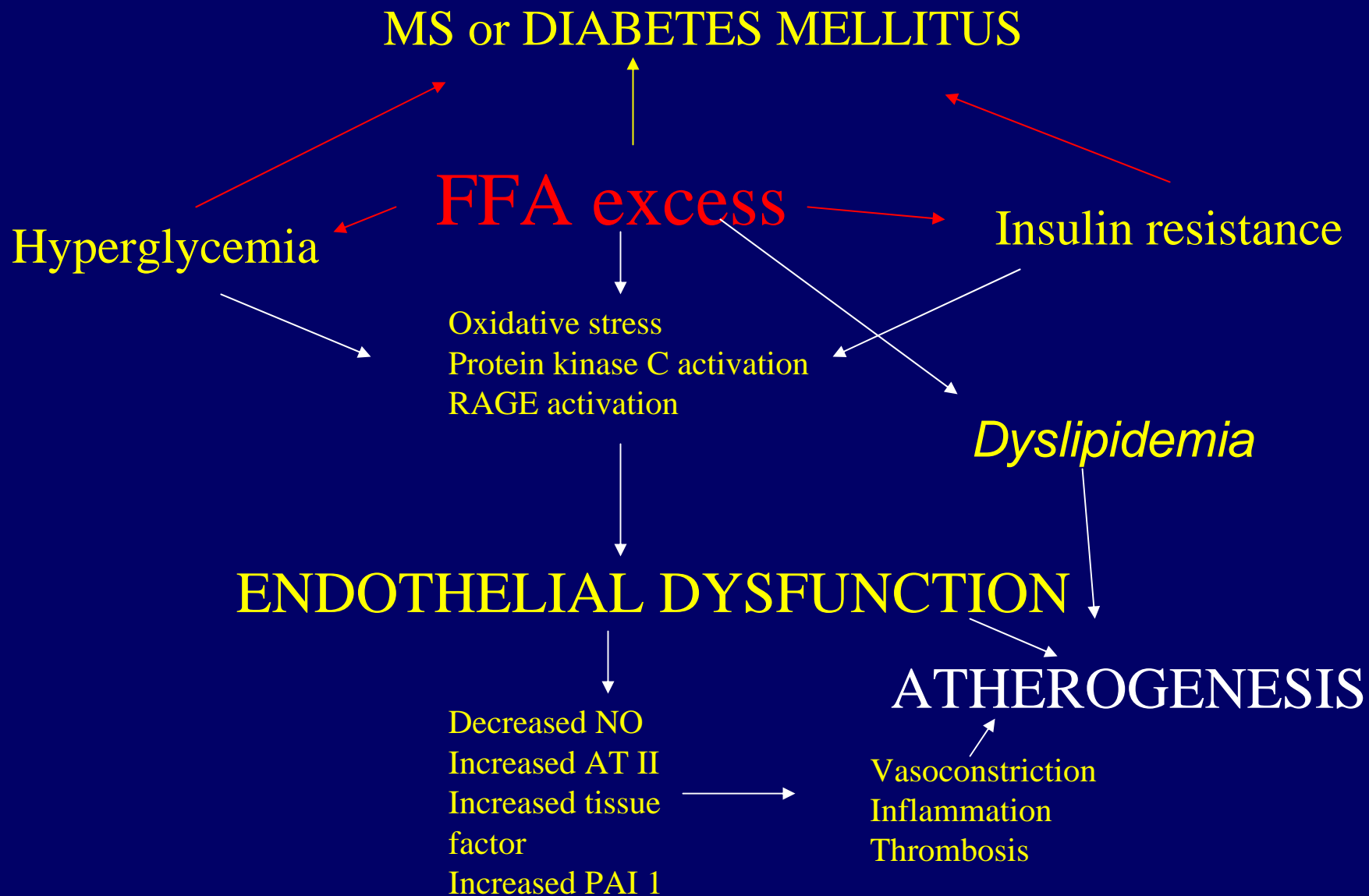


M

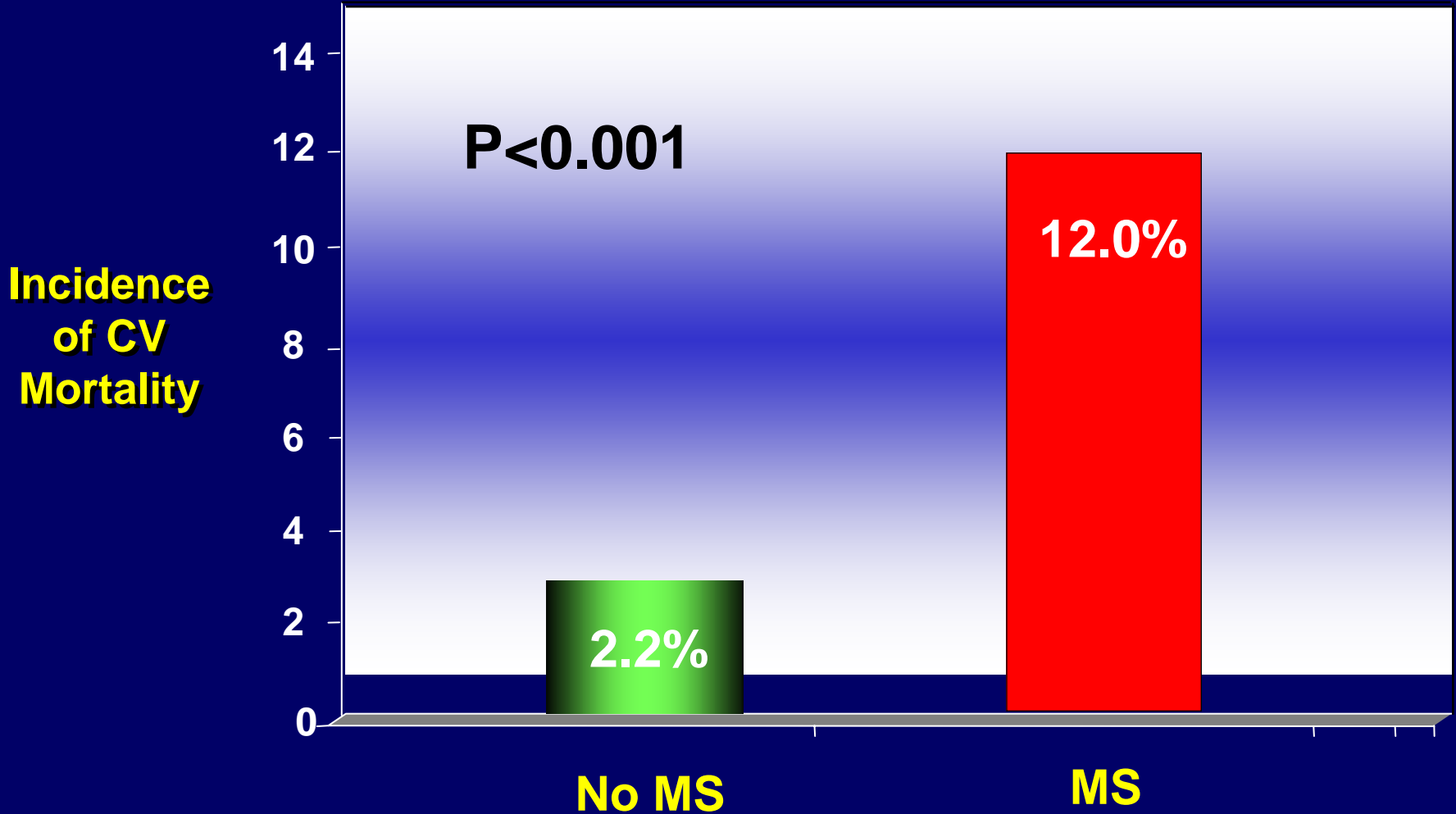
Mature audiences
Adult themes

Summary

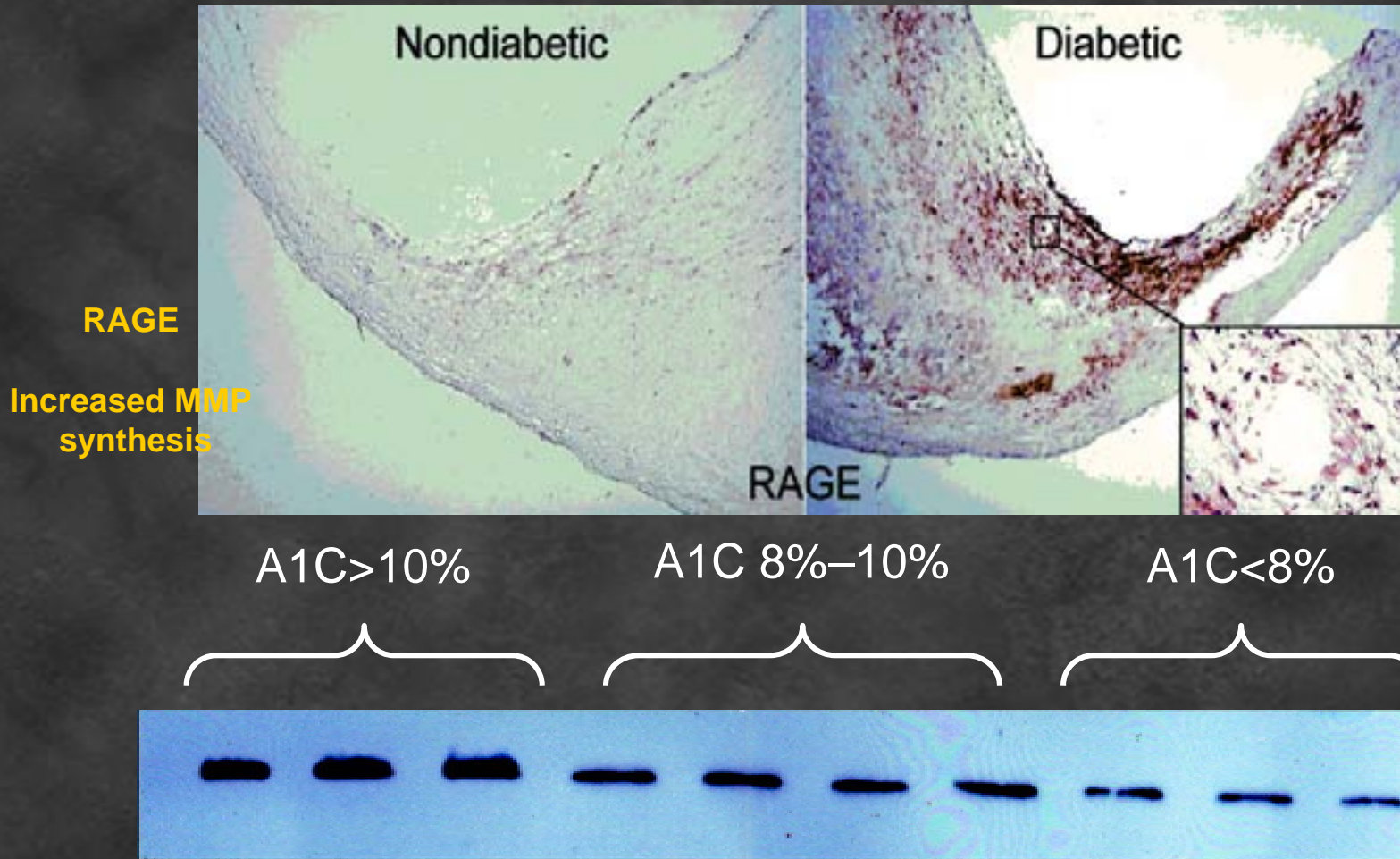
- Normal sexual function
- Hyperglycemia as a direct cause of sexual dysfunction
- Male hypogonadism and PCOS in DM
- The relationship of adiposity to abnormal sex steroid levels
- Some therapies of sexual dysfunction



Cardiovascular Mortality Associated With Metabolic Syndrome (MS)



RAGE Expression in Diabetic Atheroma



Reprinted with permission.

Cipollone F, Iezzi A, Fazia M, et al. The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: role of glycemic control. *Circulation*. 2003;108:1070–1077.

DM: sexual dysfunction/females

- Decreased vaginal lubrication associated with neural disease and chronic lower ECV
- Decreased sexual response; decreased libido; decreased genital sensation; decreased clitoral engorgement.
- Dyspareunia
- Vaginal infections; UTIs
- Early menopause/autoimmune

DM: sexual dysfunction/male

- ED: inability to attain or maintain an adequate erection
- ED: 20-85 % of male diabetics; occurs 10-15 years earlier than in non-diabetics
- ED: 5% of undiagnosed DM
- Hormonal disorders
- Retrograde ejaculation
- Associated hypertension, dyslipidemia, macro-and microvascular disease

Normal sexual arousal/female

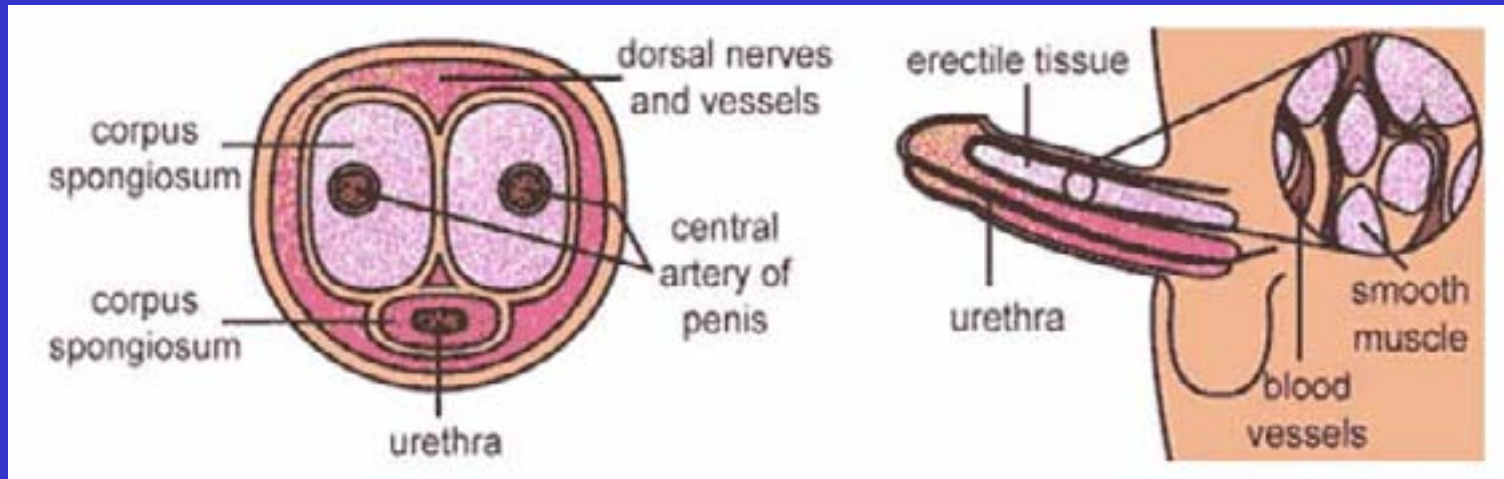
- Vaginal/clitoral blood flow: pudendal, perineal, posterior labial arteries
- Stimulation → vasocongestion and transudation of fluids for lubrication and protection
- Uterus and cervix move upward inducing vaginal ballooning
- Clitoral tumescence



Normal penile erection

- Adequate blood flow and normal neural function intrapenile blood flow
- Relaxation of smooth muscle surrounding the corpus cavernosa
- CNS stimuli leads to cholinergic release partially blocking alpha adrenergic stimulation leading to increase blood flow into the penis
- Increased NO production → increase cGMP → more vasodilatation

Normal erectile function



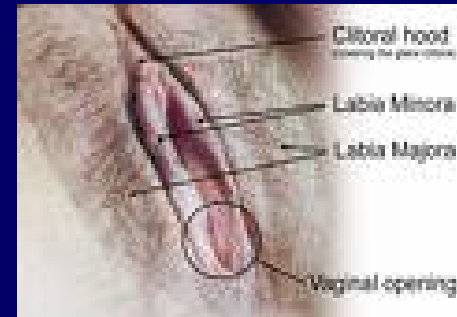
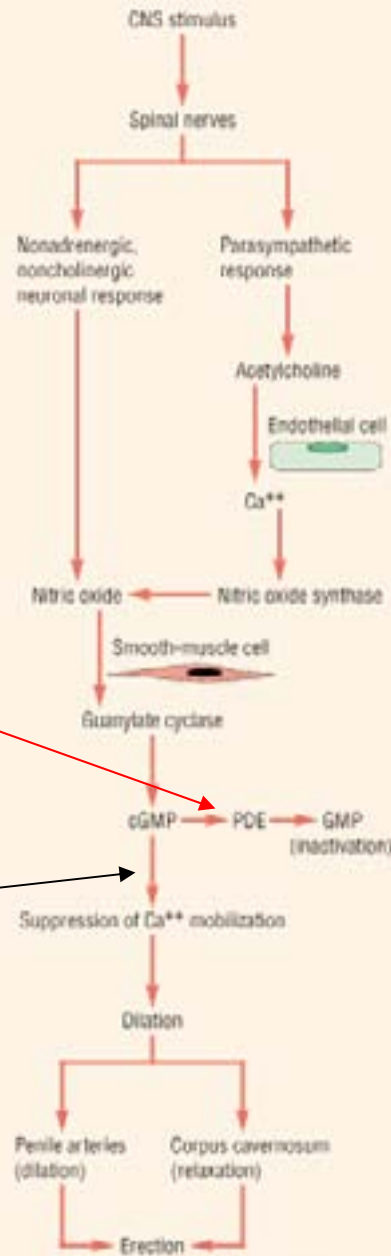
Corpora cavernosa-multiple sacs surrounded by smooth muscle

Flaccidity is maintained by contraction of smooth muscle-alpha stimulation, prostaglandins, Endothelin.



sildenafil (-)

PKC decrease in IC calcium



cGMP, cyclic guanosine monophosphate; CNS, central nervous system; GMP, guanosine monophosphate; PDE, phosphodiesterase type 5.

Adapted, with permission, from Kirby et al.¹¹

ED-etiological

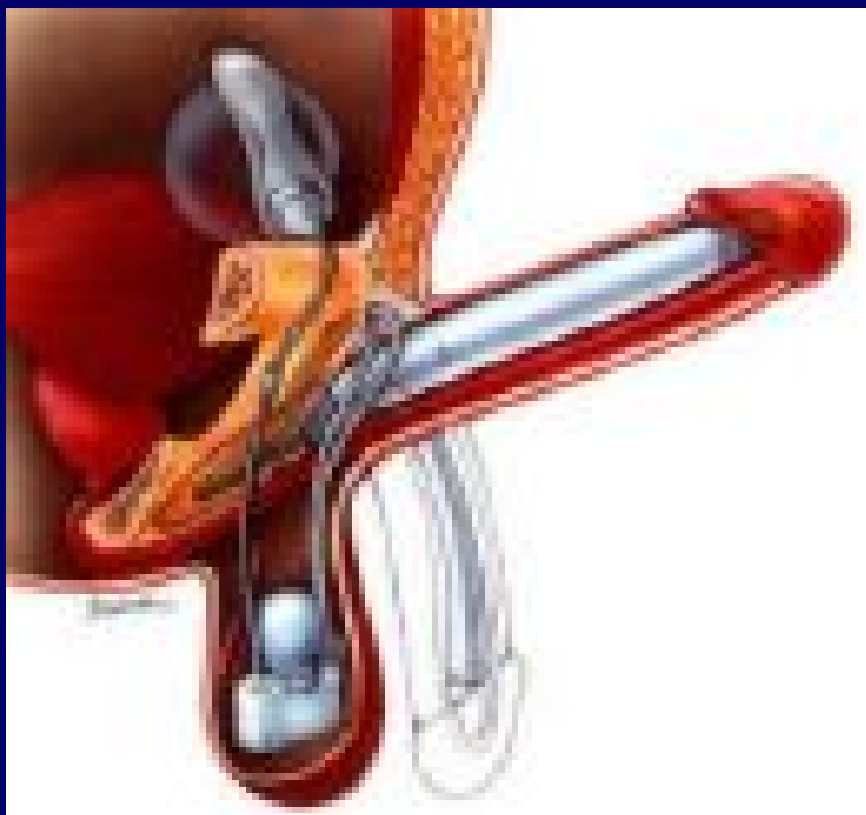
- Diabetes: decrease in the NO-induced vasodilatation
- Diabetes: macrovascular impairment
- Diabetes: decrease in autonomic-mediated smooth muscle relaxation
- Diabetes: sensory dysfunction

Therapies for ED

- PDE5 inhibitors
- Penile injections (alprostadil)/urethral suppositories
- Vacuum devices
- Penile implants



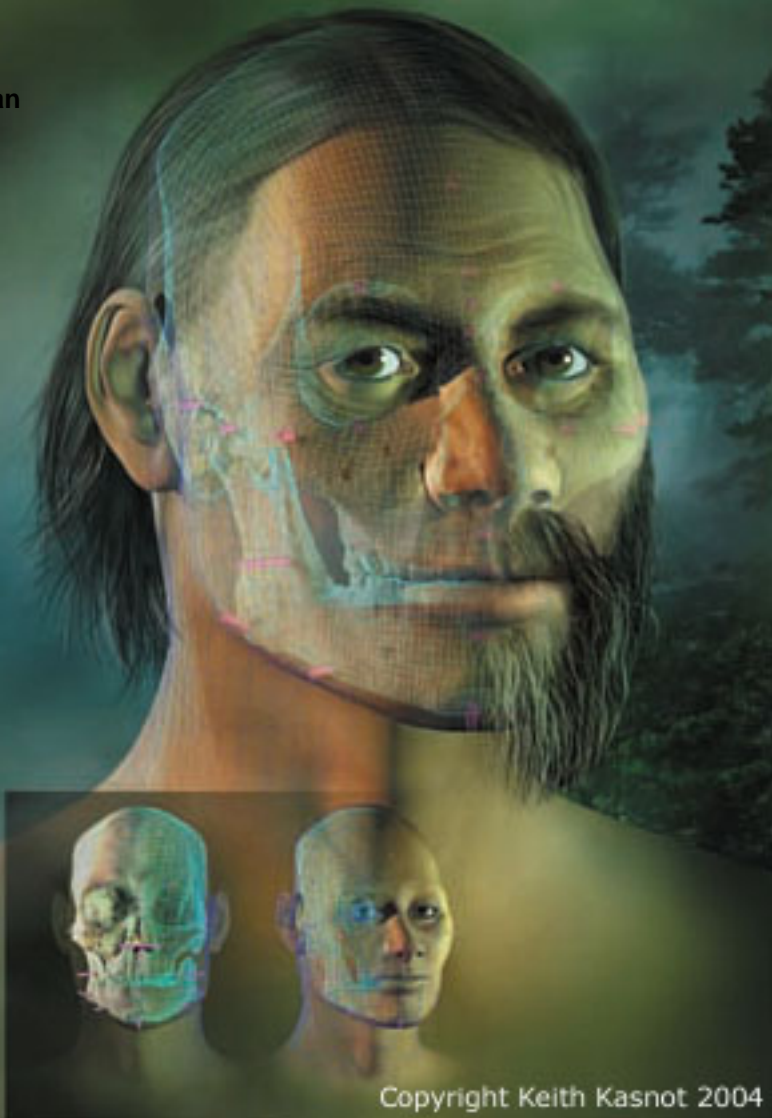




ED-history

- Medications-antihypertensives, spironolactone, antidepressants
- Drugs-marijuana, alcohol
- Testicular tumors
- CNS disease
- Hyperprolactinemia

K Man



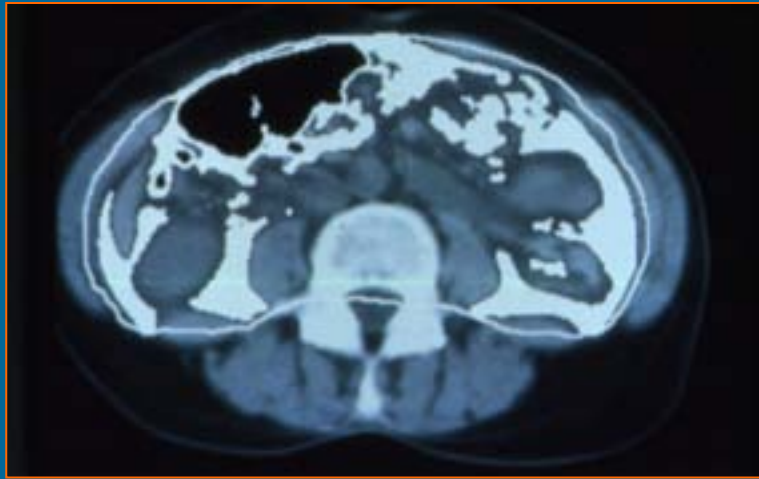
Copyright Keith Kasnot 2004

devolution

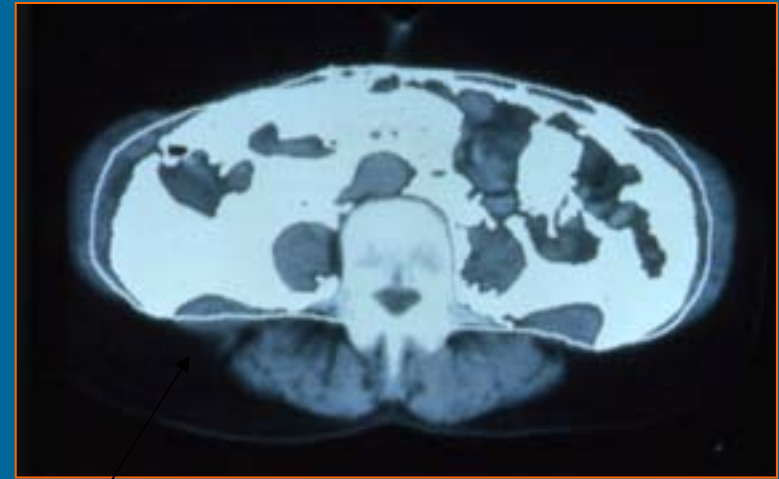


Visceral Fat Distribution

Normal vs Type 2 Diabetes

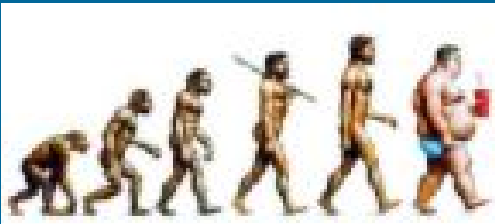


Normal



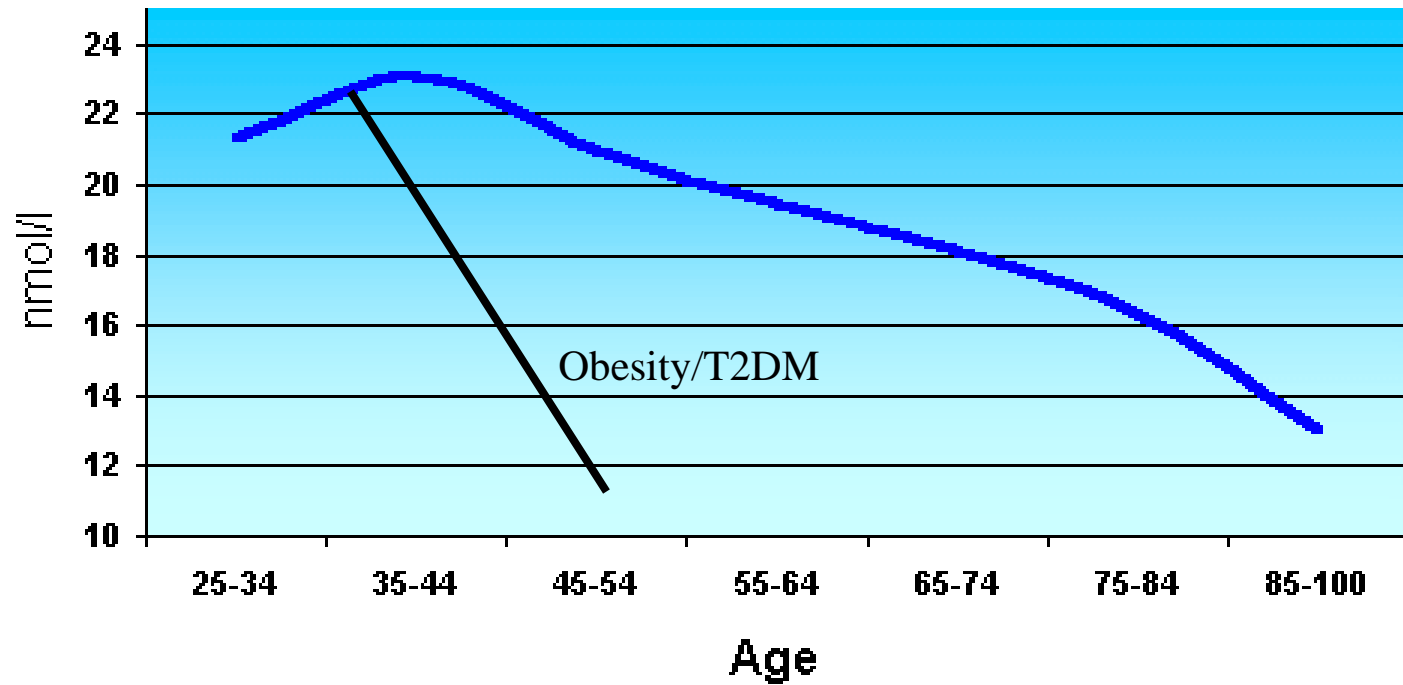
Type 2 Diabetes

macrophage



Courtesy of Wilfred Y. Fujimoto, MD.

TESTOSTERONE (plasma levels by decade)



dementia

54 inch waist

Leg ulcers

Gout



HENRY VIII

1491-1547

Six wives

Two+ mistresses

3 children from his first 3 wives

6 by mistresses, all before 1533

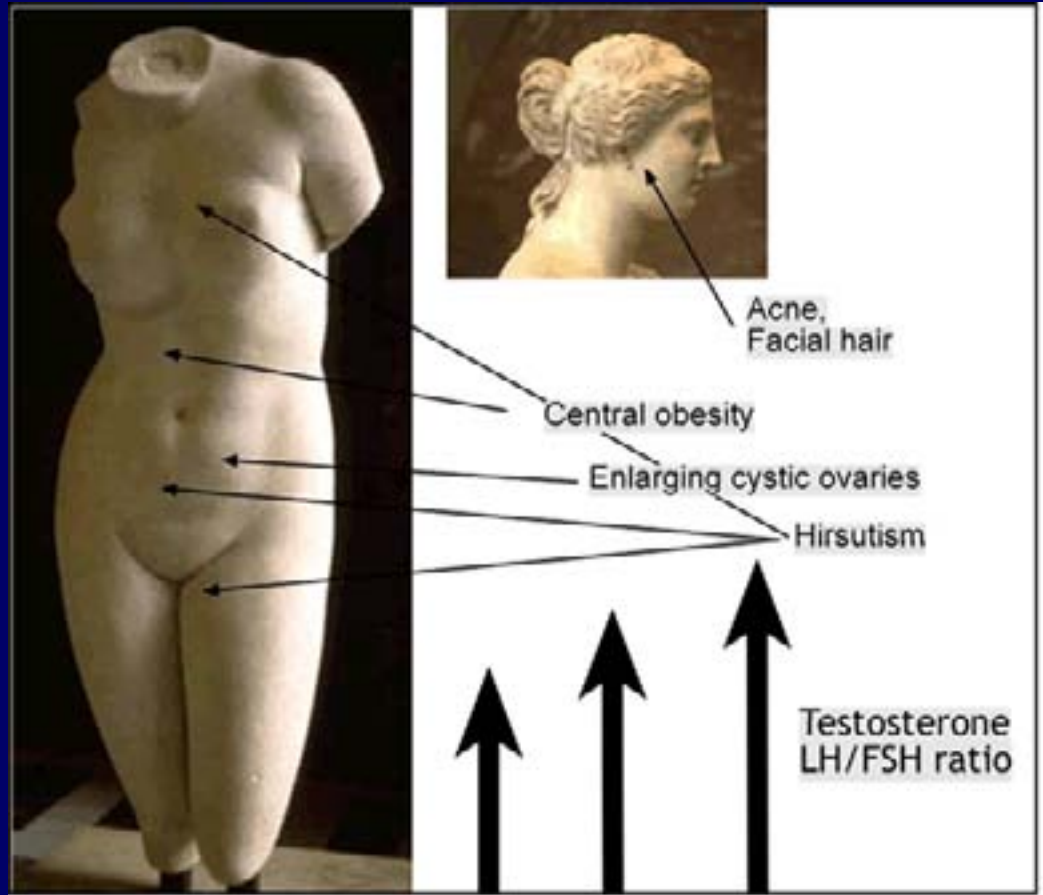


Male hypogonadism/obesity

- Mild central hypogonadism is commonly seen in DM and/or obesity
- This is related to some degree to ED, lack of a feeling of well being, decrease in muscle mass and an increase in central adiposity
- SHBG levels are lower



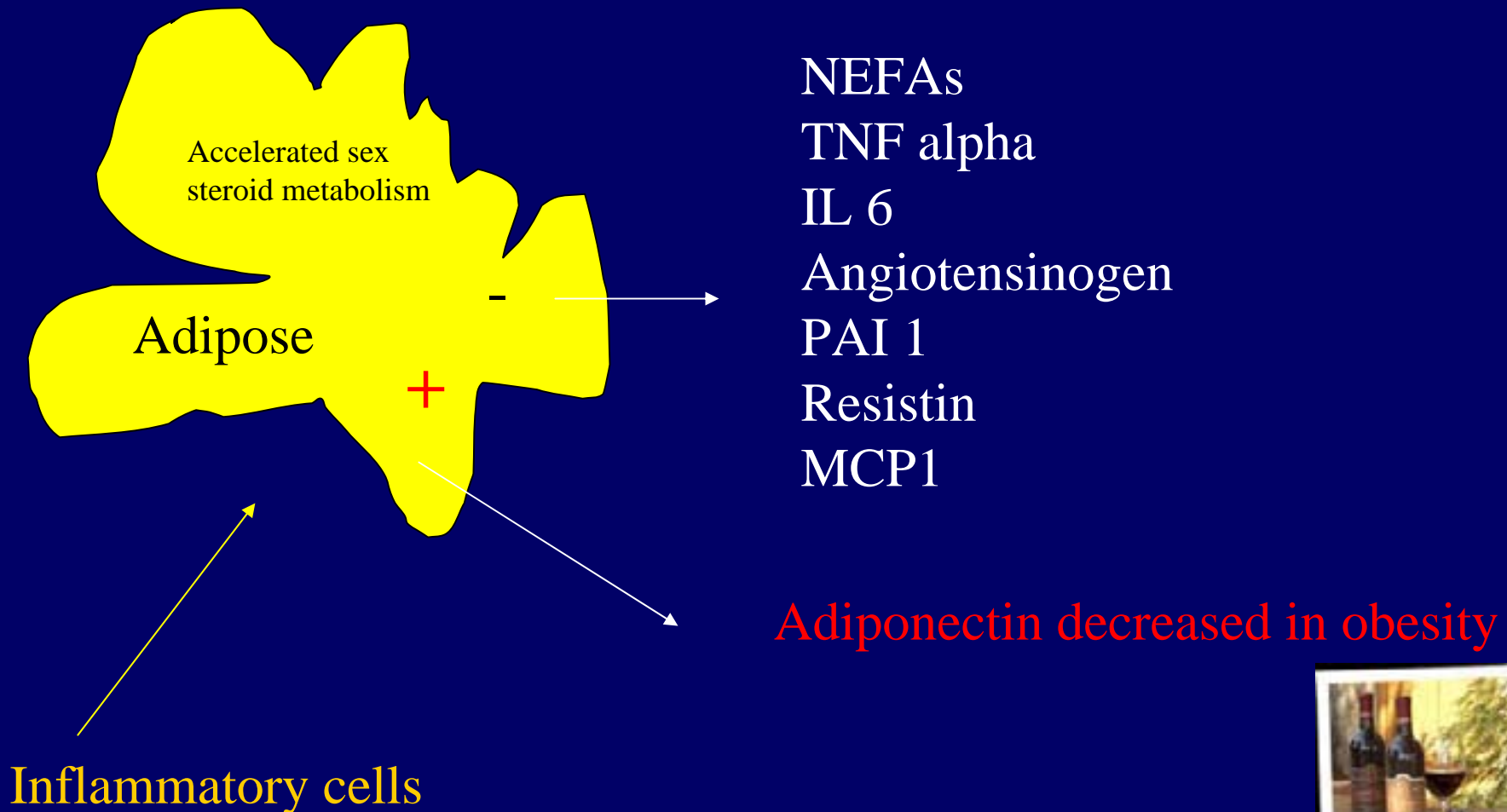
Polycystic Ovarian Syndrome



PCOS

- Described by Stein and Levinthal 1935: polycystic ovaries, androgenic characteristics, oligomenorrhea/infertility
- Most common endocrinopathy of females of reproductive age
- Hypotheses: central; ovarian; insulin resistance

FAT is ACTIVE: Adipokine production



Adipocyte as an endocrine organ

- Leptin-ob gene in mice; onset of puberty, energy balance in pregnancy, inhibition of lipogenesis. Leptin is a cytokine and can increase macrophage activity.
- Adiponectin-exclusive adipocyte complement related protein. Decreased in insulin resistant obesity. Increased with PPAR-gamma agonists.
- Adipsin-serine protease acting on the alternative pathway of complement activation.
- Acylation stimulating protein-increased in obesity; increases lipid deposition in adipocytes.
- Angiotensinogen-increased with hyperglycemia; renin, angiotensin converting enzyme and angiotensin receptors are also produced by adipose tissue.
- Resistin-induces insulin resistance; mRNA suppressed by TZDs.
- TNF-alpha-interferes with insulin signaling by increased serine phosphorylation.
- PAI-1-serine protease; disruption of fibrinolysis.
- FFAs-drives the process of insulin resistance and dyslipidemia.
- MCP-mononuclear chemoattractant protein

Adipose mass/sexuality

- Direct correlation between adiposity, especially central adiposity, and sexual function and libido
- Majority of circulating steroid hormones are from the adrenal and gonads; however, adipose tissue has a full array of activating, inactivating, and interconversion enzymes
- 100% of circulating estrogen in postmenopausal women originates in the adipose tissue; 50% of the circulating testosterone in premenopausal females

Adipose tissue/sexuality

- Aromatase: androgens → estrogens
- 17 beta HSD increases the conversion of weaker sex steroids to more potent varieties
- Central adipose has a higher 17 beta HSD/aromatase activity ratio

Macronutrient → Excess Oxidative Stress → sexual dysfunction

Caloric Excess
No Exercise



PREVENTION:

Diet/exercise
Metformin
Statin
ACEi
ARB
Acarbose
TZD

Macronutrient Accumulation

Muscle

Liver

Adipose

Endothelium

Inflammatory Response
(Oxidative mechanisms)

Atherothrombosis

T2DM

+ Genetic factors

Sexual dysfunction in DM

- Multifactorial: vascular disease, neural disease, autoimmune disorders and excessive adiposity
- The best therapy is intensive metabolic control, normalization of body weight, exercise, cessation of smoking

Potential Atherogenic & Antiatherogenic Actions in Vascular Cells

