Sexual dysfunction in diabetes mellitus

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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
MS or DIABETES MELLITUS

FFA excess

Hyperglycemia

Oxidative stress
Protein kinase C activation
RAGE activation

Insulin resistance

Dyslipidemia

ENDOTHELIAL DYSFUNCTION

Decreased NO
Increased AT II
Increased tissue factor
Increased PAI 1

ATHEROGENESIS

Vasoconstriction
Inflammation
Thrombosis
Cardiovascular Mortality Associated With Metabolic Syndrome (MS)

Incidence of CV Mortality

No MS: 2.2%
MS: 12.0%
P < 0.001

RAGE Expression in Diabetic Atheroma

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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
ED-etiologies

• 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
devolution
Visceral Fat Distribution
Normal vs Type 2 Diabetes

Normal

Type 2 Diabetes

macrophage

Courtesy of Wilfred Y. Fujimoto, MD.
HENRY VIII
1491-1547

Six wives
Two+ mistresses

3 children from his first 3 wives
6 by mistresses, all before 1533

dementia

54 inch waist

Leg ulcers

Gout
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

- NEFAs
- TNF alpha
- IL 6
- Angiotensinogen
- PAI 1
- Resistin
- MCP1

Adiponectin decreased in obesity

Accelerated sex steroid metabolism

Inflammatory cells
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 $\rightarrow$ 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

Macronutrient Accumulation

Muscle  Liver  Adipose  Endothelium

Inflammatory Response
(Oxidative mechanisms)

Atherothrombosis

T2DM

PREVENTION:
Diet/exercise
Metformin
Statin
ACEi
ARB
Acarbose
TZD

+ 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

Angiotensin Receptor 1

Insulin Receptor /AT2

PKC

Shc

IRM-1,2

NO-Mediated Vasodilation