Role of Diabetes, Metabolic Syndrome and Vascular Disease

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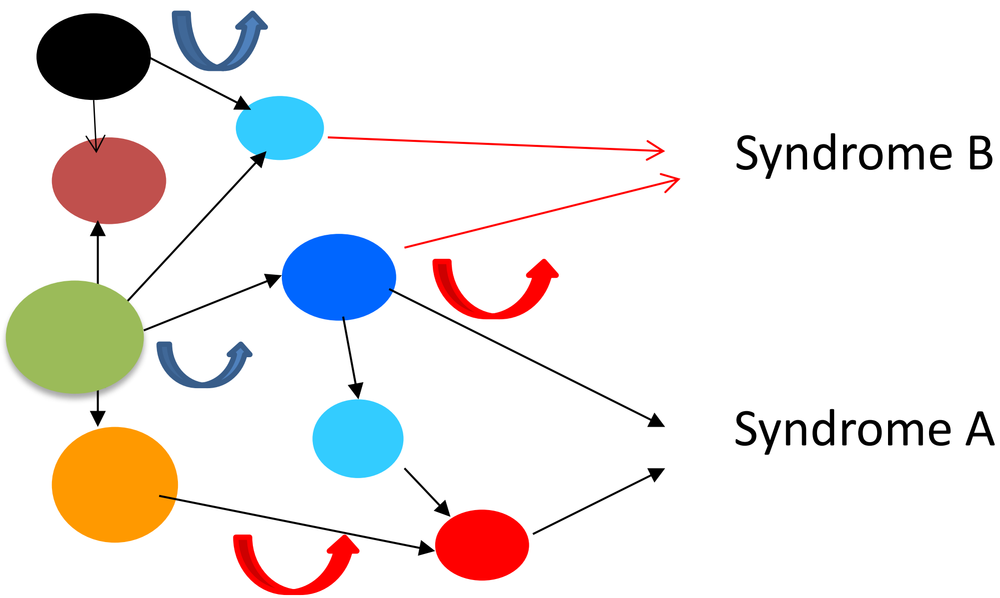
[On the way to Dartmouth-Hitchcock Medical Center and the Geisel School of Medicine]

Disclosure

- Geriatrician's perspective on translational, T1-3 science



Significance

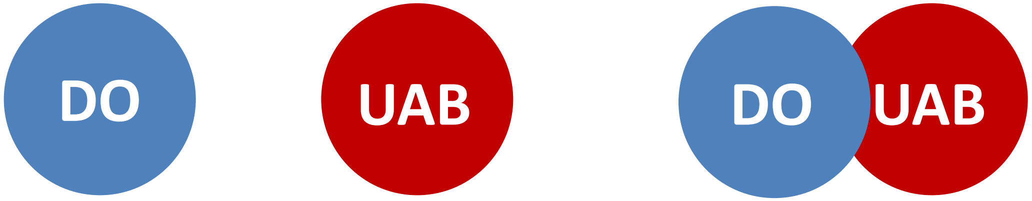
- Obesity and diabetes are epidemic in the US and increasingly across the globe, with subsequent impact on morbidity, function, mortality, and health care costs.
- Both conditions have multiple ties to metabolic syndrome (MetS) and vascular disease
- All four entities have epidemiologic association with urinary incontinence
- All four entities present valuable opportunities for translational understanding, novel clinical treatments, and prevention of UI

Syndromic structure…

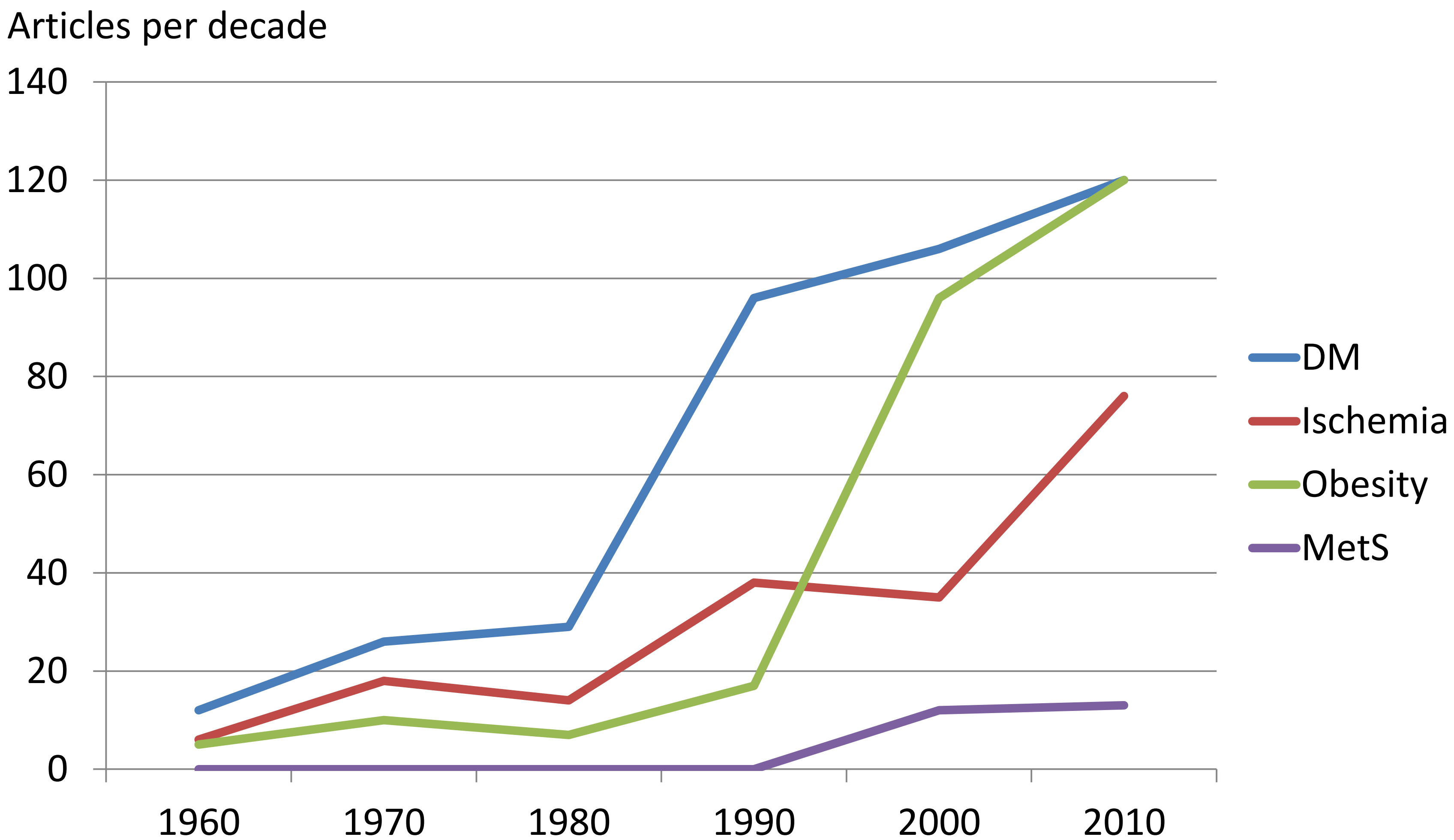
- Both obesity and diabetes are related to "downstream" vascular disease
- Metabolic syndrome (MetS) is a related and "upstream" precursor / risk factor for diabetes and vascular disease
- The hallmark of MetS – large waist circumference - trends with obesity

Parallels to aging effects on bladder

- Physiologic and mechanistic studies, especially regarding DM and UI / detrusor dysfunction, suggest parallels to the spectrum and potentially progression of age-related detrusor changes - from detrusor overactivity to the underactive bladder
- Geriatric syndromic models of disease apply particularly well to DM- and MetS-related bladder dysfunction and UI



“State of the Art Knowledge”



Diabetes mellitus

- DM increases the risk of UI approximately two-fold
- The risk applies to both incident and prevalent UI
- UI is one of the most prevalent complications of the disease
- Risk factors for UI in older persons with DM:

Risk factor	OR (95% CI)
Age > 85	3.13 (2.15-4.56)
Dependent for ambulation	1.48 (1.19-1.84)
Dependent for transfers	2.02 (1.58-2.58)
Cognitively impairment	1.41 (1.15-1.73)
On insulin	2.62 (1.67-4.13)
Higher A1c	NS (unless > 9: 1.67 [1.09-2.57])

Hsu J et al, *BMC Geriatrics.* 2014

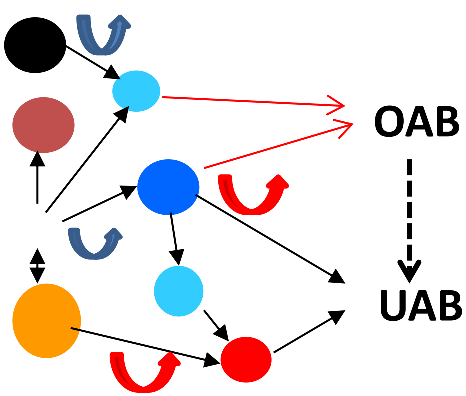
Lee SJ et al, *J Women's Health, 2013*

This is not your father's diabetic bladder…

- DBD not a distinct entity, but a time-dependent course of changes

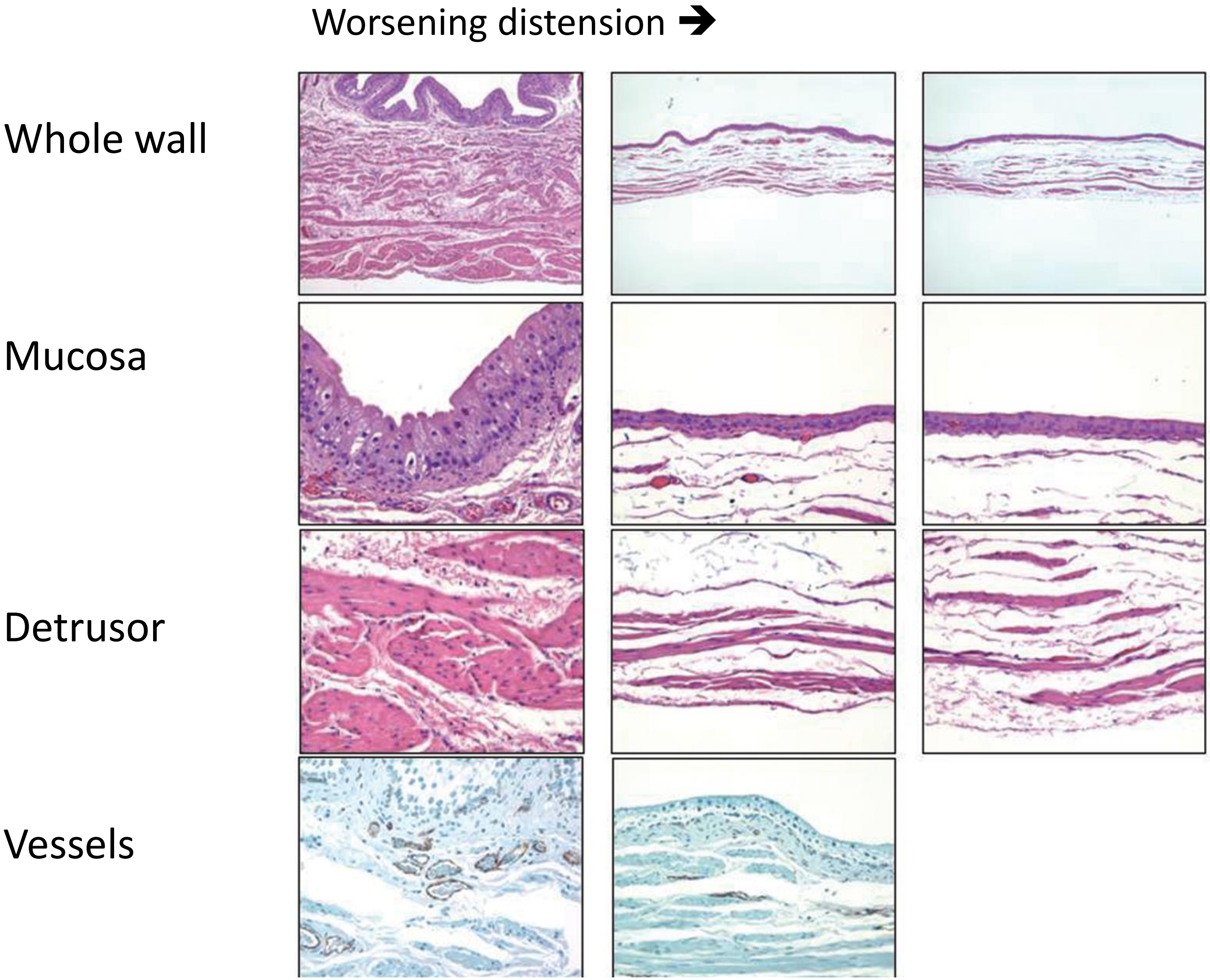
	Early Phase →	Late Phase
	Compensated Function	Decompensated Function
	Time Course/Risk factors ??	
Clinical:	**Storage problems**	**Voiding Problems**
Urodynamics:	**Overactive Bladder**	**Atonic Bladder**
In-vitro:	**Hypercontractile Detrusor**	**Hypocontractile Detrusor**

Glycosuria, over-distention



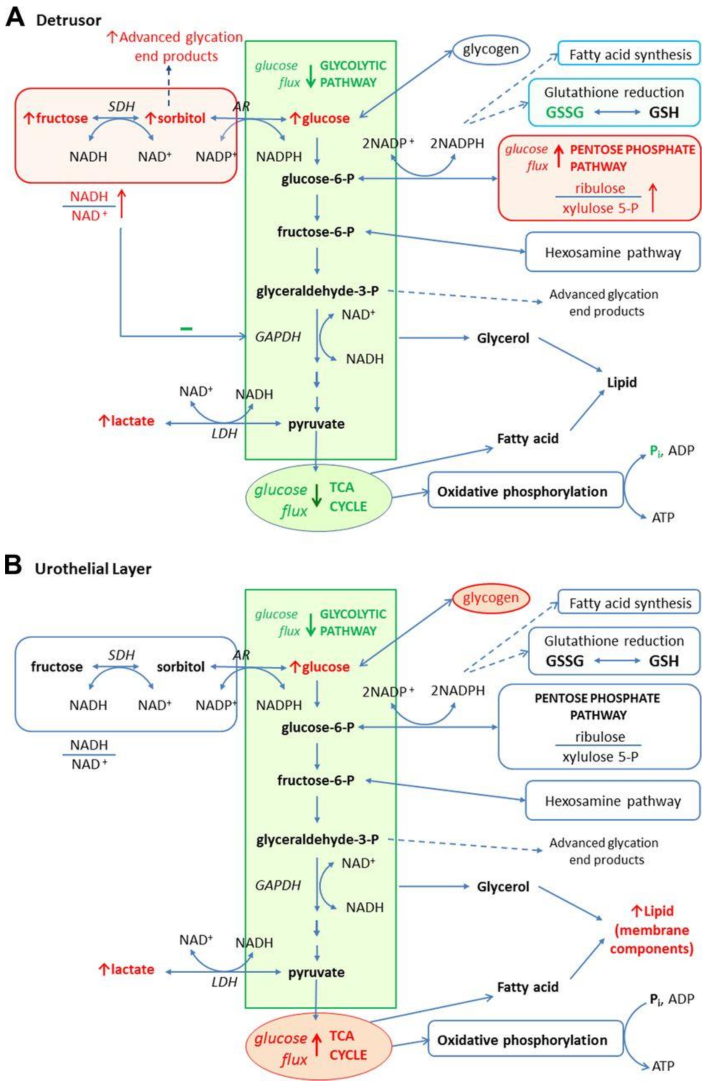
Oxidative stress
Ischemia
Inflammatory agents (eg, TGF-beta)
Alteration in collagen and elastin
Urethral function

Daneshgari F et al, *J Urol* 2009

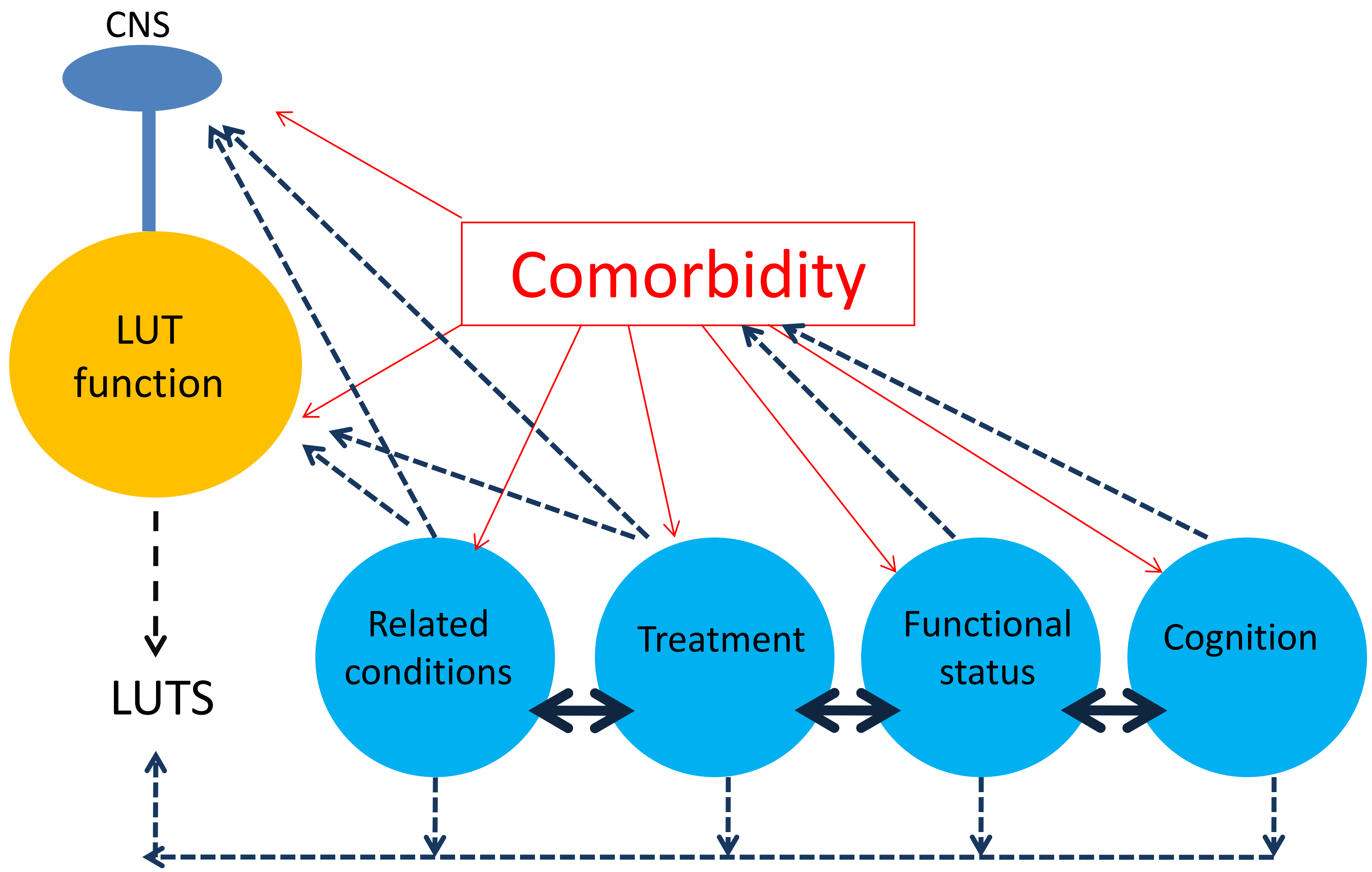


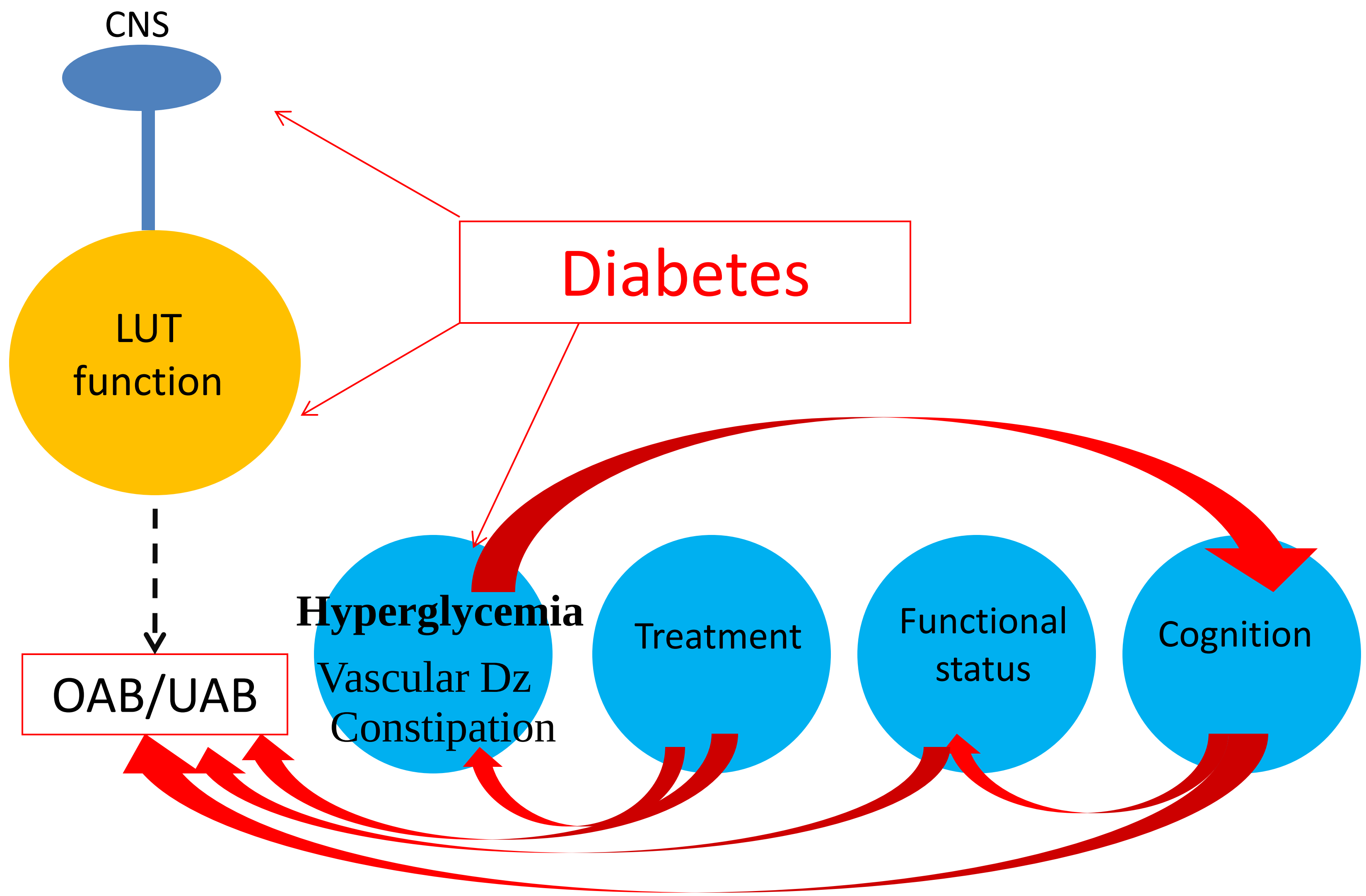
Matsumoto S and Kakizaki H, *Int J Urol* (2012) 19, 20–25

Comparison of changes in the energy generating pathways between the nondiabetic and diabetic detrusor (A) and urothelial layer (B).

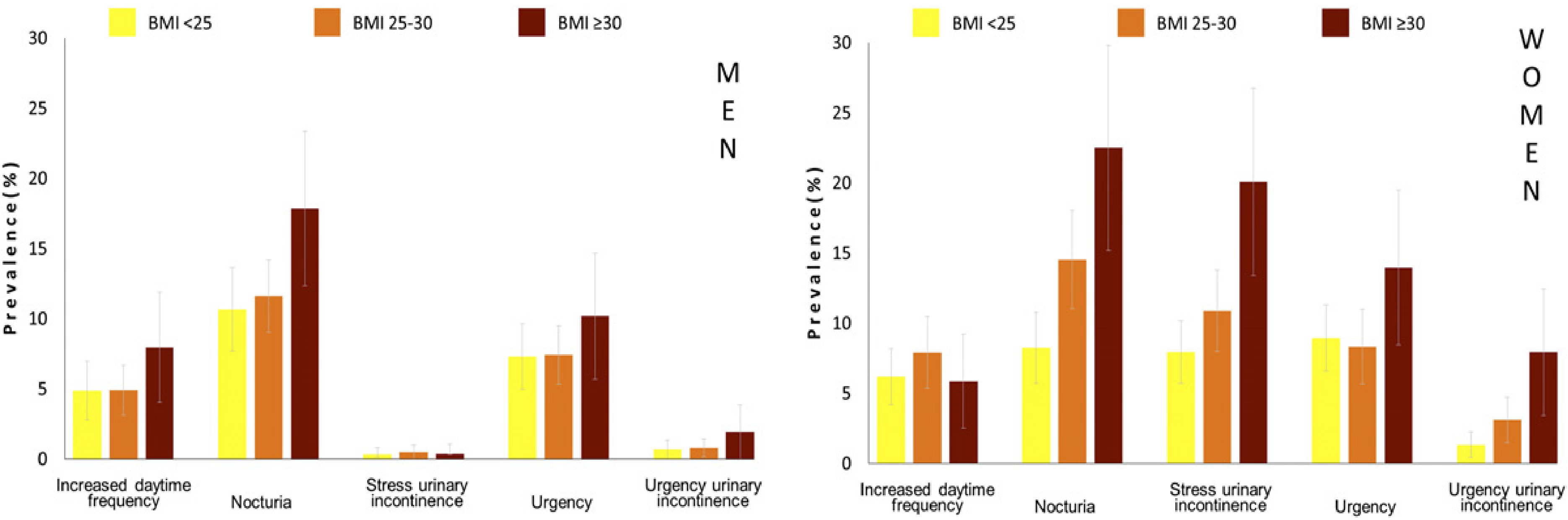


Yi Wang et al. Am J Physiol Endocrinol Metab 2016;311:E471-E479


CNS
LUT
function
Comorbidity
LUTS
Related
conditions
Treatment
Functional
status
Cognition


CNS
LUT function
Diabetes
OAB/UAB
Hyperglycemia
Vascular Dz
Constipation
Treatment
Functional status
Cognition

Obesity (high BMI): strong association with UI



OR for UI increases by 1.16 per 5 unit increase in BMI

Vaughn CP et al, *J Urol* 2013
Brown J et al, Obstet Gyn 1996

Mechanisms

- Urodynamic insights (women)
  - Increased Pabd at MCC
    - 0.4 cmH2O (95% CI=0.0,0.7) per kg/m2
    - 0.4 cmH2O (0.2,0.7) per 2 cm increase in waist circumference (WC)
  - Increased Pves at MCC
    - No association with BMI
    - 0.4 cm H2O (0.0, 0.8) per 2 cm increase in WC
- Associated comorbidity?
  - Sleep apnea and nocturia
  - Impaired mobility
  - Diabetes
  - Metabolic syndrome
  - Cardiovascular disease
  - Oxidative stress?

Richter HE et al, Int Urogyn J 2008

Weight loss decreases UI

- PRIDE (intensive)
  - At 6 mos, mean weekly number of UI episodes decreased by 47% vs 28% in the control group (P=0.01).
  - Impact was on stress but not urge UI
- Look AHEAD trial (intensive wgt loss in pts with DM)
  - Women: absolute risk diff of 3% in prevalent UI
  - Men: decreased odds of prevalent UI by 38%

Subak LL et al, NEJM 2009
Phelan S et al, J Urol 20132
Breyer BN et al, J Urol 2014

Ischemia – similar to DM?

	Early Phase →	Late Phase
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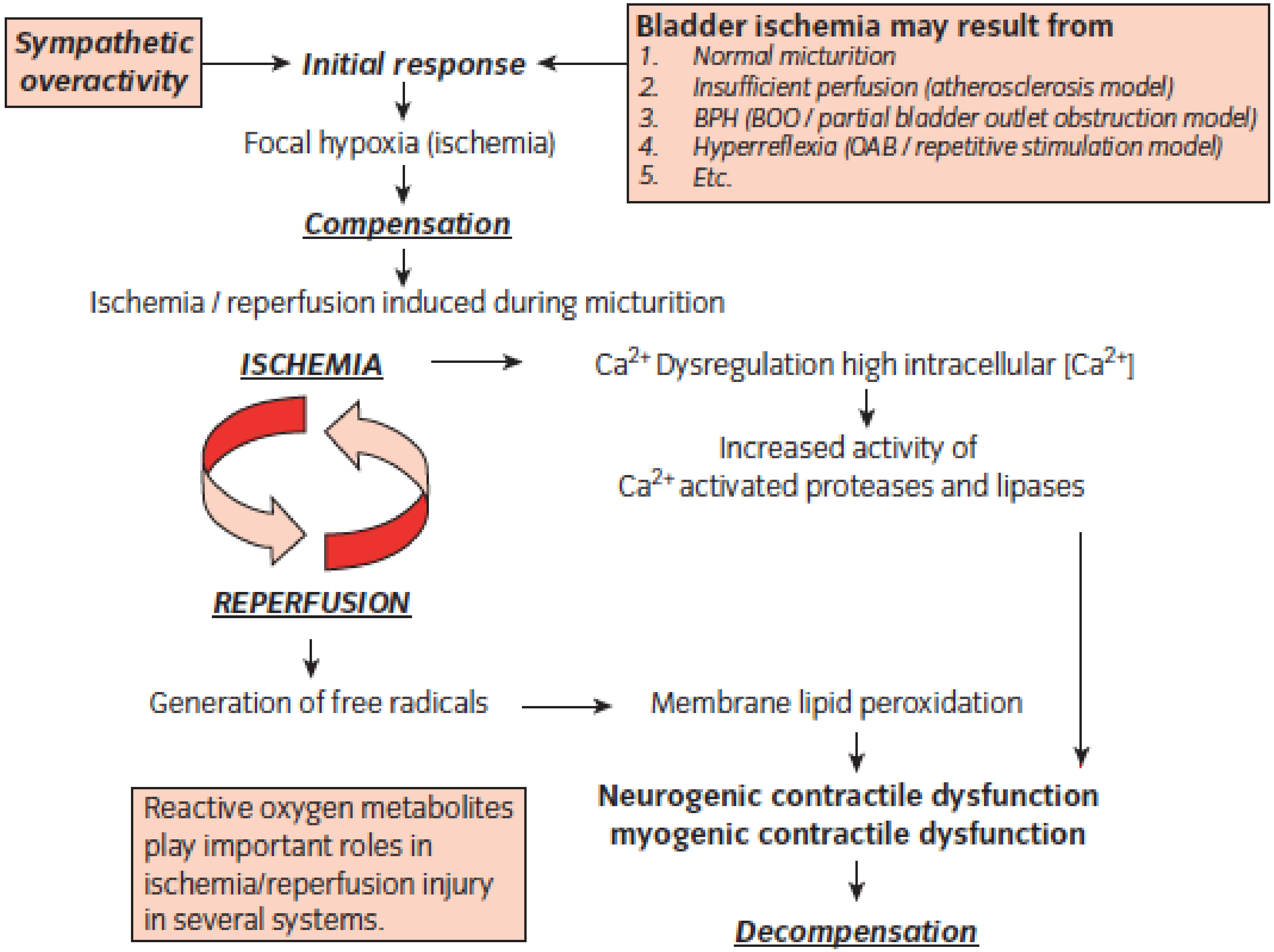
Animal models of “acute” ischemia
Increased contractility to stimulation
Moderate fibrosis

Animal models of “chronic” ischemia
Decreased contractility to stimulation
Severe fibrosis



Matsumoto S and Kakizaki H, *Int J Urol.* 2012

Potential interventions?

- Statins: decreased inflammatory and DO with impaired contractility in a rat model of cyclophosphamide-induced detrusor dysfunction
- HTN control?
- Smoking?

Metabolic syndrome

Table 1: The new International Diabetes Federation (IDF) definition

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference* with ethnicity specific values)

plus any two of the following four factors:

Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) **or specific treatment for this lipid abnormality**
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females **or specific treatment for this lipid abnormality**
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg **or treatment of previously diagnosed hypertension**
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), **or previously diagnosed type 2 diabetes** If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

** If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.*

US / Europe

Men

- $\geq$ 94 cm (37”)

Women

- >80 cm (31.4”)

Risk of UI increases with greater WC

		UI cases	Odds ratio	95%CI	*P*
WC (cm)	≤79.0	21 (7.7%)	1.000	–	0.033
	>79 to ≤86	42 (13.9%)	1.98	1.13–3.45	
	>86 to ≤94	36 (14.9%)	2.07	1.16–3.69	
	>94	39 (15.3%)	2.24	1.26–3.99	

Adjusted by age ($P = 0.77$), socioeconomic level ($P = 0.17$), diabetes ($P = 0.18$) and hypertension ($P = 0.62$).

- Observational studies suggest that the association of LUTS with MetS is strongest in men
- This gender difference may be due to prostate disease

Bunn F et al, Int J Clin Pract 2014
Krause MP et al, Age Ageing 2010

Interacting risk factors:
Metabolic Syndrome and AntiHTN Medications

LUTS symptom	Risk (OR) with Metabolic Syndrome
Incomplete emptying, mild	1.58 (1.03, 2.44)
Intermittency, mild	1.57 (1.06, 2.30)
Nocturia	1.69 (1.21, 2.36)

Odds ratios for LUTS in Men

* Thiazides: OR 2.90 (1.17 – 7.1)
* Loop diuretics: OR 2.55 (1.26 – 5.14)

Kupelian V et al, J Urol 2013; Hall SA et al BJU Int 2011

Knowledge Gaps

- Understanding the relative and attributable relationship between MetS, obesity, and vascular disease with DM-related UI and detrusor function, and similarly the related and differential impact of BMI and waist circumference (WC)
- Relationship between DM, MetS, and vascular disease with CNS changes associated with UI
- Impact of pharmacological treatment of DM (e.g., sulfonylureas, insulin, and newer classes of agents) on UI and detrusor function
- Impact of pharmacological treatment of vascular disease (e.g., antiplatelet agents, statins) on UI and detrusor function
- Synergy of aging-related changes with DM, vascular, and MetS-effects on detrusor physiology and function
- Impact of DM, MetS, and vascular disease on detrusor sensory function and the latter's link to OAB, underactive bladder, and aging related change
- Full understanding of the T1 and T2 science of the diabetic and MetS bladder

Research Opportunities

- Use of transgenic animal models to further elucidate mechanism for DM- and MetS-related bladder dysfunction.
- Translation of basic science understanding of the mechanisms of DM, MetS, and vascular disease/ischemia on detrusor function into novel interventions – pharmacologic, neurologic, and genetic
- Impact of early intervention for and prevention of obesity, DM, and MetS on incident UI
- Basic and clinical research investigating impact of pharmacologic therapy for DM, MetS, and vascular disease/ischemia on UI.

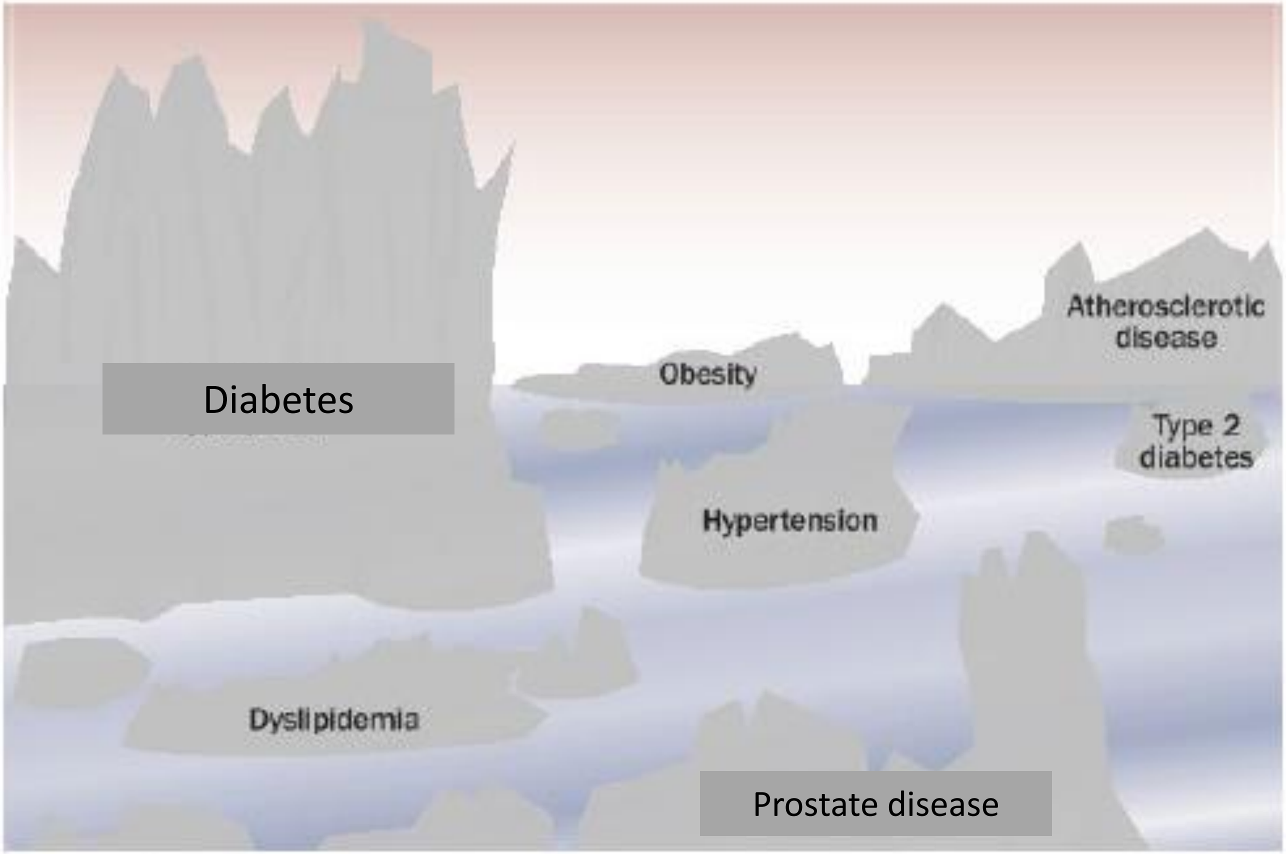


Figure 3 | As our knowledge improves, we are beginning to find that the known aspects of the metabolic syndrome—type 2 diabetes, obesity, hypertension, and others—are only the tip of the iceberg. The data suggest that BPH and prostate cancer and possibly also male hypogonadism, nephrolithiasis, OAB and ED can be considered to be new aspects of the metabolic syndrome. Abbreviations: BPH, benign prostatic hyperplasia; ED, erectile dysfunction; OAB, overactive bladder. Permission obtained from Bentham Science Publishers Ltd © Hammarsten, J. *et al.* *Curr. Hypertens. Rev.* **2**, 301–309 (2006).

Aging and UI