Metabolic Syndrome and Urologic Diseases

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Metabolic syndrome (MetS) is a complex entity consisting of multiple interrelated factors including insulin resistance, central adiposity, dyslipidemia, endothelial dysfunction and atherosclerotic disease, low-grade inflammation, and in males, low testosterone levels. MetS has been linked to a number of urologic diseases including nephrolithiasis, benign prostatic hyperplasia and lower urinary tract symptoms, erectile dysfunction, male infertility, female incontinence, and prostate cancer. This article reviews the relationships between MetS and these entities. Urologists need to be cognizant of the impact that MetS has on urologic diseases as well as on overall patient health.
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Known in the past as syndrome X, deadly quartet, and insulin resistance syndrome,[1] metabolic syndrome (MetS) generally refers to a constellation of interrelated cardiac risk factors consisting of insulin resistance (IR) (impaired insulin action), visceral obesity, atherogenic dyslipidemia, endothelial dysfunction, and systemic inflammation.[2] Throughout the years, numerous definitions of MetS have been proposed by various organizations, including the World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), International Diabetes Foundation (IDF), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), and the American Association of Clinical Endocrinologists (AACE) (Table 1). Each of the definitions shares many

Table 1
Metabolic Syndrome Definitions

	WHO (1998)	EGIR (1999)	AACE (2003)	IDF (2005)	NCEP ATP III (2005 Revision)
Required component	IR (IGT, IFG, T2DM, or additional evidence of IR)	Hyperinsulinemia[a] (plasma insulin > 75th percentile)	IR (IGT or IFG)	CO (WC)[b]	None
Criteria	Required component and ≥ 2/5 below	Required component and ≥ 2/4 below	Required component and any below based on clinical judgment	Required component and ≥ 2/4 below	≥ 3/5 below
Obesity	WHR > 0.9 (M), > 0.85 (F) or BMI > 30 kg/m^2	WC ≥ 94 cm (M), ≥ 80 cm (F)	BMI ≥ 25 kg/m^2	–	WC > 102 cm (M) > 88 cm (F)
Hyperglycemia (mg/dL)	+	+	+	Fasting glucose ≥ 100	Fasting glucose ≥ 100 or Rx
Dyslipidemia (mg/dL)	TG ≥ 150 or HDL-C < 35 (M), < 39 (F)	TG ≥ 150 or HDL-C < 39	TG ≥ 150 and HDL-C < 40 (M), < 50 (F)	TG ≥ 150 or Rx — HDL < 40 (M), < 50 (F), or Rx	TG ≥150 or Rx — HDL < 40 (M), 50 (F), or Rx
Hypertension (mm Hg)	> 140/90	> 140/90 or Rx	> 130/85	> (S), > 85 (D) or Rx	> 130 (S), > 85 (D) or Rx
Other criteria	Microalbuminuria[c]		Other features of IR[d]		

ACCE, American Association of Clinical Endocrinologists; BMI, body mass index; CO, central obesity; D, diastolic; Dx, diagnosis; EGIR, European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; IDF, International Diabetes Foundation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; Rx, pharmacologic intervention for that criterion; S, systolic; T2DM: type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHO, World Health Organization; WHR, waist-hip ratio.
+ Criteria fulfilled with required component.
[a]In patients without T2DM.
[b]Values population dependent.
[c]Urinary albumin excretion of 20 µg/min or albumin-to-creatinine ratio of ≥ 30 mg/g.
[d]This includes family history of T2DM, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to T2DM.
Adapted with permission from Huang[2] and Grundy SM et al.[13]

similarities, including the presence of criteria relating to obesity, hyperglycemia, dyslipidemia, and hypertension (HTN). However, several differences among the classifications are noted. The laboratory values that define these aforementioned criteria and the number of positive criteria necessary to be classified as having MetS vary among the organizations. Additionally, the WHO, AACE, EGIR, and IDF require the presence of certain criteria (eg, evidence of insulin resistance, hyperinsulinemia, or central obesity) to fulfill their classification of MetS, whereas the NCEP ATP III lacks this constraint. The NCEP ATP III definition is the one most used today because it incorporates the key concepts of MetS, relies on commonly used laboratory studies available to most physicians, and is less restrictive than the other classifications.[2]

Epidemiology of MetS

MetS has become quite prevalent within our society. Approximately 35% to 39% of the adult population in the United States has MetS, with similar rates in men and women.[3] This is not surprising because the percentage of overweight and obese individuals in the United States is growing, with the greatest escalation seen in the so-called superobese (body mass index [BMI] ≥ 50).[4,5] Currently, approximately 32% of our population is obese, with higher rates seen in African Americans and Hispanics.[3]

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The prevalence[6,7] and incidence[7,8] of type 2 diabetes mellitus (T2DM) are increasing as well. The United States does not appear to be unique in this trend as obesity and MetS have generally become prevalent throughout the world.[9,10]

Sadly, the growing epidemic of obesity and T2DM and their respective consequences are not limited to the adult population. In the past 30 years, the number of overweight children has more than doubled in the United States.[11] As in adults, obesity in children is associated with an increase in MetS features such as IR, HTN, dyslipidemia, and T2DM.[11,12] T2DM itself is also increasing in children and adolescents in the United States, with T2DM now accounting for approximately 20% to 25% of childhood diabetes.[12]

MetS and Cardiovascular Disease

It is well established that MetS imposes numerous cardiovascular risks. A diagnosis of MetS (or even 1 to 2 of its components) increases the risk for both cardiovascular disease (CVD) and T2DM.[13,14] One study demonstrated that men with 4 or 5 features of MetS, compared with those with none, had a 3.7-fold increase in coronary heart disease (CHD) and an impressive 24.5-fold increase in T2DM.[15] The risks of all-cause mortality as well as death from CHD and CVD were also increased.[14] Wilson and colleagues noted that more than any 3 of the following including low high-density lipoprotein (HDL) cholesterol, elevated BMI, elevated systolic blood pressure (SBP), elevated triglycerides (TG), or elevated serum glucose were associated with more than double the risk for coronary artery disease (CAD).[16]

MetS is not only associated with the aforementioned cardiovascular and systemic diseases but it also impacts a number of urologic disorders. Prior to elaborating on this relationship, we review pertinent concepts regarding MetS. Subsequently, the influence of MetS on these various urologic maladies is examined.

MetS and Inflammation

MetS has been associated with elevated levels of C-reactive protein (CRP), a nonspecific marker of inflammation, as well as the proinflammatory cytokines IL-1β, IL-6, and tumor necrosis factor-α (TNF-α).[17-19] One etiology may be inflamed adipose tissue. Obesity induces adipose cell enlargement and chemokine release, leading to macrophage infiltration of adipose tissue.[20] Macrophage infiltration further perpetuates the proinflammatory state and may account for the adipose secretion of adipokines such as IL-1β, IL-6, IL-8, CRP, and TNF-α.[20-23] Macrophage infiltration of adipose tissue has also been shown to contribute to obesity-related IR.[20,24] CRP is associated with numerous MetS features including abdominal obesity, IR and T2DM, HTN, low HDL, as well as elevated TG, IL-6, and TNF-α.[18,25] CRP has also been shown to stimulate synthesis of IL-8 in human aortic endothelial cells,[26] suggesting a role for this cytokine in MetS. A recent study determined that IL-8 is significantly elevated in heart failure patients with MetS as compared with those without MetS.[26] Higher IL-8 levels have also been noted in patients with T2DM and it has been further directly correlated with hemoglobin A1c (HbA$_{1c}$) levels.[27] Additionally, IL-6, IL-1β, and CRP are all known to impair insulin signaling so it is not surprising that they too are associated with increased risk of developing diabetes.[18,21,22] Therefore, a proinflammatory state may contribute to MetS and its features.

MetS and Endothelial Dysfunction

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acids (FFAs), and chronic inflammation may lead to endothelial damage and atherosclerosis.[2,28-30] With endothelial dysfunction, there is a decrease in vascular nitric oxide (NO) levels.[2] NO has crucial functions in maintaining vascular health. It defends against the initiation of atherosclerosis by inhibiting adhesion of platelets and leukocytes to the vascular wall as well as decreasing proliferation of vascular smooth muscle.[30] A decrease in NO levels may therefore abolish these protective functions. Increased CRP levels have been shown to decrease NO synthesis in endothelial cells.[31] Another component of MetS—hyperglycemia—also promotes increased production of free radicals such as superoxide anion resulting in NO inactivation.[30] Hyperinsulinemia and endothelial dysfunction in T2DM may contribute to increased levels of the vasoconstrictor endothelin-1 (ET-1).[30,32] Diminished insulin regulation of NO and ET-1 secondary to IR may decrease NO production while ET-1 production is maintained, thus promoting vasoconstriction.[29,33] Elevated FFAs, associated with dyslipidemia in MetS, can cause endothelial dysfunction through increased free radical production and inhibition of NO synthesis via activation of protein kinase C, a pathway that ultimately leads to decreased NO synthase (NOS)

activation.[30] Components of MetS can also lead to increased arterial stiffness.[29] AGEs formed on the vascular wall secondary to hyperglycemia lead to collagen cross-linking and loss of vascular elasticity.[29] Hyperinsulinemia and hyperglycemia may locally activate the renin-aldosterone-angiotensin system, leading to elevated angiotension-1 receptor expression and subsequent vascular fibrosis and hypertrophy.[29] These aforementioned findings demonstrate the strong relationship between MetS and endothelial dysfunction as well as the importance of NO in this physiology.

MetS and Male Hypogonadism

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even glucose and lipid metabolism.[34] Low testosterone levels are significantly associated with prevalence of MetS.[35-37] Men with prostate cancer (PCa) who undergo long-term androgen deprivation therapy (ADT) also have significantly higher rates of MetS than those who do not.[38] Numerous studies have demonstrated that MetS features such as HTN,[39,40] obesity,[36,38,41] hyperinsulinemia,[41-44] T2DM,[45,46] hyperglycemia[44,47] (including elevated HbA$_{1c}$[48]), hypertriglyceridemia,[36,41,49] elevated CRP,[47,50] as well as low HDL[38,41,47] are associated with diminished serum testosterone levels. A reduction in sex hormone-binding globulin (SHBG) has also been reported.[35,37,40,46,48] Weight loss may reverse these trends. Niskanen and colleagues[51] demonstrated that maintained weight loss in obese men

with MetS at 12 months increased free testosterone levels and reduced hypogonadism risk. At the same endpoint, they also noted a beneficial impact on insulin sensitivity, fasting plasma glucose, TG, and serum HDL levels.[51] Moreover, treatment with testosterone appears to alleviate features of MetS. Boyanov and colleagues[52] randomized 48 males with T2DM to either oral testosterone undecanoate (TU) therapy for 3 months or placebo, and demonstrated that the treatment arm had significant improvements in weight, waist-hip ratio (WHR) (a measure of abdominal obesity), and percentage of body fat. Additionally, fasting blood glucose (FBG) and HbA$_{1c}$ in the TU group significantly improved in both compared with baseline TU and control groups.[52]

A link between hypogonadism and MetS may be leptin, a 16-kDa protein synthesized and secreted mostly by adipocytes.[53,54] Leptin is believed to regulate energy intake and utilization, principally via the hypothalamus.[50] Serum leptin is directly associated with BMI[50,54] and studies have demonstrated that leptin is inversely associated with testosterone levels.[55,56] Isidori and associates[55] reported that elevated levels of leptin in obese men may lead to decreased luteinizing hormone (LH)-stimulated testosterone synthesis. Additionally, Luukkaa and colleagues[56] noted that, in elderly men without diabetes, testosterone enanthate injections significantly lowered leptin levels while increasing testosterone levels, and that 3 months after treatment was stopped, levels of both hormones

returned to baseline. Similarly, in men with T2DM and hypogonadism, testosterone replacement also resulted in significantly decreased serum leptin levels.[50]

Hypogonadism associated with MetS in males may be related to the low-grade inflammatory state known to occur in the latter. It has been reported that in Leydig cells, TNF-α inhibits steroidogenesis and IL-1 inhibits cholesterol side chain cleavage by cytochrome P450, thereby leading to diminished testosterone synthesis.[17]

Increased visceral adiposity, a feature of MetS, may contribute to hypogonadism through aromatase activity. Aromatase is an adipose enzyme that is involved in the irreversible conversion of testosterone to estrogen.[57] Logically, because persons with MetS tend to have visceral adiposity, higher aromatase activity should lower testosterone and increase estradiol levels. Indeed, Vermeulen and coauthors[58] demonstrated that obese men have significantly higher plasma estradiol levels than controls. The resultant decrease in testosterone and increase in estrogen can cause excessive visceral adipose deposition, leading to further elevated aromatase activity, creating a self-perpetuating loop coined the hypogonadal-obesity cycle.[57] The impact of aromatase has been indirectly demonstrated by experiments in which its action has been blocked. Zumoff and colleagues[59] treated 6 obese men with oral testolactone, an aromatase inhibitor, and after 6 weeks, noted significantly higher levels of testosterone and LH as well as decreased levels of estrogen compared with baseline. Elevated estrogen levels may, in turn, cause pituitary suppression leading to hypogonadotropic hypogonadism (HHG).[59] There have been inconsistent data regarding plasma levels of gonadotropins such as gonadotropin-releasing hormone (GRH),

LH, and follicle-stimulating hormone in obese individuals. Vermeulen and colleagues[58] studied pulsatile LH secretion in 8 obese men and normal controls and found a lower mean diurnal LH level, LH pulse amplitude, and sum of LH pulse amplitudes in obese individuals. Additionally, in the obese group, the sum of LH pulse amplitudes was directly associated with testosterone levels.[58] The increase in serum LH that was associated with a decrease in serum estrogen in the study by Zumoff and colleagues[59] may also be a manifestation of reduced estrogen inhibition on the normal pituitary response.

Therefore, there does appear to be a link between MetS and hypogonadism, and furthermore, MetS features such as low-grade inflammation, elevated leptin and estrogen levels, and higher aromatase activity might contribute.

MetS and Urologic Diseases
Nephrolithiasis
Much like MetS and obesity, the prevalence of nephrolithiasis in the United States and other countries is increasing.[60,61] There is evidence that these parallel changes might be linked. Studies have shown that MetS and its components (obesity/increased waist circumference, HTN, etc) are associated with increased rates of nephrolithiasis. A recent cross-sectional study from Italy demonstrated that individuals with MetS are twice as likely to have ultrasonographic evidence of nephrolithiasis.[62] Using the NHANES III (Third National Health and Nutrition Examination Survey) data, West and associates[63] similarly showed that the odds of self-reported stone disease are approximately twice as likely in individuals with MetS than those without.[63] They also demonstrated that increasing numbers of MetS components are associated with greater stone reporting:

3% with no MetS components, 7.5% with 3 components, and 9.8% with 5 components.[63] Waist circumference (WC), elevated BMI, diabetes, and HTN have also been correlated to nephrolithiasis risk.[62,64,65]

MetS may be contributing to the changing gender ratio of stone formers. Although nephrolithiasis remains more common in men than in women, there is evidence that this gender gap is decreasing. Scales and colleagues[66] reported a decrease in the man-woman ratio of inpatient discharges for kidney stones from 1.7:1 in 1997 to 1.3:1 in 2002. They hypothesized that the disproportionate increase of overweight and obese women compared with men might explain this phenomenon. Furthermore, with respect to BMI, women have a higher percentage of body fat than men, which could result in metabolic differences influencing stone risk.[64,66,67] In children, the epidemiology of nephrolithiasis is different from adults as boys are more prone to stones in the first decade of life whereas girls prevail in the second.[68]

There are a number of possible reasons for the association between MetS and nephrolithiasis. It has been demonstrated that features of MetS are associated with decreased urine pH. One study noted that increasing IR (measured by comparing glucose disposal rates via euglycemic clamp with 24-hour urine studies) is associated with more acidic urine.[69] Maalouf and associates[70] showed the same relationship, but used the homeostasis model assessment of IR. Several investigators have determined that urine pH decreases with increasing BMI.[71-74] Another study demonstrated that as the number of MetS components increased (0, 1, 2, 3, 4, 5, respectively) urine pH decreased (6.15, 6.10, 5.99, 5.85, and 5.69, respectively).[70] They also found that the components of MetS significantly

associated with urinary pH are BMI, SBP, serum glucose, and serum HDL.[70]

Low urine pH is a well-described feature of uric acid urolithiasis, so it is not surprising that people with features of MetS tend to preferentially have uric acid stones or risk factors for their development. A higher prevalence of T2DM, glucose intolerance, and hypertriglyceridemia in pure uric acid stone formers has been reported.[75] Others have demonstrated that patients with T2DM have a significantly higher prevalence of uric acid stones.[76] Li and coauthors[71] reported that a higher percentage of uric acid stone formers were obese (53.1%), as compared with those with calcium phosphate (34.3%), mixed calcium stones (38.7%), and calcium oxalate stones (42.7%). Studies have shown that BMI is also associated directly with uric acid excretion,[74,77] serum uric acid level,[74] and supersaturation of uric acid.[77] Additionally, hypertensive stone formers more commonly have uric acid stones than normotensive stone formers.[78]

MetS may impact stone risk factors that promote the formation of alternate stone types such as calcium oxalate, calcium phosphate, or mixed stones (uric acid/calcium oxalate or calcium oxalate/calcium phosphate). Lower urine pH results in more uric acid crystals, which may contribute to heterogeneous nucleation and epitaxial crystal growth.[79] Lemann and associates[80] found a positive correlation between oxalate and lean body mass estimated by urinary creatinine excretion. In a retrospective study of 1021 patients with a history of nephrolithiasis, Ekeruo and colleagues[72] demonstrated that obese individuals had a significantly higher prevalence of gouty diathesis (54%), hypocitraturia (54%), hyperuricosuria (43%), and hyperoxaluria (31%) compared with their nonobese counterparts. Additionally, calcium, oxalate, and uric

acid excretion were higher in the obese cohort and these differences were more profound as the extent of obesity increased.[72] Siener and colleagues[74] also reported a positive correlation between BMI and uric acid excretion in a group of idiopathic calcium oxalate stone formers. They noted some gender differences, reporting that BMI was positively correlated with calcium excretion in men and oxalate excretion in women.[74] Duffey and associates[81] analyzed 24-hour urine samples in morbidly obese

was not significant. Increased BMI was also indirectly associated with urinary citrate excretion, although this was seen only in men.[73] One explanation of this relationship is that BMI is inversely related to urine pH, and low urine pH results in increased citrate resorption.[82]

Bidirectional associations between HTN and nephrolithiasis have been reported. Hypertensive patients are more at risk to develop stones,[83,84] and those with stones are more likely to develop HTN.[85-87] HTN has been

uration.[91] Another group compared overweight and normal children, and found significant hypocitraturia, hyperoxaluria, and hypercalciuria in the former group.[92]

Several etiologies have been proposed for the association between MetS and risk factors for uric acid stones. As described before, low urine pH is an important and the most prevalent component of uric acid stone development. Other known risk factors include hyperuricosuria and low urinary volume.[93] Causes of low urinary pH include excessive net acid excretion (NAE) and impaired ammonium (NH_4^+) excretion resulting in poor urine buffering.[70,79] It has been demonstrated that NAE is significantly elevated in persons with MetS compared with those without the condition.[70] Causes of amplified NAE include increased dietary acid intake (via correlation between urine sulfate and NAE), decreased dietary alkali intake (via urinary potassium and NAE), or excessive endogenous acid production.[70] Ammonium is a key urinary buffer.[94] Maalouf and colleagues[70] noted that as the number of MetS features increased, ammonium excretion was impaired. One explanation may be IR, which has been linked to decreased ammonium excretion. Insulin has been shown to stimulate renal ammoniagenesis in rat,[95] canine,[96] and opossum kidney (OK) cells.[97] Additionally, Klisic and colleagues[98] demonstrated that insulin stimulates the Na+/H+ exchanger 3 (NHE3) in OKP cells (OK cells with proximal tubule characteristics). This allows tubular ammonia to be converted to ammonium, thereby trapping the molecule, which under low pH conditions within the tubule, may be the prevailing mechanism of ammonia excretion.[99] When considering these effects of insulin on the kidney, it is conceivable that IR could also impair both ammoniagenesis and ammonium excretion.[93]

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patients (mean BMI, 49.5) prior to bariatric surgery and found that greater than 97% had at least 1 risk factor for stone formation, with 80% having at least 3, the most common being low urine volume (71%). In both sexes, BMI was inversely related with urine magnesium excretion, whereas in females, BMI was also inversely associated with urinary citrate excretion.[81] Similar to Ekeruo and colleagues, they also found that elevated BMI (> 45) was strongly associated with hypercalciuria (odds ratio [OR], 18).[81] Taylor and Curhan[73] analyzed individuals with and without nephrolithiasis in the Health Professionals Follow-Up Study (HPFS) (men), Nurses' Health Study I (older women), and Nurses' Health Study II (younger women). They found that BMI was directly related to oxalate excretion in women and also detected a direct correlation between BMI and urinary calcium excretion in both the male and younger female cohorts.[73] However, individuals with a lower BMI consumed less sodium and animal protein, and when controlling for these dietary factors, the relationship between BMI and calcium excretion

shown to impact urinary stone risk factors. Positive correlations between HTN and calcium excretion in both those with a history of nephrolithiasis[88] and those without[84,89,90] have been reported. Taylor and colleagues also found this relationship in the HPFS.[77] Borghi and colleagues[84] reported that hypertensive men and women had significantly increased oxalate excretion and also found that men had increased uric acid excretion. Losito and associates[78] demonstrated that the presence of HTN was associated with lower urinary pH and citrate excretion and higher titratable acid excretion. The authors also noted an inverse association between HTN severity and urinary pH and a direct relationship with titratable acid.[78]

Studies comparing increased weight in children and nephrolithiasis are limited. Several articles, however, have found associations between being overweight and lithogenic alterations in urine composition. One study showed that, in children with a history of kidney stones, increased BMI was associated with a decrease in urine oxalate excretion and an increase in calcium phosphate supersat-

Lipotoxicity refers to the concept of excessive lipid accumulation in nonadipose tissues (eg, skeletal and cardiac myocytes, hepatocytes, pancreatic β cells) resulting in cell damage and impaired functioning.[100,101] Lipotoxicity may exist in those with MetS[100] and result in altered renal structure and function.[102] Bobulescu and colleagues[103] noted that Zucker diabetic fatty (ZDF) rats (a model of MetS) have increased TG steatosis, predominantly around the tubular portions of the kidney, and that this is associated with low urinary pH and NH_4^+ in addition to high titratable acidity. These urinary abnormalities are similar to those described in humans with MetS features. Additionally, they noted that the observed decrease in NH_4^+ excretion might be attributed to a lipotoxicity-induced reduction in NHE3 activity.[103] These investigators also incubated OK clone P cells with FFAs and found that ammonium secretion decreased as the concentration of FFA in the medium increased.[103] They also demonstrated that fat accumulation within these cells increased with higher concentrations of FFA in the medium.[103] In a follow-up study, Bobulescu and colleagues demonstrated that reduction of renal steatosis in ZDF rats improved urinary NH_4^+, increased pH, reduced titratable acidity, and additionally increased citrate and brush border NHE3 levels and activity.[94]

Evidence linking features of MetS and hypercalciuria are limited. Schwille and colleagues[104] compared males with idiopathic hypercalciuria (n = 30) with normal controls (n = 8) and noted that the former group demonstrated postprandial hyperinsulinemia and IR without hyperglycemia. Worcester and colleagues[105] demonstrated that patients with idiopathic hypercalciuria postprandially excreted more calcium (compared with normal controls) secondary to reduced tubular calcium resorption,

not an increased filtered load. Perhaps IR is the cause of this decreased resorption, resulting in hypercalciuria.[61] Because IR is a component of MetS, it is possible that this might explain hypercalciuria seen in those with HTN or increased BMI.

The cause for the positive correlation with body weight and oxalate excretion is unknown. This could be due to an increase in the endogenous synthesis of oxalate. IR may hypothetically increase the glucose pool and it is possible that the metabolism of this sugar is linked to endogenous oxalate synthesis. Figure 1 displays a diagram of the proposed associations between MetS and nephrolithiasis.

Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms
Components of MetS such as HTN, T2DM, hyperinsulinemia, abdominal obesity, and dyslipidemia have all been associated with an increased benign prostatic hyperplasia (BPH) risk.[106-110]

Hammarsten and colleagues[108] demonstrated that men with T2DM, treated HTN, and dyslipidemia had higher median average BPH growth rates. The authors further noted that annual BPH growth rate was directly associated with diastolic blood pressure (DBP) and obesity and inversely associated with HDL levels. Multivariate analysis revealed that serum insulin levels were directly correlated with total prostatic volume.[108] Ozden and colleagues[106] studied 78 men with BPH and lower urinary tract symptoms (LUTS) and determined that presence versus absence of MetS was associated with significantly higher total prostate (TP) growth rate (1.0 vs 0.64 mL/y, respectively) and median annual transition zone (TZ) growth rate (1.25 vs 0.93 mL/y, respectively). Additionally, MetS patients were noted to have significantly higher serum prostate-specific antigen (PSA) levels,[106] which may be an index for prostatic volume[106,111] and LUTS.[112]

Figure 1. *Possible mechanisms of nephrolithiasis in metabolic syndrome (MetS). Several lithogenic factors are noted in MetS including increased uric acid (UA), oxalate, and calcium (Ca^{2+}) excretion as well as decreased citrate excretion. Renal lipotoxicity may be a cause of elevated net acid excretion (NAE) in addition to decreased ammonia (NH_3) synthesis and ammonium (NH_4^+) excretion, leading to lower urinary pH. These abnormalities respectively contribute to elevated UA, Ca^{2+}, and mixed stones.*
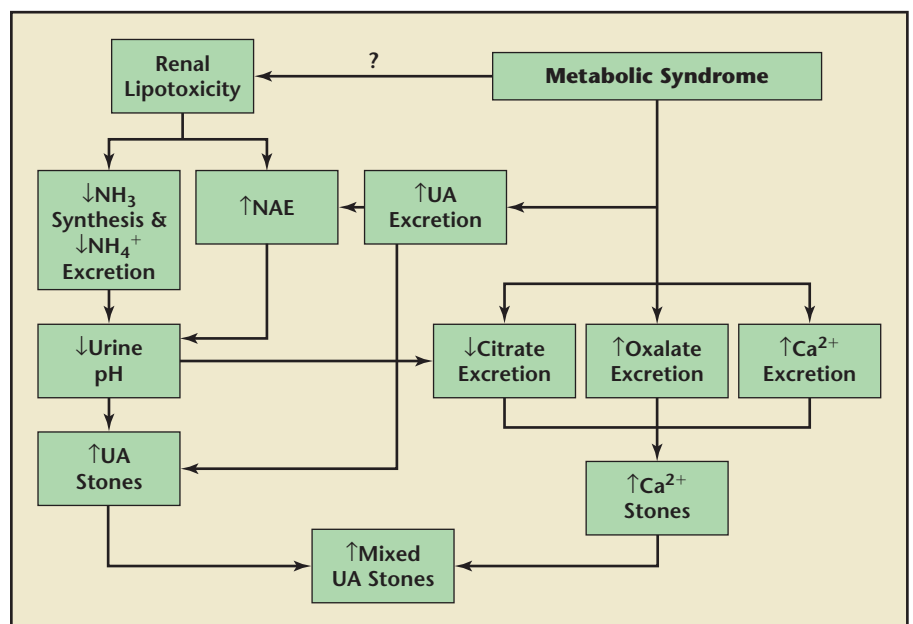
Investigators have reported conflicting associations between MetS and LUTS. Using data from the Boston Area Community Health Survey, Kupelian and colleagues[113] demonstrated that the presence of MetS was significantly associated with an elevated American Urological Association (AUA)-Symptom Index Score (score $\geq$ 2; multivariate OR, 1.68). When adjusting for age, men younger than 60 years with MetS were more likely

glucose metabolism in ventromedial hypothalamic neurons[119] leading to increased activation of α-adrenergic receptors on smooth muscle in the prostatic capsule and bladder neck.[106] This concept has been studied in both animal models and human subjects. In the rat model, elevated autonomic activity can induce BPH.[120] McVary and colleagues[121] assessed men with LUTS secondary to BPH for autonomic nervous system hyperactivity

vasculature.[122] The aforementioned findings illustrate the potential importance of NO and NOS in BPH/LUTS and thereby further link MetS with these entities as endothelial dysfunction may be present in both. Additionally, NO and NOS may also play a role in another possible etiology of BPH/LUTS and MetS—pelvic atherosclerosis. Numerous animal studies have linked atherosclerosis and chronic ischemia to bladder and prostatic changes.[120] Rabbits with induced pelvic atherosclerosis developed bladder fibrosis, smooth muscle atrophy, and decreased bladder compliance[123] as well as chronic prostatic ischemia with resultant stromal and capsular fibrosis, glandular cystic atrophy, impaired smooth muscle relaxation, and increased prostatic weight.[124,125] Moreover, it appears that in ischemic prostate models, diminished smooth muscle relaxation is regulated via an NO-dependent mechanism,[125] much like the cavernosal vascular bed.

When adjusting for age, men younger than 60 years with MetS were more likely to report intermittency, incomplete emptying, and nocturia.

to report intermittency, incomplete emptying, and nocturia.[113] Demir and associates[114] reported in a univariate analysis that MetS and its features such as HTN or treatment of HTN, elevated FBG or treatment of diabetes, and increased WC were all associated with greater BPH-related LUTS severity. Michel and colleagues[115] noted in a retrospective, multivariate analysis that HTN was directly associated with BPH-related LUTS as indexed by International Prostate Symptom Score (IPSS) and inversely with maximal flow rate (Q_{max}). Similarly, diabetes was also associated with a higher IPSS and lower baseline Q_{max}.[116] In a Japanese cross-sectional study, multivariate analysis revealed that men undergoing treatment of HTN and T2DM were more likely to report LUTS.[117] Conversely, Temml and colleagues[118] found no significant relationship between LUTS and MetS.

There is evidence of a relationship between MetS features and BPH/LUTS, and because the two are intertwined, both need to be considered when discussing pathophysiologic associations with MetS. One explanation involves hyperinsulinemia and autonomic hyperactivity. Hyperinsulinemia is associated with increased sympathetic activity via enhanced

after tilt-table testing. They demonstrated that markers of autonomic hyperactivity (BP elevation, heart rate elevation, and elevated serum or urine catecholamines) were positively associated to subjective markers of LUTS (AUA Symptom Score, Quality of Life Score, and BPH Impact Index).[121] Additional multivariate analysis showed a significant positive correlation between plasma norepinephrine levels after tilt testing and transition zone (TZ) volume.[121] McVary hypothesized that increased autonomic activity can impact α-receptors, and therefore smooth muscle contraction, throughout male genitourinary tract structures including the prostate, bladder neck, and urethra, thereby contributing to LUTS.[120] BPH/LUTS may also occur secondary to decreased NOS and NO activity in the prostate. Decreased nitrogenic (NO-related) innervation of the prostate coupled with lower NOS and NO activity in the TZ of BPH prostates has been reported.[120,122] This diminished prostatic NOS and NO activity may lead to increased smooth muscle proliferation, prostatic enlargement, and subsequent LUTS.[120] In addition, the distribution of eNOS and nNOS suggests that NO might serve to regulate regional prostatic

The RHO-kinase (ROK) system may further contribute to the MetS and BPH/LUTS relationship. The ROK pathway appears to be important in maintenance of tonic contraction or high basal tone[126] and may possibly contribute to prostate contractility. ROK causes smooth muscle contraction not by altering intracellular calcium levels but through modifying calcium sensitivity of the contractile machinery.[120,127] The impact of ROK activity on smooth muscle is thought to be via inhibition of myosin-light chain phosphatase (MLCP), thereby promoting myosin-light chain phosphorylation and contraction through actin-myosin interaction.[120,128,129] NO counteracts this by indirectly favoring the active form of MLCP.[129] On the contrary, α-adrenergic activity stimulates the ROK pathway,[120] providing a link between ROK and autonomic hyperactivity. IL-8 has also been shown

to stimulate BPH cell proliferation via the ROK pathway.[130] ET-1 stimulates this pathway as well,[120,127] and we have previously noted that ET-1 production may be increased in patients with diabetes. Takahashi and colleagues[127] demonstrated in cultured human prostatic stromal cells that ET-1–induced contraction was increased by ρ-A (a ROK activator) overexpression and decreased by ROK inhibition. Further experiments with human[127] and rat[126] prostate tissues revealed that ROK inhibition caused decreased NE-induced contraction. Rees and colleagues[126] demonstrated that human and rat prostate smooth muscle cells showed decreased proliferation in the presence of Y-27632, a ROK inhibitor. Therefore, autonomic hyperactivity, higher ET-1 and IL-8 levels in addition to lower NO levels found in MetS may result in increased ROK activity and subsequent BPH/LUTS.

We have noted the ability of IL-8 to stimulate prostatic growth, suggesting that inflammation may also play a role in BPH/LUTS. Macrophage and T-lymphocyte infiltrates are commonly found in prostate tissue removed during open prostatectomy and transurethral resection of prostate (TURP).[131] Additionally, the level of inflammation has been directly correlated with prostatic volume and IPSS.[131] Several proinflammatory cytokines are upregulated in BPH, suggesting an immunologic etiology to the inflammation.[130] In patients with BPH, seminal IL-8 levels positively correlate with LUTS via IPSS and PSA.[132] The cytokines IL-6 and IL-8 are elevated in MetS, and may contribute to inflammation in BPH/LUTS as both can be secreted by stromal cells with cytokine stimulation, and both result in proliferation of prostatic tissues.[133] Yet some question the importance of inflammation in these entities. Rohrmann and

colleagues[134] failed to show a definitive relationship between elevated CRP levels and BPH-related LUTS, but did note a stronger, albeit nonsignificant, relationship in those with MetS.

The sex hormonal milieu may further contribute to this linkage of BPH/LUTS and MetS. Similar to MetS, men with LUTS/BPH may have lower androgen and higher estrogen levels. Analyzing 260 men older than 60 years from the NHANES III Trial, Rohrmann and associates[135] noted that elevated estrogen levels and molar estradiol/testosterone ratios as well as lower androstanediol glucuronide (a metabolite of dihydroxytestosterone [DHT]) levels were associated with greater LUTS risk. Schatzl and colleagues[136] analyzed 312 men (mean age, 62.8 years) with LUTS secondary to untreated BPH and found a direct correlation between elevated estradiol levels and prostatic volume determined with transrectal ultrasound. Multivariate analysis from the Physician's Health Study also showed that increasing estradiol levels were significantly associated with BPH surgery in men with low testosterone and/or DHT levels.[137] However, others have not found evidence of such definitive relationships.[138,139] Urodynamic parameters can also be impacted by these hormonal abnormalities. Koritsiadis and colleagues[140] analyzed 25 men with confirmed bladder outlet obstruction who had undergone either TURP or suprapubic prostatectomy with hormonal measurements and urodynamics. They demonstrated a significant inverse correlation between testosterone values and detrusor pressure at the end of urinary flow and detrusor pressure at Q_{max}.[140] Additionally, they noted that low testosterone levels were associated with detrusor overactivity, defined as biphasic detrusor contraction during the filling phase.[140] Although there have been no definitive data linking

low testosterone levels to BPH/LUTS, testosterone replacement appears to improve LUTS. Haider and colleagues[141] studied hypogonadal men (mean age, 59.5 years) and demonstrated significant decreases in IPSS score and residual bladder volume after 9 months of TU treatment. Kalinchenko and colleagues[142] assessed 30 men (mean age, 51 years) with hypogonadism, and subsequently divided them into 2 treatment groups (10 with testosterone gel and 20 with TU). At the 26-week endpoint, the authors noted significant improvements in IPSS scores of both groups.[142]

A discussion of the mechanistic role that estrogens play in BPH/LUTS is germane given the aforementioned relationships. Recent experiments have shown interesting mechanisms of estrogen impact on BPH. Classically, it is known that estrogens passively cross the cellular membrane, bind an intracellular receptor (estrogen receptor [ER] α or β), and after transfer to the nucleus, function as a transcriptional regulator.[143,144] There is some evidence that high estradiol concentrations can result in upregulation of ERs in prostatic stromal cells.[145] In cultured BPH specimens, estradiol stimulates proliferation of the stromal but not epithelial component of the prostate, via intracellular ERs.[143] Additionally, Ho and associates[143] demonstrated that aromatase activity was limited to the prostatic stroma, and that this might serve to regulate local estradiol levels and subsequent proliferation. In the dog model, estrogen activation may cause formation of radical species, resulting in prostate damage and an increased susceptibility to DHT-induced growth.[146] Estrogens have also been demonstrated to induce an inflammatory response in lateral prostates of castrated rats and increasing transcript levels of IL-1β and

IL-6.[133] Interestingly, a recent study compared stromal prostate cells from normal and BPH specimens and found that both responded to lower levels of estradiol than previously believed.[144] The authors demonstrated that estradiol activates a different, nongenomic pathway in normal prostate cells, resulting in estradiol-dependent signaling via a mitogen-activated protein (MAP) kinase cascade, Erk1/2.[144] However, stromal cells derived from BPH prostate specimens responded to estradiol via the classic genomic pathway, and additionally, were noted to have consistent levels of Erk1/2 activity regardless of estradiol levels.[144] The authors hypothesized that an increased estradiol/androgen ratio, which normally occurs with aging, may evoke changes such as constitutive Erk1/2 activation, resulting in stromal proliferation and differentiation, and perhaps, BPH.[144] If MetS results in a similar alteration in the hormonal milieu, this can further explain how MetS might contribute to BPH/LUTS. Overall, the regulation and impact of estrogens on prostatic growth and BPH/LUTS is quite complex and requires further scientific inquiry.

Erectile Dysfunction

Studies have demonstrated that erectile dysfunction (ED) is up to 3 times more prevalent in individuals with MetS.[147-152] Direct relationships between ED and various components of MetS including obesity,[148,149,153-155] HTN,[148,153,155] T2DM,[156] and hypertriglyceridemia[157] have also been shown. Esposito and colleagues[150] noted that in age- and BMI-matched controls, higher ED prevalence was seen when 3 or more MetS components were present. Similarly, Bal and associates[149] demonstrated that the OR of ED increased with the number of MetS components including the following: increased WC only, 1.94;

increased WC plus abnormal HDL or TG level, 2.97; increased WC plus pathologic HDL and TG, 3.38. Using data from the Massachusetts Male Aging Study, Kupelian and colleagues[158] showed that presence of MetS in those with a BMI $<$ 25 increased ED risk approximately 2-fold. They postulated that ED could even be used to predict the development of MetS in the nonobese. Direct relationships between ED severity and MetS[149,151] as well as number of MetS features[148] have also been established. In a cross-sectional study, Heidler and colleagues noted that presence of MetS, T2DM, elevated WHR (a marker of central obesity), and HTN correlated with ED severity[151] whereas Aslan and associates reported that only T2DM is a significant risk factor for severe ED.[156]

A brief review of erectile physiology is presented to facilitate an understanding of the mechanisms by which MetS can contribute to the development of ED. An erection involves dilatation of the penile arterial bed, relaxation of the trabecular smooth muscle, and decreased venous outflow, all of which increase cavernosal pressure.[159] These events are mediated by the NO–cyclic guanosine monophosphate (cGMP) pathway. Nitrous oxide is synthesized in the endothelium of penile arteries and cavernosal sinuses and in nonadrenergic, noncholinergic nerves. This synthesis is catalyzed by NO synthases: endothelial (e)NOS, more crucial in maintaining erection; neuronal (n)NOS, more crucial in initiating erection. Nitrous oxide synthase converts L-arginine to NO, which subsequently diffuses into smooth muscle cells where it activates guanylate cyclase that converts guanosine-5-triphosphate (GTP) to cGMP. cGMP decreases intracellular calcium levels leading to vascular smooth muscle relaxation and corporal engorgement. The cGMP

is degraded by phosphodiesterase-5 in the cavernosa, thereby promoting detumescence.[160-165]

Several interrelated reasons may explain the observed relationship between MetS and ED. Hypogonadism has been associated with MetS and its association with sexual dysfunction and ED is well known. Corona and colleagues[36] demonstrated that low testosterone levels are associated with severe ED, hypoactive sexual desire, decreased nocturnal erections, and reduced intercourse frequency. The strongest association between low testosterone levels and decreased intercourse frequency and severe ED was seen in men over 62 years, suggesting that hypogonadism has a greater impact on older individuals.[36] Additionally, in men over 62 years, low testosterone levels were significantly associated with decreased penile peak systolic velocity.[36] Because testosterone has been demonstrated to increase cavernosal nNOS mRNA levels in rats,[166] hypogonadism may result in diminished NO synthesis and subsequent ED.

Another attractive etiology is atherosclerotic disease, as the same mechanisms causing CAD in those afflicted with MetS could similarly impact the penile vascular bed. Shamloul and colleagues[167] showed that, in men age $>$ 40 years, presence of arterial vasculogenic ED was significantly associated with ischemic heart disease diagnosed with cardiac stress testing. Blumentals and colleagues[168] analyzed information on 12,825 men in the Integrated Healthcare Information Services National Managed Care Benchmark Database and showed in a multivariate analysis that men with ED were almost twice as likely to have sustained a myocardial infarction. Other atherosclerotic risk factors such as prior or current smoking are associated with ED as well.[152-155] Several studies have shown that physical

activity reduces the probability of ED[147,154] and this is also known to reduce the risks of CVD and MetS.[169-171] The link between cardiac ischemic disease and ED is not surprising. Given the smaller size of the penile vasculature in relation to the coronary vessels, similar amounts of atherosclerotic burden may cause significant occlusion in the former prior to the latter, and as such, symptomatic ED might present prior to CAD.[172] In fact, many have suggested that ED can serve as a marker of early vascular disease in men.[158,173,174] In addition to diminished blood flow, atherosclerotic disease may actually lead to structural damage within the penis. Animal models of pelvic ischemia have shown similar structural alterations in bladder and prostate as well as penile tissues.[120] In rabbit cavernosa, for example, ischemia and hypercholesterolemia have been shown to induce smooth muscle atrophy and fibrosis,[175] possibly increasing ED predisposition.

Atherosclerotic disease, endothelial dysfunction, and other MetS factors may further impact penile NOS activity, and subsequently, ED. Yono and colleagues[176] demonstrated that spontaneously hypertensive rats (SHR) had diminished circulation to the penis and that this was associated with lower mRNA expression of penile nNOS and eNOS than control rats. Decreased corporal expression of these constitutive NOS subtypes was also noted in a T2DM rat model and was associated with ED.[177] Similarly, in rabbits with induced chronic penile ischemia, impaired cavernosal relaxation was again associated with decreased expression of cavernosal nNOS and eNOS and a concomitant increase in inducible (i)NOS expression.[178] This may be partially explained by the ability of iNOS to decrease eNOS synthesis both in vitro and in vivo.[179] Saenz de Tejada and

colleagues[180] analyzed penile corporal tissue from both patients with diabetes and nondiabetics with ED and found that the former group had decreased neural and endothelial-dependent smooth muscle relaxation. They concluded that a poor relaxation response was caused not by insensitivity to, but reduced synthesis or release of endothelium-derived NO.[180] Esposito and colleagues[150] compared 100 men with MetS with normal age- and BMI-matched controls and assessed ED and endothelial function (via L-arginine test). The investigators demonstrated that ED was directly associated with decreased NO availability. Chronic low-grade inflammation seen in MetS may further contribute to this phenomenon. We have previously noted that serum CRP levels are inversely related with NO synthesis. In addition, multivariate analysis has shown that markers of inflammation known to be elevated in MetS have also been demonstrated to be higher in those with ED, including (high sensitivity) CRP[150,181,182] as well as IL-1β, IL-6, and TNF-α.[181] CRP levels have been further directly correlated to extent of penile ischemia, assessed with penile Doppler studies.[182] Increased iNOS levels have been previously related to ED in animal models, and its expression is increased by IL-1β, IL-6, and TNF-α.[178]

It is known that α-adrenergic activity results in corporal smooth muscle relaxation, a concept that is exploited during treatment of priapism with α-agonists.[183,184] We have previously noted that hyperglycemia is associated with autonomic hyperactivity, and in the rat model, elevated autonomic activity was shown to induce ED.[120] This was further corroborated by a recent study demonstrating that patients with nonorganic ED had significantly higher cardiac sympathetic activity than controls.[185] In patients with BPH/LUTS, several studies have

noted that nonselective α1-antagonists such as doxazosin[186,187] and prostate-selective subtypes such as alfuzosin[188,189] lead to improvements in sexual dysfunction, including ED. In SHR, treatment with doxazosin (α1-receptor antagonist) results in increased penile blood flow as well as increased penile expression of eNOS and nNOS compared with untreated or calcium channel antagonist (nifedipine)-treated SHR.[190] Thus, excessive corporal adrenergic activity can further contribute to ED.

Features of MetS have been previously noted to stimulate the ROK pathway, which may further increase ED by inhibiting cavernosal relaxation. In T2DM rat models, ED is associated with increased cavernosal levels of a ROK receptor, ROK1, and a G-protein activator of ROK, RhoA.[177] To a lesser extent, increased cavernosal type A endothelin receptor, was also noted in this study, and these receptors are involved in regulation of vasoconstriction.[177] This finding is not surprising because ET-1 is known to stimulate the ROK pathway and elevated ET-1 levels have been associated with both T2DM[30,32] and ED.[191] The importance of ROK activity in erectile function was further demonstrated in an experiment where ROK inhibition resulted in diminished contraction of human and rat cavernosal tissue to α-adrenoreceptor stimulation with phenylephrine.[192] In rats, NO can also inhibit ROK activity, and this is believed to contribute to NO-induced erection.[193] Thus, disturbances found in MetS may result in increased ROK activation, further leading to ED.

LUTS/BPH, ED, and MetS: Common Etiological Links?
The association with ED and LUTS/BPH warrants further discussion as MetS is encountered in those afflicted with both entities. Demir

and colleagues showed that ED was the only variable found to be an independent predictor of severe LUTS.[114] Rosen and colleagues[194] found that LUTS severity was significantly associated with increased frequency of ED, ejaculatory dysfunction, and decreased sexual activity. Multiple aspects of sexual dysfunction (including libido, erectile function, ejaculation, bother due to sexual problems, and overall sexual satisfaction) have also been positively correlated with LUTS.[120,195] Several reasons for the link between ED and BPH/LUTS have been proposed, including pelvic atherosclerosis, decreased NO/NOS activity as well as increased autonomic and ROK activation.[120] The relationship of these concepts with MetS has been examined. Pelvic atherosclerosis, or more specifically ischemia, can be linked to MetS as endothelial dysfunction, atherosclerosis, and increased CVD are all features seen in MetS. Multiple aspects of MetS including IR, hyperglycemia, AGEs, FFAs, endothelial dysfunction, and

chronic inflammation all contribute to decreased NO bioavailability. Likewise, hyperinsulinemia has been shown to contribute to autonomic hyperactivity. Finally, excessive ROK activation can result in greater tonic muscle contraction contributing to both BPH/LUTS and ED. Moreover, this pathway may be augmented by ET-1, autonomic hyperactivity, and IL-8 activity. Low testosterone levels are linked definitively with ED, and some evidence suggests that deficient androgens and/or excessive estrogens may contribute to BPH/LUTS. Therefore, these processes, working independently or in concert with one another, may explain the association with both BPH/LUTS and ED. These relationships are summarized in Figure 2.

Female Incontinence

There is evidence that features of MetS may be contributing to urinary incontinence (UI) in women. A cross-sectional study from Taiwan assessed 371 women with the Incontinence-Quality of Life (I-QOL) questionnaire,

and noted that stress urinary incontinence (SUI) was the most frequent subtype reported (28.6%), followed by mixed (24.5%) and urge (16.2%) incontinence.[196] Univariate analysis showed a significant association between urinary incontinence and HTN and obesity (BMI > 27) in this study, and the latter condition significantly correlated with obesity on multivariate analysis (OR, 3.38).[196] In the Look AHEAD (Action for Health in Diabetes) trial, the prevalence of incontinence in overweight and obese women with T2DM was 27%; higher than retinopathy (7.5%), microalbuminuria (2.2%), and neuropathy (1.5%).[197] In that trial, incontinence was also associated with increasing BMI (BMI = 35-39, OR, 1.65; and BMI ≥ 40, OR, 1.84).[197]

No studies have shown direct links between MetS and SUI in women, but associations between features of MetS such as elevated BMI, abdominal obesity, diabetes, and HTN have been demonstrated. In a study of approximately 4000 women, multivariate analysis revealed that SUI was most prevalent in individuals with both obesity and diabetes (OR, 3.67). Presence of either obesity or diabetes was also associated with increased SUI prevalence (OR, 2.62 and 1.81, respectively).[198] In the Look AHEAD trial, SUI was associated with increasing BMI (BMI = 35-39, OR, 1.56; and BMI ≥ 40, OR, 1.64).[197] Multivariate analysis from HERS (Heart & Estrogen/Progestin Replacement Study) showed that SUI was 10% more likely with elevated BMI and 20% more likely with increased WHR.[199] Cross-sectional studies from China have further demonstrated that SUI is independently associated with being overweight (OR, 1.31) or obese (OR, 1.44), as well as having high WC (> 80 cm; OR, 1.38) or HTN (OR, 1.2).[200,201]

Overactive bladder (OAB) and urinary urge incontinence (UUI) are

Figure 2. *Possible mechanisms of benign prostatic hyperplasia, lower urinary tract symptoms (LUTS), and erectile dysfunction (ED) in metabolic syndrome (MetS). Features that may be seen in MetS, including pelvic atherosclerosis and ischemia, decreased nitric oxide (NO) availability, elevated sympathetic activity, low-grade inflammatory state, and elevated estrogen/testosterone ratio can contribute to benign prostatic hyperplasia (BPH), LUTS, and ED. Lower NO availability and elevated sympathetic activity can stimulate RHO-kinase activity, further exacerbating the process.*
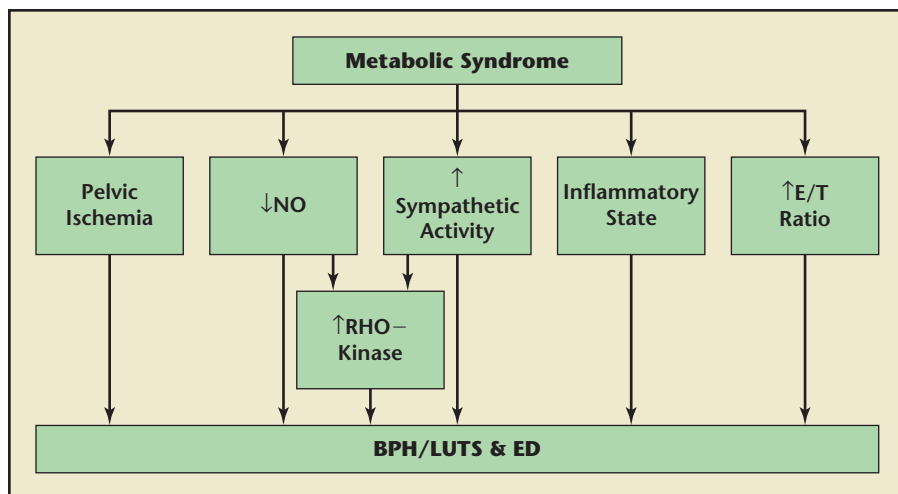
associated with MetS components as well. Lawrence and colleagues[198] noted that rates of OAB are almost 3 times higher in obese women, regardless of diabetes status. In multivariate analysis from HERS data, diabetes was significantly associated with UUI (OR, 1.5).[199] Similarly, in data from the first and second Nurses' Health Studies (NHSI and NHSII), T2DM was significantly associated with UUI in a multivariate analysis.[202] In the Look AHEAD trial, UUI had only a modest correlation with WC.[197]

Interestingly, weight loss appears to alleviate UI in women. The recent PRIDE trial (Program to Reduce Incontinence by Diet and Exercise) randomized overweight or obese women with > 10 episodes of incontinence per week to either an intensive 6-month behavioral weight loss program or a structured 4-session educational program.[203] Those in the intensive program lost more weight and their SUI improved more than the other group. However, this relationship was not seen with UUI. Bump and colleagues[204] assessed 13 morbidly obese women with urodynamic studies before and after gastric bypass surgery (prebypass mean BMI, 49.4; postbypass mean BMI, 33.1), and reported significant resolution of both SUI and UUI.

No associations between features of MetS and incontinence in males have been demonstrated.[205-208] However, a group of investigators did find a positive correlation between ED and OAB in men (OR, 1.5), which was previously noted to be more frequent in MetS.[209]

Obesity appears to be the major MetS feature associated with SUI in women. SUI occurs when intravesical pressure exceeds bladder outlet pressure either secondary to urethral hypermobility and/or an intrinsic sphincter deficiency, resulting in involuntary urine loss.[210,211] Associations between central obesity and bladder pressures have been noted. Sugerman and colleagues[212] measured intravesical pressures in anesthetized male (n = 17) and female (n = 67) patients and noted significant positive associations with obesity and central obesity. Furthermore, weight loss in morbidly obese women improved numerous SUI parameters including lower elevations in bladder pressure with maximal effort coughs, better cough pressure transmission from bladder to urethra, and lower urethral axial mobility with coughing.[204] Another etiology has been proposed by Kim and colleagues,[210] who noted that SUI is associated with increased size of retropubic space, and stated that this area might be larger in overweight women.

Components of MetS that contribute to ED and BPH/LUTS can also impact UUI and OAB. The pathophysiology of UUI is secondary to inappropriate bladder contractions during the storage phase, thereby leading to the sensation of urgency, whereas reductions in functional capacity manifest as frequency.[128] At the cellular level, detrusor contractions are stimulated by parasympathetic activity via acetylcholine (ACh) binding to muscarinic M_3 receptors.[128] Increased ROK activity is associated with MetS features, and this pathway may also contribute to increased detrusor activity not only via ACh receptors, but also purinoceptors, as well as neurokinin and bradykinin receptors.[128] Elevated ROK or RhoA activity has been associated in animal models of bladder hypertrophy as well as diabetes- and HTN-associated bladder dysfunction.[128] Bladder hypertrophy often leads to components of OAB such as urgency and frequency,[128] and we have previously noted that chronic pelvic ischemia in the rabbit also leads to increased bladder fibrosis and smooth muscle atrophy,

resulting in decreased compliance. HTN-associated bladder dysfunction has been studied. Persson and colleagues[213] demonstrated that SHR bladders exhibited reduced micturition volume, bladder capacity, and increased amplitude of nonvoiding bladder contractions, compared with control Wistar-Kyoto rats. Intrathecal doxazosin (a nonspecific α-antagonist) resulted in higher bladder capacity and diminished amplitude of nonvoiding bladder contractions, and in tissue studies, increasing norepinephrine concentrations resulted in paradoxical increases in bladder contractions.[213]

It is known that SHRs have increased bladder sympathetic innervation as well as efferent and afferent bladder neuronal hypertrophy, and that altered noradrenergic control of the micturition reflex might account for the distorted SHR bladder function.[213] Given these data as well as the positive association between α1 receptors and ROK activity, sympathetic hyperactivity may be an etiology of UUI in humans. The link between diabetes and UUI has been attributed to axonal atrophy of autonomic neurons to the bladder.[214] In streptazosin-induced diabetic rats (SIDR), findings consistent with detrusor overactivity (eg, larger gap junctions between detrusor myocytes) were seen in conjunction with degenerated nerve fibers.[214] SIDR have further demonstrated detrusor hyperactivity that is associated with increased muscarinic receptor expression and sensitivity to muscarinic stimulation.[215] Nevertheless, alternate etiologies such as increased diuresis secondary to diabetes leading to urinary frequency[202] must also be considered when discussing relationships between MetS and incontinence. These explanations between MetS and female incontinence are depicted in Figure 3.
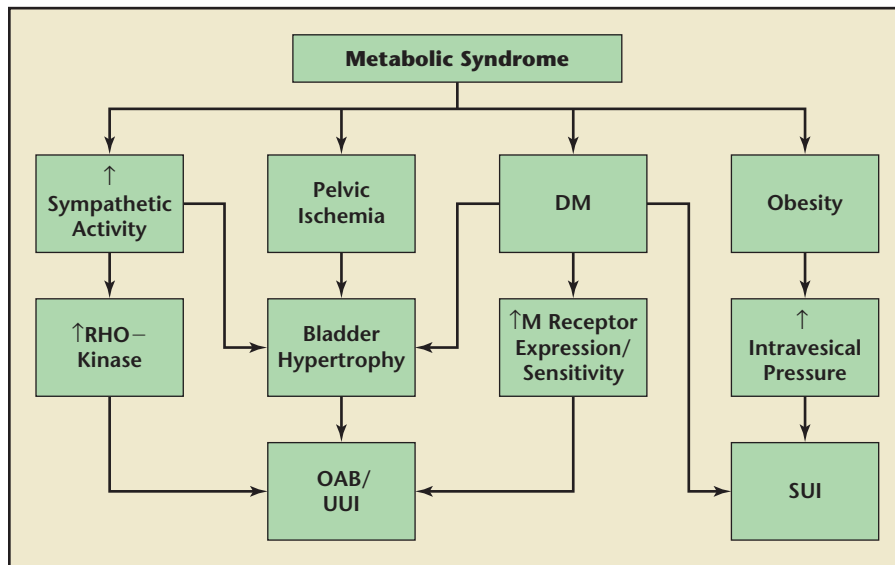
Figure 3. *Possible mechanisms of female incontinence in metabolic syndrome (MetS). Features of MetS including diabetes and obesity may contribute to stress urinary incontinence (SUI). In addition, diabetes (DM) and other possible MetS components such as elevated sympathetic activity and pelvic ischemia may further lead to overactive bladder (OAB) and urinary urge incontinence (UUI) via the denoted pathways. M receptor, muscarinic receptor.*

Male Infertility

Features of MetS have been linked to male infertility. A retrospective study revealed that overweight (BMI 25-29) and obese (BMI $\geq$ 30) men were significantly more likely to experience infertility (OR, 1.19 and 1.36, respectively) compared with lean men (BMI 20-22.4).[216] This association with higher BMI and greater infertility was maintained even after numerous adjustments, including age, partner's BMI, parity, and coital frequency.[216] A retrospective Japanese study similarly showed that men with higher BMI were less likely to experience the birth of a new child compared with lower BMI counterparts, even after adjustment for age, SBP, DBP, LDL, TG, and HbA$_{1c}$.[217] In a cross-sectional study from Qatar, male infertility was significantly related with T2DM (OR, 1.958) and HTN (OR, 2.558).[218] Multivariate analysis further revealed that obese (BMI > 30) T2DM patients were more than 3 times as likely to be infertile when compared with their thin (BMI < 25) T2DM counterparts.[218]

Numerous factors may contribute to male infertility in those with MetS features. Obesity, for example, has been demonstrated to negatively impact semen quality in several studies.[219-221] Increasing BMI is associated with low sperm motility[221,222] and ejaculate volume.[220] BMI has also been positively associated with high spermatic DNA damage as assessed by a measure of chromatin integrity, the DNA fragmentation index.[220,222] Abdominal obesity has also been inversely correlated with sperm volume, sperm count, and sperm motility.[223] Diminished sperm motility and semen volume have been noted in T2DM patients as well.[224] Hypogonadism, a condition linked to MetS, may impact fertility as testosterone initiates and qualitatively maintains spermatogenesis in humans. The ability to deliver sperm may also be influenced by MetS. Individuals with T2DM are more apt to have ED and ejaculatory dysfunction (EjD) including retrograde ejaculation and premature ejaculation.[225-228]

Several explanations may account for the seminal abnormalities noted in those with MetS features. Kasturi and colleagues[229] proposed that dyslipidemia and a proinflammatory state may result in increased reactive oxygen species (ROS) formation and subsequent lipid peroxidation of the spermatic membranes. Given that hyperglycemia is associated with increased free radical production, it may further contribute to this process in MetS. The end result may be increased DNA damage and decreased spermatic motility.[229] Obesity may increase scrotal temperature, which is thought to induce oxidative damage and apoptosis of sperm.[230] This is probably not directly related to varicocele, a condition thought to increase scrotal temperature, as varicocele is less prevalent in obese subjects.[231,232] Nevertheless, scrotal adiposity may be an underlying cause. Shafik and Olfat[233] performed scrotal dissections on men with idiopathic infertility and noted that extra and intratunicary fat distributions, which they coined scrotal lipomatosis, were more prevalent in obese subjects. They proposed that scrotal lipomatosis may lead to elevated scrotal temperatures via increased adipose insulation, venous stasis, and higher testicular position within the scrotum.[233] These investigators performed scrotal lipectomy in infertile subjects, the majority of whom were obese, resulting in increased sperm number and motility, and improved morphology.[234] The associations between MetS and male infertility are summarized in Figure 4.

Prostate Cancer

Some studies have demonstrated positive correlations between MetS, its features, and PCa. A prospective trial from Finland in which 1880 patients were followed demonstrated in a multivariate analysis that, in those with MetS, the PCa risk doubled.[235]
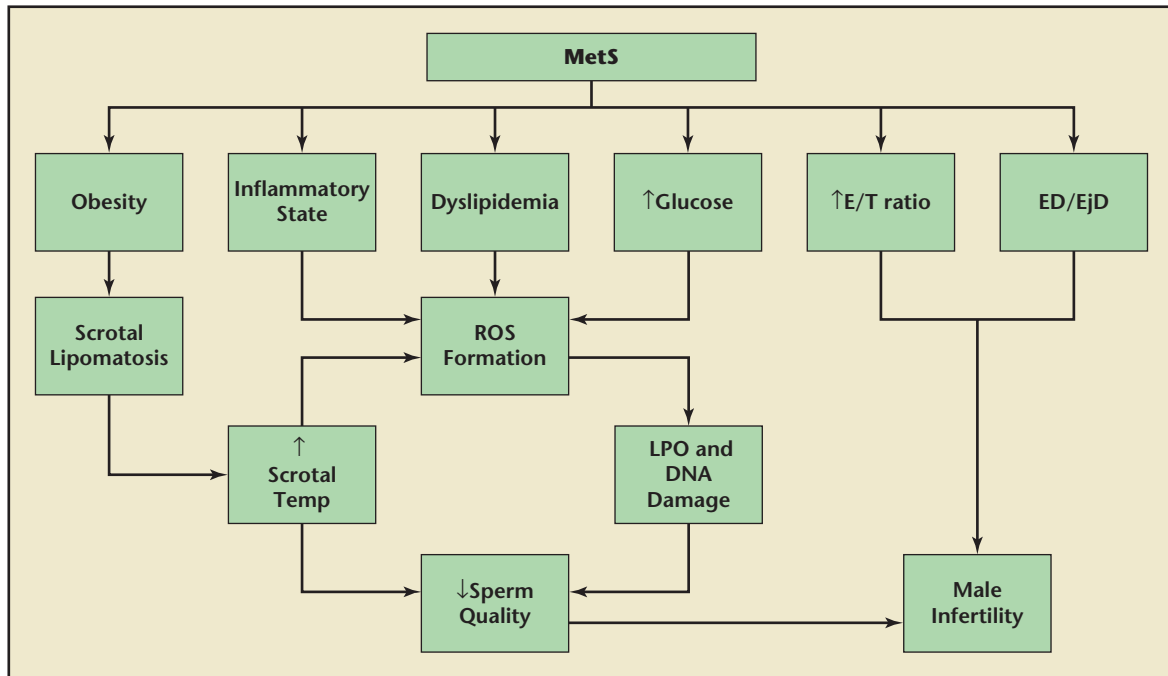
Figure 4. *Possible mechanisms of male infertility in metabolic syndrome (MetS). Several features of MetS may contribute to male infertility. Obesity might lead to scrotal lipomatosis and elevated scrotal temperatures, depressing sperm quality. This may be further augmented by dyslipidemia, hyperglycemia, and a proinflammatory state contributing to reactive oxygen species (ROS) formation and sperm damage. Other contributors may include elevated estrogen/testosterone ratio (E/T), erectile dysfunction (ED) and ejaculatory dysfunction (EjD). LPO, lipid peroxidation. Data from Kasturi SS et al.[229]*

Furthermore, those with MetS and a BMI $\geq$ 27 had a 3 times greater risk of developing PCa.[235] In univariate analysis, positive associations with PCa prevalence and hyperglycemia (OR, 7.31), low HDL-cholesterol (OR, 9.93), as well as elevated WHR, SBP, and DBP have also been noted.[236,237] Another study demonstrated that each 12-mm increase in DBP was independently associated with an 8% increase in PCa incidence.[238] Data from the Helsinki Heart Study showed that patients with an elevated BMI ($>$ 28) and SBP ($>$ 150 mm Hg) were greater than 2 times more likely to have PCa, and greater than 3 times more likely with the addition of low HDL ($\leq$ 1.05 mmol/L).[239] In a large prospective cohort study of 950,000 Norwegian men, stratification by age revealed that obese men age 50 to 59 years had a $>$ 50% increased PCa incidence compared with those with a normal BMI.[240] Additionally, a signif-

icant positive correlation with BMI and PCa incidence was shown.[240] A meta-analysis of 56 trials with 68,753 total cases demonstrated an overall 5% increased PCa risk per 5 kg/m^2 (BMI) increment.[241]

Some studies suggest that components of MetS may also result in more aggressive PCa. In the previously mentioned meta-analysis,[241] each 5-point BMI increment increased the risk of advanced PCa stage significantly (relative risk [RR], 1.12). A recent retrospective study showed that white men with a BMI $\geq$ 35 were approximately 2 to 3 times more likely to have worse pathologic findings during radical prostatectomy (including Gleason sum $\geq$ 7, positive surgical margins, extraprostatic extension, and seminal vesicle invasion) than lean counterparts (BMI $<$ 25).[242] Biochemical PCa recurrences were also higher in overweight or obese Caucasian and African-American men.[242]

Hammarsten and Högstedt[243] demonstrated that both PCa stage and grade are directly associated with BMI, waist measurement, TG, and fasting plasma insulin, and indirectly with HDL. A prospective study further demonstrated that significantly higher plasma insulin levels were noted in those who succumbed versus those who survived PCa, and moreover, PCa mortality was significantly associated with number of MetS features present.[244] Investigators have also reported positive associations among WHR, DBP, and serum PSA in those with PCa, as well as an inverse relationship between HDL and serum PSA.[236,245] Low testosterone, a condition associated with MetS, has also been linked to more severe PCa. In retrospective analysis, men with low total plasma testosterone ($<$ 3 ng/mL) had an elevated risk of high-grade PCa (Gleason sum $\geq$ 7; OR, 2.59).[246] Low testosterone levels have also

been significantly related to more advanced PCa stages[247] and positive margins in radical retropubic prostatectomy.[248] Yet other investigators have failed to find relationships between testosterone levels and risk of PCa or more aggressive PCa.[249]

There is also evidence that MetS and some of its components may actually limit the risk of PCa. Tande and colleagues followed 6429 men in the Atherosclerosis Risk in Communities (ARIC) Study and determined that MetS, either with or without diabetes, was significantly associated with a reduced risk of PCa (RR, 0.71 and 0.77, respectively).[250] Kasper and colleagues[251] demonstrated in multivariate analysis that diabetes was associated with a 17% reduced risk for total PCa, 28% reduced risk for localized PCa, 31% reduced risk for high-grade PCa, and 24% reduced risk for low-grade PCa. Further analysis demonstrated that overweight patients with diabetes (BMI $\geq$ 25) had a 19% lower PCa risk than overweight individuals without diabetes.[251] Further prospective multivariate analysis of 72,670 men from the Cancer Prevention Study II Nutritional Cohort (CPSII NC) revealed that after 4 years from diagnosis of diabetes, there was a 37% decrease in PCa incidence.[252] Similarly, data from the CPSII NC showed that diabetes decreased the incidence of both nonaggressive (stages I and II with Gleason < 8) and aggressive (stages III and IV and those with Gleason $\geq$ 8) PCa (RR, 0.71 and 0.51, respectively).[252] Other MetS features have also been shown to decrease PCa risk. In the ARIC Study, increased MetS features showed a trend toward decreasing PCa, with diabetes excluded.[250] An inverse correlation between TG and incidence of PCa has also been reported.[253] On the contrary, other investigators have found no relationship between MetS features and PCa.[238,254-256]

A number of mechanisms may play a role in how the aforementioned factors either positively or negatively influence PCa risk. Low testosterone levels may disrupt hormonal balance resulting in tumor cells that proliferate in an androgen-independent manner and a more aggressive phenotype.[247,257] Angiogenesis is crucial for tumor survival, and it has been demonstrated that androgens regulate the steady-state expression of vascular endothelial growth factor (VEG-F) in PCa models.[258] Indeed, Schatzl and colleagues[259] demonstrated that microvessel density (MVD) is inversely related to serum testosterone levels in men with newly diagnosed PCa. Low testosterone levels are also closely related to hyperinsulinemia, yet the etiology behind the relationship has not been fully elucidated.[260] Nevertheless, insulin is known to have promitotic and anti-apoptotic actions, and elevated insulin levels have been associated with increased growth in a PCa cell line (LNCaP).[261] 5 α-reductase (AR) activity has been found to be elevated in patients with T2DM and obesity[262] and may raise cancer risk through greater prostatic stimulation.[263,264] There is ample evidence that IGF-1 is linked to MetS and that it may influence the development of PCa. An increasing number of MetS components have been inversely correlated with serum IGF-1 levels as well as IGF-1/insulin growth factor-binding protein-3 (IGFBP-3) ratio, a marker of IGF-1 bioavailability.[265-267] Additionally, WC, SBP, TG, and FPG are inversely correlated with IGF-1/IGFBP-3 ratio, and HDL is directly correlated.[266] IGF-1 levels are inversely correlated with risk of T2DM development,[266] levels of HbA$_{1c}$[268] and CRP,[265] as well as HTN.[269] Significant direct relationships between IGF-1 levels and in-

creased total PCa risk as well as that for low- and high-grade PCa have also been reported.[270-273] In PCa cell lines, IGF-1 has been shown to cause proliferation and inhibit apoptosis.[251] Prostate epithelial cells have further demonstrated the ability to synthesize low levels of VEG-F in response to IGF-1 stimulation, providing a mechanism for increased angiogenesis.[274] The relationship of T2DM and PCa initially appears paradoxical. T2DM is associated with hyperinsulinemia, which itself is related to worse PCa disease. Nevertheless, T2DM has been shown to be protective for high-grade disease. This phenomenon may be due to timing. Although T2DM is associated with IR and initial hyperinsulinemia, β-islet cell desensitization and insulin depletion (termed β-cell exhaustion) may develop over time, promoting a low insulin state.[275] This concept is further corroborated by the previously mentioned findings of Rodriguez and coauthors[252] who demonstrated a decreased PCa incidence at 4 years post-diabetes diagnosis.

The chronic inflammatory state associated with MetS may contribute to increased PCa risk. We have previously mentioned that IL-1β, IL-6, TNF-α, CRP, and perhaps IL-8 are increased in MetS. TNF-α, IL-6, and IL-8 have been associated with increased PCa risk and PCa stage, as well as metastatic disease.[276-278] IL-1β has also been associated with metastatic disease.[279] IL-8 has chemotactic and angiogenic activity and can stimulate androgen-independent growth of LNCaP cells.[276,280] Both IL-1β and TNF-α have been shown to induce IL-8 expression in androgen-dependent (LNCaP) and androgen-independent (DU-145 and PC-3) PCa cell lines.[276] These cell lines have also demonstrated the ability to secrete IL-6, which might function as a paracrine
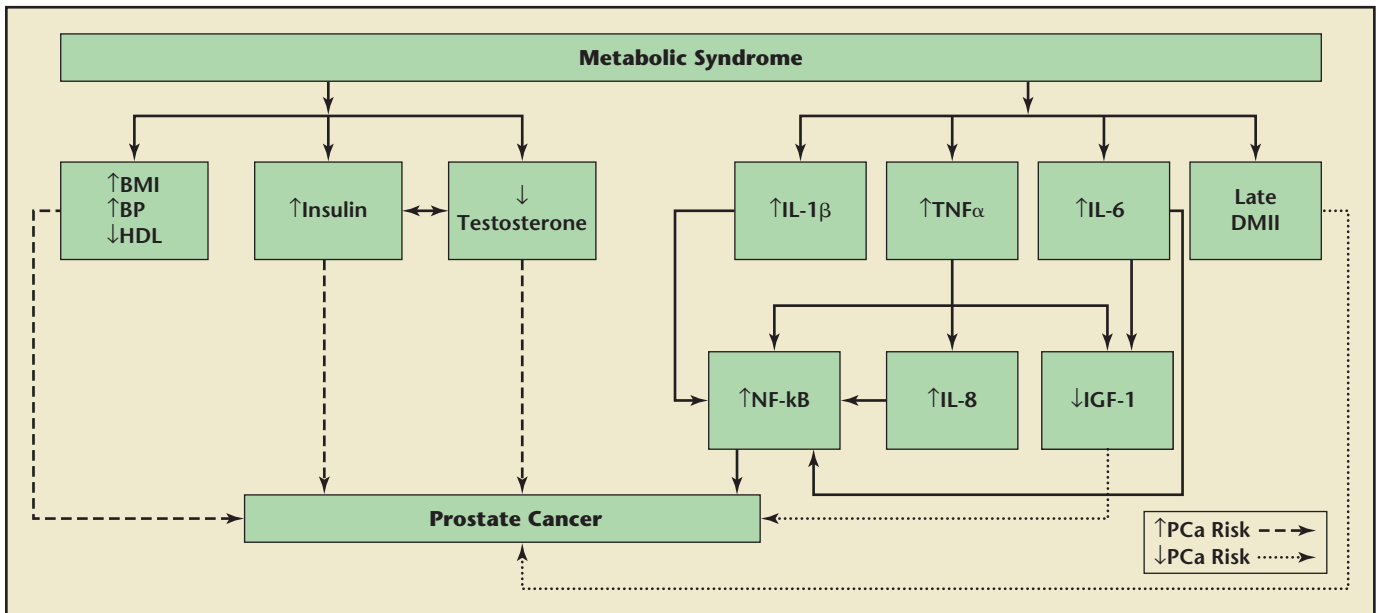
Figure 5. *Possible mechanisms of prostate cancer (PCa) in metabolic syndrome (MetS). Features of MetS such as elevated BMI, hypertension (↑BP), and low HDL levels may increase risk of PCa. Hyperinsulinemia (↑ insulin) and low testosterone levels are interrelated and may further contribute. Increases in proinflammatory cytokines might lead to prostatic malignancy via increased NF-κB (↑NF-κB) activity. However, lower IGF-1 activity seen in MetS may decrease risk of PCa. Additionally, lower PCa levels in late T2DM may be secondary to a hypoinsulinemic state.*

signal in LNCaP cells and an autocrine signal in DU-145 and PC-3 cell lines.[281] In vivo, PCa cells have shown the capacity to secrete TNF-α, and the ability of TNF-α to decrease AR expression and DHT sensitivity in LNCaP cells suggests that it may contribute to the development of androgen insensitivity in PCa.[282] Additionally, IL-1β, IL-6, IL-8, and TNF-α are known to stimulate the nuclear factor-κB (NF-κB) pathway, and this has been hypothesized as a possible link between elevated inflammatory cytokine levels and PCa development.[283] Increased NF-κB activity has been linked to PCa. In both PC-3 and DU-145 cell lines, NF-κB was shown to be constitutively activated.[284] Inverse correlations between NF-κB activity and AR sensitivity in PCa models suggests a role for NF-κB in androgen-independent PCa progression.[285] Indeed, inhibition of NF-κB in metastatic PC-3M PCa cell lines resulted in decreased VEGF and IL-8

expression, and this correlated with decreased revascularization and lymph node metastasis in prostates of nude mice.[284] Furthermore, Lessard and colleagues[286] demonstrated that, in radical prostatectomy specimens, nuclear NF-κB localization is directly related to extent of lymph node invasion. IGF-1 appears to modulate proinflammatory cytokines as it has been shown to stimulate IL-8 expression in DU-145 cells independently or synergistically with IL-1β.[276] IGF-1 can also cause IL-6, IL-8, and TNF-α expression in human immune cells.[276] Interestingly, IL-6 and TNF-α have themselves been demonstrated to decrease serum IGF-1 levels while increasing hepatic CRP synthesis,[265] possibly explaining the aforementioned inverse relationship between CRP and IGF-1. Thus, lower IGF-1 levels seen in MetS may be associated with decreased levels of these proinflammatory cytokines, thereby reducing PCa risk. However, it is

important to note that some investigators have shown no correlations between these adipokines and PCa risk.[267,287] These interactions are summarized in Figure 5.

Conclusions

MetS is a complex disorder consisting of numerous interrelated pathophysiologic entities including obesity, HTN, dyslipidemia, hyperglycemia/IR, and endothelial dysfunction. These problems and a number of systemic responses reviewed in this article may promote the development of several multifactorial urologic disorders including nephrolithiasis, ED, male infertility, BPH/LUTS, female incontinence, and PCa. Furthermore, this group of patients is subject to a number of systemic diseases that can influence quality of life and longevity. Therefore, it is important that urologists be cognizant of this disorder and the aforementioned relationships with urologic diseases.

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Main Points

- Approximately 35% to 39% of the adult population in the United States has metabolic syndrome (MetS), with similar rates in males and females. The percentage of overweight and obese individuals in the United States continues to grow, with the greatest escalation seen in the so-called "superobese".

- MetS is a complex disorder consisting of numerous interrelated pathophysiologic entities including obesity, hypertension (HTN), dyslipidemia, hyperglycemia/insulin resistance (IR), and endothelial dysfunction. These problems may promote the development of several multifactorial urologic disorders including nephrolithiasis, erectile dysfunction (ED), male infertility, benign prostatic hyperplasia/lower urinary tract symptoms, female incontinence, and prostate cancer (PCa).

- Studies have shown the MetS and its components (obesity/increased waist circumference, HTN, etc) are associated with increased rates of nephrolithiasis. A recent cross-sectional study from Italy demonstrated that individuals with MetS are twice as likely to have ultrasonographic evidence of nephrolithiasis.

- ED is up to 3 times more prevalent in individuals with MetS. Direct relationships between ED and various components of MetS including obesity, HTN, diabetes, and hypertriglyceridemia have also been shown. Atherosclerotic disease, endothelial dysfunction, and other MetS factors may further impact penile NOS activity, and subsequently, ED.

- Obesity appears to be the major MetS feature associated with stress urinary incontinence (SUI) in women. Weight loss in morbidly obese women improved numerous SUI parameters including lower elevations in bladder pressure with maximal effort coughs, better cough pressure transmission from bladder to urethra, and lower urethral axial mobility with coughing.

- Features of MetS have been linked to male infertility. A retrospective study revealed that overweight (body mass index [BMI] 25-29) and obese (BMI ≥ 30) men were significantly more likely to experience infertility (odds ratio, 1.19 and 1.36, respectively) compared with lean men (BMI 20-22.4).

- Studies have demonstrated conflicting information with regard to MetS and PCa risk. One factor may be alterations within insulin state in early versus late type 2 diabetes mellitus. Further research into this and other MetS components would be prudent and may help in better elucidating these complex relationships.

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