Metabolic syndrome and diabetes for the urologist

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Abstract

Type 2 diabetes has a number of know urological consequences. Epidemiologic and clinical data suggest a link between metabolic syndrome and prostatic diseases, such as benign prostatic hyperplasia (BPH) and prostate cancer. Recent studies have identified metformin as a viable treatment for patients with type 2 diabetes and prostate cancer.

Metabolic syndrome comprises a constellation of metabolic abnormalities that are associated with an increased risk of cardiovascular (CV) disease, type 2 diabetes, CV-specific mortality, and all-cause mortality.[1,2] The definition of metabolic syndrome varies according to different sources, but generally comprises a series of factors involving insulin resistance, increased body weight, increased lipid levels, high blood pressure and impaired glucose levels (Table 1).[3-7]

The prevalence of metabolic syndrome in Canada is estimated at 19%.[8] Dietary excess and a sedentary lifestyle are thought to contribute to the development of metabolic syndrome in genetically susceptible individuals.

The development of diabetes follows a series of stages, beginning with insulin resistance in peripheral tissues, resulting in glucose intolerance. At this stage, a postprandial rise in glucose may be the only sign of metabolic disturbance. With increased insulin resistance, the patient reaches a state of hyperinsulinemia combined with hyperglycemia – a stage that is often referred to as "pre-diabetes," during which the cells become increasingly starved for energy. During the hyperinsulinemic phase of type 2 diabetes, glucose levels rise above safe levels. Finally, during the burnout phase, beta-cells are no longer able to produce insulin. Insulin resistance occurs years before the onset of type 2 diabetes, due to genetic factors as well as environmental factors, such as sedentary lifestyle, pregnancy, nutrient intake (quantity and quality), puberty and aging. The net result is adiposity, impaired B-cell function, and impaired insulin action.

Type 2 diabetes can result in a number of urological consequences. Renal consequences may include kidney stones, pyelonephritis/inflammation or chronic renal failure. In the bladder, urinary tract infections or cystopathy/retention may develop. Infertility, andropause and erectile dysfunction are also known urological consequences of type 2 diabetes.[9]

Recent epidemiologic and clinical data suggest a link between metabolic syndrome and prostatic diseases, such as benign prostatic hyperplasia (BPH) and prostate cancer.[10] Many of the hormones, growth factors, cytokines and other mediators associated with obesity and the metabolic syndrome enable crosstalk between macrophages, adipocytes, endothelial cells and epithelial cells, which is implicated in carcinogenesis (including growth signaling, inflammation, and vascular alterations).[11] A recent study at the University of Toronto found that men with 3 or more components of the metabolic syndrome had a 38% higher odds of being diagnosed with prostate cancer than men with no risk factors.[12] These men also had a 52% higher odds of being diagnosed with clinically significant prostate cancer and a 43% higher odds of being diagnosed with high-grade prostate cancer (Gleason 7 or higher). These findings suggest a biologic gradient with increasing number of metabolic risk factors. As well, androgen deprivation therapy, used in the treatment of prostate cancer, can induce alterations similar to those of metabolic syndrome, including increased obesity, decreased insulin sensitivity and altered lipid profiles.[13]

Recent data suggest that men with type 2 diabetes and prostate cancer have improved survival when treated with the biguanide oral hypoglycemic agent metformin. Among men with diabetes in a population-based, retrospective cohort of 3837 patients, cumulative duration of treatment with the antidiabetic metformin following a diagnosis of prostate cancer was associated with declines in both all-cause mortality and prostate cancer-specific mortality.[14] However, despite these findings of improved survival in men with an existing diagnosis of prostate cancer, metformin does not seem to prevent the development of prostate cancer in men with type 2 diabetes. A retrospective review of 5306 diabetic men with prostate cancer and 26 530 matched controls

Table 1. Indications for bone mineral density testing[5]

Clinical measure	WHO (1998)[3]	ATP III (2001)[4]	IDF (2005)[5]	AHA/NHLBI (2005)[6]	IDF & AHA/NHLBI Joint Interim (2009)[7]
Insulin resistance	**Mandatory** IGT, IFG, T2DM, or lowered insulin sensitivity* **plus any 2 of the following**	None, but any 3 of the following 5 features	None	None, **but any 3 of the following 5 features**	
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥102 cm in men or ≥88 cm in women†	**Mandatory** Increased WC (population specific) **plus any 2 of the following**	WC ≥102 cm in men or ≥88 cm in women†	Ethnicity/pop-specific WC
Lipid -High TG -Low HDL	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women Or use of specific drug for this (nicotinic acid or fibrate)	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women Or use of specific drug for this (nicotinic acid or fibrate)
Blood pressure	≥140/90 mmHg	≥130/85 mmHg	≥130 mmHg systolic or ≥85 mmHg diastolic or on hypertension medication	≥130/85 mmHg or medical treatment for hypertension	≥130/85 mmHg or medical treatment for hypertension
Glucose	**Mandatory** IGT, IFG, or T2DM	>110 mg/dL (includes diabetes)‡	≥100 mg/dL (includes diabetes)	>100 mg/dL (includes diabetes)‡	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria				

AHA: American Heart Association; ATP III: Adult Treatment Panel III; HDL-C: High-density lipoprotein cholesterol; IDF: International Diabetes Foundation; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; NHLBI: National Heart, Lung, and Blood Institute; T2DM: type 2 diabetes mellitus; TG: triglycerides; WC: waist circumference; WHO: World Health Organization. *Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation. †Some men can develop multiple metabolic risk factors when the waist circumference is only marginally increased (e.g., 94 to 102 cm). These patients may have a strong genetic contribution to insulin resistance and may benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. ‡In 2001, a fasting plasma glucose of 110 mg/dL (6.1 mmol/L) or higher was defined as elevated. In 2004, the definition was revised to 100 mg/dL (5.6 mmol/L) or higher, in accordance with the American Diabetes Association's updated definition of IFG.[16-18]

found no association between cumulative metformin use and the risk of developing prostate cancer.[15]

The Metformin Active Surveillance Trial (MAST) study is currently exploring whether metformin will delay progression of prostate cancer. A total of 404 men with low-risk prostate cancer undergoing active surveillance have been randomly assigned to receive metformin (850 mg bid) or placebo for 3 years. The primary end point is time to progression, defined as the need for primary prostate cancer therapy (e.g., prostatectomy, radiation or hormone therapy) as a result of pathological progression.

Conclusion

Type 2 diabetes and metabolic syndrome are important factors in many aspects of prostate cancer. Recent evidence has shown that metformin may be a viable treatment for patients with type 2 diabetes and prostate cancer. Ongoing studies are exploring the possibility that metformin may also play a role in the progression of early stage prostate cancer.

Regardless of a diagnosis of prostate cancer, the urologist should be aware of the potential effects of diabetes and metabolic syndrome on the prostate and other urological systems.

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