For many years, the concept of ‘men’s health’ has been largely focused on prostatic disease and other male-specific urological conditions. However, while urological conditions are without doubt important contributors to the health and quality of life of men, it is cardiovascular disease (CVD), type 2 diabetes mellitus and other elements of the ‘metabolic syndrome’ that present the biggest threats to men in terms of morbidity and premature death.

There is growing evidence that we can place many common urological conditions as part of the ‘metabolic syndrome’. Patients presenting with these conditions, both to primary and secondary care, could be considered therefore as offering us a ‘gateway’ to improve their wider health. Assessment of risk factors and identifying the presence of features of the metabolic syndrome allows the physician to address future risk of diabetes, cardiovascular disease and urological conditions and potentially impact on future quality of life, morbidity and mortality.

Metabolic syndrome and common urological conditions: looking beyond the obvious

JONATHAN REES AND MIKE KIRBY

Awareness of the link between the metabolic syndrome and many common urological conditions should encourage all physicians to assess the patient presenting with these conditions for underlying metabolic syndrome and cardiovascular risk.

Figure 1. Identification of the presence of features of the metabolic syndrome (central obesity, high blood pressure and high blood sugar) allows the physician to address future risk of diabetes, cardiovascular disease and urological conditions (“Carol and Mike Werner/Visuals Unlimited, Inc./Science Photo Library”)
WHAT IS ‘METABOLIC SYNDROME’?
Over the years a number of definitions have been proposed for the components of metabolic syndrome. All definitions recognise similar components that comprise the syndrome, but differ in exact thresholds – however, there is a consensus that metabolic syndrome is extremely common and growing in prevalence at an alarming rate.

The US definition1 (NCEP ATP III) requires more than three of the following criteria to be met:
• Central obesity (waist circumference >102cm in men, >88cm in women)
• Impaired fasting glycaemia or type 2 diabetes mellitus
• Dyslipidaemia – raised low-density lipoprotein-cholesterol
• - or raised triglycerides
• Hypertension (blood pressure >130mmHg systolic or >85mmHg diastolic or on treatment)

The International Diabetes Federation definition2 is more applicable to other nationals due to the smaller waist circumference:
• Central obesity (Table 1) Plus at least two of the following:
  - Raised triglycerides – ≥1.7mmol/l (150mg/dl) (or on treatment for this lipid abnormality)
  - Lowered high-density lipoprotein-cholesterol – <1.03mmol/l (40mg/dl) males or <1.29mmol/l (50mg/dl) females (or on treatment for this lipid abnormality)
  - Hypertension – blood pressure ≥130/85mmHg (or on treatment for previously diagnosed hypertension)
  - Insulin resistance – fasting plasma glucose ≥5.6mmol/l (100mg/dl) or previously diagnosed type 2 diabetes mellitus

The pathophysiology of metabolic syndrome is principally related to peripheral insulin resistance, endothelial dysfunction and systemic inflammation. It is also hypothesised that all these factors may relate to visceral adiposity, including non-alcoholic hepatosteatosis (or fatty liver), particularly associated with central abdominal obesity and far more prevalent in men than women.3 These factors combine to create a unifying link between CVD, type 2 diabetes, obesity, hypertension and dyslipidaemia.

A sedentary lifestyle is the biggest risk factor and means that in western countries metabolic syndrome is highly prevalent, with estimates that almost 40 per cent of the adult population of the USA is affected.4 Patients with metabolic syndrome are twice as likely to die of heart attack or stroke and have a fivefold greater risk of developing type 2 diabetes.5

LOWER URINARY TRACT SYMPTOMS
Large-scale studies have shown that men with three or more components of the metabolic syndrome have an increased risk of lower urinary tract symptoms (LUTS; odds ratio 1.8).6 A history of diabetes or hypertension is particularly associated with LUTS, with odds ratios of 1.67 and 1.76, respectively. In diabetic men, the risk of LUTS increases with increasing glycosylated haemoglobin (HbA1c). Both benign prostatic enlargement and overactive bladder (OAB) syndrome are linked to the metabolic syndrome.

Benign prostate disease
There is a strong evidence base to place benign prostate hyperplasia (BPH) within metabolic syndrome. The pathological basis of this association is complex, with hyperinsulinaemia, sympathetic overactivity, sex hormone changes and inflammation all believed to play a part.7 Hammarsten et al8 examined this hypothesis in detail by searching the literature for evidence of links with established aspects of the metabolic syndrome – BPH was found to be linked with 21 out of 22 of these factors (Box 1).

Prostate volume, PSA level (used as a surrogate marker of prostate volume) and severity of LUTS have been shown to increase with increasing waist circumference,9 with mean PSA increasing from 1.87ng/ml in men with waist circumference less than 90cm to 3.96 in men with waist circumference over 100cm. Obese men are 30 per cent more likely to develop LUTS compared to non-obese men, and men in the highest quartile of physical activity are 29 per cent less likely to develop LUTS than their sedentary peers, having allowed for body mass index.10 Data on more than 2000 men participating in the Olmsted County cohort study showed that men on statins had a 6.5– to 7-year delay in the new onset of moderate to severe LUTS compared with those not taking statins, again suggesting a significant metabolic component in the development of symptomatic LUTS.11

Further evidence of this association is seen in the strong link between LUTS/BPH and erectile dysfunction (ED). As will be seen in later sections, the association between ED and aspects of the metabolic syndrome is well established. In the Multinational Study of the Ageing Male, more than 12,000 men aged 50–80 were assessed: 31 per cent had moderate to severe LUTS, 48.7 per cent had a degree of ED and in each age decade the risk of ED was closely related to the presence and severity of LUTS, with a relative risk of 3.1 in men with moderate LUTS, increasing to 5.9 in those with severe LUTS.12 The presence of more severe LUTS was seen to be a bigger risk factor for ED than increasing age.

<table>
<thead>
<tr>
<th>Waist circumference (cm)</th>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td>Euroid</td>
<td>≥94</td>
<td>≥80</td>
</tr>
<tr>
<td>South Asian</td>
<td>≥90</td>
<td>≥80</td>
</tr>
<tr>
<td>Chinese</td>
<td>≥90</td>
<td>≥80</td>
</tr>
<tr>
<td>Japanese</td>
<td>≥85</td>
<td>≥90</td>
</tr>
</tbody>
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Table 1. Definition of central obesity by racial origin

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Increased fasting plasma insulin
Increased body length
Increased free oestradiol level
Type 2 diabetes mellitus
Lower serum high-density lipoprotein level
Higher diastolic blood pressure
Atherosclerotic disease
Lower sex hormone-binding globulin level
Treated hypertension
Higher serum uric acid
Increased waist measurement
Increased fat body mass

**Box 1. Aspects of metabolic syndrome linked to benign prostatic hyperplasia**

- Increased fasting plasma insulin level
- Increased free oestradiol level
- Lower sex hormone-binding globulin level
- Increased body length
- Increased body mass index
- Increased body weight
- Increased waist measurement
- Increased waist-to-hip ratio
- Increased fat body mass
- Type 2 diabetes mellitus
- Atherosclerotic disease
- Treated hypertension
- Higher systolic blood pressure
- Higher diastolic blood pressure
- Lower serum high-density lipoprotein–cholesterol
- Higher serum uric acid
- Higher serum alanine aminotransferase

Overtactive bladder
Metabolic syndrome causes overactivity of the autonomic nervous system – parasympathetic activity causes detrusor contraction, so overactivity may therefore contribute to OAB.13 Animal studies show that fructose-fed rats not only develop metabolic syndrome but a large proportion also develop detrusor instability.14 Several of the aspects of metabolic syndrome (type 2 diabetes, reduced high-density lipoprotein, raised triglyceride, ED and hypertension) have been shown individually to be associated with increased incidence of OAB.13 The incidence of OAB increases with obesity, with rates almost three times higher in obese women, regardless of diabetic status.14 Uzun15 studied patients with OAB in Turkey and found metabolic syndrome was diagnosed in 201 (64 per cent) of 313 patients with OAB and 73 (35 per cent) of 208 patients without OAB (p=0.002). A larger waist circumference, greater body mass index, low high-density lipoprotein level, and incidence of hypertension were significantly greater statistically in the OAB group than in the controls.

**Prostate cancer**
It is hypothesised that high circulating insulin levels indirectly drive hepatic production of insulin-like growth factor 1 and that this combined effect acts as a ‘fertiliser’, generating a microenvironment that promotes prostate tumour growth.8 There is a growing body of evidence showing that obesity is associated with an increase in aggressive prostate cancer, increased risk of failure of radical therapy and increased prostate cancer-specific mortality.16 A Spanish study of more than 2400 men showed that overall prostate cancer risk was the same in men with and without metabolic syndrome, but high-grade (Gleason 8–10) tumours were seen in 35.9 and 23.9 per cent, respectively (p<0.001) and advanced disease rates were 17 and 12 per cent, respectively.17

So, what is the evidence that exercise and lifestyle can impact on men with prostate cancer? Increased physical activity appears to offer a small protective effect on subsequent risk of developing prostate cancer, strengthening the well-established argument for all men to maximise exercise levels for a variety of health benefits.18

Kenfield and colleagues19 followed 2705 men diagnosed with prostate cancer over 10 years, monitoring activity levels. They showed that the number of deaths in total was 36 per cent lower in men who walked on average an hour per day. It was 49 per cent lower in men taking three or more hours of vigorous activity each week, with 61 per cent fewer deaths.

Research is starting to explore why exercise might be protective. It may have an impact on energy balance and fat distribution. First, this is important, as fat and obesity are strongly associated with a higher risk of cancer recurrence. Second, activity can influence sex hormones, which affect some cancer receptors. It may also act on DNA damage and recovery. We know that lack of exercise and poor diet also contribute to other cardiovascular diseases, which can occur as a result of hormone therapy for prostate cancer. Generally only 30–40 per cent of the adult population take the recommended amount of exercise before being diagnosed with prostate cancer. This falls off during treatment and in aftercare. A recent study of men with prostate cancer found that only 4 per cent had the levels of vigorous activity to impact on cure.

**Renal calculi (nephrolithiasis)**
The incidence of nephrolithiasis is increasing in western countries, in parallel with the increase in the prevalence of obesity and metabolic syndrome.20 A large cross-sectional analysis of more than 12 000 men in the US showed that kidney stones were more common among obese than normal-weight individuals (11.2 versus 6.1 per cent, respectively; p<0.001), with both diabetes and obesity strongly related to kidney stone risk in multivariable models.20

Studies have suggested that individuals with metabolic syndrome are twice as likely to have stone disease,21,22 with the risk of stone formation increasing alongside increasing numbers of components of the metabolic syndrome itself. The exact mechanism for this association is not fully understood, but it is postulated that metabolic syndrome is associated with changes in the urine, including lowering of pH, decreased excretion of citrate and increased excretion of calcium and uric acid, leading to increased risk of uric acid and calcium stone formation.23

By contrast with observational findings, there is no strong evidence for causal associations between uric acid and ischaemic heart disease or blood pressure.24 However, evidence supports a causal effect between body mass index and uric acid level and hyperuricaemia. This finding strongly suggests body mass index as a confounder in observational associations,
and suggests a role for elevated body mass index or obesity in the development of uric acid-related conditions.

Studies have also suggested an increased risk of subsequent stroke or myocardial infarction in patients with a history of nephrolithiasis.\(^{25,26}\)

**ERECTILE DYSFUNCTION**
The link between ED and elements of the metabolic syndrome is well established and the risk of ED can be seen to increase in line with the number of elements of the metabolic syndrome present in the patient.\(^8\) This association is now widely recognised in clinical practice, both in primary and secondary care. All patients with ED should be assessed at the time of initial assessment for the presence of diabetes and a full cardiovascular risk profile carried out. The presence of hypogonadism should be considered.

Erectile dysfunction is a strong marker of cardiovascular risk – a recent review found that, compared with patients without ED, the patient with ED has a 44 per cent increased risk of cardiovascular events, 62 per cent for myocardial infarction, 39 per cent for cerebrovascular events, 25 per cent for all-cause mortality and 19 per cent for cardiovascular mortality.\(^{27}\) The authors concluded that the risk posed by ED on future cardiovascular events is of a similar magnitude to more established risk factors such as hypertension, diabetes or dyslipidaemia. The Princeton Consensus panel recommend that sexual function is incorporated into cardiovascular risk assessment for all men, and discuss extensively the management of cardiovascular risk in the ED patient.\(^{28}\)

**HYPOGONADISM**
Studies have demonstrated that multiple aspects of metabolic syndrome are closely linked with low serum testosterone levels (Figures 2–4).\(^{29–32}\) Patients receiving androgen deprivation therapy for prostate cancer have significantly increased rates of metabolic syndrome. Weight loss in obese men with metabolic syndrome has been shown to increase testosterone levels and reduce the complications of long-term hypogonadism.\(^{33}\)

**BLADDER CANCER**
There is limited evidence of a link between metabolic syndrome and bladder cancer, but a recent systematic review and meta-analysis of cohort studies found a relative risk of 1.10 (\(p=0.013\)) in men with metabolic syndrome compared with those without.\(^{34}\) Comorbidities such as ischaemic heart disease are common in bladder cancer patients, but there is clearly a confounding issue as a result of the high prevalence of cigarette smoking in bladder cancer patients. There has been extensive work to try to identify a link between bladder cancer and type 2 diabetes, with some studies suggesting an increased risk – however, again, potential confounders exist, as the diabetic population is more likely to have regular urine testing, which may account for a higher incidence of bladder cancer.\(^{35}\)
TESTICULAR CANCER

Testicular cancer patients have an increased risk for CVD, which might be related to the increased prevalence of the metabolic syndrome in this group of patients.36 A recent study assessed the prevalence of metabolic syndrome and the 10-year CVD risk in a cohort of 255 testicular germ cell tumour survivors (median age, 38.7 years; interquartile range, 31–48) at a mean of 7.8 years after anticancer treatment, and compared these with data obtained from 360 healthy men. The survivors had an age-adjusted increased risk for metabolic syndrome of 1.9 compared with that of healthy controls. The risk for metabolic syndrome was highest in survivors treated with combination chemotherapy (odds ratio 2.0) and in survivors with testosterone levels in the lowest quartile (odds ratio 2.5).

CONCLUSION

The medical literature increasingly supports the idea of a link between metabolic syndrome and many common urological conditions. An awareness and understanding of this connection should encourage all physicians to assess the patient presenting with these conditions for underlying metabolic syndrome and cardiovascular risk. The literature suggests that, as a minimum, a number of baseline investigations should be carried out: blood pressure measurement, a fasting lipid profile (and formal cardiovascular risk profile using established algorithms such as Qrisk), assessment for diabetes using fasting glucose or HbA1c, measurement of weight and body mass index, or ideally the measurement of abdominal circumference (as central obesity is a far more sensitive marker of risk than body mass index).

Identification of features of the metabolic syndrome allows for tailored lifestyle intervention, in terms of increasing exercise, dietary changes, weight loss, smoking cessation advice and alcohol moderation. Medical management of hypertension, diabetes, dyslipidaemia and CVD may be required according to national guidelines.

Declarations of interests: none declared.

REFERENCES


