

Diabetes and the urologist: a growing problem

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The incidence of diabetes continues to increase dramatically; this incidence is predominantly of the type-2 form which clusters together with other comorbidities of hypertension and lipid abnormalities, to form the metabolic syndrome. These conditions will have an increasing impact on

urological practice, with erectile dysfunction, hypogonadism, voiding difficulties and urinary tract infections all more common in these patients. These symptoms might be the initial presentation of previously undiagnosed diabetes and it is important to recognise this condition early to avoid later

complications including end-stage renal failure.

KEYWORDS

urology, metabolic syndrome, diabetes mellitus

INTRODUCTION

The incidence of diabetes mellitus (DM) continues to increase dramatically; recent projections of the lifetime incidence of DM are likely to increase to 32.8% in males and 35.8% in females in those born in America after 2000 [1]. This increase is predominantly in type-2 DM, which is primarily related to obesity; this clusters together with the other comorbidities of hypertension and lipid abnormalities seen in the metabolic syndrome. DM is associated with an earlier onset and increased severity of urological symptoms including erectile dysfunction (ED), hypogonadism, voiding difficulties and UTIs. These symptoms might be the initial presentation of DM and it is important that the urologist recognises this condition early. Diabetic nephropathy is also a common sequelae, with 20–30% of patients with DM type-1 and -2 affected. Ultimately, some might progress to end-stage renal failure (ESRF) requiring renal transplantation. Surgery in patients with DM is common and it is important to have a thorough understanding of this condition to optimize patient care and clinical outcome.

BLADDER DYSFUNCTION

Over half of men and women with DM have bladder dysfunction [2,3]. While the condition is not generally life-threatening it can be associated with severely debilitating symptoms. The classic triad of diminished bladder sensation, poor contractility, and increased postvoid residual urine volume are known as diabetic cystopathy (DC). The

prevalence of DC is unrelated to the sex or age of the patient but it does increase with the duration of DM [4]. DC is most likely to represent end-stage bladder failure. While the classic symptoms of DC are infrequent voiding, difficulty initiating voiding, and fullness after voiding, Brown *et al.* [5] stated that these are relatively uncommon. Indeed, frequency and urgency associated with detrusor instability might be a more common feature, with 39–61% of patients having some degree of problem [2].

Treatment options for patients with DC include conservative (e.g. pelvic floor training), pharmacological and surgical. Initial treatment should be conservative, with careful surveillance necessary for the secondary complications of DC. UTIs are the most common complication due to the presence of residual urine. With progressive worsening of the condition, prolonged retention can give rise to VUR and hydronephrosis. Pyelonephritis, nephrolithiasis, and sometimes urosepsis can also develop. Finally, uraemia might develop after continuing damage to the kidney due to diabetic glomerulosclerosis [6].

The pathophysiology of DC is not entirely understood but it has been most often attributed to diuresis-induced hypertrophy and metabolically induced neuropathy [7]. The underlying neurophysiology of DC reveals a sensory and autonomic dysfunction. Recently there has been renewed interest in the role of nerve growth factor (NGF) in the development of DC. NGF is an essential survival factor for neuronal populations of the peripheral and CNS. Down-regulation of bladder NGF can

lead to a sensory neuropathy commonly seen in DC. Tong and Chen [8] suggested that a decrease in the expression of NGF and its receptor might be responsible for the pathogenesis of DC, while hyperglycaemia is part of the cause of these changes. This raises the possibility of supplemental NGF therapy to reverse the detrimental effect of DC on the urinary bladder. Certainly some success was reported using gene-transfer therapy; Sasaki *et al.* [9] successfully used a replication-defective herpes simplex virus vector expressing NGF to treat DC in a rat model. Another potential therapy is N-hexacosanol, which is a neurotrophic substance derived from the tropical plant, *Hygophylla erecta* (Hochr.). N-hexacosanol recently showed promising results in reversing DM-induced bladder dysfunction in a rat model [10]. While its mechanism of action is not entirely clear, real-time PCR and immunohistochemistry showed that N-hexacosanol treatment appears to coincide with a reversal of the up-regulation of muscarinic M₂ and M₃ receptor mRNAs. Whilst the evidence for both these treatments is preliminary, they are promising and warrant further investigation.

URINARY INCONTINENCE

This can also be a troublesome complication of DM, particularly in women, with an estimated 30–100% greater risk [11]. Incontinence might or might not relate to overflow incontinence secondary to DC, and can present as either urge incontinence or stress incontinence, with the latter the most common [12]. Treatment options for women with urinary incontinence include

conservative (pelvic muscle training), medical and surgical, but there is also evidence that interventions that delay the onset of DM can also prevent urinary incontinence.

The Diabetes Prevention Program consisted of a randomized controlled trial conducted at 27 centres in the USA involving nearly 2000 women, with a mean follow-up of 2.9 years. This trial showed that intensive lifestyle intervention, involving weight loss and exercise, reduced the incidence of DM among women with impaired glucose tolerance [13], and furthermore, it substantially reduced the prevalence of weekly stress incontinence. Weight loss was thought to account for most of this protective effect and it was suggested that as little as 5–10% reduction in weight would confer this protective effect.

DM AND BPH

There is a high prevalence of LUTS in men, which appears to increase linearly with age. It is important to fully evaluate all individuals who present with LUTS as there are many other conditions apart from BPH that might be responsible [14]. DM is obviously one condition that might be responsible for LUTS, and the distinction between DC and LUTS secondary to BPH is difficult to disentangle. Furthermore, early work suggested that DM increases prostate size, consistent with BPH [15]. In particular, hyperinsulinaemia secondary to the insulin resistance present in type-2 DM might be a prospective risk factor for developing BPH. Dahle *et al.* [16] examined the role of obesity and insulin levels on the pathogenesis of BPH in 502 men (200 with BPH, 302 controls). They reported an increased relative risk of 2.47 for men with insulin levels in the highest quartile ($>9.76 \mu\text{U/mL}$) compared to those in the lowest quartile ($<5.87 \mu\text{U/mL}$). There was a similar increased effect with increased abdominal obesity. This is in agreement with Ozden *et al.* [17], who examined the effect of the metabolic syndrome on a small cohort of 78 patients with BPH; they noted that those with the metabolic syndrome and BPH had a statistically significant further increase in prostate growth. Hammarsten and Hogstedt [18] reported that the median annual prostate growth rate was faster in men with metabolic disease, non-insulin-dependent DM, treated hypertension, obesity and dyslipidaemia, than in men with no metabolic disease. On multivariate analysis only fasting plasma

insulin and age became significant. Recently, the same group reported that the metabolic syndrome and hyperinsulinaemia are also prospective risk factors for death from prostate cancer [19]. They suggested that insulin levels could be used as a marker for the aggressiveness of prostate cancer, regardless of the patients' stage, grade and PSA level. Obviously more work is needed to confirm any association.

There are several plausible explanations for the association of hyperinsulinaemia and BPH; the former has a stimulant effect on the sympathetic nervous system [17] and this could affect the dynamic component of the obstruction in BPH. Doxazosin, an α -blocker used in the treatment of BPH, is known to decrease insulin levels while increasing insulin sensitivity [20]. Another potential explanation is the pathway involving the polypeptide growth factor IGF; this is a strong mitogen and increases cellular proliferation in the prostate. The systemic use of IGF-1 in rats over a short period results in increases in prostate weight by up to 29% [21]. At present, the precise underlying mechanism is unknown.

UTIs

Women with DM are at greater risk of both symptomatic and asymptomatic UTI. Whilst there is little available information in male patients or those with type-1 DM, postmenopausal women with type-2 DM have double the risk of a symptomatic UTI. The risk is further increased by three to four times in those taking oral hypoglycaemics or those with insulin-controlled DM, indicating a possible association between increased incidence and severity of DM [5]. The complications of symptomatic UTI are also increased, with women with type-1 DM at greater risk of developing pyelonephritis and subsequent impairment of renal function [22]. Other clinical manifestations that are unique or strongly associated with DM include renal abscess formation and papillary necrosis. Furthermore, diabetic patients are commonly infected with species other than *Escherichia coli*, in particular *Klebsiella*, and other Gram-negative rods, enterococci and group B streptococci [22,23].

Recently the importance of asymptomatic bacteriuria (AB) in patients with DM has been questioned. Studies have shown that AB

occurs at two to three times the frequency in women with DM, but whether all AB should be treated is particularly relevant. One significant prospective randomized controlled study of 105 women followed for up to 36 months showed that screening and treatment of episodes of AB had no impact on overall occurrence of UTI or hospitalization [24].

ED

Male sexual dysfunction is troublesome for a substantial number of men with DM. Concurrent comorbid risk factors include obesity, hypertension, lipid disorders, coronary heart disease and smoking, i.e. many of the features of the metabolic syndrome. Estimates of the prevalence of ED and DM are 20–71% [25]. In one study, the prevalence of ED increased steadily from 6% in men aged 20–24 years, to 52% in those aged 55–59 years, and peaked at 55–95% in men aged >60 years [26]. One case-controlled study found smokers with DM to have twice the risk of ED than non-smokers with DM [27]. Furthermore, in men the relative risk of ED increases with poor glycaemic control, and Rhoden *et al.* [28] noted that the severity of ED correlates with glycosylated haemoglobin (HbA_{1c}) levels. Severe ED was noted in 9% of patients with HbA_{1c} levels of $<8\%$, vs 40% in those with HbA_{1c} levels of $\geq 8\%$. ED is also recognized as a marker symptom for men with as yet undiagnosed DM [29]. In 1985, Gatling *et al.* [30] studied a UK population of 90 660 people and reported that the prevalence of undiagnosed DM was 1.01%. A more recent smaller study found the prevalence to be higher, at 4.7%, with a further 3.7% having abnormal fasting blood glucose suggesting possible impaired glucose tolerance [31]. This difference might reflect the increasing prevalence of this condition.

There are several pharmacological treatment options for men with ED and DM, in particular the phosphodiesterase type 5 inhibitors (PDE-5Is). However, the importance of lifestyle changes must not be overlooked, as shown by Esposito *et al.* [32], who reported a significant improvement in erectile function scores. A large meta-analysis of 11 randomized, double-blind, placebo-controlled trials of sildenafil in patients with DM found improved erections in 59% of patients with type-1 and 63% with type-2 DM [33]. This compares with an 83% improvement in men with ED who do

not have DM. Newer PDE-5Is that are also potent inhibitors of cGMP might offer improvements in ED. A recent study with tadalafil noted that 76% of patients reported improved erections [34].

HYPOGONADISM

Men with DM have a high incidence of hypogonadism, and it was suggested that it might be an additional component of the metabolic syndrome [35]. Recently, Laakson *et al.* [36] reported that hypogonadism can predict the subsequent development of DM and metabolic syndrome in middle-aged men. They also suggested that in addition to being an early marker of metabolic syndrome or overt DM, hypogonadism might also be involved in the pathogenesis of these disease processes. Most of the differences in testosterone levels between men with DM and men without might be due to low levels of sex-hormone-binding globulin. Free testosterone levels decline with increasing age and obesity, making many men with type-2 DM testosterone-deficient. Testosterone-replacement therapy (TRT) might improve the sensitivity to insulin therapy in hypogonadal, overweight men [37]. Recently, Kirby *et al.* [38] indicated that TRT might not only treat hypogonadism but also slow or halt the progression from metabolic syndrome to overt DM. In addition, in men, the use of testosterone to treat the metabolic syndrome might also prevent the urological complications commonly associated with such chronic disease states, including ED and voiding dysfunction.

DIABETIC NEPHROPATHY

DM is the leading cause of ESRF; exceeding a threshold creatinine value of 1.5 mg/dL results in a linear increase in morbidity and mortality. Once ESRF has developed the outcome is uniformly poor, with 5-year survival rates of 20%. This increased mortality is largely due to associated cardiovascular disease. Currently, there are three main renal-replacement therapies available, i.e. haemodialysis, peritoneal dialysis or kidney transplantation. Haemodialysis is the most commonly used therapy. Chantrel *et al.* [39] reported the poor prognosis of patients with DM who progressed to renal-replacement therapy, noting that 32% of them were dead within 8 months. The most important

independent predictor of patient survival with haemodialysis treatment is age.

The exact cause for diabetic nephropathy is not well understood. Whilst the development of hypertension and renovascular insufficiency is undoubtedly a significant factor, Geerlings *et al.* [40] suggested that AB might be important in deteriorating renal function. Genome screening showed several potential markers that might predispose some patients with DM to developing diabetic nephropathy. Chew *et al.* [41] noted an association between the apolipoprotein ϵ 4 allele and an increased likelihood for the development of acute renal failure after cardiac surgery.

RENAL TRANSPLANTATION

Renal transplantation is usually cadaveric or sometimes from a living-related donor, and the treatment of choice in patients with end-stage diabetic nephropathy. Whilst minimally invasive techniques have reduced the peri-operative morbidity associated with donation, the numbers of patients with DM undergoing transplantation is very low, at 8.4% of Italian men who were on renal replacement therapy, and 16% of such patients in the USA [42]. Unfortunately, patient and graft survival rates remain slightly worse than in patients with no DM, and selection criteria are crucial and include age <65 years, absence of severe cardiovascular or cerebrovascular disease, absence of significant sepsis, and absence of life-limiting comorbidity.

In these patients assessment of the coronary vasculature is routine. The diabetogenic effects of immunosuppressive agents often require an increased insulin dose after transplantation. In addition, dyslipidaemia might also be exacerbated by the immunosuppressive therapy, which also increases the risk of subsequent neoplastic disease.

One particularly promising strategy for patients with type-1 DM and ESRF is simultaneous pancreas and kidney transplantation (SPKT). One recent study showed that patients undergoing SPKT have a significant survival advantage over cadaveric kidney transplant recipients [43]. The results compared to living-donor kidney recipients are equivocal. Furthermore, SPKT improves several secondary complications of DM, including gastric and bladder function,

metabolic impairment, and autonomic polyneuropathy.

SURGERY

DM is the commonest surgical endocrinopathy; while an extensive review of the peri-operative management of the patient with DM is not in the remit of this review, a few points can be emphasised. First, before embarking on major surgery it is crucial that glycaemic control is optimized with a target HbA_{1c} of <7%. Second, peri-operative metabolic changes in sympathetic and endocrine hormone levels, together with the required period of 'nil by mouth', necessitate careful monitoring of blood glucose to avoid hypo- and hyperglycaemia. Several studies showed that poor peri-operative glucose control is associated with adverse postoperative outcomes. Kaplin *et al.* [44] evaluated 400 patients with DM having a coronary artery bypass graft and compared their outcomes with nearly 900 controls without DM. Maintaining strict glycaemic control by i.v. insulin infusion resulted in similar mortality rates in both groups. This result compares favourably with the National Cardiac Surgery Database, which indicates a 46% higher mortality in those with DM than in those without. This finding is also true for the acutely unwell patient requiring a stay in the intensive care unit. Furthermore, poor metabolic control impedes wound healing in general. Several studies indicated that the overall rate of wound infection might be as high as 10 times more in patients with DM than without. Zerr *et al.* [45] reported an interventional study in patients undergoing coronary artery bypass grafting; patients who were started during surgery on an i.v. infusion of insulin had lower rates of sternal infections than those on a s.c. insulin regimen.

There are several different regimens for the peri-operative management of the patient with DM, and no consensus on which is best; therefore, close liaison with the endocrine team is essential. The goals of establishing normoglycaemia, avoiding ketosis and reducing mortality and morbidity are the key.

CONCLUSION

With the incidence of DM and the metabolic syndrome continuing to increase rapidly, they are bound to have an increasing impact on

urological practice. Early recognition of DM is important to reduce cardiovascular mortality and improve survival. Interventions that prevent or delay the onset of DM might also prevent many of the urological complications, including DC and ED. Furthermore, early recognition of the metabolic syndrome might allow intervention to delay or arrest the progression to overt DM. Future work is necessary to delineate the exact benefit of TRT in hypogonadism and the metabolic syndrome. Finally, strict blood glucose monitoring for those patients undergoing surgery will also provide improved surgical outcomes. It is critical that urologists take an overall view of the health of patients with DM, and a collaborative approach is necessary between the specialist DM team, family care practitioners and the urological team [46].

CONFLICT OF INTEREST

None declared.

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Abbreviations: DM, diabetes mellitus; ED, erectile dysfunction; ESRF, end-stage renal failure; DC, diabetic cystopathy; NGF, nerve growth factor; AB, asymptomatic bacteriuria; HbA_{1c}, glycosylated haemoglobin; PDE-5I, phosphodiesterase type 5 inhibitor; TRT, testosterone-replacement therapy; SPKT, simultaneous pancreas and kidney transplantation.