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Concurrent improvement of the metabolic syndrome and lower urinary tract symptoms upon normalisation of plasma testosterone levels in hypogonadal elderly men

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Summary

Central obesity in adulthood, the metabolic syndrome, erectile failure and lower urinary tract symptoms (LUTS) are all associated with lower-than-normal testosterone levels, although the relationship between testosterone and LUTS appears weak. The metabolic syndrome is associated with an overactivity of the autonomic nervous system. Alternatively, the metabolic syndrome is associated with markers of inflammation, such as C-reactive protein (CRP), maybe signalling intraprostatic inflammation. A large cohort of 95 middle-aged to elderly hypogonadal men (T levels 5.9–12.1 nmol l^{-1}) were treated with parenteral testosterone undecanoate and its effects on the metabolic syndrome {waist circumference, cholesterol, CRP and LUTS [residual bladder volume (RBV), International Prostate Symptoms Score (IPSS), prostate volume, prostate-specific antigen (PSA)]} were evaluated. Along with the improvements of the metabolic syndrome, there was a significant decline of the values of the IPSS, RBV and CRP. There was a (low) level of correlation between the decline of waist circumference and residual volume of urine but not with IPSS and prostate size. Along with the improvement of the metabolic syndrome upon testosterone administration, there was also an improvement of the IPSS and of RBV of urine and CRP. The mechanism remains to be elucidated.

Introduction

Elderly men suffer from several health problems that were hitherto regarded as distinct entities and treated by different medical disciplines, but they actually appear to be largely inter-related. At the epidemiological level, an association between central obesity in adulthood, the metabolic syndrome, erectile failure and lower urinary tract symptoms (LUTS) has been established (Rohrmann *et al.*, 2007). Population studies show a frequency of moderate-to-severe LUTS from 8 to 31% of men in their 50s, increasing to 27–44% of men in their 70s. But many men experience symptoms of LUTS much earlier in life. LUTS is an important determinant of quality of life (Robertson *et al.*, 2007).

A common denominator of the above ailments is lower-than-normal testosterone levels occurring in a significant proportion of elderly men and increasing with age (Kaufman & Vermeulen, 2005).

Many studies have tried to establish a relationship between the levels of sex steroids and benign prostate hyperplasia, and a few studies have analysed the relationship between circulating testosterone and LUTS symptoms. One study found that hypogonadism was seen in approximately one-fifth of elderly men with LUTS, but it had no impact on symptom status (Schatzl *et al.*, 2003).

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Another study found a relation between symptoms of LUTS and plasma total and bio-available testosterone but this relationship disappeared after statistical adjustment for age (Litman *et al.*, 2007). No consistent correlations were found between total and calculated free testosterone and symptoms of LUTS in another study (Rohrmann *et al.*, 2007). But a recent study of clinical bladder outlet obstruction found that low testosterone levels were negatively correlated with detrusor pressure at urethral closure and with detrusor pressure at maximum flow, thus promoting detrusor overactivity (Koritsiadis *et al.*, 2008). In the rabbit, testosterone appeared to have a positive effect on bladder capacity and on compliance defined as rate of volume change per unit pressure (Celayir, 2003).

A recent study provided supporting evidence that stress conditions could be associated with the development and aggravation of prostatic disease. It was found that body mass index (BMI), age and greater diastolic blood pressure reactivity correlated with a greater transition zone volume, greater total prostate gland volume, greater post-void residual bladder volume (RBV) and more severe LUTS (Ullrich *et al.*, 2007).

Inflammatory infiltrates are frequently found in and around nodules in benign prostate hyperplasia (BPH) (Rohrmann *et al.*, 2005). The presence of the metabolic syndrome might be a mediator of this association because it is associated with elevated serum C-reactive protein concentration, a nonspecific marker of inflammation (Teoh & Verma, 2007). Thus, linking the metabolic syndrome to LUTS and elevated circulating C-reactive protein concentrations may be an indicator of intraprostatic inflammation in symptomatic BPH (Rohrmann *et al.*, 2005; Teoh & Verma, 2007).

Insulin resistance is associated with hyperinsulinaemia. Insulin, because of its biochemical similarities with insulin-like growth factor, can promote growth (Renehan *et al.*, 2006). This might play a role in the development of prostate hyperplasia (Hammarsten & Hogstedt, 2001).

As indicated above, with a more integrative approach to the ailments of the ageing male, the age-related decline of plasma testosterone levels has been found to be a feature of erectile failure and central obesity in elderly men with proven successes of administration of testosterone to correct lower-than-normal levels (Isidori *et al.*, 2005; Kapoor *et al.*, 2005; Shabsigh *et al.*, 2005; Kaplan *et al.*, 2006; Allan *et al.*, 2008). This study analysed the effects of normalisation of plasma testosterone levels in elderly men on the features of the metabolic syndrome and of LUTS.

Patients and methods

A cohort of 117 men aged between 34 and 69 years (mean ± SD = 59.5 ± 6.0), with plasma testosterone levels between 5.9 and 12.1 nmol l^{-1} (mean ± SD = 9.4 ± 1.7) were studied. They had sought urological consultation for a number of reasons: erectile dysfunction, questions about their testosterone status or a variety of urological complaints. Upon clinical and laboratory investigation, they were found to have subnormal plasma total testosterone levels (24 men had plasma levels of testosterone between 5.9 and 7.0 nmol l^{-1}, 29 between 7.0 and 9.0, 46 between 9 and 10.5 and 18 between 10.5 and 12.1). The indication for testosterone treatment was signs and symptoms of late-onset hypogonadism and a subnormal plasma testosterone level.

They received treatment with parenteral testosterone undecanoate 1000 mg for 12 months, with injections following the established recommendations: an interval of 6 weeks between the first two injections and thereafter every 12 weeks. Hereupon, plasma testosterone returned to the physiological range.

They were followed up for 12 months at intervals of 3 months. At each visit, blood was sampled between 8.00 and 11.00 hours after overnight fasting. Plasma testosterone, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and C-reactive protein (CRP) were measured using standardised routine laboratory methods. Body weight, BMI, waist circumference, post-void RBV and prostate volume (PV) were measured using Sonoace SA 8000 SE with ultrasound probes; for abdominal measurement of residual bladder urine volume, a probe with 3–7 MHz and for PV, a transrectal probe of 5–12 MHz were used. The International Prostate Symptoms Score (IPSS) was assessed. The waist circumference was measured midway between the upper hip bone and the uppermost border of the right iliac crest. Waist circumference measurements were always carried out by the same expert nurse. Weight and height were recorded and BMI was calculated by dividing the weight (kg) by the square of height (m). Complaints of LUTS are progressive with ageing and therefore, the study population was divided into quartiles and it was analysed whether testosterone administration had a different impact in the younger versus the older men. Further, it was analysed whether men with higher scores of the IPSS (with clinically significant complaints) improved to a degree that represented a significant clinical improvement. All patients gave their informed consent to be included in this study, which was approved by the hospital's ethical review board for investigation in human subjects.

All analysis was performed using STATA (Stata Corp, College Station, TX, USA). Comparison of mean between two different time points was performed using either paired *t*-test for normally distributed variables or signed rank test for variables not normally distributed. The significant level of testosterone effect on metabolic and

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LUTS parameters was determined using linear mixed model (West *et al.*, 2007). The effect of testosterone was adjusted for age by categorising the samples into four groups according to age using quartiles. Correlation between LUTS parameters was determined using Spearman rank correlation.

Results

Over the first 9 months, there was a progressive rise of plasma testosterone levels, significantly different from each previous measurement ($P < 0.001$). Thereafter, no further rise of testosterone levels was found. Body weight, BMI and waist circumference also declined significantly over the study period (Fig. 1).

The level of blood glucose remained constant over the study period. The levels of cholesterol and triglycerides had significantly improved ($P < 0.001$) after 3 months of testosterone administration and these improvements were progressive over the following 9 months of the study (Fig. 1). Testosterone levels appeared to be significantly associated with the levels of triglycerides over the first 6 months ($P < 0.001$). This effect was no longer significant after 6 months of testosterone administration. Testosterone levels were not significantly associated with the waist size, BMI, blood levels of cholesterol or CRP. However, when adjusted for age, testosterone levels were found to be significantly associated with the level of cholesterol too ($P = 0.01$).

There was no significant correlation between the change of metabolic parameters and IPSS score or RBV.

Serum CRP had declined after 3 months of testosterone treatment and declined progressively over the next 9 months. A similar pattern was observed for IPSS scores (Fig. 2). There was a significant correlation ($P < 0.05$) between the level of CRP and IPSS score though at a low level ($r^2 = 0.39$). The post-void RBV had decreased significantly ($P = 0.001$) after 9 months of testosterone treatment (Fig. 3). PV was not significantly affected over the 12-month study period (Fig. 3). The levels of CRP were significantly ($P < 0.05$) correlated with the RBV ($r^2 = 0.30$). However, there were no significant correlations between the decreases of CRP and IPSS score or the decrease RBV neither the change of PV. While a significant decrease of IPSS was observed, only four patients had IPSS which qualified as clinically relevant LUTS. In these four patients, IPSS declined from 17 to 11, from 18 to 13, from 19 to 12 and from 17 to 11.

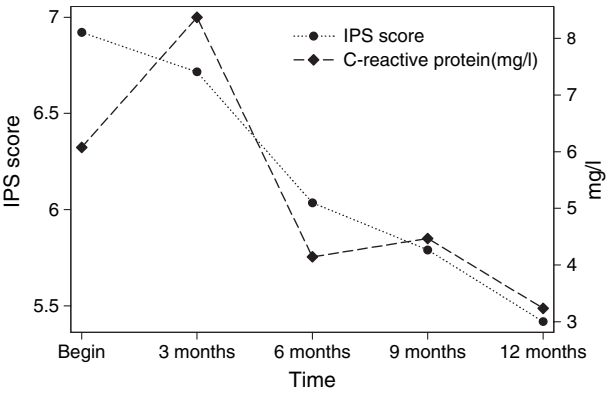

Fig. 2 Mean of C-reactive protein and International Prostate Symptom Score (IPSS) over the study period in 117 men receiving treatment with testosterone undecanoate.

Discussion

This study found that normalisation of plasma testosterone levels in elderly men with the features of the metabolic syndrome not only improved the metabolic syndrome, but also led to an improvement of the IPSS and of the RBV, while there was no significant change in

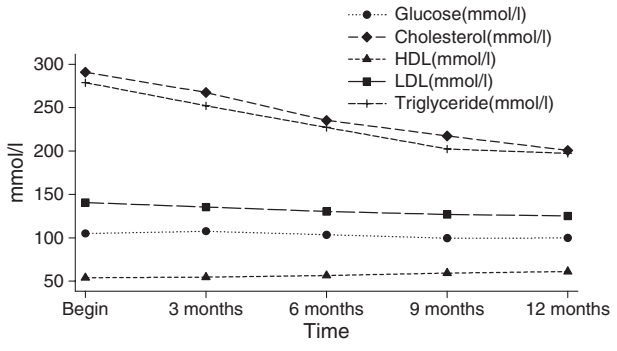

Fig. 1 Mean of metabolic parameters over the study period in 117 men receiving treatment with testosterone undecanoate.

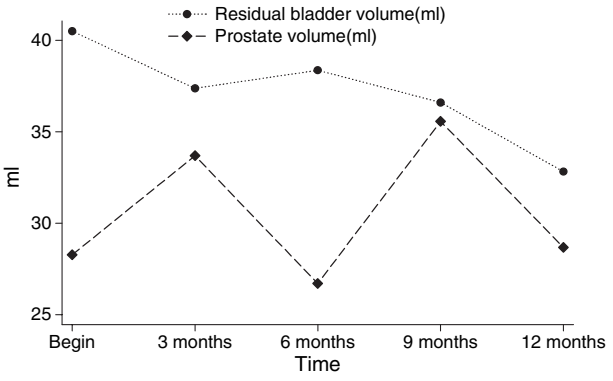

Fig. 3 Mean residual bladder volume and prostate volume over the study period in 117 men receiving treatment with testosterone undecanoate.

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prostate size. While occurring concurrently, a statistically significant correlation between the improvement of features of the metabolic syndrome and the improvements in the IPSS and RBV could not be established.

The theoretical basis for the concurrence in improvement of the metabolic syndrome and the IPSS and the RBV remains unclear from this study. Testosterone itself might not be the 'prime mover' of the effect on structures of the urinary tract anatomically and functionally related to LUTS, although androgen receptors have been found to a large extent in the epithelial cells of the urethra and the bladder (Rosenzweig *et al.*, 1995). In another study, the role of testosterone and its metabolites on maintaining the reflex activity in the pelvic part of the autonomic nervous system was demonstrated (Keast, 1999). Others have postulated the influence of testosterone on postsynaptic nongenomic receptors, which are suppressing detrusor activity (Watkins & Keast, 1999; Hall *et al.*, 2002). Castration resulted in significant alterations in the activities of citrate synthase-thapsigargin sensitive Ca(2+) ATPase (Sarco/Endoplasmic Reticulum Ca(2+)ATPase [SERCA]) and choline acetyl-transferase as markers for mitochondrial function, sarcoplasmic reticular calcium storage and release, and cholinergic nerve function, in the bladder body, base, urethra and corpora (Juan *et al.*, 2007).

Not only in the penis but also in other parts of the urogenital tract, nitric oxide (NO) acts as a nonadrenergic noncholinergic neurotransmitter and the action of testosterone on the urogenital tract may be mediated by this system (Filippi *et al.*, 2007). There is an increasing evidence for a link between erectile dysfunction (ED) and LUTS, the metabolic syndrome, pelvic atherosclerosis with its associated Rho-kinase activation/endothelin pathway, the NOS/NO theory and the autonomic hyperactivity (McVary, 2006). As a further substantiation of the role of androgens in the urogenital tract, NO synthase in an earlier study had appeared to be androgen-dependent in the urogenital tract of the rat (Chamness *et al.*, 1995). Meanwhile, a large number of clinical studies have convincingly shown that phosphodiesterase inhibitors have a beneficial effect on LUTS (Truss *et al.*, 2001; Sairam *et al.*, 2002; Montorsi *et al.*, 2004; McVary, 2006; Mulhall *et al.*, 2006; Uckert *et al.*, 2006; Andersson *et al.*, 2007; McVary *et al.*, 2007). Studies treating one condition (e.g. ED) and measuring the impact on the other (e.g. LUTS) should further contribute to support this common link. But yet it is not possible to provide a comprehensive picture of the impact of testosterone (and its deficiency) on the lower urinary tract.

Studies trying to explain the epidemiological relationship between the metabolic syndrome and LUTS hypothesised that the metabolic syndrome is associated with an overactivity of the autonomic nervous system (Rosmond *et al.*, 1998; Bjorntorp & Rosmond, 2000) for which hyperinsulinaemia, a key element of the metabolic syndrome, may be responsible (Rosmond *et al.*, 1998; Bjorntorp & Rosmond, 2000). This overactivity of the autonomic nervous system is supposedly not responsible for the development of LUTS but plays a key role in increasing the severity of LUTS above an intrinsic basal intensity that is determined by the genitourinary anatomical/pathophysiological characteristics of other ailments leading to LUTS (McVary *et al.*, 2005; Kasturi *et al.*, 2006). There is supporting evidence that stress conditions could be associated with the development and aggravation of prostatic disease. It was found that BMI, age and greater diastolic blood pressure reactivity correlated with a greater transition zone volume, greater total prostate gland volume, greater post-void RBV and more severe LUTS (Ullrich *et al.*, 2007). The improvement of features of the metabolic syndrome upon testosterone administration may also account for the improvement in the IPSS scores.

Inflammatory infiltrates are frequently found in and around the nodules in benign prostate hyperplasia (BPH) (Rohrmann *et al.*, 2005). The presence of the metabolic syndrome might be a mediator of this relationship because it is associated with elevated serum CRP concentration, a nonspecific marker of inflammation (Teoh & Verma, 2007). Thus, the metabolic syndrome might be linked to LUTS and elevated circulating CRP concentrations as an indicator of intraprostatic inflammation in symptomatic BPH (Rohrmann *et al.*, 2005; Teoh & Verma, 2007). In this study, CRP levels showed a quantitatively significant decline upon testosterone administration to men with features of the metabolic syndrome and elements of LUTS. The precise mechanism of the decline of CRP levels upon testosterone administration remains unclear at present. CRP levels are associated with the severity of the metabolic syndrome and improvement of the metabolic syndrome upon testosterone administration might lead to a reduction of CRP levels (Lemieux *et al.*, 2001).

The first mention of effects of testosterone on bladder function was reported by Holmang *et al.* (1993) who found an increase in peak urinary flow and mean urine volume voided in a testosterone-treated group of men compared with placebo treatment. In recent times, there has only been preliminary evidence that men with LUTS benefit from treatment with testosterone in the form of abstracts. The first data on this subject have shown that normalisation of testosterone levels has a positive effect on LUTS in men with BPH and late-onset hypogonadism (LOH) (Mskhalaya *et al.*, 2006). A recent presentation confirmed that testosterone treatment of men with LOH improved bladder function.

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Bladder capacity increased and detrusor pressure was lower at maximal flow (Karazindiyanoğlu & Çayan, 2007). The results of another pilot study (Mskhalaya *et al.*, 2007) also showed a positive effect of testosterone undecanoate therapy on LUTS in men with LOH. The results of Mskhalaya *et al.* (2006) have now been accepted for publication in a peer-reviewed journal.

In a series of earlier papers, we have tested the effects of testosterone administration on a number of variables relating to the ailments of the ageing male. The studies were not specifically designed to investigate the effects of testosterone administration to elderly on symptoms of LUTS, but the effects of testosterone treatment on the IPSS were recorded. In the first study, the effects of administration of parenteral testosterone undecanoate (TU) over 12 months were analysed (Saad *et al.*, 2007). There were positive clinical effects of administration of TU on the IPSS and also on parameters of the metabolic syndrome, progressive over the 12-month study period. As the effects were progressive over the 12 months of the study, it is likely that the effects occur gradually over a period of time following testosterone administration. In the second study, the effects of testosterone gel in a dose of 50 mg day^{-1} over 9 months on symptoms of LOH were compared with those of parenteral TU. The higher plasma levels of T generated with TU than with T gel (50 mg day^{-1}) were more effective in reducing the scores on the IPSS, probably indicating that there is a relationship between plasma levels of testosterone and their effects on LUTS. The third study investigated the effects of testosterone gel in a dose of 50 mg day^{-1} over 9 months, which had a positive effect on scores of the IPSS. Subsequently, these men shifted their testosterone treatment to administration of parenteral TU (Saad *et al.*, 2008a). There were positive clinical effects of administration of T gel on the IPSS and also on the parameters of the metabolic syndrome, and there was a significant further improvement of the IPSS when TU was administered after 9 months of administration of T gel when plasma T levels rose to higher levels than with T gel (Saad *et al.*, 2008b).

Conclusions

It is common for ageing men to experience urinary problems subsumed under the umbrella term LUTS. LUTS is epidemiologically linked to ED and the metabolic syndrome and the latter appears to be related to the circulating levels of testosterone. At an epidemiological level, the relationship between LUTS and testosterone levels has been more difficult to demonstrate and the relationship between LUTS and circulating levels of testosterone may be indirect. The relationship between the metabolic syndrome and LUTS may be based on the fact that the metabolic syndrome is associated with an overactivity of autonomic nervous system (Bjorntorp & Rosmond, 2000; Kasturi *et al.*, 2006; Ullrich *et al.*, 2007). The metabolic syndrome is associated with nonspecific inflammation. Some studies investigating the effects of restoration of plasma testosterone levels in elderly men to normal found a positive effect on variables of the metabolic syndrome, on CRP (a marker of nonspecific inflammation) on one hand and on scores of the IPSS on the other. We found a concurrent improvement of features of the metabolic syndrome and LUTS scores upon normalisation of circulating levels of testosterone in elderly men. Our study has some important limitations. The study was neither placebo-controlled nor blinded. The men in this study were not selected for the severity of LUTS scores and a large number had only mild symptoms. However, the evidence that testosterone treatment has a beneficial effect on LUTS must be regarded as preliminary but in view of the impact that LUTS has on the quality of lives of elderly men (Robertson *et al.*, 2007), this relationship is worthy of further investigation.

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