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Original article

PERMANENT LOW NORMAL TESTOSTERONE AND LOWER URINARY TRACT SYMPTOMS IN MEN 35 - 45 YEARS OF AGE

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ABSTRACT

In our outpatient practice, we are increasingly seeing men aged 35 to 45 years who have permanent low normal testosterone levels.

Aim We set out to investigate whether there is an association between permanent low normal testosterone levels and lower urinary tract symptoms in young men.

Patients and Methods For the period from January 2013 to December 2015 at the Andrology office at Hospital "St. Sofia", we examined 73 men aged 35 to 45 years with normal or elevated body mass index, permanent low normal testosterone level and micturition disorders. In order to compare the results we obtained, at the very beginning of the study, we selected a control group of 20 healthy men of the same age.

Results We obtained, although within reference ranges, significantly lower values for total testosterone in the 73 men with micturition disorders we studied, compared with those in the control group without micturition disorders.

Conclusions

1. Our study shows that in some men at a young age, some deviation in normal testosteronå secretion occurs, with a concomitant decrease in maximum urine flow, which is remarkably different from the same indicator in their peers with a high normal testosterone level.

2. We identify permanent low normal testosterone, overweight, and obesity as predictors of initial lower urinary tract symptoms in young men.

3. According to our study, the altered E2/T ratio is also relevant to the initial onset of lower urinary tract symptoms in young men.

Keywords: testosterone, estradiol, BMI, LUTS,

INTRODUCTION

In our outpatient practice, we are increasingly seeing men aged 35 to 45 years with permanent low normal testosterone (T). In the present study, we looked for an association between these levels and lower urinary tract symptoms (LUTS).

The obesity associated decrease in T levels is multifactorial and may be due to increased conversion of T to estradiol (E2) in peripheral adipose tissue. [1] Recent studies support the contention that obesity in men is accompanied by decreased T levels. On the other hand, the negative correlation found between T and body mass index (BMI), and between T and body weight, is consistent with the assumption that these factors alone are more important to its lower levels than aging. [2, 3]

According to the guidelines defined for clinical practice by the Endocrine Society, the sub-normal T level for men should be between 300 and 1000 ng/ml (10.4 - 34.7 nmol/l). [4, 5] The recommendations of the International Society of Andrology (ISA), the International Society for the Study of Aging Men (ISSAM), the European Association of Urology (EAU) and the American Society of Andrology (ASA), define a minimum T level of 230 ng/ml (7.98 nmol/l), and for total testosterone values between 230-300 ng/ml (7.98 -10.4 nmol/l), recommend additional measurement of free testosterone. [6]

In younger men, the decrease in T levels is due to environmental factors, prior testicular infections or injuries, acquired conditions such as obesity, diabetes, anabolic steroid or drug use. [1]

While some authors were able to demonstrate an association between LUTS and serum T levels, [7] others found none in their studies. [8] In men, androgen levels decrease with age, while those of estradiol (E2) remain constant, increasing the E2/T ratio. According to some authors, the changed attitude is associated with the development of LUTS. [9, 10] There is clear evidence in the literature regarding the links between metabolic syndrome and LUTS. [11] Kwon et al., 2013 examined risk factors associated with the progression of benign prostatic hyperplasia in men with moderate to severe LUTS and showed a correlation with an increasing number of metabolic syndrome components. [12] The close relationship between it, lower androgen levels and LUTS has been demonstrated in animal models by Vignozzi L et al. 2012. [13]

The International Prostate Symptom Score (IPSS) is an eight-question written screening tool used to screen for, rapidly diagnose, track the symptoms of and suggest treatment for LUTS resulting from benign prostatic

hyperplasia. The International Committee on Benign Prostatic Hyperplasia adopts the "eight questions" score and labeled it IPSS. [14]

Uroflowmetry, particularly maximum urinary flow (Qmax) can predict the natural history of LUTS, [15, 16] and is the most valued parameter for predicting obstruction. [16, 17]

AIM

We set out to investigate whether there is an association between permanent low normal T and LUTS in men aged 35 to 45 years.

MATERIALS AND METHOD

For the period from January 2013 to December 2015 in the Department of Andrology, Hospital "St. Sofia" we examined 73 men aged 35 to 45 years with normal and elevated BMI and permanent low normal T level. From the beginning of the study, we established a control group of patients of the same age, who underwent a prophylactic examination in our office. They were clinically healthy with normal body weight, not using drugs or testosterone preparations. All patients were informed in detail and signed a written consent to participate in the present study.

We developed a questionnaire by selecting questions from IPSS, which we adapted for the purposes of our study. Each question had 5 point-equivalent responses, which helped us in statistically processing the results. Table 1.

Table 1. Questionnaire

	none	1 time per 5-6 urinations	less than half time	about half time	nearly always
1. In the past month, how often have you urinated in less than 2 hours?	0	1	2	3	4
2. In the past month, how often have you had difficulty delaying urination?	0	1	2	3	4
3. In the past month, how often has the urinating flow been weak?	0	1	2	3	4
4. In the past month, how many times have you gotten up to urinate at night?	none 0	One time 1	Two times 2	Three times 3	Four times 4
SCORE					

We tested each man's T level three times over 20-30 days [18] and E2 and SHBG once. We performed mandatory blood collection after 30 min of rest between 8.00 and 9.00 AM in the clinical laboratory of the Hospital. Hormonal analysis was performed with a mini Vidas apparatus of Bio-Mérieux company and standard reagents by radioimmunological analysis. The standard values for T 10,4 - 29,0 nmol/L, E2 41,4-159 pmol/L and SHBG men aged between 20 and 49 3-54.1 nmol/L were determined by the manufacturer. The mean values of the three T samples in the male control group were 19.4-24.64 nmol/, which we assumed to be a high normal level in accordance with the guidelines set for clinical practice by the Endocrine Society. [4, 5] In our study, we included men with a first sample T level below 19.0 nmol/L, after double confirmation of the initial result. According to the guidelines defined for clinical practice by the Endocrine Society (4, 5), the recommendations of ISA, ISSAM, EAU and ASA, [6] depending on the mean values of the three T samples, we defined three sublevels in the reference range as follows: high normal testosterone level 19,4-24,64 nmol/l and low normal testosterone level 8,60 - 14,28 nmol/l. In order to standardize the units, we converted the E2 level from pmol/l to nmol/l by dividing its value by 1000. We used the average T value of the three studies to calculate the E2/T ratio. We calculated the Free androgen index (FAI) using the formula: FAI = (100xT)/ SHBG. [18]

According to the WHO criteria for normal and overweight and depending on the T level, all 93 men were divided into 5 groups as follows:

Group 1 (reference group) - **20** men with normal BMI 18,5-24,99 and high normal T level.
Group 2 - **18** men with normal BMI (18.5-24.99), low normal T level.
Group 3 - **27** overweight men (BMI 25-29.99) low normal T level.
Group 4 - **16** men with grade I obesity (BMI 30-34,99), low normal T level.
Group 5 - **12** men with grade II obesity (BMI 35-39,99), low normal T level.

Seminal fluid and urine were examined microbiologically twice over a 5-7 days period. For each patient we performed ultrasonography of kidneys and bladder, using an NS2 device manufactured by Mindray with a 3.5 MHz transducer for abdominal organs, and a uroflowmeter MMS Flowstar model for uroflowmetry. After emptying the bladder of the patient, we performed a repeat ultrasound examination looking for residual urine. Following the recommendations of the European Association of Urology, we used the maximum urinary flow rate (Qmax) with a standard value >/= 15 ml/sec. [17]

We compared the results of all 73 men with LUTS

included in our study with those of 20 healthy men in the control group. For processing the survey data, we used the statistical software IBM SPSS STATISTICS Version 25. Wå used: Independent Samples T-Test, parametric coefficient of linear correlation – Pearson, non-parametric linear correlation coefficient – Spearman.

RESULTS

On table 2 we present general data on the 93 men we examined.

Table 2. General data on the 93 men we examined

Parameter		Mean ± SD	Range	SD	P
Age (year)					
	Group 1	40.950 ± 2.743	37 - 45		
	Group 2	40.611 ± 2.789	37 - 45		
	Group 3	40.741 ± 2.640	37 - 45		
	Group 4	41.500 ± 2.338	37 - 45		
	Group 5	42.750 ± 1.913	39 - 45		
BMI (kg/m^2)					
	Group 1	21.947 ± 1,434	19.71 - 24.68		
	Group 2	21.694 ± 1.314	19.44 - 23.80		
	Group 3	27.250 ± 1.066	25.34 - 28.84		
	Group 4	32.654 ± 1.213	31.26 - 34.81		
	Group 5	37.359 ± 1.049	35.91 - 38.94		
T (nmol/l)					
	Group 1	21.576 ± 0.993	19.04 - 24.64		
	Group 2	12.095 ± 1.436	10.63 - 15.18	1 – 2 group	p<0.001
	Group 3	11.800 ± 1.590	9.72 - 15.09	1 – 3 group	p<0.001
	Group 4	10.680 ± 1.089	9.01 - 13.05	1 – 4 group	p<0.001
	Group 5	10.236 ± 1.339	8.60 - 13.20	1 – 5 group	p<0.001
E2 (nmol/l)					
	Group 1	0.038 ± 0.005	0.031 - 0.049		
	Group 2	0.080 ± 0.008	0.072 - 0.093	1 – 2 group	p<0.001
	Group 3	0.074 ± 0.009	0.056 - 0.092	1 – 3 group	p<0.001
	Group 4	0.074 ± 0.010	0.057 - 0.094	1 – 4 group	p<0.001
	Group 5	0.085 ± 0.006	0.076 - 0.094	1 – 5 group	p<0.001
FAI					
	Group 1	78.854 ± 6.113	70.53 - 88.41		
	Group 2	44.983 ± 2.199	41.48 - 48.40	1 – 2 group	p<0.001
	Group 3	44.640 ± 3.368	40.75 - 52.30	1 – 3 group	p<0.001
	Group 4	48.454 ± 2.420	44.94 - 53.77	1 – 4 group	p<0.001
	Group 5	49.053 ± 4.160	43.40 - 56.63	1 – 5 group	p<0.001
E2/T					
	Group 1	0.002 ± 0.000	0.0015 - 0.0019		
	Group 2	0.007 ± 0.001	0.0041 - 0.0088	1 – 2 group	p<0.001
	Group 3	0.006 ± 0.001	0.0042 - 0.0081	1 – 3 group	p<0.001
	Group 4	0.007 ± 0.001	0.0055 - 0.0090	1 – 4 group	p<0.001
	Group 5	0.008 ± 0.001	0.0061 - 0.0110	1 – 5 group	p<0.001
Q max (ml/sec)					
	Group 1	16.075 ± 0.634	15.2 - 16.8		
	Group 2	15.200 ± 1.324	12.4 - 16.8	1 – 2 group	p<0.033
	Group 3	14.741 ± 0.776	13.4 - 16.8	1 – 3 group	p<0.001
	Group 4	14.194 ± 0.965	12.3 - 15.6	1 – 4 group	p<0.001
	Group 5	13.892 ± 1.026	12.3 - 15.8	1 - 5 group	p<0.001
QS					
	Group 1	0.000 ± 0.000	0 - 0		
	Group 2	3.500 ± 1.790	1 - 7		
	Group 3	4.370 ± 1.245	2 - 7	2 - 3 group	p<0,035
	Group 4	6.000 ± 1.211	4 - 8	2 – 4 group	p<0.001
	Group 5	5.500 ± 1.931	3 - 8	2 – 5 group	p<0,009

BMI – body mass index, T – total testosterone, E2 – estradiol, FAI – free androgen index, Qmax – maximum urinary flow, QS - questionnaire score.

The absence of scores in the responses of the men of the first group showed the absence of micturition disorders in them. In the rest of them, we found that more than half (57.5%) urinated with a frequency of fewer than two hours in less than half the time, mild difficulty in postponing the posture in 38.4%, thinning of the stream in less than half to about half the time in 80.8% and 60.3% visited the toilet-room at least once a night. The maximum urinary flow rate was above 15 ml/sec in all 20 men of group one, below 15 ml/sec in 7 (39%) of group two, 17 (63%) of group three, in 12 (75%) of group four, in 11 (92%) of group five. (Fig 1, 2)

Fig. 1. Mean values of Qmax compared with those of T in men of different groups

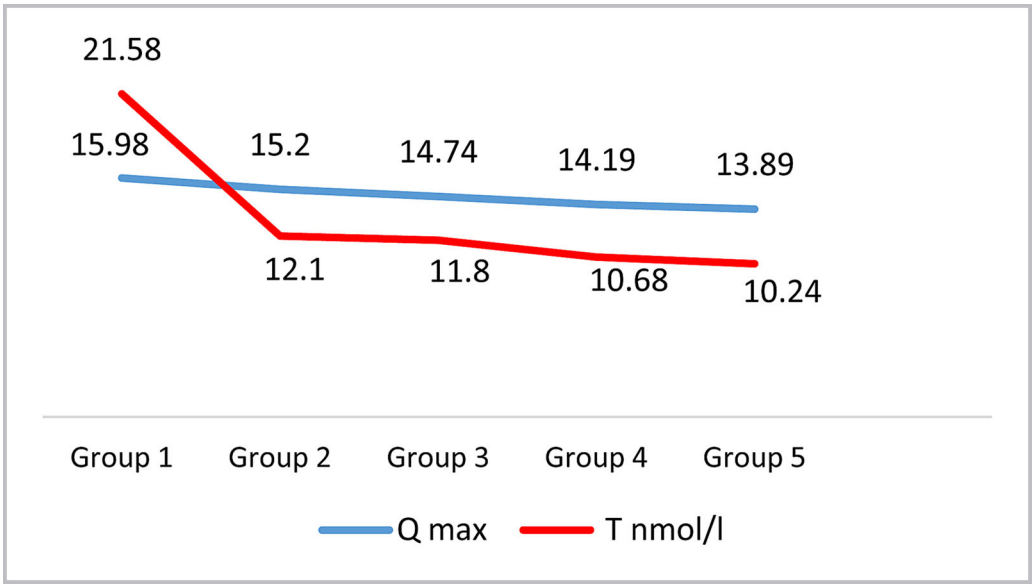
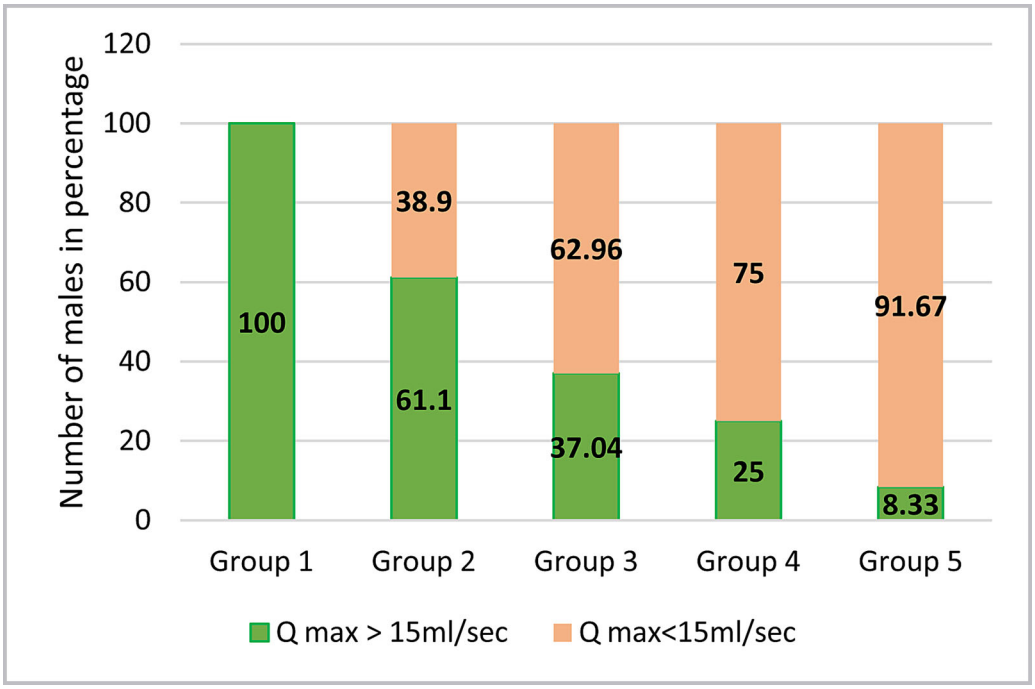


Fig.2 Number of men expressed a percentage of men with Qmax above and below 15 ml/sec in different groups



On repeat ultrasound examination of men in groups one, two and three, we found no residual urine, and we found residual urine in 1 (6%) of group four and 2 (17%) of group five.

In men of the control group, microbiological examinations of urine and ejaculate showed no growth. Mycoplasma, urea plasma, chlamydial or mixed infection was isolisted in the ejaculate of 10 (13.9%) of the 73 patients studied. Antibiotic treatment with a tetracycline preparation for 10 days was performed in all these men, and control microbiological examinations were negative, but micturition disorders remained persistent after therapy.

The correlation dependences that we established during the statistical processing are presented in table 3.

Table 3. Correlation dependencies

	T	FAI	E2	E2/T	BMI	Quest.	MUF
T	1.000						
FAI	,469**	1.000					
E2	-,473**	-,454**	1.000				
E2/T	-,831**	-,466**	,833**	1.000			
BMI	-,634**	-0.155	,329**	,517**	1.000		
QS	-,691**	-,283**	,372**	,458**	,548**	1.000	
Qmax	,583**	,343**	-,331**	-,488**	-,608**	-,667**	1.000

(p< 0,05*, p < 0,001**). BMI – body mass index, T – total testosterone, E2 – estradiol, FAI – free androgen index, Qmax – maximum urinary flow, QS - questionnaire score

DISCUSSION

From the outset, it is necessary to note that when reporting all indicators, it is imperative to consider the age of patients. We did not find a similar study in the available literature and therefore compared our results where possible with those conducted in adults. We proved the long-term persistence of moderate and low normal T levels with three blood draws over a period of 20 to 30 days. [18] All men in the control group had a high normal level and those in groups two to five had a moderate and low normal T level in all three samples. A double microbiological examination of urine and ejaculate was performed in order to exclude an inflammatory process as the cause of LUTS.

The lack of scores from the responses of the men in group one did not allow the calculation of significant differences between the reference group and the others. We found such significant differences between group two and groups three, four, and five. In our study, we observed relatively minor micturition disorders, with obstructive having some predominance over irritative symptomatology. While some authors were able to show a dependency between LUTS and serum T levels [7], others found no significant correlation between them. [8] With our finding of a high negative correlation between the number of points and theT level, we demonstrate the importance of a low normal T level as a predictor of initial LUTS. There is clear evidence in the literature regarding the association between metabolic syndrome and LUTS [11, 12, 13], and we found a significant positive correlation between questionnaire scores and BMI without looking for features of metabolic syndrome. It is more difficult to explain the low normal level of T in the men of the second group with normal BMI and LUTS. One possibility is that weight gain is not the only cause, but that there is another one related to lifestyle or harmful habits in men, which is a prerequisite for low-normal T and LUTS without an increase in BMI. Another is that these men had low normal T and LUTS at the time of the study but had not yet experienced weight gain.

We found a moderate negative correlation between the number of questionnaire items and E2. The dependence we found showed its lesser importance as a prerequisite for micturition disorders. A similar result was obtained between the questionnaire and FAI scores. In men, while serum androgen levels decline with age, E2 levels remain constant, increasing the E2/T ratio, and this altered relationship is clearly associated with the development of LUTS according to some authors. [9, 10] We found a significant positive correlation between the questionnaire scores and the E2/T ratio, but in our study, although within reference limits, in addition to a decrease in the T level, we also found an increase in that of E2 and significantly higher E2/T values.

Considering the recommendations of some authors, we used Qmax with a normal value for it >/= 15 ml/sec in the diagnosis of patients with lower urinary tract symptoms. [15, 16, 17] We found significant differences in average Qmax values between the control and other groups. These were absent between groups two to five, but the trends of increasing numbers of men whose Qmax is below 15 ml/sec and decreasing mean Qmax values with decreasing mean T were clearly evident. The significant and high correlations we found indicated the importance of T level, E2/T ratio and BMI as predictors of lower Qmax values. With the moderate correlations we found, we report the lesser importance of E2 and free testosterone for the lower Qmax values. We found residual urine in only three men, and this result we associated with the age of the examined patients.

CONCLUSION

1. Our study shows that in some men at a young age, some deviation in normal T secretion occurs, with a concomitant decrease in Qmax, which is remarkably different from the same indicator in their peers with a high normal T level.

2. We identify permanent low normal T, overweight and obesity as predictors of initial LUTS in men 35 to 45 years of age.

3. According to our study, the altered E2/T ratio is also relevant to the initial onset of LUTS in young men.

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