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LONG-TERM PERSISTENCE OF MODERATE OR LOW NORMAL TESTOSTERONE LEVELS AND PROSTATE GLAND VOLUME IN MEN 35–45 YEARS OLD

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Abstract

In our outpatient practice, we are increasingly seeing men aged from 35 to 45 years who have a long-term persistence of moderate or low normal testosterone levels. We aimed to investigate whether there is a link between long-term persistence of moderate or low normal testosterone levels and prostate volume. For the period from January 2013 to December 2015 in the Department of Andrology of "St. Sofia" Hospital we investigated 73 men aged 35 to 45 years with normal or elevated body mass index and long-term persistence of moderate or low testosterone levels. To compare our results, at the beginning of the study we formed a control group of 20 healthy men of the same age. The prostate volume was calculated by ultrasound. We obtained, within the reference range, significantly lower values for total testosterone ($p < 0.001$) and higher prostate volume ($p < 0.001$) in the 73 men we investigated compared to those in the control group. In some men at a young age, certain deviations in the normal secretion of testosterone occur, in parallel with an increase in total prostate volume, which differs significantly from the same indicator in their peers with a high normal level of testosterone. In most cases overweight or obesity were a prerequisite for young men to increase their prostate volume, but with a weaker correlation dependence than testosterone. Without going into cellular processes, we determined that long-term persistence of moderate or low normal testosterone levels, was a prerequisite for men aged between 35 and 45 years to increase their prostate volume.

Key words: testosterone, prostate volume, BMI

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Introduction. In our outpatient practice, we are increasingly seeing men aged 35 to 45 years with long-term persistence of moderate or low testosterone (T) levels. In this study, we present the changes in prostate gland volume (TPV) that we observed in men from 35 to 45 years of age with a low normal T level. In younger men, the decline in T level is due to environmental factors, previous infections, testicular trauma or acquired conditions such as obesity, diabetes, anabolic steroid or drug use [1].

The obesity-related decline in testosterone levels is multifactorial. This may be due to increased conversion of T to estradiol (E2) by peripheral adipose tissue [1]. Recent studies support the contention that obesity in men is accompanied by a decreased T level. 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 ageing [2, 3].

According to Endocrine Society clinical practice guidelines, the morning T level for men should be between 300 and 1000 ng/ml (10.4–34.7 nmol/l) [4, 5]. Recommendations from the International Society of Andrology (ISA), the International Society for the Study of Ageing Men (ISSAM), the European Association of Urology (EAU), and the American Society of Andrology (ASA) determine the minimum T level of 230 ng/ml (7.98 nmol/l), and for this androgen values between 230–300 ng/ml (7.98–10.4 nmol/l), they recommend an additional measurement of free testosterone (FT) [6].

According to Berry et al. [7], the normal prostate reaches 20 ± 6 grams in men between the ages of 21–30 years. This weight remains constant if benign prostatic hyperplasia (BPH) does not develop. The prevalence of BPH after the 3rd decade is only 8%. After the age of 50, 50% of men have pathological changes in the prostate gland. The analysis of BPH lesions shows that the process starts probably before the patient turns 30. Its early development in men aged 31 to 50 is characterized by a doubling of the prostate weight in about 4.5 years [7].

Many theories explain the progression of BPH. These include embryonic awakening, the influence of androgens, estrogens, ageing, and inflammation in this process [8–13]. In some studies, the authors reported no or weak correlation between serum testosterone levels (total or bioavailable), TPV and International Prostate Symptom Score (IPSS) [12, 14]. Serum androgen levels in men decrease with advancing age, but E2 levels remain constant, increasing the E2/T ratio. According to some authors, this change is closely related to the development of BPH [15, 16]. Others have reported a correlation between serum E2 levels and TPV [17]. Last but not least, E2 levels in stromal cells of BPH patients increase during ageing and this is most likely related to high expression of the aromatase enzyme [18]. Evidence suggests that prostate growth rate is higher in patients with metabolic disorders [19].

We set out to investigate whether there is an association between long-term

persistence of moderate or low-normal T and change in TPV in men aged from 35 to 45 years.

Patients and method. For the period from January 2013 to December 2015 in the Department of Andrology of "St. Sofia" hospital we examined 73 men aged between 35 and 45 years with normal and elevated BMI and long-term persistence of moderate or low normal T level. We determined TPV in all patients. 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 tested each man's T level three times over 20–30 days and E2 and SHBG levels once [20]. We performed the blood collection after a mandatory 30-minute rest period between 8.00 and 9.00 hours in the clinical laboratory of the hospital. Hormonal analysis was performed with a mini Vidas apparatus of Bio-Mérieux company and standard reagents to it according to the radioimmunological analysis method. Normal values for T (10.4–29.0 nmol/L), E2 (41.4–159 pmol/L) and SHBG (3–54.1 nmol/L) in men between 20 and 49 years were determined by the manufacturer. The mean values of the three T samples in the male control group were 19.0–25.0 nmol/L. We considered these values to be highly normal, in accordance with the guidelines set for clinical practice by the Endocrine Society [4, 5]. Men with a T level from the first sample below 19.0 nmol/L were included in our study after second and third confirmation of the initial result. According to the guidelines set for clinical practice by the Endocrine Society recommendations of ISA, ISSAM, EAU, and ASA, and depending on the mean values obtained from the three T samples, we defined three sublevels within the reference range. They were as follows: high normal testosterone level 19.00–25.0 nmol/l, moderate normal testosterone level 10.40–19.0 nmol/l, and low normal testosterone level 7.98–10.4 nmol/l [4–6]. In order to standardize the units, we converted the E2 level from pmol/l to nmol/l by dividing its value by 1000. To calculate the E2/T ratio, we used the mean T value of the three studies. We calculated the free androgene index (FAI) using the formula: $\mathrm{FAI} = (100 \times \mathrm{T})/\mathrm{SHBG}$ [20].

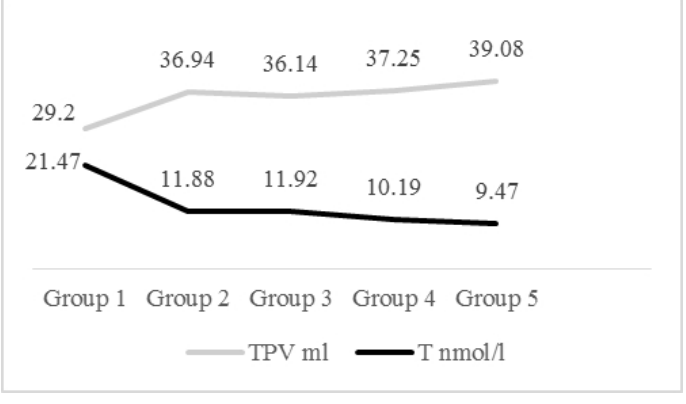
According to the WHO criteria for normal and overweight and depending on the T level, all 93 men were divided into 5 groups as follows:

1. Group 1 (reference group) – **20** men with normal BMI 18.5–24.99 and high normal T level.
2. Group 2 – **18** men with normal BMI (18.5–24.99), moderate and low normal T level.
3. Group 3 – **27** overweight men (BMI 25–29.99), moderate and low normal T level.

4. Group 4 – **16** men with grade I obesity (BMI 30–34.99), moderate and low normal T level.
5. Group 5 – **12** men with grade II obesity (BMI 35–39.99), moderate and low normal T level.

We performed bladder and prostate ultrasonography on each patient. We used the "NS2" device of the company "Mindray" with a 3.5 MHz transducer for abdominal organs. We performed the ultrasound examination with a well-filled bladder, looking for pathological changes inside its lumen in different projections. We scanned the prostatic gland with transversal, longitudinal and oblique sections measuring transverse, longitudinal and oblique dimensions in turn. TPV was calculated by the formula: TPV = 0.52.a.b.c. We compared the results of all 73 men included in our study with those of the control group. We used the statistical software IBM SPSS STATISTICS Version 25 to process the study data. We used: Independent Samples T-Test, parametric coefficient of linear correlation – Pearson, non-parametric linear correlation coefficient – Spearman.

Results. The overall data obtained from the 93 men we studied are presented in Table 1, and the correlations between T, FAI, E2, E2/T ratio, BMI, and TPV in Table 2.



T – total testosterone, TPV – total prostate volume

Fig. 1. Mean T values compared with mean TPV values

In all 93 men, the prostate was sharply and well demarcated with two lateral lobes that had a homogeneous hypoechoic echostructure. In the men from the control group, TPV was the lowest 29.2 ml, which is shown in Table 1. With the decrease in T level, we found a gradual increase in TPV in the groups. It was highest 39 ml in men of the fifth group (Fig. 1). The presence of a mean lobe size of 4–6 mm (mean 5.0 mm) was found in 3 (17%) of men in group 2, in 5 (19%) in group 3, in 7 (44%) in group 4, and in 6 (50%) in group 5 (Fig. 2).

T a b l e 1

The general data obtained in the 93 men studied by us

Parameter		Mean ± SD	Range	SD	p
Age (yr)	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	35.9–38.94		
T (nmol/l)	Group 1	21.576 ± 0.993	19.04–24.64		
	Group 2	12.199 ± 1.436	10.63–15.18	1–2 group	$p < 0.001$
	Group 3	11.962 ± 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	$p < 0.001$
SHBG (nmol/l)	Group 1	27.473 ± 1.854	24.35–30.52		
	Group 2	27.149 ± 3.146	21.44–33.57	1–2 group	$p = 0.698$
	Group 3	26.956 ± 4.390	22.43–35.71	1–3 group	$p < 0.035$
	Group 4	22.036 ± 1.690	19.33–24.57	1–4 group	$p < 0.001$
	Group 5	20.840 ± 1.661	18.63–23.31	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	$p < 0.001$
TPV (ml)	Group 1	29.200 ± 2.331	25–33		
	Group 2	37.111 ± 3.027	31–42	1–2 group	$p < 0.001$
	Group 3	36.607 ± 2.998	29–41	1–3 group	$p < 0.001$
	Group 4	36.875 ± 3.138	30–41	1–4 group	$p < 0.001$
	Group 5	38.083 ± 3.528	37–42	1–5 group	$p < 0.001$

BMI – body mass index, T – total testosterone, E2 – estradiol, SHBG – sex hormone binding globuline, FAI – free androgen index, TPV – total prostate volume

T a b l e 2

Correlations between mean T, FAI, E2, E2/T ratio, BMI and TPV

	T	FAI	E2	E2/T	BMI	TPV
T	1.000					
FAI	.469**	1.000				
E2	–.473**	–.454**	1.000			
E2/T	–.831**	–.466**	.833**	1.000		
BMI	–.634**	–.155	.329**	.517**	1.000	
TPV	–.526**	–.286**	.472**	.518**	.418**	1.000

($p < 0.05^{*}$, $p < 0.001^{**}$). BMI – body mass index, T – total testosterone, E2 – estradiol, FAI – free androgen index, TPV – total prostate volume

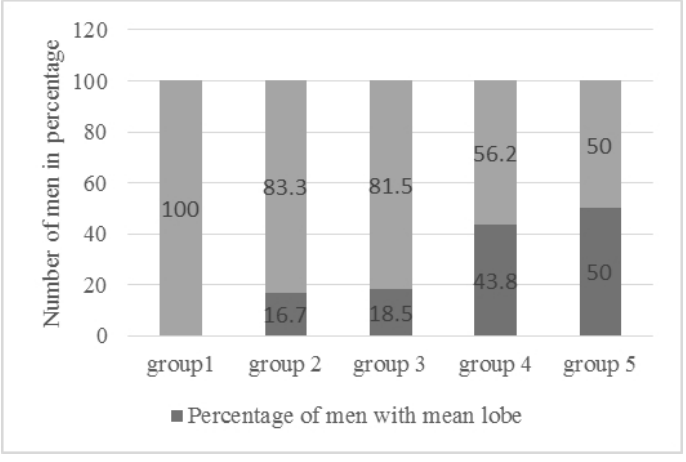


Fig. 2. Number of men expressed as percentage with and without mean lobe in different groups

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 [20]. 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.

One study performed at autopsy, determined the normal prostate weight in young men in grams [7]. We measured gland dimensions by ultrasound and calculated TPV in milliliters. Values in men in the control group were slightly higher but relatively similar to those reported in the cited study. This indicates

that men with a high normal T level between 35 and 45 years of age have a TPV approximately equal to that of men between 21 and 30 years of age. After analysis of BPH lesions, the same authors concluded that the process probably begins between 31 and 50 years of age [7].

Our results show that, although minimal, the increase in TPV, visualized by ultrasound, is detected in men after 37 years of age. Most likely, histological lesions are detected much earlier, before the increase in TPV can be ultrasonographically detected.

We found significant differences in TPV values between men in the control and other groups. No such differences were found between groups two to five, but there was a clear trend for an increase in TPV with a decrease in T level. The presence of a middle lobe of the prostate is an important change that we found in the course of our study, and the men with it increased in number with the decrease in the level of T and the increase in BMI in the fourth and fifth groups.

Many theories try to explain how BPH develops, and most often the authors look for the causes in sex hormones [8–13, 15, 16]. Most studies report no or weak correlation between serum T levels (total or bioavailable) and TPV [13, 14]. We found a significant negative correlation between mean T levels and TPV. We found significant differences in T levels between men in the control and other groups. No such differences were found in men from groups two to five. In our study, we found the lowest mean T level in men of groups four and five, where TPV was also the highest (Table 1).

Overweight or obesity on the one hand is a prerequisite for a low normal T level [2, 3]. On the other hand, an irregular metabolism is maintained inside the prostate, which increases its growth rate [10]. Like several other authors, we found a significant positive correlation between BMI and TPV, but the negative correlation between T and TPV in our study was superior in strength to that between BMI and TPV.

It is more difficult to explain the low normal T level in men of the second group with normal BMI and increased TPV. One possibility is that weight gain is not the only cause, but that there is another one related to lifestyle and unhealthy habits in men, which is also a prerequisite for low normal T level and increased TPV. The other is that these men had a low normal T level and increased TPV at the time of the study, but weight gain had not yet occurred in them.

The lower FAI values we found are the result of lower T levels. The moderate negative correlation we found with TPV confirms the results of other authors on the lesser importance of FT as a prerequisite for increasing TPV [13, 14].

In parallel with the long-term persistence of a moderate or low normal T level, we observed a high normal E2 level and a significant change in E2/T ratio values. Some authors have shown a correlation between serum E2 levels and TPV [16].

Our results demonstrated a significant positive correlation between E2 and TPV, but weaker than that with T (Table 2). We found a similar relationship,

close to that of T, between E2/T and TPV. We found the highest normal level of E2 and the highest values of the E2/T ratio in men of group five, who had the highest TPV. Our results confirm the opinion of other authors that the E2/T ratio is closely related to the development of BPH [15]. The presence of mean prostate volume was an important factor and men with it increased in number as the T level decreased and BMI increased in groups four and five.

Conclusions.

1. In some men at a young age, certain deviations in the normal secretion of T occur, in parallel with an increase in TPV, which differs significantly from the same indicator in their peers with a high normal level of T.
2. Without going into cellular processes, we think the long-term persistence of moderate or low normal testosterone levels, were a prerequisite for men aged between 35 and 45 years to increase their prostate volume.
3. In most cases overweight or obesity were a prerequisite for young men to increase their prostate volume, but with a weaker correlation dependence than T.

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