MEDICAL SCIENCES

INCREASED VALUES OF THE E2/T RATIO, TOTAL PROSTATE VOLUME AND LOWER URINARY TRACT SYMPTOMS IN MEN AGED 37 TO 45 YEARS. CROSS-SECTIONAL PILOT CLINICAL STUDY

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https://doi.org/10.5281/zenodo.10138046

Abstract

Introduction

We were looking for a relationship between total prostate volume, lower urinary tract symptoms and increased values of the E2/T ratio in young men.

Materials and Methods

We have examined 73 men aged 37 to 45 with lower urinary tract symptoms and increased values of the E2/T ratio. We use an appropriate questionnaire, diagnostic ultrasound and uroflowmetry as methods to evaluate total prostate volume, residual urine, and the maximum urinary flow. We selected a control group of 20 men of similar age without lower urinary tract symptoms.

Results

In the patients with lower urinary tract symptoms, we observed, though within the reference limits, significantly decrease in the level of serum testosterone below average values for a prolonged period and increased values of the E2 and E2/T ratio, compared to those of the control group ($p<0.001$). We found significant differences between the studied patients and those of the control group in a number of points in the answers to the questions ($p<0.001$), E2/T ratio ($p<0.001$), total prostate volume ($p<0.001$) and the maximum urinary flow ($p<0.001$).

Conclusion

Our study shows that some young men with lower urinary tract symptoms have some reduction in normal testosterone secretion and an increase in estradiol/testosterone ratio values that are significantly different from the same values in their peers without lower urinary tract symptoms. According to our results, overweight and obesity are important, but not a necessary condition for the occurrence of lower urinary tract symptoms and the increase of total prostate volume.

Keywords: LUTS**,** prostate volume, E2/T ratio, young men

INTRODUCTION

In our study, we focused on a group of young men with lower urinary tract symptoms and **increased values of the estradiol/testosterone (E2/T) ratio**. The human prostate consists of glandular and fibromuscular tissue located in three histological zones: central, peripheral, and transitional, the latter of which benign prostatic hyperplasia (BPH) develops in adult men [1]. The transitional zone, located in the periurethral region of the gland, represents approximately 5% of its total volume. The reasons responsible for its proliferation are still not fully understood [1].

Androgens are probably not the only hormones responsible for the development of BPH. Some authors have suggested that estrogens may also affect the normal function of the prostate gland by potentiating pathological growth [2], and studies suggest that excessive estrogenization may contribute to the higher incidence of BPH currently observed in the aging male population. The levels of serum and intraprostatic E2 increase in men with age, and patients with a greater total prostate volume (TPV) usually maintain high levels of serum E2 [3, 4]. According to Ho S. et al. (2008) this is associated with high aromatase expression [5]. In men, while serum androgen levels decline with age, E2 levels remain constant, increasing the E2/T ratio. Some authors consider this altered attitude to be a prerequisite for the development of BPH/ lower urinary tract symptoms (LUTS) [6]. Others have demonstrated a relationship between the rise in serum E2 levels and TPV [7, 8] and found no relationship between the decrease in serum T and TPV [8].

Although aging and hormonal changes appear to be the two main factors responsible for the development of BPH [9], data also show that the growth rate of the prostate is higher in patients with metabolic disorders such as insulin resistance syndrome, abdominal obesity, hypertension, hyperglycemia, and decreased low-density lipoprotein [10].

The 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 [11]. Uroflowmetry, particularly maximum urinary flow (Qmax) can predict the natural history of LUTS, [12, 13] and is the most valued parameter for predicting obstruction [13, 14].

The aim of this study was to look for a correlation between LUTS, TPV and E2/T ratio in young men.

MATERIALS AND METHODS

Study site, design, and population

From January 2013 to December 2019, we examined 73 men aged 37 to 45, with a LUTS and with normal and elevated body mass index (BMI). We also selected a control group of 20 clinically healthy men of the same age without LUTS, who have not used drugs or testosterone preparations.

Institutional Review Board Statement

All subjects gave their verbal and written informed consent taking part before the study. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of the Hospital (IC code: No3 / 28.11.2022) for studies with humans.

Clinical and laboratory evaluation

In our study we used the questionnaire by selecting questions from the IPSS. Each question had five point-equivalent responses, which helped us statistically process the results. The questionnaire was completed at the end of the third month at the last blood collection for serum T.

We tested each man's T level three times every 45 days for a period of 3 months. We also tested that of E2 once at the third blood collection for serum T. Furthermore, we did a blood collection after a mandatory 30-minute rest period between 8.00 am and 9.00 am after an overnight fast. Hormonal analysis was performed with a Mini Vida's apparatus from Bio-Mérieux Company and standard reagents were added according to the radioimmunological analysis method. Normal values for T (10.4–29.0 nmol/L) and E2 (41.4–159 pmol/L) were determined by the manufacturer. To standardize the measurement 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 average T value from the three samples. Seminal fluid and urine were examined microbiologically twice in a period of 5-7 days after the third blood collection for serum T. A microbiologist performed the tests for Trichomonas vaginalis, Neisseria gonorrhea, Chlamydia trachomatis, Ureaplasma parvum, Ureaplasma urealyticum, Mycoplasma hominis and Mycoplasma genitalium. The latter were performed with the one-step rapid test, an immune chromatographic test for in vitro diagnostics by Ameritech for Chlamydia and Mycoplasma system plus by Liofilchem diagnostic for Mycoplasma and Ureaplasma.

Ultrasonographic technique and uroflowmetry

After the third blood collection for serum T we also 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 with a well-filled bladder (250-350 ml of urine), then we invited the patient to urinate, performing uroflowmetry as well. The diagnosis was carried out with a "MMS flowstar" uroflowmeter. After emptying the bladder, we continued the ultrasound examination, looking for the presence of residual urine. TPV was calculated by the formula: TPV = 0.52.a.b.c. [ml] (a - transverse dimension, b - longitudinal dimension, c - oblique dimension). From all parameters of uroflowmetry, following the recommendations of the EAU, we used only Qmax with an accepted normal value >/= 15 ml/sec [14].

RESULTS

There were 73 participants with LUTS, serum T level 8,60-14,28 nmol/L, serum E2 level 0,056 – 0,094 nmol/L, E2/T ratio 0,042 – 0,0110 and 20 clinically healthy men of the same age, serum T level 19,04-24,64 nmol/L, serum E2 level 0,031 – 0,049 nmol/L , E2/T ratio 0,0015 – 0,0020 without LUTS. The average age of the examined was 41,401±2,420, while that of controls was 40,950 ±2,743. According to the criteria of the World Health Organization for normal and overweight [15] and depending on the E2/T ratio, the group of 93 men was divided into 5 groups as follows:

1. First (control) group – 20 men with BMI 18.50-24.99 and E2/T ratio: 0.002 ± 0.000
2. Second group – 18 men with BMI 18.50-24.99 and E2/T ratio: 0.007 ± 0.001
3. Third group – 27 men with BMI 25.00-29.99 and E2/T ratio: 0.006 ± 0.001
4. Fourth group – 16 men with BMI 30.00-34.99 and E2/T ratio: 0.007 ± 0.001
5. Fifth group – 12 men with BMI 35.00-39.99 and E2/T ratio: 0.008 ± 0.001

In our study, there were men with normal BMI values, but with increased E2/T ratio, and this necessitated their special place as a separate (second) group, different from the control one, and from the other groups. The other demographic, clinical, and laboratory parameters are as shown in Table 1, the correlation dependencies are summarized in Table 2. The comparison curves, obtained from the average E2/T ratio and the questionnaire score (QS), the TPV and the Qmax, are as shown in Figures 1, 2, 3.

Table 1.

The general data of the 93 men studied by us.

Parameter	Mean ± SD[1]	Range
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
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
Group 4	6.000 ± 1.211	4 - 8
Group 5	5.500 ± 1.931	3 - 8
BMI		
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	9.69 - 14.28
Group 3	11.800 ± 1.590	9.72 - 13.82
Group 4	10.680 ± 1.089	9.01 - 13.05
Group 5	10.236 ± 1.339	8.60 - 13.20
E2 (nmol/L)		
Group 1	0.038 ± 0.005	0.031 - 0.049
Group 2	0.080 ± 0.008	0.072 - 0.093
Group 3	0.074 ± 0.009	0.056 - 0.092
Group 4	0.074 ± 0.010	0.057 - 0.094
Group 5	0.085 ± 0.006	0.076 - 0.094
E2/T		
Group 1	0.002 ± 0.000	0.0015 - 0.0019
Group 2	0.007 ± 0.001	0.0041 - 0.0088
Group 3	0.006 ± 0.001	0.0042 - 0.0081
Group 4	0.007 ± 0.001	0.0055 - 0.0090
Group 5	0.008 ± 0.001	0.0061 - 0.0110
TPV (ml)		
Group 1	19.200 ± 2.331	15 - 23
Group 2	27.111 ± 3.027	21 - 32
Group	26.607 ± 2.998	19 - 31
Group 4	26.875 ± 3.138	20 - 31
Group 5	28.083 ± 3.528	27 - 32
Qmax (ml/sek)		
Group 1	16.075 ± 0.634	15.2 - 16.8
Group 2	15.200 ± 1.324	12.4 - 16.8
Group 3	14.741 ± 0.776	13.4 - 16.8
Group 4	14.194 ± 0.965	12.3 - 15.6
Group 5	13.892 ± 1.026	12.3 - 15.8

QS-questionnaire score, BMI – body mass index, T – total testosterone, E2 – estradiol, E2/T ratio – estradiol/testosterone ratio, TPV – total prostate volume, Qmax – maximum urinary flow

Table 2

Correlation dependencies

	QS	T	E2	E2/T	BMI	TPV	Qmax
QS	1,000						
T	-,682**	1,000					
E2	,372**	-,473**	1,000				
E2/T	,644**	-,829**	,833**	1,000			
BMI	,548**	-,634**	,329**	,517**	1,000		
TPV	,556**	-,526**	,472**	,518**	,418**	1,000	
Q max	-,667**	,583**	-,331**	-,488**	-,608**	-,263**	1,000

QS–questionnaire score, BMI – body mass index, T – total testosterone, E2 – estradiol, E2/T ratio – estradiol/testosterone ratio, TPV – total prostate volume, Qmax – maximum urinary flow

Mean T values nmol/L compared with mean QS, TPV and Q max are presented on Fig.1, Fig.2, and Fig.3.

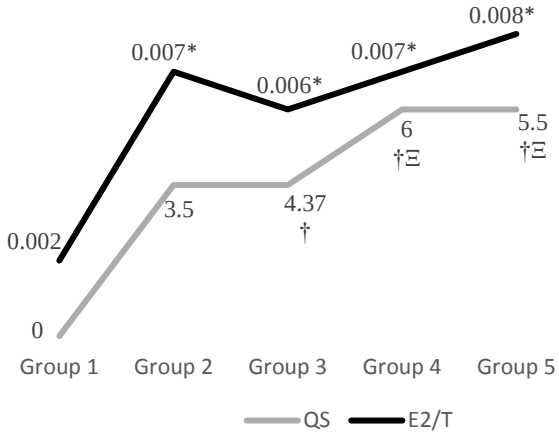

Fig.1 Mean E2/T values compared with mean questionnaire score (QS)
** - significant difference 1 with 2, 3, 4 and 5 group; † - significant difference 2 with 3, 4 and 5 group; Ξ - significant difference 3 with 4 and 5 group; ◊ – significant difference 4 with 5 group*

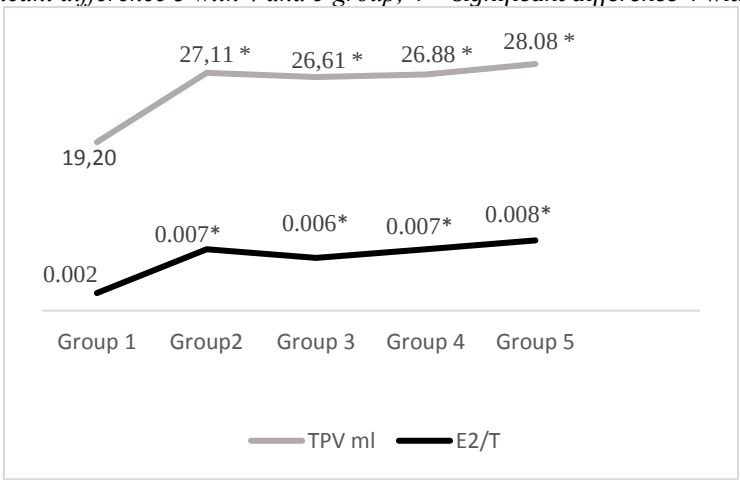

Fig.2 Mean E2/T values compared with mean TPV values in ml.
** - significant difference 1 with 2, 3, 4 and 5 group; † - significant difference 2 with 3, 4 and 5 group; Ξ - significant difference 3 with 4 and 5 group; ◊ – significant difference 4 with 5 group*

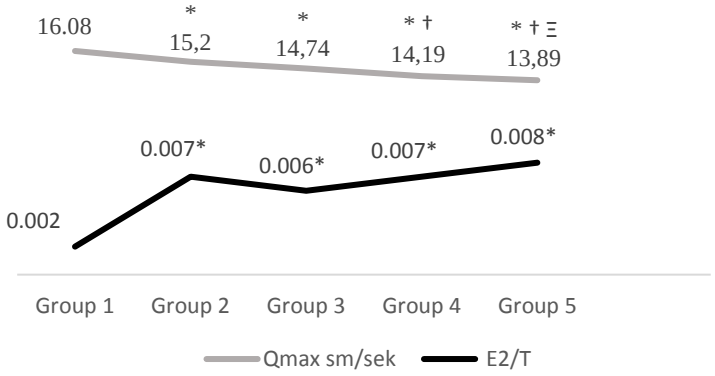

Fig.3 Mean E2/T values compared with mean Qmax values
** - significant difference 1 with 2, 3, 4 and 5 group; † - significant difference 2 with 3, 4 and 5 group; Ξ - significant difference 3 with 4 and 5 group; ◊ – significant difference 4 with 5 group*

Data analysis

The age, BMI, serum T level, E2, E2/T, QS, TPV and Qmax values in the five groups were entered into the IBM SPSS STATISTICS Version 25 statistical software. Descriptive and evaluation methods - averages and standard deviation were derived for the age, BMI, serum T level, E2, E2/T, QS, TPV and Qmax values. Hypothesis testing methods (parametric) - T-test for two independent samples (Independent Samples T-Test) were derived for the age, BMI, serum T level, E2, E2/T, QS, TPV and Qmax values. Correlation analysis - Parametric coefficient of linear correlation – Pearson were derived for BMI, serum T level, E2, E2/T, QS, TPV and Qmax values. The critical significance level that we used was $p \leq 0.05$.

Microbiological analysis

As regards men in the control group, urine and ejaculate microbiological examinations mark no growth. Mycoplasma genitalium, Ureaplasma urealyticum or Chlamydia trachomatis were isolated in the ejaculate in 9 (12.33%) of the 73 patients studied. Antibiotic treatment with a tetracycline preparation was applied for 10 days to all these men. Control microbiological examinations were negative, but the LUTS remained persistent after therapy.

Ultrasonic parameters

In all 93 men the prostate was sharply and well defined with two lateral lobes that had a homogeneous hypoechoic structure. The presence of a mean lobe size of 4-6 mm (mean 5.0 mm) was found in 7 (38,9%) of men in second group, in 11 (40,7%) in a third group, in 7 (43,8%) in the fourth group, and in 6 (50%) in the fifth group. Fig.4

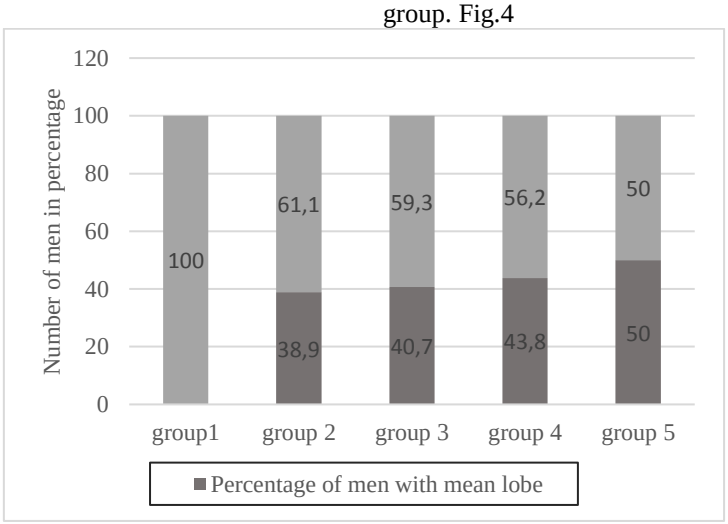

Fig.4 Number of men expressed as percentage with and without mean lobe in different groups.

DISCUSSION

In our cross-sectional pilot clinical study, we describe deviations, although within reference limits in E2/T ratio, in a group of young men with LUTS, compared to the same parameters in those of the control group without LUTS. In available literature, we did not find similar studies and compared our results, where possible, with similar studies conducted in men with late-onset hypogonadism. After the three blood collections every 45 days for a period of 3 months, we proved that the serum T levels are below the average values of the standard for a prolonged period. Serum E2 test was performed at the third blood collection for T at the end of the third month. Thus, we were sure that throughout the period the men studied had a serum T level below the average values of the standard for a prolonged period, which suggests that the change in the E2/T ratio is also for a prolonged period. As the level of serum T decreased, we observed an increase in the level of E2 within reference limits and a significant change in the

values of the ratio E2/T (p<0,001). Some authors show a relationship between serum levels of E2 and TPV [7]. Our results demonstrated a significant positive correlation dependence between E2 and TPV (r = ,472**, p<0.001), but weaker than that with T. However, we found a similar dependence, close to that of T, between E2/T and TPV (r = ,518**, p<0.001). We found the highest values of the E2/T ratio in the men of the fifth group, who had the largest TPV. The transition zone, which is in the periurethral region of the gland, represents approximately 5% of its total volume. The reasons responsible for its proliferation are still not fully understood [1]. The presence of a middle lobe of the prostate is an important change that we found during our study, and the men with it increase in number with the increase in the E2/T ratio especially in the fourth and fifth groups. We do not exclude the possibility that in rest of the men there is some histological growth of the transitory zone, which, however, we cannot detect with our available ultrasound technique. Our results show that the increase in TPV in young men begins at the transition zone, where both T and E2 receptors are present. It appears that, in addition to the decrease in the serum T level, it is the increase in the E2/T ratio in young men that accounts for the initial increase in the mean fraction originating from the transition zone. Our opinion coincides with the opinion of other authors who conducted studies in adult men, who also identified it as clearly related to the development of BPH [6].

Overweight or obesity, on the one hand, is a prerequisite for a change in the E 2/T ratio and on the other hand, for impaired metabolism in the cells and intercellular space of the prostate [16]. The latter is considered by some authors to be a factor in increasing the speed of its growth [16]. Like several other authors, we found a significant positive correlation between BMI and TPV (r =, 418**, p<0.001) [17], but a correlation between E2/T and TPV (r =, 518**, p<0.001) in our study was superior in strength to that between BMI and TPV, i.e. in our opinion the increase in the E2/T ratio is more important for the increase in TPV.

The absence of points from the men's answers to the questionnaire (relating to micturition disorders) did not allow the calculation of significant differences between the control and the other groups. We found such between the second and third (p<0.035), second and fourth (p<0.001), and second and fifth (p<0.009) groups. In our study, we observed relatively minor micturition disorders, with obstructive having some predominance over irritative symptomatology. Our results show a high positive correlation between number of points and E2/T ratio (r =, 644**, p<0.001) which demonstrate its importance as a predictor of initial LUTS. In our study, we found a significant positive correlation between the number of points from the questionnaire and BMI (r = ,548**, p<0.001), even though the patients studied by us lacked the signs of metabolic syndrome.

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 [13]. We found significant differences in the average Qmax values only between the control and the other groups (p<0.001), but the trends of decreasing mean Qmax values and increasing numbers of men whose Qmax is below 15 ml/sec with increasing in the E2/T ratio were evident. We found a high negative correlation between the number of points from questionnaire and Qmax (r = -.667**, p<0.001), significant negative correlations between E2/T ratio and Qmax (r = -,488**, p<0.001) and a high negative correlation between BMI and Qmax (r = - ,608** , p<0.001) According to our results, an increased BMI is an important, but not a prerequisite, considering the men of the second group, which however, is of a greater importance for the onset of LUTS than for the increase in TPV.

We found residual urine in only three men, and this result we associate with the age of the examined patients. Some authors hypothesize that LUTS is induced by inflammation [18].

We performed a double microbiological examination of urine and ejaculate in order to rule out an inflammatory process as a cause of LUTS. Our study showed that even after antibiotic treatment, where necessary and negative repeat results, LUTSs persisted. Therefore, based on our own study, our opinion is that in young men, not only prostatic gland infections or sclerosis of the bladder neck are important for the occurrence of micturition disturbances, but also the change in E2/T ratio, when the level of serum T is below the average values of the norm for a prolonged period.

We found a moderate negative correlation between the TPV and Qmax (r = -,263**, p<0.001), demonstrating the weak dependence of the urine stream on the TPV in young men. This observation of ours coincides with the opinion of most authors in the scientific literature who have conducted studies on adult men [13]. However, as the mean E2/T ratio increased across groups, we observed an increase in TPV, the appearance of a middle lobe, and an increase in the number of questionnaire items associated with LUTS.

LIMITATIONS

1. The study is cross-sectional in terms of most parameters, except the serum T level, which was followed three times over three months and does not allow us to say how these changes would develop in the future by the lifestyles of the same patients.

2. The number of examined patients included in the study is relatively small and we intend to expand it in the future.

3. It would be interesting to include a maximum number of patients with LUTS and with a normal BMI in a future study to identify some lifestyle factors and their harmful habits, in which we observe a decrease in the level of serum T below the average values of the standard and an increase in the values of E2 /T.

CONCLUSIONS:

Our study shows that some young men with LUTS have some reduction in normal testosterone secretion and an increase in E2/T values that are significantly different from the same values in their peers without LUTS. According to our results, overweight and obesity are important, but not a necessary condition for the occurrence of LUTS and the increase of TPV.

Author Contributions: All authors involved in the preparation of this article have given their consent to the published version of the manuscript.

Acknowledgments: The authors of this study thank Assoc. Prof. Mircho Vukov (mathematician and epidemiologist) who helped with the statistics.

Data Availability: The data used to support the findings of this study are available from the corresponding author upon request.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: Disclosure Statement: The authors declare that they have no conflict of interest.

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