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Color Doppler Ultrasound of the Testis in Young Men with a Serum Testosterone Level below the Average Values of the Standard for a Prolonged Period

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ABSTRACT

Introduction: This study aimed to correlate the testicular volume, ultrasound imaging, and blood flow parameters, determined using color Doppler ultrasonography in young men with a testosterone level below the average values of the standard for a prolonged period.

Material and Methods: From January 2013 and December 2019, we examined 73 men aged 37 to 45 years with a testosterone level below the average values of the standard for a prolonged period and a 20 age-matched men with a testosterone level above the average values of the standard. We use color Doppler ultrasound as a method to evaluate the volume, ultrasound imaging and Doppler parameters of the testicular blood flow.

Results: We obtained significantly lower but still within the reference range values for total testosterone ($p<0.001$), compared to those of the control group. We found no differences in the ultrasound characteristics of the testicular parenchyma and significant differences between testicular volumes in patients with a testosterone level below the average values of the standard for a prolonged period and those in the control group. In the color Doppler ultrasound we recorded fluctuations only in the blood flow of a aa.intratesticularis, expressed in a slight increase in the resistance index.

Conclusions: Ultrasonography of young men with a serum T level below the average values of the standard for a prolonged period found no reduction in testicular volume and no change in the ultrasound characteristic of the parenchyma, which suggests to us that this is not a congenital condition, but cannot answer the question of whether it will lead to structural changes in the testicles in the future and if so what. The non-significant increase in RI in the intratesticular arteries in all examined men is a non-specific indicator that directs the specialist's attention to additional testing of total testosterone in patients with complaints from the male reproductive system.

Keywords: Color Doppler Ultrasound, Testosterone, Young Men

Introduction

In our study, we focused on the testicular volume, ultrasound imaging, and blood flow parameters, determined using color Doppler ultrasonography (CDU) in young men with a testosterone level below the average values of the standard for a prolonged period. Clinical examination of their external genitalia is one of the most important steps in assessing their condition. Determination of testicular volume (TV), tone and consistency provides indirect information on both spermatogenesis and hormonal function [1]. Diagnostic ultrasound scanning of the scrotal contents has already been proven greater capabilities than clinical examination [2]. It is safe and effective, with the ability to rapidly define pathology, and has become the primary imaging modality for the evaluation of the testes and paratesticular structures. Color Doppler imaging of the vessels adds additional information and enhances the diagnostic capability of ultrasound scanning [3]. According to Sayfan J. et al. 1988 high-frequency ultrasound serves as a diagnostic method not only for evaluating scrotal pathology but also for accurate determination of TV [4]. It outperforms the Prader orchidometer and other conventional orchidometers by eliminating inaccurate measurement due to thick scrotal walls or the cremaster muscle [5,6]. Regardless of the method, no consensus has yet been reached on TV reference limits, and currently different values have been proposed depending on the ethnic characteristics of men [6]. Determination of testicular volume is important and provides valuable information on spermatogenesis and steroid hormone production [7]. A number of authors define smaller TV as a clinical sign, both for impaired sperm quality and hypogonadism [8]. The true prognostic value of TV for clinical practice in mild and moderate seminal damages and low-normal T level still remains unclear, due to the lack of validated cut-off values for testicular volume/function.

Along with TV measurement, high-frequency ultrasound enables detailed imaging of testicular structure. Ultrasound evaluation, according to the guidelines of the European Association of Urology,

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is in the recommendations for examining men for infertility [9]. Normally, the echogenicity of the testicular parenchyma increases during puberty and resembles the standardized structure of the normal thyroid gland [10]. However, the structural evaluation of the testes is subjective and depends on the experience of the operator [6]. Inhomogeneity is defined as the lack of uniform structure that characterizes normal testicular parenchyma. For its quantitative determination in the USA, a 5-level scale has been proposed which however is not unanimously accepted by all researchers [11]. However, some authors conclude that testicular parenchymal inhomogeneity is an informative marker of testicular function, both spermatogenesis and T production [12,13]. Others believe that the inhomogeneity of the testicular parenchyma adds no meaningful information to the assessment of male hypogonadism, but is an extremely useful indicator in infertility research. Due to the difficulty to categorize the ultrasound imaging of the testes and to objectify an operator-independent parameter, the same authors choose to evaluate a dichotomous variable (presence/absence of characteristic). According to them, this classification is easily applicable in clinical practice and can provide useful information about the functionality of the testes [14].

Global delineation of blood flow is essential for the pathology of any organ [15]. Middleton W. et al. 1989 first demonstrated the capabilities of CDU to assess extra- and intratesticular blood flow in healthy men [16]. It is a fast and accurate method for measuring blood flow and vascular impedance. The resistance index (RI) is the most widely used in clinical practice and Lefort C. et al. 2001 recommend its measurement also during the examination of the scrotal contents [17,18]. Its increase most often suggests intratesticular ischemia [19]. A retrospective study concluded that an intratesticular RI greater than 0.6, is associated with reduced total sperm motility, reduced testicular size, and elevated FSH, supporting the use of this parameter as an independent indicator of testicular function [20].

According to the guidelines, defined for clinical practice by the Endocrine Society, the normal T level for men should be between 10.4 - 34.7 nmol/L [21,22]. 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 7.98 nmol/L and for total testosterone values between 7.98-10.4 nmol/L, recommend additional measurement of free testosterone [23].

The aim of this study was to investigate the diagnostic capabilities of CDU in young men with a testosterone level below the average values of the standard for a prolonged period.

Material and Methods

Study Site, Design, and Population

This cross-sectional comparative study was carried out at the Department of Andrology of a tertiary hospital from January 2013 to December 2019. The study population comprised 73 young males with a testosterone level below the average values of the standard for a prolonged period and 20 age-matched men with a testosterone level above the average values of the standard.

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 involving humans.

Participants Selection

Consenting men with a testosterone level below the average values of the standard for a prolonged period aged 37 to 45 years, were recruited consecutively from the andrology office. Consenting age-matched men with with a testosterone level above the average values of the standard were also recruited consecutively from the andrology office. Exclusion criteria were absence of congenital or acquired disease of the genital system (testicular and epididymal cysts, hydrocele, funiculocele, varicocele), absence of inflammatory or infectious disease in the last six months, and no use of testosterone preparations.

Clinical and Laboratory Evaluation

The testes of all men were examined clinically in supine and upright positions. We tested each man's T level three times every 45 days for a period of 3 months. Furthermore, we performed blood collection after a mandatory 30-minute rest period between 8.00 am and 9.00 am after an overnight fast. Fasting venous blood sample, for serum T, was drawn from the antecubital veins of subjects under sterile conditions. Hormonal analysis was performed with a Mini Vidas apparatus from Bio-Mérieux Company and standard reagents were added according to the radioimmunological analysis method. The manufacturer has determined the normal values for men T (10.4-29.0 nmol/L).

Ultrasonographic Technique

All ultrasound examinations were performed using a Mindray Ultrasonography machine (model NS-2; Shenzhen Mindray Bio-medical Electronics, Nanshan, Shenzhen, China, 2012) with Doppler facility equipped with high Frequency (7.5 MHz) transducer. All men were examined in the supine position, with the thighs retracted and the scrotum resting on them. In the ultrasound scan, we used standard and consistent longitudinal, transverse and oblique sections. We determined the ultrasound characteristics of the testicular parenchyma, the TV and the parameters of the blood flow peak systolic velocity (PSV), end diastolic velocity (EDV) and resistance index (RI) in the three arteries: a.testicularis, a.capsularis, aa. intratesticularis (Figure 1, Figure 2).

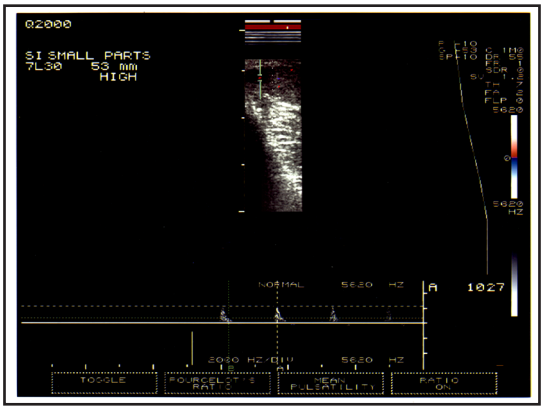

Figure 1: PSV and EDV a. Testicularis

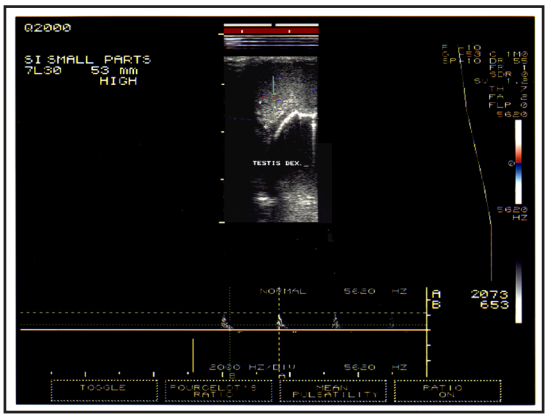

Figure 2: PSV and EDV aa. Intratesticularis

We calculated RI according to the formula: RI = PSV - EDV /PSV [16,24]. The ultrasound examinations were carried out by the same urologist (with thirty-two years of experience in the field of color Doppler ultrasound of the scrotum and scrotal contents) to eliminate interobserver variability. The transducer output and receiver gain setting were optimised for each participant. All sonographic measurements were taken thrice, and the mean values were recorded for each subject, to ensure accuracy of the measurements and reduce intraobserver error. We compared the results of all 73 men included in our study with those of the control group.

Results

Demographic, Clinical, and Laboratory

There were 73 participants with a serum T level below the average values of the standard for a prolonged period 8,60-14,28 nmol/L and an 20 age matched participants with a serum T 19,04-24,64 nmol/L. 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 World Health Organization for normal and overweight and depending on the T level, the group of 93 men was divided into 5 groups as follows [25]:

1. First (control) group - 20 men with BMI 18.50-24.99 and serum T: 21.576 ± 0.993 nmol/L
2. Second group - 18 men with BMI 18.50-24.99 and serum T: 12.199 ± 1.436 nmol/L
3. Third group - 27 men with BMI 25.00-29.99 and serum T: 11.962 ± 1.590 nmol/L
4. Fourth group - 16 men with BMI 30.00-34.99 and serum T: 10.680 ± 1.089 nmol/L
5. Fifth group - 12 men with BMI 35.00-39.99 and serum T: 10.236 ± 1.339 nmol/L

In our study, there were men with normal BMI values, but with a testosterone level below the average values of the standard for a prolonged period, and this necessitated their special place as a separate (second) group, different from the control and from the other groups. The other demographic, clinical, and laboratory parameters are as shown in Tables 1 and 2. Only the serum T level showed a statistically significant difference between cases and controls.

Table 1: The mean values for the TV, PSV, EDV and RI of a.testicularis, a.capsularis and aa. intratesticularis with the standard deviation obtained in the 93 men studied by us

Group	Right testicle Mean ± SD	Right testicle Range	Left testicle Mean ± SD	Left testicle Range
	TV (ml)	TV (ml)	TV (ml)	TV (ml)
Group 1	21.785 ± 2.379	17.9 - 28.8	21.675 ± 2.442	17.7 - 28.6
Group 2	21.794 ± 2.375	17.5 - 27.8	21.656 ± 2.574	17.1 - 27.5
Group 3	21.530 ± 2.678	17.4 - 26.7	21.389 ± 2.588	17.0 - 26.3
Group 4	21.819 ± 2.772	17.4 - 26.3	21.800 ± 2.910	17.3 - 26.1
Group 5	21.692 ± 2.409	17.6 - 26.5	21.567 ± 2.668	17.4 - 26.3
	TA PSV (sm/sec)	**TA PSV (sm/sec)**	**TA PSV (sm/sec)**	**TA PSV (sm/sec)**
Group 1	19.124 ± 3.350	12.83 - 26.98	19.081 ± 3.348	12.48 - 26.74
Group 2	18.932 ± 3.809	12.48 - 25.43	19.073 ± 3.801	12.23 - 25.43
Group 3	19.482 ± 3.777	14.23 - 26.32	19.357 ± 4.118	14.23 - 26.39
Group 4	19.423 ± 2.284	15.53 - 25.58	19.401 ± 2.278	15.24 - 25.39
Group 5	19.661 ± 2.570	14.91 - 23.65	19.468 ± 2.573	14.55 - 23.49
	TA EDV (sm/sec)	**TA EDV (sm/sec)**	**TA EDV (sm/sec)**	**TA EDV (sm/sec)**
Group 1	3.401 ± 0.851	1.99 - 4.81	3.468 ± 0.849	2.00 - 4.77
Group 2	3.383 ± 0.847	2.50 - 4.83	3.403 ± 0.851	2.45 - 4.62
Group 3	3.492 ± 0.722	2.71 - 5.00	3.447 ± 0.863	2.66 - 4.75
Group 4	3.406 ± 0.572	2.51 - 4.18	3.401 ± 0.569	2.78 - 4.06
Group 5	3.513 ± 0.650	2.98 - 3.91	3.562 ± 0.649	2.91 - 3.99
	TA RI	**TA RI**	**TA RI**	**TA RI**
Group 1	0.824 ± 0.016	0.80 - 0.86	0.823 ± 0.016	0.80 - 0.86
Group 2	0.821 ± 0.017	0.80 - 0.84	0.822 ± 0.016	0.80 - 0.84
Group 3	0.822 ± 0.023	0.80 - 0.84	0.823 ± 0.021	0.80 - 0.84
Group 4	0.824 ± 0.015	0.81 - 0.84	0.821 ± 0.017	0.81 - 0.84
Group 5	0.823 ± 0.020	0.80 - 0.84	0.824 ± 0.021	0.80 - 0.83

	CA PSV (sm/sec)	CA PSV (sm/sec)	CA PSV (sm/sec)	CA PSV (sm/sec)
Group 1	9.642 ± 3.493	5.63 - 14.35	9.503± 3.472	5.31 - 14.03
Group 2	9.540 ± 3.748	6.68 - 13.89	9.557 ± 3.339	6.57 - 13.64
Group 3	9.593 ± 3.629	6.31 - 13.76	9.511 ± 3.631	6.75 - 13.64
Group 4	8.954 ± 4.144	6.85 - 12.29	8.868 ± 4.123	6.92 - 11.90
Group 5	9.371 ± 3.728	7.25 - 10.88	9.153 ± 3.742	7.16 - 10.81
	CA EDV (sm/sec)	**CA EDV (sm/sec)**	**CA EDV (sm/sec)**	**CA EDV (sm/sec)**
Group 1	3.233 ± 0.752	1.95 - 4.73	3.188 ± 0.750	1.91 - 4.49
Group 2	3.221 ± 0.740	2.46 - 4.72	3.248 ± 0.727	2.33 - 4.64
Group 3	3.264 ± 0.605	2.27 - 4.81	3.204 ± 0.609	2.14 - 4.46
Group 4	3.021 ± 0.768	2.33 - 4.06	2.976 ± 0.771	2.35 - 3.77
Group 5	3.104 ± 0.724	2.46 - 3.56	3.078 ± 0.721	2.56 - 3.57
	CA RI	**CA RI**	**CA RI**	**CA RI**
Group 1	0.665 ± 0.018	0.64 - 0.68	0.663 ± 0.018	0.60 - 0.68
Group 2	0.663 ± 0.020	0.63 - 0.68	0.660 ± 0.018	0.63 - 0.68
Group 3	0.660 ± 0.020	0.63 - 0.68	0.659 ± 0.021	0.64 - 0.68
Group 4	0.662 ± 0.023	0.64 - 0.68	0.656 ± 0.020	0.64 - 0.68
Group 5	0.667 ± 0.034	0.65 - 0.68	0.668 ± 0.032	0.65 - 0.68
	ITA PSV (sm/sec)	**ITA PSV (sm/sec)**	**ITA PSV (sm/sec)**	**ITA PSV (sm/sec)**
Group 1	4.085 ± 3.423	2.85 - 7.96	4.089 ± 3.416	3.17 - 7.93
Group 2	4.175 ± 3.749	3.21 - 5.64	4.357 ± 3.561	3.24 - 5.86
Group 3	4.036 ± 3.509	3.17 - 4.97	4.121 ± 3.507	3.21 - 5.26
Group 4	4.021 ± 4.005	3.17 - 5.76	4.062 ± 4.008	3.43 - 4.87
Group 5	4.152 ± 4.299	3.36 - 5.20	3.898 ± 4.296	3.74 - 4.90
	ITA EDV (sm/sec)	**ITA EDV (sm/sec)**	**ITA EDV (sm/sec)**	**ITA EDV (sm/sec)**
Group 1	1.548 ± 0.578	1.14 - 2.85	1.532 ± 0.574	1.25 - 1.82
Group 2	1.731 ± 0.659	1.22 - 3.30	1.643 ± 0.745	1.20 - 2.77
Group 3	1.523 ± 0.558	1.20 - 1.94	1.538 ± 0.555	1.22 - 1.95
Group 4	1.547 ± 0.568	1.20 - 2.13	1.511 ± 0.571	1.30 - 1.79
Group 5	1.578± 0.666	1.24 - 1.98	1.589 ± 0.664	1.42 - 1.86
	ITA RI	**ITA RI**	**ITA RI**	**ITA RI**
Group 1	0.617 ± 0.014	0.60 - 0.64	0.616 ± 0.014	0.60 - 0.65
Group 2	0.621 ± 0.011	0.61 - 0.65	0.621 ± 0.014	0.61 - 0.63
Group 3	0.623 ± 0.018	0.61 - 0.65	0.622 ± 0.017	0.61 - 0.64
Group 4	0.626 ± 0.067	0.60 - 0.64	0.627 ± 0.061	0.61 - 0.65
Group 5	0.627 ± 0.076	0.61 - 0.64	0.627 ± 0.077	0.61 - 0.64

Table 2: Age, BMI and mean T value obtained in the 93 men studied by us

Parameter	Mean ± SD	Range
Age (years)		
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/m²)		
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 *†‡ Ξ	35.91 - 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
group 3	11.962 ± 1.590*	9.72 - 15.09
group 4	10.680 ± 1.089*	9.01 - 13.05
group 5	10.236 ± 1.339*	8.60 - 13.20

* - significant differences between 1 and 2, 3, 4, 5 group
† - significant differences between 2 and 2,3, 4, 5 group
‡ - significant differences between 3 and 4, 5 group
Ξ - significant differences between 4 and 5 group

Data Analysis

The age, BMI, serum T level, TV, PSV, EDV and RI 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, TV, PSV, EDV and RI values. Hypothesis testing methods (parametric) - T-test for two independent samples (Independent Samples T-Test) were derived for the age, BMI, serum T level, TV, PSV, EDV and RI

values. P ≤0.05 was considered statistically significant at 95% confidence interval.

B-Mode Ultrasound Parameters of the Testis

In men from the control group the mean TV of the right testicle was 21.785 ± 2.379 ml and of the left testicle 21.675 ± 2.442 ml. In the studied men the mean TV of the right testicle was 21.709 ± 2.5585 ml and of the left testicle 21.603 ± 2.685 ml. We found no significant differences between right and left testis volumes in all men, significant differences between the testicular volumes of control and study men (p = 0.155) and correlational dependencies between serum T level and TV. During the high-frequency ultrasound examination in all men, we found a normal fine-grained ultrasonic structure of the testicular parenchyma (Table 1).

Doppler Indices of Testicular Arteries

There was no statistically significant difference in PSV, EDV and RI between control and other groups, as well as between the second and fifth groups and correlational dependencies between serum T level and RI. Only the mean values of the RI of the intratesticular arteries in men from second, third, fourth and fifth groups were slightly elevated but without significant differences compared to those of the control group (Table 1).

Discussion

In our cross-sectional pilot clinical study, we describe deviations, although within reference limits in serum T level, B-mode ultrasound parameters of the testis and Doppler indices of testicular arteries in a group of young men, compared to the same parameters in those of the control group. 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. CDU 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. We found significant differences in average T values between the control and other groups (p<0,001). This was not established between the second, third, fourth, and fifth groups, but we observed a clear trend of a gradual decrease in their level with increasing BMI.

Physical examination is one of the most important steps in the evaluation of patients with diseases of the genital system. Determining the volume, tone and consistency of the testes provides indirect information, both on spermatogenesis and hormonal function [1]. Ultrasound diagnostic scanning of the scrotum has already been proven to have greater capabilities compared to a simple clinical and physical examination [2]. Evaluation of the testes with CDU is recommended in male infertility according to the guidelines of the European Association of Urology [9]. No consensus has yet been reached on the reference limits for TV, and currently different values have been proposed depending on ethnic, environmental and geographical factors [6]. In our study, the testicular volume in all men was 21-22 ml. We found no significant differences in the mean testis volume of men from the control and other groups, in the mean testis volume of men within the second and fifth groups, and between the mean left and right testis volume in all men (p = 0.155). The true prognostic significance of TV in patients with a testosterone level below the average values of the standard for a prolonged period in our opinion still remains unclear, due to the lack of validated cut-off values for testis volume/function.

Along with the measurement of TV, high-frequency ultrasound enables precise visualization of the testicular structure. However, the evaluation of the testicular parenchyma by ultrasound is subjective and depends on the experience of the operator [6]. Due to the difficulty to categorize the echostructure of the testes with ultrasound and to objectify an operator-dependent parameter, modern authors propose to evaluate a dichotomous variable (presence/absence of characteristic). This classification, according to them, is easily applicable in clinical practice and can provide useful information about testicular functionality [14]. Most authors describe inhomogeneity of the testicular parenchyma in hypogonadism and infertility, concluding that the change in the testicular parenchyma is an informative marker of testicular function, both for spermatogenesis and T production [11,12]. In our study, we found no inhomogeneity in testicular structure in men with a testosterone level below the average values of the standard for a prolonged period, in contrast to the studies conducted by the above authors in hypogonadism. Our study shows that serum T level below the average values of the standard for a prolonged period is not a congenital condition, but cannot answer the question of whether this will lead to structural changes in the testicles in the future and if so, what.

Middleton W. et al. 1989 first demonstrated the capabilities of CDU to assess extra- and intratesticular blood flow in healthy men [16]. It is a rapid and accurate method for measuring blood flow and vascular impedance. RI is most widely used in clinical practice and Lefort C. et al. 2001 recommend its measurement also during ultrasound of the scrotal contents [17,18,26]. In our study, we did not detect pathological changes in the blood flow parameters (PSV, EDV and RI) of the right and left testicular and capsular arteries. Only the mean values of the RI on the right and the left intratesticular arteries in men from the second, third, fourth and fifth groups were slightly elevated but without significant differences, compared to those of the control group. The largest difference in RI, although insignificant, was found between the control and the fourth group, and between the control and the fifth group, where the men were obese. It is most likely, in our opinion that the increase in RI values is due to the metabolic disorders and not to a serum T level below the average values of the standard for a prolonged period. As a lower serum T level is a prerequisite for obesity and metabolic disorders, and conversely obesity and metabolic disorders are a prerequisite for a lower T level, an increase in the intratesticular artery RI above 0.60 requires further laboratory evaluation of the fat profile and the T level in such men.

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, in the future, we are considering expanding it.

3. It is of interest to include a maximum number of patients with a normal BMI and a serum T level below the average values of the standard for a prolonged period in a future study, which would indicate whether or not there was an increase in RIs in the intrathestial arteries.

Conclusions

CDU of young men with a serum T level below the average values of the standard for a prolonged period found no reduction in testicular volume and no change in the ultrasound characteristic of the parenchyma, which suggests to us that this is not a congenital condition, but cannot answer the question of whether it will lead to structural changes in the testicles in the future and if so what. The non-significant increase in RI in the intratesticular arteries in all examined men is a non-specific indicator that directs the specialist's attention to additional testing of total testosterone in patients with complaints from the male reproductive system.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy regulations.

Conflicts of Interest: Disclosure statement: The authors declare no conflict of interest.

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