ABSTRACT

In our practice, we are increasingly seeing men aged from 37 to 45 years’ old 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 negative change in seminal fluid parameters 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 37 to 45 years with normal or elevated body mass index, permanent low normal testosterone level, and negative change in seminal fluid parameters. 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 negative change in seminal fluid parameters, compared with those in the control group without seminal damages (p<0.001). We found a high correlation relationship between the level of testosterone and the results of the first (r = 0.614, p<0.001) and second spermograms (r = 0.662, p<0.001).

Conclusions:

1. Our study shows that in a number of men at a young age, some decrease in normal testosterone secretion occurs, with a concomitant negative change in seminal fluid parameters, which is remarkably different from the same parameters in their peers with a high normal testosterone level.
2. We identify permanent low normal testosterone, overweight and obesity as predictors, signaling a possible negative change in seminal fluid parameters.
3. We can say that if obesity plays some role in seminal damages, the mechanism in most cases is most likely related to the sustained permanent low normal testosterone level, as a result of increased adipose tissue.

Keywords: low normal testosterone, BMI, seminal damages.

INTRODUCION

In our outpatient practice, we are increasingly seeing men aged 37 to 45 years with permanent low normal total testosterone (T). De Kretser D. 1979 reviews the endocrinological aspects of male infertility, beginning with the physiological interrelationship of the hypothalamus-pituitary-gonad. According to him, the reduced secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland leads to impaired testicular function and infertility. However, in such men, gonadotropin deficiency accounts for less than 5% of the causes. An increase in the values of LH and a decrease in those of T are found in about 30% of men with severe testicular damage and are indicative of interstitial cell failure. [1] Pierrepoint C. et al. 1982 measured plasma concentrations of LH, FSH, prolactin, T, and estradiol in men with normal fertility and in infertile men, finding that plasma LH, FSH, prolactin, and T levels were significantly different in fertile than in infertile men with or no sperm in the ejaculate. [2] Low T values are found in approximately 15% of subfertile men. [3] Although androgens are essential for spermatogenesis, it is unclear whether low T levels may have a negative impact on sperm parameters in men belonging to infertile couples. Furthermore, the question of whether an endocrine evaluation should be included in the initial evaluation of the subfertile man remains controversial. In their study, DiGuardo F. et al. 2020 found that most patients in the low T group also had subnormal seminal fluid parameters. [3] Meeker J. et al. 2007 demonstrated a study in which they investigated the influence and predictive ability of reproductive and thyroid hormones on sperm quality among men who were partners in infertile couples, finding that levels of FSH, LH, inhibin B, T and free testosterone were associated with seminal parameters. [4] Jorgensen N. et al. 2016 presented another large retrospective analysis in men with a mean age of 19 years, finding that serum T levels were not associated with total sperm count and concentration, percentage of motile and morphologically normal sperm. [5] Olesen I. et al. 2018 are holding one study comparing
In a recent study, we examined 73 men aged 37 to 45 years with permanent low normal T level, normal or elevated BMI and negative change in seminal fluid parameters. We selected a control group of 20 clinically healthy men of the same age, who have not used 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 serum T level three times every 45 days for a period of 3 months [17] We performed the blood collection after a mandatory 30-minute rest period between 8.00 and 9.00 hours in the morning after an overnight fast. 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 serum T (10.4-29.0 nmol/L), in men were determined by the manufacturer. The mean values of the three T samples in the male control group were 19.04-24.64 nmol/L. We considered these values to be high degree of normality the serum T level, in accordance with the guidelines set for clinical practice by the Endocrine Society. [14, 15]. Men with a serum 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 two sublevels within the reference range. They were as follows: high degree of normality the serum T level 19.04-24.64 nmol/L and low normal serum T level 8.60-14.28 nmol/L. [14, 15, 16]

According to the World Health Organization criteria for normal and overweight [18] and depending on the T level, all 93 men were divided into 5 groups as follows: 1. Group 1 - 20 men with normal BMI (18,50-24,99) and high normal T level. (reference group) 2. Group 2 - 18 men with normal BMI (18,50-24,99) and permanent low normal T level. 3. Group 3 - 27 overweight men (BMI 25.00-29.99) and permanent low normal T level. 4. Group 4 - 16 men with grade I obesity (BMI 30.00-34,99) and permanent low normal T level. 5. Group 5 - 12 men with grade II obesity (BMI 35.00-39,99) and permanent low normal T level.

In our study, there were men with normal BMI values, but with long term persistence of medium or low normal T levels, and this necessitated their separation into a separate (second) group, different from the control and other groups.

Spermograms were performed on all men twice, during a period of 25-30 days after 4-5 days of sexual abstinence. The men excreted material in a specially adapted room in the hospital, and the examination was carried out up to two hours after masturbation by a reproductive biologist, according to the World Health Organization (WHO) criteria described in the human reproduction program 2021. [19]

Microbiological examination of seminal fluid and sterile urine was performed twice over a period of 5-7 days. A specialist microbiologist performed the tests for Tri-
chomonas vaginalis, Neisseria gonorrhoeae, 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.

We compared the results of all 73 men with seminal damages 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. We used: Independent Samples T-Test, chi-square test, parametric coefficient of linear correlation – Pearson, non-parametric linear correlation coefficient – Spearman.

RESULTS

On table 1 we present general data on the 93 men we examined.

Table 1. General data on the 93 men we examined

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>40.950 ± 2.743</td>
<td>37 - 45</td>
</tr>
<tr>
<td>Group 2</td>
<td>40.611 ± 2.789</td>
<td>37 - 45</td>
</tr>
<tr>
<td>Group 3</td>
<td>40.741 ± 2.640</td>
<td>37 - 45</td>
</tr>
<tr>
<td>Group 4</td>
<td>41.500 ± 2.338</td>
<td>37 - 45</td>
</tr>
<tr>
<td>Group 5</td>
<td>42.750 ± 1.913</td>
<td>39 - 45</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>21.947 ± 1.434</td>
<td>19.71 - 24.68</td>
</tr>
<tr>
<td>Group 2</td>
<td>21.694 ± 1.314</td>
<td>19.44 - 23.80</td>
</tr>
<tr>
<td>Group 3</td>
<td>27.250 ± 1.066</td>
<td>25.34 - 28.84</td>
</tr>
<tr>
<td>Group 4</td>
<td>32.654 ± 1.213</td>
<td>31.26 - 34.81</td>
</tr>
<tr>
<td>Group 5</td>
<td>37.359 ± 1.049</td>
<td>35.91 - 38.94</td>
</tr>
<tr>
<td>T (nmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>21.576 ± 0.993</td>
<td>19.04 - 24.64</td>
</tr>
<tr>
<td>Group 2</td>
<td>12.199 ± 1.436</td>
<td>9.69 - 14.28</td>
</tr>
<tr>
<td>Group 3</td>
<td>11.962 ± 1.590</td>
<td>9.72 – 13.82</td>
</tr>
<tr>
<td>Group 4</td>
<td>10.680 ± 1.089</td>
<td>9.01 - 13.05</td>
</tr>
<tr>
<td>Group 5</td>
<td>10.236 ± 1.339</td>
<td>8.60 - 13.20</td>
</tr>
</tbody>
</table>

BMI – body mass index, T – total testosterone

Normospermia was found in all men of the first group in the first and second seminal examinations. In the patients of the second to fifth groups, from mild oligozoospermia with asthenozoospermia to moderate oligozoospermia with asthenoteratozoospermia with the decrease in serum T level, especially in the fourth and fifth groups. We found a high correlation relationship between the level of T and the results of the first (r = 0.614, p<0.001) and second spermograms (r = 0.662, p<0.001).

DISCUSSION

According to some authors, infertility affects 15-20% of couples, and in 20-50% the cause of infertility is the male factor. [20] De Kretser D. 1979 examines the endocrine aspects of male infertility, establishing increased levels of LH and low T levels in about 30% of men with severe testicular damage and defined them as indicators of interstitial cell failure. Routine semen analysis remains the main standard for the evaluation of infertility. [1] In our study, we performed two seminal examinations on each patient 25-30 days apart, all of which were evaluated by a reproductive biologist according to the laboratory manual for the examination and processing of the WHO human sperm 2021. [19] Jorgensen N. et al. 2016 presented a large retrospective analysis finding that serum levels of T were not associated with concentration, total number, percentage of motility and normal sperm.

Fig. 1. The number of men in the individual groups expressed in percentages with different degrees of the spermograms damages

In men of the control group, microbiological examinations of urine and ejaculate showed no growth. Mycoplasma genitalium, Ureaplasma urealyticum and Chlamydia trachomatis was iso-listed in the ejaculate of 9 (12.3%) 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 seminal damages remained persistent after therapy.
morphology. Other authors demonstrated a varying degree of decrease in the number of sperm, along with a decrease in serum levels of T. [2, 3, 4, 6, 7] According to DiGuardo F., et al. 2020 low T levels are found in approximately 15% of subfertile men. In their study, they found that most patients in the low T group also had subnormal seminal fluid parameters. [3] In our study in the control group men who had a high normal T level, normozoospermia was established. In all the others, we found negative change in seminal fluid parameters of varying severity from a mild degree oligozoospermia with asthenozoospermia to moderate degree oligozoospermia with asthenozoospermia or asthenoteratozoospermia. The analysis of the results showed that the largest number of men (31 men or 42.5%) were with mild degree oligozoospermia with asthenozoospermia and the least number (15 men or 20.6%) with moderate degree oligozoospermia with asthenoteratozoospermia. Using the chi-square test, we found significant differences between the results of seminal examinations of men from the first and the other groups p<0.001. Our results demonstrate that in parallel with the decrease in the average of T level from the second to the fifth group, the percentage of men with mild degree oligozoospermia with asthenozoospermia decreases and that of men with moderate degree oligozoospermia with asthenoteratozoospermia increases. We found a high correlation relationship between the level of T and the results of the first (r = 0.614, p<0.001) and second spermograms (r = 0.662, p<0.001). DiGuardo F., et al. 2020 recently presented a study in men with low T and severe or very severe oligoasthenozoospermia. [3] Our results show that permanent low normal T level is also a prerequisite for seminal disorders, but they are milder than those presented in men with low T. McDonald A. et al. 2010 and McDonald A. et al. 2013 found no evidence of a relationship between increased BMI and sperm parameters. [8, 9] Other authors believe that overweight and obesity are associated with an increased prevalence of oligozoospermia or azoospermia. [10, 11, 13] In our study we confirm the opinions of recent authors, as in the groups with increased BMI, we observed from mild degree oligozoospermia with asthenozoospermia to moderate degree oligozoospermia with asthenoteratozoospermia. Furthermore, with increasing BMI, the number of men with mild oligozoospermia and asthenospermia decreased, and that of men with moderate oligozoospermia and asthenoteratozoospermia increased.

It is more difficult to explain the permanent low normal T level in men from the second group with normal BMI and negative change in seminal fluid parameters. 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 are also a prerequisite for permanent low normal T level and negative change in seminal fluid parameters. Another possibility is that these men had permanent low normal T and negative change in seminal fluid parameters at the time of the study but prior to the weight gain. Our results unequivocally show that overweight or obesity is an important, but not mandatory prerequisite for the negative change in seminal fluid parameters.

We performed the double microbiological examination of urine and ejaculate in order to exclude an inflammatory process as the cause of the negative change in seminal fluid parameters. Our results show that even after antibiotic treatment, where necessary and negative repeat results, seminalological disorders of the same degree of severity continued to persist.

CONCLUSIONS

1. Our study shows that in a number of men at a young age, some decrease in normal testosterone secretion occurs, with a concomitant negative change in seminal fluid parameters, which is remarkably different from the same parameters in their peers with a high normal testosterone level.

2. We identify permanent low normal testosterone, overweight and obesity as predictors, signaling a possible negative change in seminal fluid parameters.

3. We can say that obesity plays some role in negative change in seminal fluid parameters, the mechanism in most cases is most likely related to the sustained low normal T level, as a result of increased adipose tissue.

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