Case Reports and Reviews: Open Access

Original Article| Vol 4 Iss 2

Changes in the Hypothalamic-Pituitary-Gonadal Axis in Men Aged 37 to 45 Years With a Testosterone Level Below the Average Values of the Standard for a Prolonged Period

Georgi Lazarov[1*] and Vladislav Mladenov[2]

[1]Department of Molecular Immunology, Institute of Biology and Immunology of Reproduction, Bulgarian Academy of Sciences and Hospital in Obstetrics and Gynecology "St. Sofia", Andrological Office, Sofia, Bulgaria

[2]Clinic of Urology, Medical University, UMBAL Alexandrovska, Sv G. Sofijski" Str., Sofia, Bulgaria

[*]Corresponding author: Lazarov G, Department Molecular Immunology, Institute of Biology and Immunology of Reproduction, Bulgarian Academy of Sciences, Sofia, Bulgaria, Tel: +3598873191; E-mail: doctorlazarov30@gmail.com

Received: September 15, 2023; **Accepted:** October 22, 2023; **Published:** October 31, 2023

Abstract

Background: ***In our study, we focused on a group of young patients with a testosterone level below the average values of the standard for a prolonged period and the changes in the hypothalamic-pituitary-gonadal axis.*** ***Methods:*** ***From January 2013 to December 2019 at the Andrological office we examined 73 men aged 37 to 45 years with normal or elevated body mass index and a testosterone level below the average values of the standard for a prolonged period. We selected a control group of 20 age-matched men.*** ***Results:*** ***In the patients, we obtained, although within reference limits, reliably lower values for total serum testosterone compared to those of the control group (p<0.001). We found significant differences in mean levels of sex hormone binding globulin, estradiol, luteinizing and follicle stimulating hormones, estradiol/testosterone ratio, and the free androgen index values between the study men and those of the control group (p<0.001).*** ***Conclusions:*** ***Our studies unequivocally show that even at a young age, some men, regardless of their BMI, have certain deviations in the normal secretion of testosterone and its carrier in the blood. Along with that, changes in the hypothalamic-pituitary-gonadal axis were observed, which, although not yet out of the reference values, differed significantly from the same parameters in their peers with a high degree of normality the serum testosterone level. The changes we have found are mostly discrete, probably reversible with lifestyle changes, but if ignored can lead in older age to a prominent climacteric-like state and hypogonadism.***

Keywords: ***Testosterone, Estradiol, FAI, E2/T ratio, LH, FSH, Joung mem.***

Citation: Lazarov G and Mladenov V. Changes in the hypothalamic-pituitary-gonadal axis in men aged 37 to 45 years with a testosterone level below the average values of the standard for a prolonged period. Case Rep Rev Open Access. 2023;4(2):135.

1. Introduction

Clinical definition of hypogonadism refers to decreased testicular function, as compared to what is expected for age, involving an impaired hormone secretion by Leydig cells (androgens, insulin-like factor 3) and/or Sertoli cells (anti-Müllerian hormone, inhibin B) and/or a disorder of spermatogenesis [1]. In our study, we focused on a group of young mens with a testosterone level below the average values of the standard for a prolonged period and the changes in the hypothalamic-pituitary-gonadal axis. In fact, minimal androgen requirements for elderly men remain poorly defined and are likely to vary between individuals [2]. In young men, decreased in the serum T levels are associated with genetic or congenital abnormalities, environmental factors, past infections or testicular injuries, acquired conditions such as obesity, diabetes, anabolic steroid use, and medications [3]. A European study on ageing in men found that 73% of those with reduced androgen levels were overweight or obese [4]. The decrease in the serum T level is multifactorial and may be the result of its increased conversion to estradiol (E2) by peripheral adipose tissue and/or a decrease in the level of sex hormone binding globulin (SHBG) [3]. Kumanov P et al support the proposition that male obesity is accompanied by a reduction in T levels, by highlighting that the negative correlation found between T and body mass index (BMI) as well as between T and body weight is consistent with the assumption that these factors themselves are more important for lower T levels than ageing [5]. Svartberg J et al identified waist circumference, not BMI, as an important predictor of low T levels [6]. According to Rosario Pivonello et al T deficiency is associated with, and predicts, an increased risk of developing metabolic disorders. On the other hand, is highly prevalent in obesity, metabolic syndrome and type-2 diabetes mellitus. In functional hypogonadism, as well as in late-onset hypogonadism, the relationship between hypogonadotropic hypogonadism and metabolic disorders is bidirectional, and a vicious circle between the two components has been documented [7]. In elderly men, as a result of increased activity of the enzyme aromatase and the increase in fat mass, serum levels of androgens decrease and those of E2 remain constant, increasing the E2/T ratio [3], [8]. However, E2 levels are strongly positively associated with waist-to-hip ratio [9] and visceral adipose tissue [8]. Relationships between androgen-estrogen activity and anthropometric parameters of obesity vary in younger versus older healthy men [10].

According to the guidelines defined for clinical practice by the Endocrine Society, the sub-normal T level for men should be between 10.4 - 34.7 nmol/L [11], [12]. The recommendations of the International Society of Andrology (ISA), the International Society for the Study of Aging Men (ISSAM), 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 [13]. Scovell JM et al. demonstrated in their study that the hypogonadal symptoms in men aged <40 years can be associated with a serum T level of <400 ng/dL (13.87 nmol/L) [3]. Salonia A et al. define a minimum lower limit in adult men below which hormone replacement therapy is indicated 12.00 nmol/L [14].

2. Aim

A clinically oriented study to investigate changes in the hypothalamic-pituitary-gonadal axis in young men with a testosterone level below the average values of the standard for a prolonged period.

3. Materials and Methods

3.1 Study Site, Design, and Population

From January 2013 to December 2019, we examined 73 men aged 37 to 45 with a serum T level below the average values of the standard for a prolonged period with normal and elevated body BMI. We also selected a control group of 20 clinically healthy men of the same age who have not used drugs or testosterone preparations.

3.2 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.

3.3 Clinical and Laboratory Evaluation

We tested each man's T lewel three times every 45 days for a period of 3 months. We also tested that of the SHBG, the E2, the luteinizing hormone (LH), the follicle stimulating hormone (FSH) once after the third blood collection for serum T. Furthermore, we performed the blood collection after a mandatory 30-minute rest period between 8.00 a.m. and 9.00 a.m. after an overnight fast. Hormonal analysis was performed with a mini Vidas apparatus from Bio-Mérieux company and standard reagents were added to it according to the radio-immunological analysis method. Normal values for T (10.4–29.0 nmol/L), E2 (41.4–159 pmol/L), and SHBG men (20–49 years) 3-54.1 nmol/L, LH 0.6-12.1 U / L, FSH up to 12.1 U/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. To calculate the value of free testosterone, we used the free androgen index (FAI) formula, which is sufficiently informative and easily applicable in clinical practice:

FAI = (100xT)/SHBG

4. Results

4.1 Demographic, Clinical, and Laboratory

There were 73 participants with a serum T level is below the average values of the standard for an prolonged period of time 8,60-14,28 nmol/L, and 20 clinically healthy men of the same age, 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 World Health Organization criteria for normal and overweight, and depending on the T level [15], all 93 men were divided into 5 groups as follows:

- First (control) group – 20 men with BMI 18.50-24.99 and serum T: 21.576 ± 0.993 nmol/L
- Second group – 18 men with BMI 18.50-24.99 and serum T: 12.199 ± 1.436 nmol/L
- Third group – 27 men with BMI 25.00-29.99 and serum T: 11.962 ± 1.590 nmol/L
- Fourth group – 16 men with BMI 30.00-34.99 and serum T: 10.680 ± 1.089 nmol/L
- 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 serum T 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 Table 1. The Mean values of serum T compared with those of SHBG, FAI, E2, FSH, and LH are presented to Fig.1, Fig. 2, Fig. 3, and Fig. 4.

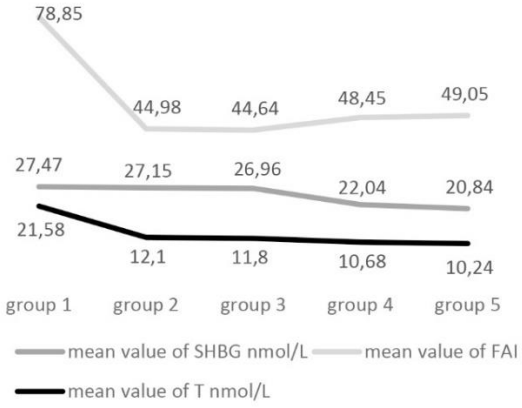
Table 1: The General Data Obtained From the 93 Men Studied by us.

Parameters	**Average ± SD**	**Range**	**Established difference between**
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/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	12.199 ± 1.436	9.69 – 14.28	1-2‡ group
Group 3	11.962 ± 1.590	9.72 – 13.82	1-3‡ group
Group 4	10.680 ± 1.089	9.01 - 13.05	1-4‡ group
Group 5	10.236 ± 1.339	8.60 - 13.20	1-5‡ group
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

Group 3	0.074 ± 0.009	0.056 - 0.092	1-3 ‡ group
Group 4	0.074 ± 0.010	0.057 - 0.094	1-4 ‡ group
Group 5	0.085 ± 0.006	0.076 - 0.094	1-5 ‡ group
SHBG (nmol/l)			
Group 1	27.473 ± 1.854	24.35 - 30.52	
Group 2	27.149 ± 3.146	21.44 - 33.57	
Group 3	26.956 ± 4.390	22.43 - 35.71	1-3* group
Group 4	22.036 ± 1.690	19.33 - 24.57	1-4‡; 2-4‡; 3-4‡ group
Group 5	20.840 ± 1.661	18.63 - 23.31	1-5‡; 2-5‡; 3-5‡ group
FAI			
Group 1	78.854 ± 6.113	70.53 - 88.41	
Group 2	44.983 ± 2.199	41.48 - 48.40	1-2‡ group
Group 3	44.640 ± 3.368	40.75 - 52.30	1-3‡ group
Group 4	48.454 ± 2.420	44.94 - 53.77	1-4‡ group
Group 5	49.053 ± 4.160	43.40 - 56.63	1-5‡ group
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
Group 3	0.006 ± 0.001	0.0042 - 0.0081	1–3‡ group
Group 4	0.007 ± 0.001	0.0055 - 0.0090	1–4‡ group
Group 5	0.008 ± 0.001	0.0061 - 0.0110	1–5‡ group
FSH (U/L)			
Group 1	8.200 ± 0.671	7.0 - 9.4	
Group 2	6.276 ± 1.264	3.6 - 8.4	1–2‡ group
Group 3	6.342 ± 1.404	4.5 - 8.9	1–3‡ group
Group 4	4.642 ± 1.434	2.7 - 6.7	1-4‡; 2-4‡; 3-4‡ group
Group 5	3.884 ± 0.841	2.7 - 5.5	1-5‡; 2-5‡; 3-5‡ group

LH (U/L)			
Group 1	7.875 ± 1.635	5.2 -10.7	
Group 2	6.729 ± 1.607	4.6 - 8.9	1–2* group
Group 3	6.744 ± 1.633	2.9 - 9.3	1–3* group
Group 4	4.029 ± 1.162	2.5 - 6.6	1-4‡; 2-4‡; 3-4‡ group
Group 5	3.813 ± 0.959	2.4 - 5.4	1-5‡; 2-5‡; 3-5‡ group

*- p<0.05; † - p<0.01; ‡ - p<0.001; BMI - body mass index, T – testosterone, E2 – estradiol, SHBG – sex hormone globulin, FAI – free androgen index, E2/T - estradiol/testosterone ratio, FSH - follicle stimulating hormone, LH - luteinizing hormone.



. **Fig.1.** Mean values of serum T compared with those of SHBG and FAI.

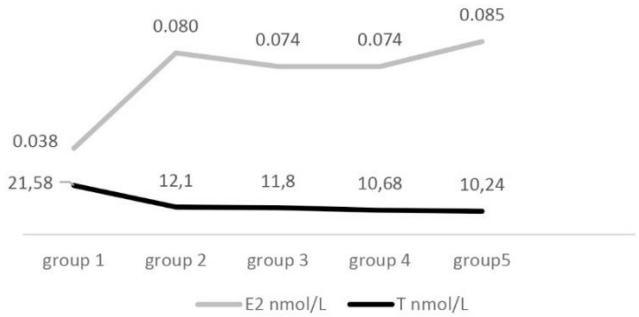


Fig. 2. Mean E2 values compared with those of serum T.

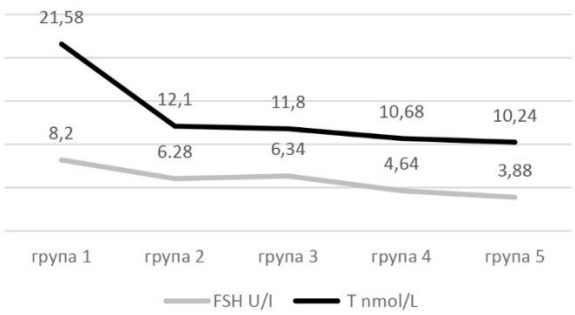


Fig. 3. Mean FSH values, compared with those of serum T.

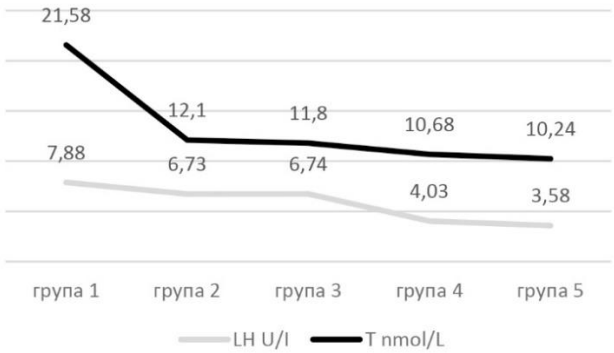


Fig. 4. Mean LH values, compared with those of serum T.

4.2 Data Analysis

The age, BMI, serum T level, SHBG, FAI, E2, E2/T ratio, LH and FSH values of 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, SHBG, FAI, E2, E2/T ratio, LH and FSH values. Hypothesis testing methods (parametric) - T-test for two independent samples (Independent Samples T-Test) were derived for the age, BMI, serum T level, SHBG, FAI, E2, E2/T ratio, LH and FSH values. The data were analyzed by Georgi Lazarov and Vladislav Mladenov.

5. Discussion

In our study, we focused on a group of young mens with a serum T level below the average values of the standard for a prolonged period and with changes in the hypothalamic-pituitary-gonadal axis, compared to the same parameters in those of the control group. We found a single similar study in our available literature and compared our results, where possible, with similar ones conducted in young and elderly men. The mean level of the three samples of serum T in the men we studied was below 13.85 nmol/L except for one in the second group which was 14.28 nmol/L. Our results match the values reported by Scovell JM et al. which associated some hypogonadal symptoms in men aged <40 years with a serum T level <400 ng/dL (13.87 nmol/L) [3]. In addition, a large percentage of men (68.49%) in our study had a mean T value of the three samples below that determined by Salonia A, et al. minimum threshold for adult men (12.00 nmol/L) when hormone replacement therapy is indicated [14]. With the triplicate examination of serum T within three months

in the men we studied, we were certain that throughout the period the men had a serum T level below the average values of the standard for a prolonged period. Our study clearly shows that in parallel with the increase in BMI there is a decrease in the mean level of serum T in the groups to low normal values. This relationship has been demonstrated by a number of authors in late onset-hypogonadism as well [5]-[7]. Of interest however, are the men of the second group with a normal BMI, in whom we observe the same deviations in the values of serum T level, as in those with overweight and obesity, which is more difficult to explain. One possibility is that weight gain is not the only cause, but that there is another one related to lifestyle or unhealthy habits, which is also a prerequisite for a reduced androgen levels, without an increase in BMI. The other possible thesis is that these men were studied at a time when a reduced androgen levels was found, but an increase in body weight had not yet occurred, and in this sense, we can suspect the leading role of the decrease in T in future health trouble, most of which is already obesity. In our study nearly 75% of the examined patients were overweight or obese, and about 25% were of normal body weight. Our results confirm the conclusion of other authors in late-onset hypogonadism, according to which 73% of men with reduced T levels are overweight or obese [4].

An increase in the level of SBHG is observed in elderly men [5], [11]. In our study, we observed a decrease in SHBG values, being lowest in men from the fourth and fifth groups, and a trend towards a slight increase in FAI between the third and fourth (8.53%) and third and fifth groups (9.88 %). It is possible in the young men with obesitas that as a biological mechanism, the decrease in total T levels is compensated by a slight increase in FT levels.

In late-onset hypogonadism, all authors report a relatively constant level of E2, with a low level of T [3], [8]. Our results show a significant difference in the E2 level between the men of the control and other groups ($p<0.001$). A relatively higher values, although within reference limits, in the E2 level are observed even in the patients of the second group, and after a minimal decrease in the third and fourth groups, they increased again in the fifth group. Our results demonstrate variability in androgen-estrogen activity compared to that at late-onset hypogonadism. Since our study is cross-sectional, it is difficult to determine the sequence over time: does the appearance of low normal T levels and relatively higher, although within reference limits E2 level lead to an increase in BMI or vice versa, we accept the opinion of other authors as well , that the process is most likely bidirectional [7].

In our study, we logically found a significant difference in the values of E2/T ratio between the control and the other groups. The increase in E2/T ratio values starts from the second and remains almost unchanged until the fifth group. A recent study in late-onset hypogonadism reported increased E2/T ratio values at the expense of decreased T and constant or slightly elevated E2 levels [3], [8]. In our study, along with the decrease in the mean T value to a low and low normal level, we reported an increase in the mean E2 value within reference limits and obtained higher values of the E2/T ratio. The dependence we found shows that the E2/T ratio also varies compared to that at late-onset hypogonadism.

We found significant differences in LH and FSH levels between men from the control and other groups ($p<0.001$), as well as between the second and fourth, third and fourth, second and fifth, and third and fifth groups ($p<0.001$). An

exception was the significant difference obtained for LH between the first and second groups ($p<0.036$), most likely due to the lack of difference in the body weight of the men. In parallel with the decrease in the mean T level from the second to the fifth group and the increase in the mean value of BMI from the third to the fifth group, we observed a gradual decrease in that of FSH and LH. These results show us that we do not have solid grounds to claim that the leading endocrinological change in the hypothalamic-pituitary-gonadal axis is only the T reduction. The relatively low levels of FSH and LH in the men of the fourth and fifth groups, who have the highest BMI, suggest the possibility that the changes are central, i.e., at the level of the hypothalamus-pituitary, as admitted by some authors [7]. Most likely, the lower T concentration in our patients with obesity may reflect impaired Leydig cell function combined with an inadequate response of gonadotropins. The very fact that FSH and especially LH do not respond adequately to the lowering of T and instead of showing a tendency towards a compensatory increase in their secretion, these gonadotropins decrease permanently shows that the central units contribute significantly to changes in the hypothalamic-pituitary-gonadal axis in overweight or obese young men. It is also possible that the increase in E2, although within reference limits, considering the conversion of T to E2, participates in lowering the level of gonadotropins, especially LH, according to the principle of negative feedback. Therefore, the early-onset hypogonadism in the studied young men most likely has a mixed (primary and secondary) genesis.

6. Limitations

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 same patients' lifestyles. The number of examined patients included in the study is relatively small, and in the future, we are considering expanding it. It is of interest to additionally include a maximum number of patients with a normal BMI in a future study, which would indicate certain factors on the lifestyle and their harmful habits, which are a prerequisite for the changes in the hypothalamic-pituitary-gonadal axis.

7. Conclusion

Our study unequivocally shows that even at a young age, some men, regardless of their BMI, have certain deviations in the normal secretion of T and its carrier in the blood. Along with that, changes in the hypothalamic-pituitary-gonadal axis were observed, which, although not yet out of the reference values, differed significantly from the same parameters in their peers with a high degree of normality the serum T level. The changes we have found are mostly discrete, probably reversible with lifestyle changes, but if ignored can lead in older age to a prominent climacteric-like state and hypogonadism.

8. Author Contributions

All authors reviewed and approved the final manuscript and have contributed equally to this work.

9. Funding

This research received no external funding.

10. Data Availability Statement

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

11. Acknowledgments

The authors would like to thank Assoc. Prof. Mircho Vukov (a mathematician and epidemiologist) who helped with the statistics.

12. Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

1. Rey RA, Grinspon RP, Gottlieb S, et al. Male hypogonadism: An extended classification based on a developmental, endocrine physiology-based approach. Andrology. 2012;1(1):3-16.
2. Kaufman JM and Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev. 2005;26(6):833-76.
3. Scovell JM, Ramasamy R, Wilken N, et al. Hypogonadal symptoms in young men are associated with a serum total testosterone threshold of 400 ng / dl. BJU Int. 2015;116(2):142-146.
4. Poobalan A and Aucott L. Obesity among young adults in developing countries: a systemic overview. Curr Obes Rep. 2016;5(1):2-12.
5. Kumanov P, Tomova A, Robeva R, et al. Influence of aging and some lifestyle factors on male gonadal function: A study in Bulgaria. Andrologia. 2007;39(4):136-140.
6. Svartberg J, von Mühlen D, Sundsfjord J, et al. Waist circumference and testosterone levels in community dwelling men. The Tromsø study. Eur J Epidemiol. 2004;19(7):657-663.
7. Pivonello R, Menafra D, Riccio E, et al. Metabolic disorders and male hypogonadotropic hypogonadism. Front Endocrinol. 2019;10:article 345.
8. Vermeulen A, Kaufman JM, Goemaere S, et al I. Estradiol in elderly men. Aging Male. 2002;5(2):98-102.
9. Jankowska EW, Rogucka EA, Medraś M, et al. Relationships between age-related changes of sex steroids, obesity, and body fat distribution among healthy Polish males. Med Sci Monit. 2000;6(6):1159-1164.
10. Jankowska EW, Medras M, Rogucka EA. Body mass index, waist/hip ratio and androgen- estrogenic activity in younger versus older Polish men. Aging Male. 2000;3(4):177-184.
11. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore longitudinal study of aging. J Clin Endocrinol Metab. 2001;86(2):724-731.
12. Bhasin S, Buckwalter G. Testosterone supplementation in older men: a rational idea whose time has not yet come. J Androl. 2001;22(5):718-731.
13. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur Urol. 2009;55(1):121-130.

14. Salonia A, Bettocchi C, Capogrosso P, et al. EAU guidelines on sexual and reproductive healt. Diagnostic Evaluation of Late-Onset Hypogonadism. 2023: 248-312p.
15. Weir CB and Jan A. BMI classification percentile and cut off points. StatPearls. 2022.

Citation: Lazarov G and Mladenov V. Changes in the hypothalamic-pituitary-gonadal axis in men aged 37 to 45 years with a testosterone level below the average values of the standard for a prolonged period. Case Rep Rev Open Access. 2023;4(2):135.