MEDICAL SCIENCES

CHANGES IN THE BLOOD GLUCOSE AND SERUM LIPIDS IN MEN AGED 37 TO 45 YEARS WITH A TESTOSTERONE LEVEL BELOW THE AVERAGE VALUES OF THE STANDARD FOR A PROLONGED PERIOD

Lazarov G.,
MD, PhD(corresponding author): Department of Molecular Immunology, Institute of Biology and Immunology of Reproduction, Bulgarian Academy of Sciences, 73 Tzarigradsko shose Blvd., 1113 Sofia; Hospital in Obstetrics and Gynecology "St. Sofia", Andrological Office, 2 Mihalaki Tashev Str., 1330 Sofia, Bulgaria
ORCID ID: https://orcid.org/0000-0001-7373-4302
Mladenov V.
MD, PhD Clinic of Urology, Medical University, UMBAL Alexandrovska, "Sv. G. Sofijski" Str. №1, 1431 Sofia, Bulgaria
ORCID iD: https://orcid.org/0000-0002-7409-8085
https://doi.org/10.5281/zenodo.10008818

Abstract

Introduction

In our study, we focused on a group of young men's with a testosterone level below the average values of the standard for a prolonged period and the changes in the *blood* glucose and serum lipids values.

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 *blood* glucose and serum lipids 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. Along with that, changes in the blood glucose and serum lipids were observed, which, differed significantly from the same parameters in their peers with a high degree of normality the serum testosterone level. The changes we have found, probably (?) reversible with lifestyle changes, but if ignored can lead to metabolic syndrome at a later age.

Keywords: testosterone, glucose, serum lipids, young mem

INTRODUCTION

In our study, we focused on a group of young men's with a testosterone level below the average values of the standard for a prolonged period and the changes in the *blood* glucose and serum lipids values.

In younger men the decrease in the level of total testosterone (T) is due to congenital or acquired conditions that negatively affect its production in the testicles **[1, 2]** , as well as environmental factors preceding testicular infection or injury, acquired conditions such as obesity, diabetes, anabolic steroids and drugs. **[2]**

The prevalence of obesity among young men is increasing at a rapid rate and is expected to triple over the next decade. **[3]** An analysis looking at adolescents and young adults using the National Health and Nutrition Examination Survey (NHANES) demonstrated statistically significant increase in their body mass index (BMI) from 1999 to 2016. A European study on aging in men found that 73% of those with reduced androgen levels were overweight or obese. The measured serum T of those with BMI>30 kg/sq.m. was on average 5 nmol/l lower compared to normal weight subjects. **[4**] The obesity related decrease in T level is a multifactorial process and may be due to a decrease in SBHG and /or increased conversion of T to estradiol (E2) by peripheral adipose tissue. **[2]**

Many studies also support the claim that obesity in men is accompaniedby a decrease in T levels [**5, 6, 7, 8**], which in very obese individuals may reach very low values. **[9]** Serum T level is lower in middle aged men with visceral obesity and correlates directly with cholesterol and high density lipoprotein (HDL). These data highlight the major role of obesity in the decline of testicular function. However, a systematic review of placebo-controlled trials involving older men with low or low-normal T levels reported minor changes in major lipid fractions: total cholesterol, low-density lipoprotein (LDL), HDL and triglycerides. **[10, 11, 12, 13]** Study by Chosich J. et al. 2017 found that increased levels of serum lipids suppress the release of gonadotropins from the pituitary gland, which may explain the decreased androgen levels in this group of patients**. [14]**

Type 2 diabetes mellitus, which is increasing at an annual rate of 4.8%, compared to 1.8% for type 1, further contributes to the reduced T levels in obese young men**. [15]** The studies by Kumanov Ph. et al 2007 men with diabetes mellitus and hypertension had lower levels of the hormone compared to their peers who did not

have these diseases. **[15]** A similar observation was reported by Mulligan T. et al. 2006 and Zhong O. et al. 2021. **[16, 17]** Based on a large-scale study of middle-aged men who were not diabetic, Tsai E. et al. 2004 argued that the negative association between T and insulin resistance is mediated by body adipose tissue. Its relevance to lower T levels in general, as well as to androgen deficiency in the elderly population, is beyond doubt! **[18]** Type 2 diabetes mellitus further contributes to reduced serum T levels in young obese men. **[19]** It is important to note, however, that low T levels can also lead to obesity. **[2]**

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. [**20, 21]** 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.**[22]** Scovell JM et al. 2015 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). **[2]** Salonia A et al. 2023 define a minimum lower limit in adult men below which hormone replacement therapy is indicated 12.00 nmol/L. **[23]**

AIM: A clinically oriented study to investigate changes in the *blood* glucose and serum lipids in young men with a testosterone level below the average values of the standard for a prolonged period.

MATERIALS AND METHODS

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.

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.

Clinical and laboratory evaluation

We tested each man's T level three times every 45 days for a period of 3 months. We also tested that of the total cholesterol, the LDL, the HDL, the triglycerides and the *blood* glucose 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. Biochemical studies were performed with an A15 apparatus from the company Biosystems. Hormonal analysis was performed with a mini Vida's 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), *blood* glucose (2,8-5,6 mmol/L), total cholesterol (to 5.0 mmol/L), LDL (to 3,0 mmol/L), HDL (above 1.0 mmol/L) and triglycerides (to 2,0 mmol/L) were determined by the manufacturer.

RESULTS

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:

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 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 and the correlation dependences in table 2.

Table 1.

The general data obtained from the 93 men studied by us

Parameter	Average ± 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/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
Total cholesterol (mmol/L)		
group 1	4.705 ± 0.214	4.3 - 5.0
group 2	5.117 ± 0.543	4.5 - 6.2
group 3	5.063 ± 0.515	4.5 - 6.3
group 4	6.500 ± 0.859	5.1 - 7.4
group 5	6.342 ± 0.966	5.0 - 7.6
LDL (mmol/L)		
group 1	2.325 ± 0.241	1.95 - 2.81
group 2	2.659 ± 0.337	2.32 - 3.41
group 3	2.724 ± 0.507	2.43 - 4.82
group 4	3.801 ± 0.849	2.47 - 4.87
group 5	3.654 ± 0.821	2.48 - 4.54
HDL (mmol/L)		
group 1	1.686 ± 0.187	1.46 - 1.98
group 2	1.506 ± 0.150	1.23 - 1.74
group 3	1.490 ± 0.128	1.24 - 1.94
group 4	1.370 ± 0.088	1.24 - 1.52
group 5	1.323 ± 0.118	1.15 - 1.53
Triglycerides(mmol/L)		
group 1	1.486 ± 0.172	1.19 - 1.69
group 2	1.643 ± 0.092	1.47 - 1.84
group 3	1.794 ± 0.525	1.54 - 3.78
group 4	3.155 ± 0.849	1.54 - 4.27
group 5	3.196 ± 1.131	1.68 - 5.23
Blood glucose (mmol/L)		
group 1	4.865 ± 0.160	4.6 – 5.1
group 2	5.017 ± 0.667	4.6 – 7.6
group 3	5.193 ± 0.646	4.5 – 6.8
group 4	6.619 ± 1.026	4.9 – 8.2
group 5	6.367 ± 1.045	5.0 – 8.1
Testosterone (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

Table 2

Correlation dependences of glucose, total cholesterol, HDL, LDL, triglycerides and T

	T	total cholesterol	HDL	LDL	triglycerides	glucose
T	1,000					
total cholesterol	-,600**	1,000				
HDL	,526**	-,717**	1,000			
LDL	-,615**	,804**	-,760**	1,000		
triglycerides	-,657**	,770**	-,749**	,820**	1,000	
glucose	-,479**	,665**	-,638**	,659**	,679**	1,000

The Mean values of serum T compared with those of *blood* glucose, total cholesterol, HDL, LDL and triglycerides are presented to Fig.1, Fig.2 and Fig.3

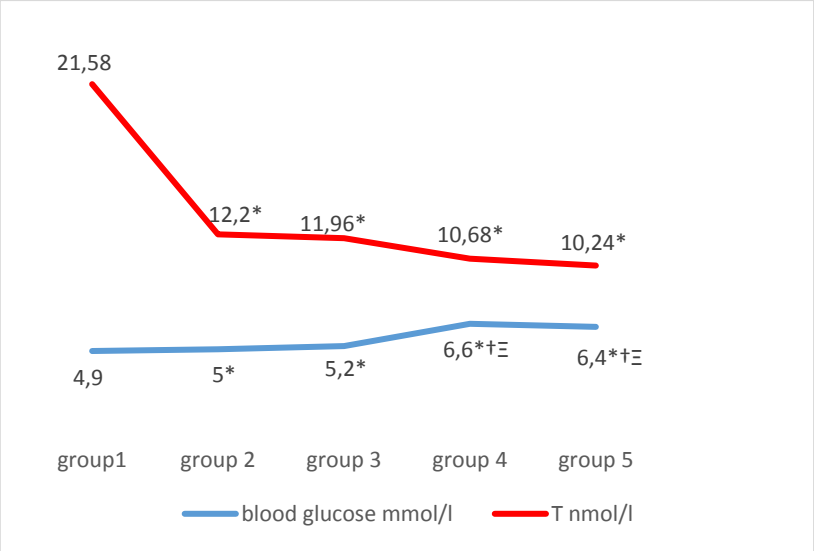

Fig.1 Comparison of the curves obtained from the average values of blood *glucose in the different groups with those of T*

* - significant difference group 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

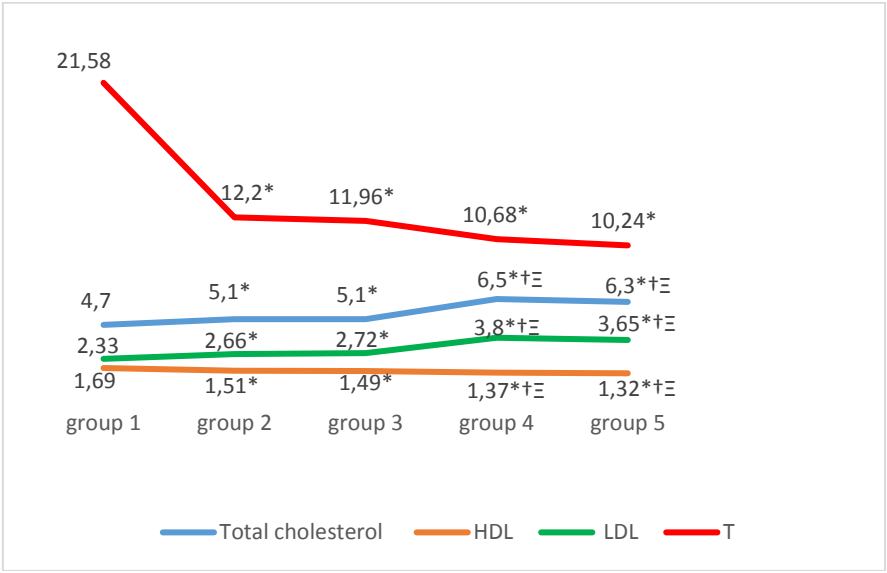

Fig.2 The average values of total cholesterol, HDL, LDL compared with those of T.

* - significant difference group 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

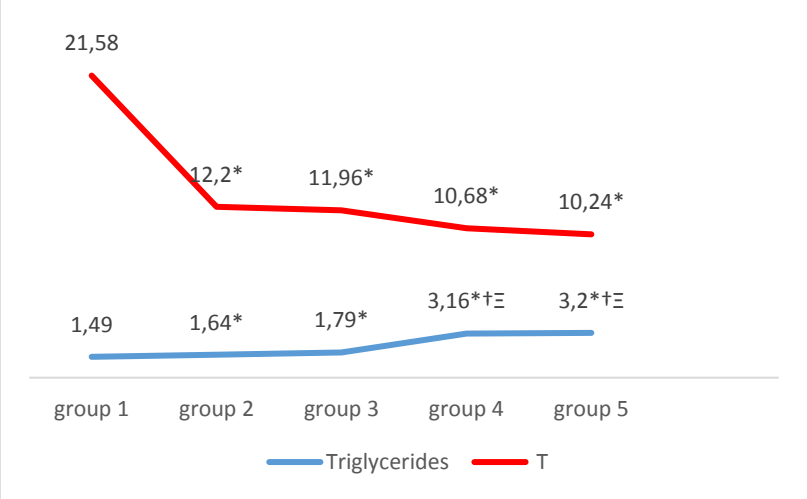

Fig.3 The average values of triglycerides, compared with those of T.

* - significant difference group 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, *blood* glucose, total cholesterol, HDL, LDL, and triglycerides 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, *blood* glucose, total cholesterol, HDL, LDL, and triglycerides values. Hypothesis testing methods (parametric) - T-test for two independent samples (Independent Samples T-Test) were derived for the age, BMI, serum T level, *blood* glucose, total cholesterol, HDL, LDL, and triglycerides values.

The data were analyzed by Georgi Lazarov and Vladislav Mladenov.

DISCUSSION

In our study, we focused on a group of young men's 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. 2015, which associated some hypogonadal symptoms in men aged <40 years with a serum T level <400 ng/dL (13.87 nmol/L). **[2]** 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. 2023 minimum threshold for adult men (12.00 nmol/L) when hormone replacement therapy is indicated. **[23]** 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, 8]** 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]**

Serum T level is lower in middle-aged men with visceral obesity and correlates directly with cholesterol and high-density lipoprotein. **[15]** However, a systematic review of placebo-controlled trials involving elderly men with low or low-normal T levels reported minor changes in major lipid fractions. [**10, 11, 12, 13]** In our study, nearly 30% of men had elevated total cholesterol values, nearly 42% had elevated LDL values, about 50% had elevated triglycerides values, and 38% had decreased HDL values. In contrast to the above-mentioned studies, we reported slightly larger differences between the mean values in men from the control group and the highest mean value in the other groups of the main lipid fractions, respectively total cholesterol (1.8 mmol/L), LDL (1.5 mmol/L), HDL (0.4 mmol/L) and triglycerides (1.7 mmol/L). For the mean values of total cholesterol, LDL, HDL and triglycerides, we found significant differences between the control and other groups ($p<0.001$), as well as between the second and fourth, third and fourth, second and fifth, third and fifth groups ($p<0.001$). A significant difference was absent only between the second and third groups. Along with the decrease in the mean T level in the groups, we

observed an increase in the values of total cholesterol, LDL, triglycerides and a decrease in those of HDL, as well as an increase in the number of men with these indicators outside the norm. We found the most patients, even among those from the second group, with elevated triglycerides values. We found a high negative correlation between T and total cholesterol (r = -.600**, p<0.001), between T and LDL (r = -.615**, p<0.001) and between T and triglycerides (r = -, 657**, p<0.001) and a significant positive correlation between T and HDL (r = .526**, p<0.001). Our results show that with a decrease in the level of serum T below the average values of the norm for a prolonged period, there is a negative change in the serum lipids, without being able to determine with certainty which occurs first: the decrease of the serum T or the change in values in the serum lipids, assuming that the process is two-way. Of interest is the higher percentage of men from the second group with increased values of total cholesterol, LDL and especially triglycerides (the percentage approaches those of the fourth and fifth groups), as well as with lowered values of HDL, compared to those of men from the third group. Most likely, in addition to overweight or obesity, there are other lifestyle factors and harmful habits in patients that are a prerequisite for the decrease of serum T below the average values of the norm for a prolong period and disturbances in the fat profile. The largest number of men with elevated triglycerides values found by us, even among those in the second group, and the high negative correlation between T and triglycerides suggest that of all parameters of the serum lipids, triglycerides is most closely related to the level of serum T in young men.

Based on a large-scale study of middle-aged men who were not diabetic, Tsai E. et al. (2004) argue that the negative relationship between T and insulin resistance is mediated by body adipose tissue. **[18]** Type 2 diabetes mellitus further contributes to reduced serum T levels in young obese men. **[19]** According to some authors, the diabetic men studied diabetes and hypertension had lower levels of the hormone compared to their peers who did not have these diseases. On the other hand, a lower T level is associated with a worse prognosis of these diseases. **[15, 16]** In our study, nearly 27% of men had elevated *blood* glucose values. We also found significant differences in the mean values of *blood* glucose between the control and other groups (p<0.001), as well as between the second and fourth, third and fourth, second and fifth, third and fifth groups (p<0.001). We did not find a significant difference between the second and third groups, most likely due to the minimal difference in T level and/or the small difference in BMI in these men. Along with the decrease in the level of T in the groups, we observed an increase in the values of *blood* glucose, as well as an increase in the number of men with values above the norm. We found a significant negative correlation between T and *blood* glucose (r = -.479**, p<0.001). Our results show that a decrease in the level of T below the average values of the norm for a long period of time is a prerequisite for an increase in *blood* glucose, without being able to say which occurs first, the decrease in the level of T or an increase in the value of *blood* glucose defining the process, like other authors, as bidirectional. **[15, 16]**

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 same patients' lifestyles.
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 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 *blood* glucose and the serum lipids values.

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. Along with that, changes in the blood glucose and serum lipids were observed, which, differed significantly from the same parameters in their peers with a high degree of normality the serum testosterone level. The decrease of the serum T level below the average values for a prolonged period is an important prerequisite for the elevated blood glucose values and the change in the serum lipid with which the clinicians should take into account in the future. The changes we have found, probably (?) reversible with lifestyle changes, but if ignored can lead to metabolic to more serious metabolic disorders at a later age.

Author Contributions: All authors reviewed and approved the final manuscript and have contributed equally to this work

Funding: This research received no external funding.

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.

Acknowledgments: The authors thank Assoc. Prof. Mircho Vukov (a mathematician and epidemiologist) helped with the statistics.

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

References:

1. Cohen J, Nassau D, Patel P et al. Low testosterone in adolescents and young adults. Front Endokrinol, 2020; 10(1): 916-920. doi: 10.3389/fendo.2019.00916.
2. Scovell J, 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(1): 142-146. doi: 10.1111/bju.12970.
3. Peterson M, Belakovskiy A, McGrath R et al. Testosterone deficiency Weakness and Multymorbidity in Men Sci Rep, 2018; 8(1): 1-9. doi: 10.1038/s41598-018-24347-6.
4. Poobalan A. Aucott L. Obesity among young adults in developing countries: a systemic overview.

Curr Obes Rep, 2016; 5(1): 2-13. doi: 10.1007/s13679-016-0187-x.

5. Ma J, Wang B, Li H et al. Assotiation between obesity-associated markers and semen quality parameters and serum reproductive hormones in Chinese infertile men. Reprod Biol Endocrinol, 2020; 18(95): 351-359.

6. Macdonald A, Stewart A, Farquhar C. Body mass index in relation to semen quality and reproductive hormones in New Zealand men: a cross sectional study in fertility clinics. Hum Reprod 2013; 28(12): 3178-3187. doi: 10.1093/humrep/det379.

7. Pivonello R, Menafra D, Enrico Riccio E et al. Metabolic Disorders and Male Hypogonadotropic Hypogonadism Front Endocrinol, 2019 (10) doi.org/10.3389/fendo.2019.00345

8. Salas-Huetos A, Maghsoumi-Norouzabad L, James E et al. Male adiposity, sperm parameters and reproductive hormones: an updated systemic review and collaborative meta-analysis. Obes Rev, 2021, 22(1): 154-162. doi: 10.1111/obr.13082.

9. Wu F, Tajar A, Pye S et al. Hypotalamic-pituitary-testicular axis disruptions in older men are differentialy linked to age and modifiable risk factors: the Europen Male Aging Study. J Clin Endocinol Metab, 2008; 93(7): 2737-2745. doi: 10.1210/jc.2007-1972.

10. Ferrando A, Sheffield-Moore M, Yeckel C et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab, 2002; 282(3): 601–607. doi: 10.1152/ajpendo.00362.2001.

11. Kenny A, Prestwood K, Gruman C et al. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci, 2002; 57(7): 460–465. doi: 10.1093/gerona/57.7.m460.

12. Page S, Amory J, Bowman F et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab, 2005; 90(3): 1502–1510. doi: 10.1210/jc.2004-1933.

13. Snyder P, Peachey H, Berlin J et al. Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. Am J Med, 2001; 111(4): 255–260. doi: 10.1016/s0002-9343(01)00813-0.

14. Chosich J, Bradford A, Allshouse A et al. Acute recapitulation of the hyperinsulinemia and hyperlipidaemia characteristic of metabolic syndrome suppresses gonadotropins. Obesity, 2017; 25(3): 553-60. doi: 10.1002/oby.21754.

15. Kumanov Ph, Tomova A, Robeva R et al. Influence of ageing and some lifestyle factors on male gonadal function: a study in Bulgaria. Andrologia, 2007; 39(4): 136-140. doi: 10.1111/j.1439-0272.2007.00780.x.

16. Mulligan T, Frick M, Zuraw M et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract, 2006; 60(7): 762–769. doi: 10.1111/j.1742-1241.2006.00992.x

17. Zhong O, Lin J, Wang J et al. Association of diabetes and obesity with sperm parameters and testosterone levels: a meta-analysis. Diabetol Metab Syndr, 2021; 13(1): 109-113. doi: 10.1186/s13098-021-00728-2.

18. Tsai E, Matsumoto A, Fujimoto W et al. Association of bioavailable, free and totaltestosterone with insulin resistance. Diabetes Care, 2004; 27(4): 861-868. doi: 10.2337/diacare.27.4.861.

19. Levine H, Jorgensen N, Martino-Andrade A et al. Temporal trends in sperm count: a systemic revive and meta-regression analysis. Hum Reprod Update, 2017; 23(6): 646-659. doi: 10.1093/humupd/dmx022.

20. Bhasin S, Buckwalter J. Testosterone supplementation in older men: a rational idea whose time has not yet come. J Androl, 2001; 22(5): 718-731.

21. Harman S, Metter E, Tobin J 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 doi: 10.1210/jcem.86.2.7219.

22. 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 Urology, 2009; 55(1): 121-130. doi: 10.1530/EJE-08-0601

23. Salonia A, Rastrelli G, Wilken N et al. Pediatric and adult onset hypogonadism. Nat Rev, 2019; 5(1): 1-21. doi: 10.1038/s41572-019-0087-y.