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An assessment of clinical importance of low libido in the evaluation of men with late-onset hypogonadism**

Ocena przydatności klinicznej zaburzeń libido w rozpoznawaniu hipogonadyzmu późnego u mężczyzn

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S u m m a r y

Aim. We evaluated the relationship between total testosterone levels, libido and erecrile functions (ED) among men with sexual dysfunction and late-onset hypogonadism (LOH).

Material and methods. 334 men over 50 years with LOH and sexual dysfunctions (low libido and/or ED) were invited to complete the International Index of Erectile Function questionnaire (IIEF-5), as a diagnostic tool for ED and libido was assessed using modified the Brief Sexual Function Inventory questionnaire (BSFI). Serum total testosterone (TT) were measured. Linear regresion model were used to analyze the factors that are associated with sexual dysfunctions and testosterone levels.

Results. Mean patient age was 64 ± 9.2 years (range 50 to 78). Of the men 51% had low, 37% moderate and 12% high libido. Mean serum total testosterone levels among men with low, moderate and high libido were 2.4, 2.9 and 3.3 ng/mL respectively, and differences among means were statistically significant ($p < 0.01$). There was significant inverse relationship between BSFI score and total testosterone ($r = -0.3481$, $p < 0.05$) and BSFI score and age ($r = -3382$, $p < 0.02$). Moreover, there was significant inverse relationship between IIEF-5 score and total testosterone ($r = -0.3123$, $p < 0.002$) and IIEF-5 score and age ($r = -0.3463$, $p < 0.02$). These relationships were significant after adjustment for age and BMI.

Conclusions. Erectile dysfunctions are more specific symptom of late-onset hypogonadism than low libido and correlated negatively with testosterone levels. Total testosterone level is an inadequate measure of sexual dysfunctions in men over 50 years.

Key words: men, testosterone, libido, erectile dysfunctions

S t r e s z c z e n i e

Cel pracy. Oceniano związki pomiędzy stężeniem testosteronu, libido oraz zaburzeniami wzwodu u mężczyzn z hipogonadyzmem późnym (LOH) oraz zaburzeniami seksualnymi.

Materiał i metody. Badano 334 mężczyzn > 50. roku życia z hipogonadyzmem późnym oraz zaburzeniami seksualnymi (obniżone libido i/lub zaburzenia wzwodu). Badani wypełniali ankiety oceniające funkcje erekcyjne (International Index of Erectile Function – IIEF-5) oraz libido (zmodyfikowany kwestionariusz Brief Sexual Function Inventory = BSFI). Oznaczano stężenia testosteronu całkowitego (TT).

Wyniki. Wiek pacjentów wynosił średnio 64 ± 9,2 lat (od 50 do 78 lat). W badanej grupie 51% miało niskie libido, 37% umiarkowane oraz 12% wysokie libido. Średnie stężenie testosteronu całkowitego wśród pacjentów z niskim, umiarkowanym oraz wysokim libido wynosiło odpowednio 2,4, 2,9 oraz 3,3 ng/mL, a róznice pomiędzy grupami były znamienne statystycznie ($p < 0,01$). Stwierdzono istotną ujemną korelację pomiędzy wskaźnikiem BSFI a stężeniem testosteronu całkowitego ($r = -0,3481$, $p < 0,05$) oraz wskaźnikiem BSFI a wiekiem chorych ($r = -3382$, $p < 0,02$). Wykazano również istotną ujemną korelację pomiędzy wskaźnikiem IIEF-5 a stężeniem testosteronu całkowitego ($r = -0,3123$, $p < 0,002$) oraz wskaźnikiem IIEF-5 a wiekiem chorych ($r = -0,3463$, $p < 0,02$). Wykazane korelacje były istotne po wytrąceniu wpływu wieku i wskaźnika masy ciała (BMI).

Wnioski. Zaburzenia wzwodu są bardziej specyficznym objawem hipogonadyzmu późnego u mężczyzn niż obniżone libido i korelują ujemnie ze stężeniem testosteronu całkowitego. Oznaczanie stężenia testosteronu całkowitego nie jest wystarczającym narzędziem diagnostycznym wszystkich zaburzeń seksualnych u mężczyzn.

Słowa kluczowe: meżczyźni, testosteron, libido, zaburzenia wzwodu

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Accompanying the aging process are certain critical conditions that are often associated with decreased testosterone, such as decreased sense of well-being, depression, decreased libido and increased erectile dysfunction (ED) (1). Associated with aging decreasing of total testosterone (TT) levels is named Late-Onset Hypogonadism (LOH) (2). Testosterone is a major androgen which is essential for the development and maintenance of male sexual characteristics. However, the physiological role of TT in male sexual behavior is not well understood. Results of several studies about the relationship between TT and sexual behavior have been conflicting or not significant. Probably, the most specific symptoms of this process are ED. However, testosterone deficiency is linked to multiple causes of metabolic syndrome as well as ED and may be a central factor in the pathology of ED (3). Moreover, there is wide individual variability in the threshold of serum TT below which impairment of sexual function becomes evident (4, 5). Testosterone enhance libido in some patient but a causal relationship between altered androgen levels, ED and libido is still discussed (6). Nevertheless, measurement of serum TT level has become standard clinical practice in the evaluation of ED and especially decreased libido.

Moreover, management of LOH is difficult because there is not wide accepted low limit of normal TT levels. Guidelines from the Endocrine Society have defined LOH as a TT level of less than 200 ng/dL. These low levels must occur in conjunction with one or more of the signs and symptoms of hypogonadism (6). In contrast, the American Society of Andrology has stated that symptomatic men with reliable TT levels less than 300 ng/dL should be considered hypogonadal (7) and in recommendations of The International Society for the Study of the Aging Male symptomatic, aged men with reliable TT levels less than 350 ng/dL can be considered hypogonadal (2).

We used modified the Brief Sexual Function Inventory (BSFI) as a validated instrument for assessing libido (8) and the International Index of Erectile Function questionnaire (IIEF-5) as tool to assessing ED to evaluate the relationship between libido, ED and TT levels and clinical importance of low libido in the evaluation of men with LOH.

MATERIAL AND METHODS

Our study included 334 men treated in Department of Endocrinology, Medical Centre for Postgraduate Education in Warsaw with a primary complaint of LOH. LOH was defined as as a TT level of less than 350 ng/dL in conjunction with one or more of the signs and symptoms of hypogonadism like low sex drive (libido), ED or lack of nocturnal erections. We excluded patients with obvious preexisting conditions that strongly contribute to sexual dysfunction, such as diabetes mellitus, renal failure or a history of surgery in the pelvic cavity and, especially patients with insufficiency of hypophysis and primary hypogonadism. Men were also excluded from analysis due to recent or current hormone replacement therapy at the time of evaluation, noncompletion of the questionnaire and unavailable or missing testosterone results. Obesity is defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more. Hyperlipidemia was considered to be present if the participant reported having received the diagnosis or if he was receiving medication for the condition.

Patient age was over 50 years (from 50 to 78 years; mean age 64 ± 9.2 years). Erectile function was assessed according to the International Index of Erectile Function (IIEF-5). Possible scores on the IIEF-5 are 1 to 25 and erectile dysfunction was classified into 5 categories based on the scores, namely severe – 1 to 7, moderate – 8 to 11, mild to moderate – 12 to 16, mild – 17 to 21 and none – 22 to 25. Libido (sexual drive) was assessed according to the Brief Sexual Function Inventory questionnaire (BSFI) and scores were categorized as low – 0 to 3, moderate – 4 to 4 or high – 6 to 8.

Blood samples were collected between 8:00 and 9:00 a.m. Endocrinological data including luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) – using Immulite 2000; DPC United States kids, TT – using Coat-a-Coat; Siemens United States kids – were evaluated. TT, LH and FSH were measured by radioimmunoassay and prolactin was measured by chemiluminescent immunometric assay.

Statistical analysis was performed using Statistica software. The p values were calculated with the use of Fisher's exact test and Student's t-test. Plus-minus values are means ±SD. All relationships were assessed by linear univariate and multivariate regression analysis to determine factors which affected the testosterone levels and to reduce bias in a cross-sectional study.

RESULTS

A total of 334 men with LOH and sexual dysfunctions were evaluated in the study. Mean patient age was 64 ± 9.2 years (range 50 to 78). All men had their TT, LH, FSH and PRL levels checked at least once. Of the 334 men, 8% had TT levels < 200 ng/dL, 22% – 200-250 ng/dL, 32% – 250-300 ng/dL and 37% – 300-350 ng/dL. Mean TT concentration was 3.05 ± 0.25 ng/mL. Mean LH and FSH levels were just below high limits of normal range and mean prolactin levels were in normal range. Hormones levels are shown in table 1.

Of the men 51% had low, 37% moderate and 12% high libido according to BSFI questionnaire (fig. 1a). Mean serum TT levels among men with low, moderate and high libido were 2.4 ± 0.3, 2.9 ± 0.4 and 3.3 ± 0.5 ng/mL respectively, and differences among means were statistically significant ($p < 0.01$) (tab. 2). LInear regression analysis showed that there was significant inverse relationship between BSFI score and TT ($r = -0.3481$, $p < 0.05$) and BSFI score and age ($r = -3382$, $p < 0.02$).

Of the men 53% had mild, 30% mild to moderate, 12% moderate and 5% severe ED according to IIEF-5

Table 1. Mean hormones levels and percentage of patients in four cutpoints of TT levels and in all patients.

	Total testosterone levels				
	< 200 ng/dL	200-250 ng/dL	250-300 ng/dL	300-350 ng/dL	All patients
No. pts. (%)	29 (8)	72 (22)	109 (33)	124 (37)	334 (100)
Total testosterone (ng/dL)	1.64 ± 0.2	2.35 ± 0.19	2.73 ± 0.22	3.26 ± 0.21	3.05 ± 0.25
LH (IU/L)	7.2 ± 0.75	6.5 ± 0.6	6.1 ± 0.6	6.4 ± 0.8	6.6 ± 1.2
FSH (IU/L)	7.4 ± 1.1	7.1 ± 0.8	6.5 ± 0.9	6.7 ± 0.7	6.8 ± 0.9
Prolactin (ng/mL)	14 ± 3.7	12.1 ± 2.9	15.3 ± 3.7	12.3 ± 3.8	12.3 ± 3.5

Table 2. TT levels and degree of libido according to BSFI score in four cutpoints of TT levels and in all patients.

	BSFI score			
	No. pts.	low	moderate	high
< 200 ng/dL	29	1.5 ± 0.2	1.8 ± 0.2	No patients
200-250 ng/dL	72	2.1 ± 0.1	2.3 ± 0.2	No patients
250-300 ng/dL	109	2.6 ± 0.2	2.8 ± 0.1	2.85 ± 0.1
300-350 ng/dL	124	3.1 ± 0.2	3.2 ± 0.2	3.4 ± 0.1
All patients	334	2.4 ± 0.3	2.9 ± 0.4	3.3 ± 0.5*

*significant differences between all groups ($p < 0.01$).
variables of BSFI score and TT ($r = -0.3481$, $p < 0.05$)
variables of BSFI score and age ($r = -3382$, $p < 0.02$).

questionnaire (fig. 1b). Mean serum TT levels among patients with ED classified as severe, moderate, mild to moderate and mild were 2.1 ± 0.3, 2.5 ± 0.4, 3.1 ± 0.4 and 3.3 ± 0.4 ng/mL, respectively.and differences among means were statistically significant ($p < 0.02$) (tab. 3). Moreover, linear regresion analysis showed that there was significant inverse relationship between IIEF-5 score and TT ($r = -0.3123$, $p < 0.002$) and IIEF-5 score and age ($r = -0.3463$, $p < 0.02$).

Multivariate linear regression analysis showed that relationships between TT and IIEF-5 score and between TT and BSFI score were significant after adjustment for age and BMI.

DISCUSSION

In our study we demonstrated that ED are more specific symptom of late-onset hypogonadism than low libido and correlated negatively with testosterone levels. This hypothesis is based on statystcal analysys, which showed that there were inverse relationships between BSFI score and TT and between IIEF-5 score and TT, but correlation of IIEF-5 score (tool for assessment of erectile functions) with TT levels was more statistical significant. Than low libido seems to have more clinical importance in the evaluation of men with LOH.

It is now generally accepted that even among healthy adults, there is age related decrease in total testosterone levels. Furthermore, the prevalence of abnormally low serum testosterone levels even among men with erectile dysfunction is generally high, especially in population over 50 years (9).

Table 3. TT levels and degree of ED according to IIEF-5 scale in four cutpoints of TT levels and in all patients.

	IIEF-5 score				
	No. pts.	mild	mild to moderate	moderate	severe
< 200 ng/dL	29	No patients	1.9 ± 0.1	1.7 ± 0.2	1.6 ± 0.3
200-250 ng/dl	72	2.4 ± 0.2	2.4 ± 0.2	16,217 mm	2.1 ± 0.4
250-300 ng/dL	109	2.8 ± 0.1	2.7 ± 0.2	2.7 ± 0.3	2.6 ± 0.2
300-350 ng/dL	124	3.4 ± 0.1	3.3 ± 0.1	3.2 ± 0.3	3.1 ± 0.4
All patients	334	3.3 ± 0.4	3.1 ± 0.4	2.5 ± 0.4	2.1 ± 0.3*

*significant differences between all groups ($p < 0.02$).
variables of IIEF score and TT ($r = -0.3123$, $p < 0.002$)
variables of IIEF-5 score and age ($r = -0.3463$, $p < 0.02$)

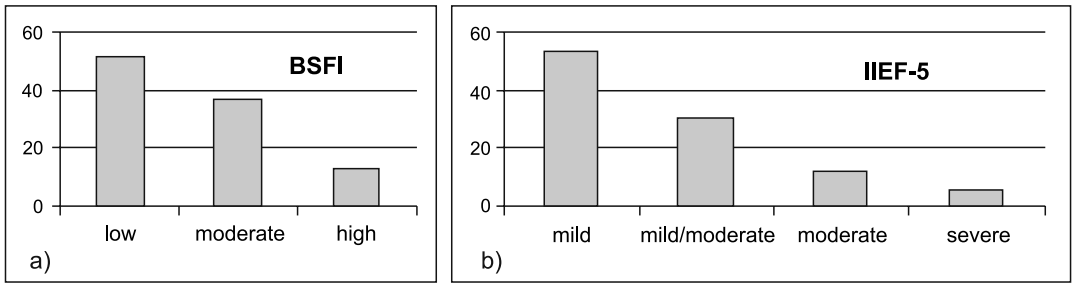

Fig. 1. The prevalence (%) of low, moderate and high libido according to BSFI score (a) and mild, mild to moderate, moderate and severe ED according to IIEF-5 score (b) in all patients.

Sexual dysfunctions (reduced libido and ED) are widely considered the most prominent symptomatic reflection of hypogonadism in men (10, 11).

Erectile dysfunctions are the most important problem in elderly patients with symptoms of LOH. In the Massachusetts Male Aging Study the prevalence of complete erectile dysfunction tripled from 5% to 15% between subject ages 40 and 70 years (9). Today it is well accepted that erectile dysfunction is related to aging and it is also believed, that serum testosterone concentration decreases with age (about 1%/per year) (12, 13).

LOH is defined by ISSAM as a biochemical syndrome associated with advancing age and characterized by specific signs and symptoms in combination with an unequivocally low total testosterone level of less than 350 ng/dL and decreased levels of free testosterone (2). The Polish Endocrine Society guidelines defined LOH similar to ISSAM guidelines (14). To date, no robust data sets have described of what prevalence of men with ED can be expected to meet these guidelines in Polish population of elderly men.

It is uncertain to what extent age related decline in testosterone production explains the age related increase in the prevalence of erectile dysfunction. Nevertheless, routine serum testosterone level determination is currently an accepted and common practice in the evaluation of men seeking evaluation for erectile dysfunction (2, 6, 15).

Testosterone replacement therapy is regarded as a promising treatment for the symptoms of LOH, including sexual dysfunctions. However. It is still unclear, how often patients who report low libido truly have hypogonadism and indications to replacement therapy.

Previous study showed, that testosterone replacement therapy has been associated with increases in sexual functioning and mood (16-17) but the association between naturally occurring TT levels and libido are not completely understood. Decreased libido is a concern often expressed by aging patients, but may be associated with both psychosocial and organic organic factors.

The aging process is itself often accompanied by a decline in sexual functioning (18, 19). The specific range of TT values that is associated with sexual dysfunctions in men, especially low libido, may differ by patient. Moreover, sexual functions and TT levels may be also influenced by androgen receptor polymorphism associated with the androgen receptor gene polymorphic repeat length (CAG RL) (20, 21).

However, recent studies have suggested that sexual dysfunctions are closely connected with testosterone deficiency. Wu et al. in European Male Aging Study (EMAS) studied the association between aging-related testosterone deficiency and late-onset hypogonadism in men (22). They sought criteria for identifying late-onset hypogonadism in the general population on the basis of an association between symptoms and a low testosterone level. In this study symptoms of poor morning erection, low sexual desire and erectile dysfunction were significantly related to the testosterone level. Increased probabilities of the three sexual symptoms were discernible with decreased testosterone levels (ranges, 2.3 to 3.7 ng/mL) for TT Morover, only the three sexual symptoms had a syndromic association with decreased testosterone levels. An inverse relationship between an increasing number of sexual symptoms and a decreasing testosterone level was observed. So, LOH can be defined by the presence of at least three sexual symptoms associated with TT level of less than 11 nmol per liter (3.2 ng/mL).

Travison et al.analyzed data on men enrolled in the Massachusetts Male Aging Study (MMAS) to assess the significance of the association between aging men's self-reports of libido and serum TT concentrations (23). They showed, that libido and TT levels displayed a significant association. However, the difference in mean TT levels between those subjects with low libido and those without was small. In conclusion thay summarized, that libido and TT concentrations are strongly related at the population level. However, the value of individual patient reports of reduced libido as indicators of low T levels is open to question.

In our cross-sectional study we observed inverse correlation between TT levels and degree of erectile dysfunctions and low libido. The tools used in our study are very simple and meb be used in outclinic patient. Moreover, testosterone measurements also is widely available and relative not expensive. It seems resonable to looking for testosterone deficiency in all patient wiath sexual dysfunctions but especially in those with erectile dysfunctions, becouse these sexual problems probably are the most specific symptoms of late-onset hypogonadism in men.

The effects of testosterone treatment on parameters of sexual functioning have been demonstrated (17, 24-26) but it must be pointed, that testosterone treatment is not always sufficient to restoring sexual potency. In men with hypogonadism and sexual dysfunctions testosterone treatment there was an improvement in sex drive and erectile function only in the first month after reaching normal plasma testosterone which subsequently declined in the following months of the follow-up (26).

Many of the issues affecting its accuracy can be cited as weaknesses in our data set. The testosterone measurements were not repeated in our sample set, total testosterone alone might not accurately describe the subject's bioavailable or free testosterone and our study did not obtain the free testosterone or SHBG levels. It is also important to remember that our model in no way established a causal link between low testosterone and sexual dysfunctions; the two conditions might simply overlap and they have probaly two separate pathophysiologic pathways.

BIBLIOGRAPHY

1. Lunenfeld B, Nieschlag E: Testosterone therapy in the aging male. Aging Male 2007; 10(3): 139-153.
2. Wang C, Nieschlag E, Swerdloff R et al.: ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Aging Male 2009; 1: 5-12.
3. Traish A, Guay A, Feeley R et al.: The Dark Side of Testosterone Deficiency: I. Metabolic Syndrome and Erectile Dysfunction. J Androl 2009; 30: 10-22.
4. Salmimies P, Kockott G, Pirke KM et al.: Effects of testosterone replacement on sexual behavior in hypogonadal men. Arch Sex Behav 1982; 11: 345-350.
5. Gooren LJ: Androgen levels and sex functions in testosterone treated hypogonadal men. Arch Sex Behav1987; 16: 463-469.
6. Bhasin S, Cunningham GR, Hayes FJ et al.: Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2006; 91: 1995-2010.
7. American Society of Andrology: Testosterone replacement therapy for male aging: ASA position statement. J Androl 2006; 27: 133-134.
8. O'Leary, MP, Fowler JF, Lenderking WR et al.: A brief male sexual function inventory for urology. Urology 1995; 46: 697-704.
9. Feldman HA, Goldstein I, Hatzichristou DG et al.: Impotence and its medical and physiological correlates: results od the Massachusetts Male Aging Study. J Urol 1994; 151: 54-61.
10. Morley JE: Testosterone and behavior. Clin Geriatr Med 2003; 19: 605-616.
11. Matsumoto AM: Andropause: clinical implications of the decline in serum testosterone levels with aging in men. J Gerontol Med Sci 2002; 57: M76-M99.
12. Harman SM, Metter EJ, Tobin JD et al.: Longitudinal effects of aging on serum total and free testosterone levels in health men. J Clin Endocrinol Metab 2001; 86: 724-731.
13. Feldman HA, Longcope C, Derby CA et al.: Age trends in the level of serum testosterone and other hormnes in middle-aged men: longitudinal results from Massachusetts Male Aging Study. J Clin Endocrinol Metab 2002; 87: 589-598.
14. Rabijewski M, Zgliczyński W: Pathogenesis, management and treatment oh hypogonadism in men. Pol J Endocrinol 2009; 3: 222-233.
15. Wespes E, Amar D, Hatzichristou K et al.: Guidelines on Erectile Dysfunction. European Urology Association 2008 www.eau.com
16. Seftel AD, Mack RJ, Secrest AR et al.: Restorative increases in serum testosterone levels are significantly correlated to improvements in sexual functioning. J Androl 2004; 25: 963-972.
17. Wang C, Cunningham G, Dobs A et al.: Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004; 89: 2085-2098.
18. Ebert T, Jockenhovel F, Morales A et al.: The current status of therapy for symptomatic late-onset hypogonadism with transdermal testosterone gel. Eur Urol 2005; 47: 137-146.
19. Vermeulen A: Diagnosis of partial androgen deficiency in the aging male. Ann Endocrinol (Paris) 2003; 64: 109-114.
20. Krithivas K, Yurgalevitch SM, Mohr BA et al.: Evidence that CAG repeat in the androgen receptor gene is associated with the age-related decline in serum androgen levels in men. J Endocrinol 1999; 162: 137-142.
21. Seidman SN, Araujo AB, Roose SP et al.: Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. Biol Psychiatry 2001; 50: 371-376.
22. Wu F, Tajar A, Heynon JM et al.: Identification of late-onset hypogonadism in middle-aged and elderly men. N Eng J Med 2010; 363(2): 123-135.
23. Travison T, Morley JE, Araujo A et al.: The Relationship between Libido and TestosteroneLevels in Aging Men. J Clin Endocrinol Metab 2008; 91: 2509-2513.
24. Yassin AA, Saad F: Improvement of sexual functions in men with late-onset hypogoonadism treated with testosterone only. J Sex Med 2007; 4: 20-28.
25. Arver S, Dobs AS, Meikle AW et al.: Improvement of sexual function in testosterone deficient men treated for 1 year with a permeation enhaced testosterone transdermal system. J Urol 1996; 155: 1604-1608.
26. Rabijewski M, Kubuj M, Zgliczyński S: The efficacy and safety of testosterone replacement therapy in elderly men with hypogonadism. Pol J Endocrinol 2003; 3: 293-300.

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