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Research Article

Low Testosterone Levels Predict a High Prevalence of Cardiovascular Risk Factors

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Keywords

- Testosterone; Cardiovascular risk; Hypertension; Diabetes

Abstract

Background: Epidemiological studies suggest an inverse correlation of testosterone with the prevalence of cardiovascular risk factors, but most of these trials evaluated a small population with selected co-morbidities only.

Aim: The present trial evaluated the association of testosterone concentrations with the prevalence of cardiovascular risk factors in a broad general population of all ages throughout Germany.

Methods: Association of testosterone concentrations with prevalence of hypertension and diabetes as well as body mass index and waist circumference were analysed in 14,171 men between 2011 and 2016. Age dependent analysis was performed corresponding to categorization (18-40 years, 41-60 years, 61-80 years and >80 years).

Outcomes: Valid information regarding prevalence of hypertension, diabetes and body mass index were obtained via a personal interview. Waist circumference was measured in 3,074 men.

Results: Prevalence of hypertension and diabetes as well as body mass index and waist circumference were significantly increased in hypogonadal men with testosterone concentrations <2.5ng/ml ($p<0.001$), but also in patients with border zone testosterone concentrations (2.5-3.5ng/ml, $p<0.001$). Age-related categorization of participants did not reveal any significant impact of age on association of testosterone concentrations with cardiovascular risk factors.

Clinical implications: Data from the current trial highlight the importance to screen for low testosterone concentrations even in younger patient with symptoms of a testosterone deficiency syndrome, providing the opportunity to prevent cardiovascular events by an early detection and treatment of the underlying cardiovascular risk.

Strengths & Limitations: Recent studies are widely limited by a restrictive patient selection or study population´s age, whereas the current study was performed in a broad general population of more than 14,000 men aged between 18 and 104 years. However, data are limited to a cross-sectional and non-prospective study design.

Conclusion: The results reveal a strong and age independent association of low testosterone concentrations with cardiovascular risk factors in a broad general population of more than 14,000 men aged between 18 and 104 years.

INTRODUCTION

Testosterone concentrations in men were thought to decrease with increasing age, starting with the age of 30-40 years [1,2]. The testosterone deficiency syndrome (TDS) is defined by low testosterone concentrations in addition to symptoms related to the physiological effects of low testosterone, which include reduced sexual activity, fatigue, reduced strength and depressed mood.[3] Incidence of the TDS increases with age and may affect 30-50% of men older than 70 years [3]. Irrespective of the male genital and reproductive system, the symptoms of low testosterone levels are attributable to the broad range of physiological effects of testosterone affecting multiple organ systems including muscles, fat, bone, peripheral nerves, but also the cardiovascular system.[4] Several trials and meta-analyses demonstrated an increasing all-cause and particularly cardiovascular mortality in men with low testosterone concentrations [5,6]. This coherence was as well shown in patients with proven cardiovascular disease, i.e. coronary heart disease, or renal failure and is suggested to be more distinctive in those cardiovascular high-risk-patients [5-8].

Increased cardiovascular morbidity and mortality in men with low testosterone concentrations may be attributed to a cross-link between testosterone and the cardiovascular risk factors, although available data are inconclusive. Recent trials suggest an association of low testosterone levels with an increased incidence and prevalence of diabetes and increased body mass index, which might be related to impaired insulin sensitivity and

increased body fat percentage [4,9]. Regarding the relationship between testosterone and blood pressure, available data are rather inconsistent. Epidemiological studies suggest an inverse correlation of testosterone with blood pressure, but testosterone replacement was associated with increased blood pressure or a high incidence of hypertension in several trials [10,11].

However, majority of these trials focused on specific cardiovascular risk factors and merely evaluated a small population with selected co-morbidities. The present trial evaluated the association of testosterone concentrations with the prevalence of cardiovascular risk factors in a broad general population of all ages throughout Germany.

MATERIAL AND METHODS

Study population

Between 2011 and 2016 testosterone concentrations were evaluated in more than 20,000 men in the context of informative presentations throughout Germany. In 14,171 men, valid information regarding prevalence of hypertension, diabetes and body mass index were obtained via a personal interview. Waist circumference was measured in 3,074 men. For age dependent analysis, participants were categorized in four groups (18-40 years, 41-60 years, 61-80 years and >80 years). The investigation conforms with the principles outlined in the Declaration of Helsinki, informed consent was obtained from all participants.

Measurement of testosterone concentrations

Blood samples were collected between 9am and 2pm to exclude circadian variation of testosterone levels. Samples were analysed by Bioscientia Med Lab Service, Ingelheim, Germany using an ElectroChemiLumineszenz ImmunoAssay from Roche Diagnostics, Switzerland (Elecsys Testosterone II). Testosterone concentrations were expressed in ng/ml, with <2.5ng/ml as threshold for hypogonadism and an additional border zone of 2.5-3.5ng/ml.

Statistical analysis

All data are expressed as mean±standard deviation (SD). Statistical significance was assumed at a p-level <0.05. Prevalence of hypertension and diabetes was analysed with the chi-square-test. Means of age, body mass index and waist circumference between groups were compared with the unpaired t-test and the one-way-ANOVA with Newman-Keul post hoc analysis were applicable. Statistical analysis was performed with PSPP for MacOs.

RESULTS

Information about prevalence of hypertension, diabetes mellitus and body mass index could be obtained from 14,171 men, waist circumference was measured in 3,074 men. Baseline characteristics of participants are shown in Table 1.

Prevalence of hypertension and diabetes as well as body mass index and waist circumference were significantly increased in hypogonadal men with testosterone concentrations <2.5ng/ml (Table 2a). Further analysis of border zone testosterone concentrations (2.5-3.5ng/ml) suggests a linear association of testosterone concentrations with prevalence of hypertension, diabetes, BMI, and waist circumference (Table 2b).

Age-related categorization of participants did not reveal any significant impact of age on association of testosterone concentrations with cardiovascular risk factors (Figure 1a-d). Further analysis of the total cardiovascular risk, combining the prevalence of hypertension, diabetes and/or the body mass index indicates a more than threefold risk for having two or three risk factors with a decreased testosterone concentration (<2.5ng/ml) (Figure 2).

DISCUSSION

The testosterone deficiency syndrome affects numerousness men after a certain age, and, in particular low testosterone concentrations might be related to an increased cardiovascular risk owing to the physiological actions of testosterone [3,5] However, these studies are widely limited by a restrictive patient selection or study population´s age [12-14]. The results of the current study reveal a strong and age independent association of

Table 1: Detailed characteristics of participants.

	Total (mean±SD)
Age (yrs)	58.9±13.6 (18-104)
Body mass index (kg/m²)	27.1±3.9
Waist circumference (cm)	101.7±12.9
Hypertension (%)	17.4
Diabetes mellitus (%)	6.98
Testosterone-concentration (ng/ml)	4.2±1.7
Hypogonadism (%) (testosterone <2.5ng/ml) total 18-40yrs 41-60yrs 61-80yrs 81-100yrs	 13.7 12.0 13.7 14.2 13.4
Border zone hypogonadism (%) (testosterone 2.5-3.5ng/ml) total 18-40yrs 41-60yrs 61-80yrs 81-100yrs	 23.0 20.3 24.1 22.6 19.8

Baseline characteristics were evaluated in 14,171 men, except waist circumference (3,074 men). Age - mean±SD (range), body mass index/waist circumference/testosterone concentrations - mean±SD.

Table 2a: Prevalence of cardiovascular risk factors in hypogonadal men.

	Testosterone <2.5ng/ml	Testosterone >2.5ng/ml	p-value
N (%)	1,944 (13.7)	12,227 (86.3)	
Age (yrs)	59.3±13.1	58.8±13.7	n.s.
Hypertension (%)	23.3	16.5	<0.001
Diabetes mellitus (%)	10.8	6.4	<0.001
Body mass index (kg/m²)	29.5±4.6	26.8±3.7	<0.001
Waist circumference (cm)	109.1±15.6	100.6±12.0	<0.001

In hypogonadal men, prevalence of hypertension, diabetes mellitus, body mass index and waist circumference were significantly increased. Age/body mass index/waist circumference - mean±SD.

Table 2b: Prevalence of cardiovascular risk factors in hypogonadal and borderzone hypogonadal men.				
	Testosterone <2.5ng/ml	**Testosterone 2.5-3.5ng/ml**	**Testosterone >3.5ng/ml**	**p-value**
N (%)	1,944 (13.7)	3,258 (23.0)	8,969 (63.3)	
Age (yrs)	59.3±13.1	58.7±13.0	58.8±14.0	n.s.
Hypertension (%)	23.3	18.5	15.7	<0.001
Diabetes mellitus (%)	10.8	7.6	5.9	<0.001
Body mass index (kg/m²)	29.5±4.6	27.9±3.9	26.3±3.5	<0.001
Waist circumference (cm)	109.1±15.6	104.2±11.5	99.2±11.5	<0.001
Prevalence of hypertension, diabetes mellitus, body mass index and waist circumference increased with decreasing testosterone concentrations. Age/body mass index/waist circumference - mean±SD.				

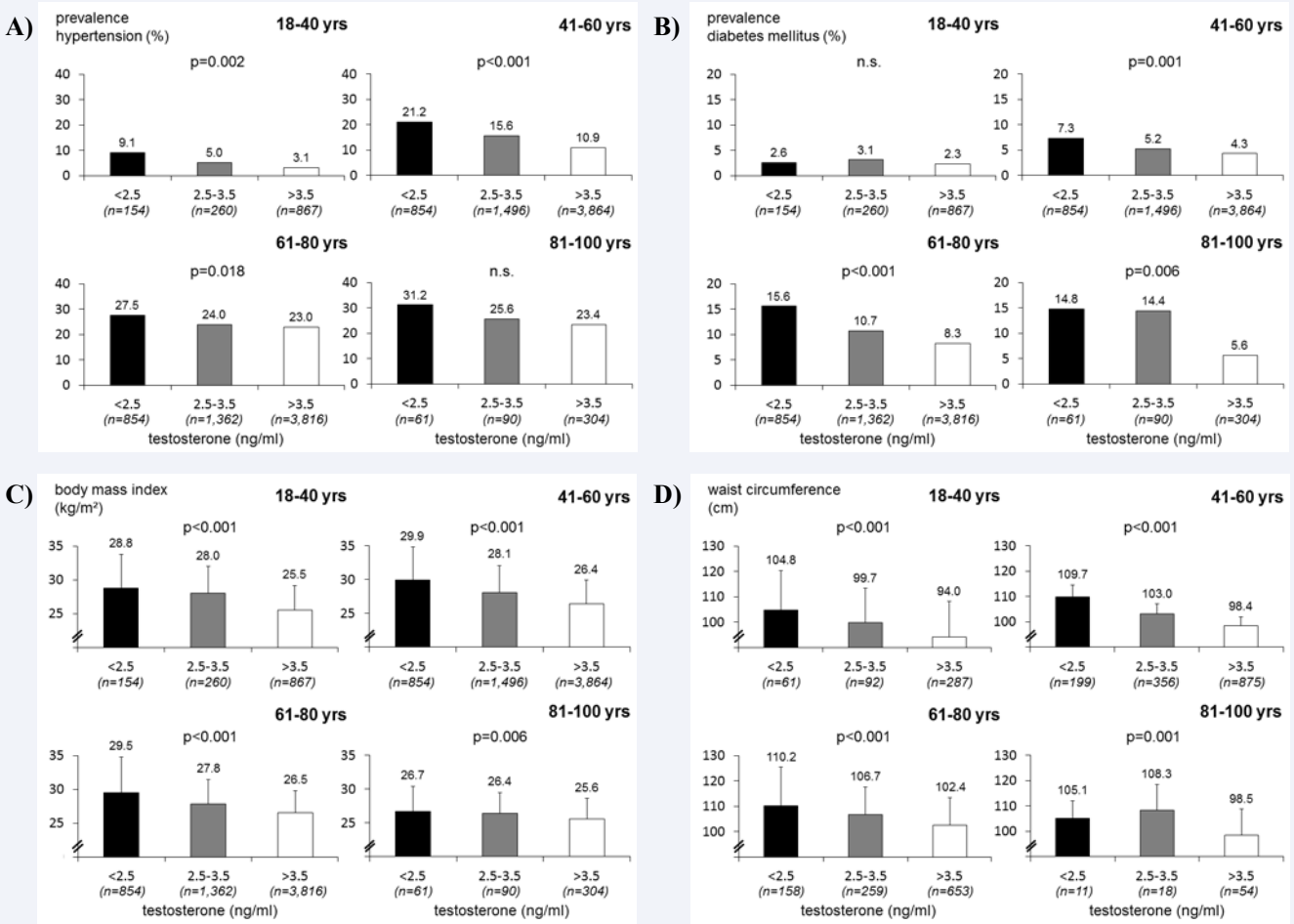

Figure 1 Prevalence of cardiovascular risk-factors in hypogonadal men is independent of age.

low testosterone concentrations with cardiovascular risk factors in a broad general population of more than 14,000 men aged between 18 and 104 years.

Decreasing testosterone concentrations were described in the aging male, with about 30-50% of men aged above 70 years with additional symptoms related to the testosterone deficiency syndrome [1,3]. Prevalence of decreased testosterone concentrations was high in the general population evaluated in the present study. Hypogonadism was present in about 13%, border-zone hypogonadism in 27% of the study population. Interestingly, the relation of hypogonadism, border-zone hypogonadism and normal testosterone concentrations was robust throughout all age-classifications, indicating that there is only a slight or even missing age-dependency of testosterone concentrations in men. Interpretation of this conflicting data remains speculative. Probably there is an increase of testosterone related symptoms with age which lead to a more pronounced detection or screening for decreased testosterone-concentrations. Testosterone concentrations itself might be stable for several decades.

Prevalence of hypertension, diabetes, body mass index and waist circumference increased significantly in hypogonadal, and to a less, but still significant extent in border-zone hypogonadal

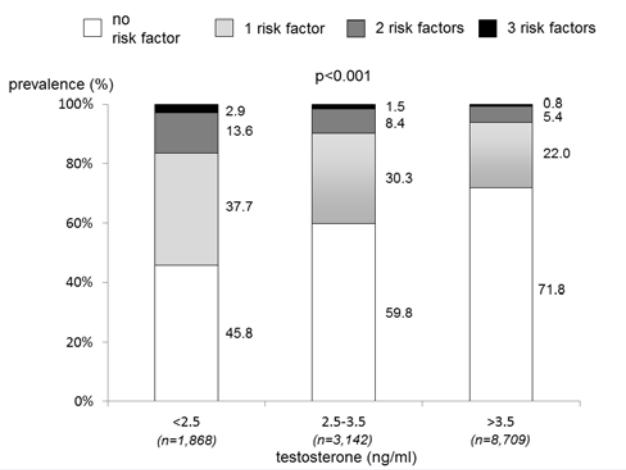

Figure 2 Cardiovascular risk-factor cumulation in hypogonadal men.

men. This result clearly indicates a testosterone-concentration dependent effect on the prevalence of cardiovascular risk-factors. This is in line with several trials demonstrating an association of low testosterone levels with an increased prevalence of risk factors referring to the metabolic syndrome [4,9]. In a recent male health survey in China, low total testosterone, free testosterone and bioavailable testosterone concentrations were significantly associated with a higher incidence of hypertension during a four-year follow-up [15]. Moreover, another trial revealed significantly lower total serum testosterone concentrations in patients with type 2 diabetes mellitus and an inverse relation of testosterone with body mass index and waist circumference [16]. Therefore, the American Association of Clinical Endocrinologists recommend a screening for hypogonadism in all men with type 2 diabetes mellitus with increased body mass index (>30kg/m^2) or waist circumference over 104cm [17].

In contrast, a reverse mechanism might be still up for debate. Several prospective observational studies describe the development of low testosterone levels in patients with a metabolic syndrome, or at least enhanced visceral fat mass [18,19]. These effects might be related to a peripheral conversion from testosterone to estrogen leading to a central inhibition of testosterone production and exacerbating the vicious cycle of obesity and low testosterone concentrations [20]. Thus, it is not completely clear, whether low testosterone is a cause or consequence of the metabolic syndrome. Nevertheless, most trials indicate that low testosterone is predictive of cardiovascular risk factors as hypertension, diabetes mellitus and increased body mass index, suggesting testosterone as a potential marker of overall cardiovascular risk. Moreover, the NHANES III-trial demonstrated an inverse correlation of testosterone with the incidence of diabetes independent of adipositas [21]. This indicates that low testosterone-levels might be the cause of an increased cardiovascular risk. Thus, further mechanism leading to low testosterone-levels as peripheral conversion to estrogen might enhance these effects, but are not suggested to be an epiphenomenon only.

The results of the present study support these data. In border-zone hypogonadal men, cardiovascular risk was significantly increased with a further rise in hypogonadal men with testosterone levels below 2.5ng/ml. More than fifty percent of these men did have one or more cardiovascular risk factors (hypertension, diabetes, increased body mass index). Moreover, the association of low testosterone concentrations with an increased prevalence of hypertension, diabetes and an increased body mass index or waist circumference was shown to be independent of age. To our knowledge, independency of age was demonstrated for the first time in such a broad general population. Physicians should be aware of this result and may screen for low testosterone concentrations even in younger patient with symptoms of a testosterone deficiency syndrome. Detection of low testosterone concentrations and subsequent screening for cardiovascular risk in young male patients provides the opportunity to prevent cardiovascular events by treatment of underlying cardiovascular risk factors according to recent guidelines.

Testosterone replacement treatment is clearly indicated in hypogonadal men with symptoms of a testosterone deficiency syndrome, but effects on cardiovascular risk factors and even cardiovascular risk are contrary. The Osteoporotic Fractures in Men-study revealed an association of high testosterone levels with a reduced risk of cardiovascular events in elderly men, which may lead to the assumption, that testosterone replacement in hypogonadal men might be beneficial [22]. Beneficial effects of testosterone treatment are likely on diabetes, body mass index and waist circumference, subsequently leading to a reduced mortality in those patients [23,24]. However, duration of testosterone exposure might play an important role. In an intention to treat observational cohort study of more than 10,000 men in Canada, short time treatment with testosterone was associated with increased mortality and cardiovascular events; whereas long-term exposure reduced this risk [25]. Effects of testosterone treatment of hypertension were similar. Several trials showed an increase of systolic blood pressure after testosterone treatment, but epidemiological studies suggest an inverse association of testosterone replacement with incidence or prevalence of hypertension [10,11]. Formulation and duration of exposure of testosterone replacement may be responsible for these conflictive results. Altogether, testosterone replacement treatment is suggested to have beneficial effects on cardiovascular risk factors and mortality, but due to the lack of randomized prospective trials it may not be recommended in this indication currently.

CONCLUSIONS

The results of the current study reveal a strong and age independent association of low testosterone concentrations with cardiovascular risk factors in a broad general population of more than 14,000 men aged between 18 and 104 years. These data highlight the importance of screening for low testosterone concentrations even in younger patient with symptoms of a testosterone deficiency syndrome. Further evaluation of cardiovascular risk may provide the opportunity for an early prevention of cardiovascular events in those patients.

REFERENCES

1. Wu FC, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab. 2008; 93: 2737-2745.

2. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. 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: 724-731.

3. Traish A.M. Adverse health effects of testosterone deficiency (TD) in men. Steroids. 2014; 88: 106-116.

4. Morgentaler A, Zitzmann M, Traish AM, Fox AW, Jones TH, Maggi M, et al. Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions. Mayo Clin Proc. 2016; 91: 881-896.

5. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol. 2013; 169: 725-733.

6. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011; 96: 3007-3019.

7. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. Heart. 2010; 96: 1821-1825.

8. Carrero JJ, Qureshi AR, Parini P, Arver S, Lindholm B, Bárány P, et al. Low serum testosterone increases mortality risk among male dialysis patients. J Am Soc Nephrol. 2009; 20: 613-620

9. Wang C, Jackson G, Jones TH, Matsumoto AM, Nehra A, Perelman MA, et al. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. Diabetes Care. 2011; 34: 1669-1675.

10. Torkler S, Wallaschofski H, Baumeister SE, Völzke H, Dörr M, Felix S, et al. Inverse association between total testosterone concentrations, incident hypertension and blood pressure. Aging Male. 2011; 14: 176-182.

11. Velho I, Fighera TM, Ziegelmann PK, Spritzer PM. Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review. Andrology. 2017; 5: 881-888.

12. Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Salonen R, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol. 2003; 149: 601-608.

13. Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab. 2005; 90: 2618-2623.

14. Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, et al, Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care. 2004; 27: 1036-1041.

15. Jiang Y, Ye J, Zhao M, Tan A, Zhang H, Gao Y, et al, Cross-sectional and longitudinal associations between serum testosterone concentrations and hypertension: Results from the Fangchenggang Area Male Health and Examination Survey in China. Clin Chim Acta. 2018; 487: 90-95.

16. Schianca GP, Fra GP, Brustia F, Bellan M, Pirovano A, Gualerzi A, et al, Testosterone Plasma Concentration is Associated with Insulin Resistance in Male Hypertensive Patients. Exp Clin Endocrinol Diabetes. 2017; 125: 171-175.

17. Goodman N, Guay A, Dandona P, Dhindsa S, Faiman C, Cunningham GR; AACE Reproductive Endocrinology Scientific Committee. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF TESTOSTERONE AND CARDIOVASCULAR RISK. Endocr Pract. 2015; 21: 1066-1073.

18. Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, et al, The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: a prospective cohort study. J Clin Endocrinol Metab. 2005; 90: 712-719.

19. Tsai EC, Boyko EJ, Leonetti DL, Fujimoto WY. Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. Int J Obes Relat Metab Disord. 2000; 24: 485-491.

20. Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. J Clin Endocrinol Metab. 1993; 76: 1140-1146.

21. Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson WG, et al, Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care. 2007; 30: 234-238.

22. Ohlsson C, Barrett-Connor E, Bhasin S, Orwoll E, Labrie F, Karlsson MK, et al, High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol. 2011; 58:1674-1681.

23. Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S. Long-Term Testosterone Therapy in Type 2 Diabetes Is Associated with Decreasing Waist Circumference and Improving Erectile Function. World J Mens Health. 2020; 38: 68-77.

24. Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S. Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors. BJU Int. 2019; 123: 519-529.

25. Wallis CJ, Lo K, Lee Y, Krakowsky Y, Garbens A, Satkunasivam R, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. Lancet Diabetes Endocrinol. 2016; 4: 498-506.

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