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The associations between serum sex hormones, erectile function, and sex drive:

the Olmsted County study of urinary symptoms and health status among men

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Abstract

Few studies have examined the association between sex hormone serum levels, erectile function, and sex drive. Using data from the Olmsted County Study of Urinary Symptoms and Health Status among Men we examined the associations between sex hormone serum levels, erectile function, and sex drive. During 1989-1991, Caucasian men ages 40-79 years were randomly selected from Olmsted County, MN, and in the sixth year of follow-up questions on sexual function from the Brief Male Sexual Function Inventory were added and included biennially thereafter with assays for estradiol, testosterone, and bioavailable testosterone levels. Out of 414 men, 294 had a regular sexual partner and androgen measurements at the fourteenth year of follow-up. These cross-sectional results suggest the relationship between sex hormones and sexual function is complex. Total testosterone and erectile function were significantly correlated even after adjustment for age ($r = 0.12$, $p = 0.04$). Conversely, total testosterone was not significantly correlated with sex drive ($r = 0.08$, $p = 0.17$). Bioavailable testosterone was significantly correlated with both erectile function and sex drive ($r = 0.16$, $p = 0.01$ and $r = 0.20$, $p = 0.001$, respectively). However, these associations disappeared after age-adjustment ($r = 0.04$ and $r = 0.09$). This suggests that the age-related decline in sexual function may be due to age-related declines in levels of bioavailable testosterone rather than total testosterone levels.

Keywords

Erectile dysfunction; hypogonadism; androgens; Estradiol; aging; cohort study

INTRODUCTION

Sexual dysfunction, and in particular, erectile dysfunction and low sex drive, is a common health problem affecting more than 150 million men [1]. A strong association between sexual

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dysfunction and age has been seen, with up to 10% of men in their 40's and up to 80% of men in the 70's or older affected [2]. Sexual dysfunction has also been shown to have a profound negative effect on the quality of life of affected men [3-5].

It is well documented and widely accepted that sex hormones influence the growth and development of the male reproductive tract, including secondary sex characteristics [6]. Additionally, in animal models, androgens have been shown to play an essential role in the initiation and maintenance of penile erections [7] and a currently recommended use of testosterone therapy is to improve sexual function [8]. However, a systematic review and meta-analysis of 17 trials by Boloña and colleagues [9] showed that testosterone replacement in men was associated with minimal improvements in satisfaction with erectile function and moderate improvements in sex drive. Additionally, it is not clear whether testosterone therapy is safe and effective in aging men [10], and the Institute of Medicine has recommended that further studies are necessary to assess the risks and benefits of androgen replacement therapy in men with sexual dysfunction [11].

Therefore, testosterone therapy remains controversial [12-14] and randomized clinical studies are lacking. Furthermore, McKinlay [15] has suggested that important scientific questions such as clearly defining androgen deficiency, understanding intra-subject and longitudinal variability and determining the most valid and reliable methods of measurement need to be answered before an optimal randomized controlled trial can be initiated. The effectiveness and long-term health implications of testosterone replacement therapy in men are unknown [16] and current testosterone replacement therapy is based on anecdotal information. Furthermore, in many instances only erectile function is reported with no mention of sex drive changes.

Due to the multiple variables involved in sexual function, including age, hormone levels, sex drive, and interactions between these variables, defining clear associations may be difficult. Therefore we used the Brief Male Sexual Function Inventory for urology developed by O'Leary [2,17]. This instrument encompasses the five domains of sexual function, including sex drive, erectile function, ejaculation function, perceptions of problems in each area, and overall satisfaction. Stratifying sexual function into separate domains allows clearer examination of the associations with age and hormone levels.

A population-based cohort study could therefore provide important baseline information regarding levels of sex hormones and the associations between such hormones and various components of sexual function in community men. To this end, we evaluated the associations between serum sex hormones, erectile function, and sex drive in our population-based cohort entitled "The Olmsted County Study of Urinary Symptoms and Health Status among Men".

METHODS

The Olmsted County Study of Urinary Symptoms and Health Status among Men was initiated in December 1989 and details have been published elsewhere [18-20]. Briefly, this is a community-based, prospective cohort study of randomly selected Caucasian men 40-79 years of age on January 1, 1990 from Olmsted County, Minnesota [21]. After exclusion for pre-existing conditions and treatments, 3,874 men were invited to join the study and of these 2,115 agreed to participate (55% participation rate). A 25% random sub-sample of the study cohort (n = 537) was invited to complete a detailed clinical urologic examination; 475 (88%) participated. The cohort was actively followed on a biennial basis using a similar protocol to the initial examination. During the second and third round of visits, men who did not participate in the follow-up were replaced by men randomly selected from the community (n = 332). Since that time the study has been maintained as a closed cohort. Men participating in the clinical subset gave written consent at each round, prior to the clinical examination.

In the sixth year of follow-up, questions on sexual function from the previously validated Brief Male Sexual Function Inventory [2,17] were added and included biennially thereafter (Appendix). Erectile function was evaluated from the responses to questions about (1) how often men had partial or full erections when sexually stimulated, (2) how often were their erections firm enough for sexual intercourse, and (3) how much difficulty they had in getting an erection, all in the past 30 days. Similarly, sex drive was evaluated with responses to two questions; (1) how many days men felt sexual drive and (2) how they would rate their level of sexual drive. Responses for each question were scored on a scale from 0 to 4 with domain scores equaling the sum of the individual questions comprising the domain. For categorical analyses, the cut-points were determined based on examination of their distribution in the entire population and sensitivity analyses [22]. They were defined as follows: low sex drive if the sexual drive domain score was ≤ 2 and erectile dysfunction if the erectile function domain score was ≤ 3.

Furthermore, in the fourteenth year of follow-up, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), was administered to evaluate physical and mental health [23]. The five questions directly assessing mental health status were evaluated in the current study. A mental health score was calculated, randing from 0 to 100 [23].

A history of incident myocardial infarction and positive angiography were ascertained via a detailed medical record review and by electronic ascertainment from the Mayo Clinic Medical Index, respectively [24]. History of diabetes and hypertension were based on self-report at baseline. Furthermore, in the fourteenth year of follow-up, the questionnaire included items on cigarette smoking and assessed whether men had smoked at least 100 cigarettes in their lifetime and, if yes, whether they currently smoked. Former smokers were asked how long ago they stopped smoking and for how many years they smoked. Based on the questionnaire responses, smoking status was categorized as a current/ever smoker versus a never smoker [25].

In the fourteenth year of follow-up, hormone levels were measured on 294 men participating in the clinic subset. The median (Q1,Q3) time of blood draw was 9:32 am (8:44 a.m.-11:00 a.m. A high sensitivity double antibody radioimmunoassy was used to measure estradiol (Diagnostic Products Corp. Los Angeles, Ca 90045). Estradiol assays were run twice for each individual and the mean of the two values was used in the analysis. A competitive chemiluminescent immunoassay on the ACS-180 automated immunoassay system (Bayer Diagnostics Corp., Tarrytown, NY 10591) was used to measure total testosterone. Total testosterone represents the sum of bioavailable testosterone and testosterone bound to sex hormone binding globulin. Bioavailable testosterone was calculated as the product of the percent bioavailable testosterone and total testosterone by using ammonium sulfate to differentially precipitate sex hormone binding globulin following equilibration of the serum sample with trace amounts of tritium labeled testosterone [26].

Intra-assay and inter-assay CVs were assessed at multiple levels for each assay as a quality control measure. The intra-assay coefficients of variation (CVs) for estradiol were 18.3%, 3.8%, and 7.2% at 3.6, 40.4, and 297 pg/mL, respectively. Inter-assay CVs for estradiol were 8.1% at 16.0 pg/mL, 4.7% at 31.1 pg/mL, and 4.9% at 119 pg/mL. Intra-assay CVs for testosterone were 8.0%, 4.1%, and 3.2% at 98, 442, and 984 ng/dL, respectively. Inter-assay CVs for testosterone were 10% at 74 ng/dL, 8% at 605 ng/dL, and 8% at 1335 ng/dL. Intra-assay CV was 5.4 at 14.1% of bioavailable testosterone. Inter-assay CVs for bioavailable testosterone were 7.5 at 28.4%, 4.9 at 41.9%, and 4.9 at 50.8% [26].

Under separate Institutional Review Board approval, a random subset of 20 men each received morning and afternoon blood draws on days 1, 2, 7, 30 and 60 to assess monthly, daily, and

diurnal variation in testosterone levels. The mean measurements were 329.7 ng/ml for testosterone and 78.5 ng/ml for bioavailable testosterone. For testosterone, the standard deviations and coefficients of variation (CV) were 19.9 (6.0%), 0.9 (<1.0%), and 49.0 (14.9%) for monthly, daily, and diurnal variation, respectively. For bioavailable testosterone, the standard deviations (CV) were 9.2 (11.7%), 4.5 (5.7%), and 13.0 (16.6%) for monthly, daily and diurnal variation, respectively.

To evaluate correlations of sex hormone serum levels with erectile function and sex drive, data from 294 men in the 14th year of follow-up (2004) were analyzed using Spearman correlation coefficients, with and without adjustments for age, with correlation coefficients. Because previous work has shown that self-reported sexual function can be heavily influenced by the availability of a regular sexual partner [17], only men with a regular sexual partner were included in the analyses. Logistic regression was used to calculate odds ratios (OR) to assess the associations between sex hormone levels and sexual function. Cut-points for serum sex hormones were based on the median serum level with values greater than or equal to the median as the reference. Other cut-points for sex hormone serum levels with sexual function, and sex drive showed similar results. A multivariable model was constructed to simultaneously evaluate the potential confounding effects of age, hypertension, diabetes, coronary heart disease, mental health status, and smoking history. All statistical analyses were completed using SAS (SAS Institute, version 8.2, Cary, NC). An alpha of $p < 0.05$ was considered significant.

All study procedures were approved by the Mayo Foundation and Olmsted Medical Center Institutional Review Boards.

RESULTS

Of the 414 men who participated in the clinic subset in 2004, 294 (71%) had a regular sexual partner and androgen measurements, and were included in the analyses. The median (25th, 75th percentile) age for the men was 63.1 (57.9, 68.5) years. There were 48 (16.3%) men with erectile dysfunction and 55 (18.7%) men with low sex drive. Table 1 shows the distribution of the erectile function domain, sex drive domain, and serum sex hormone levels. Both median erectile function domain and sex drive domain scores decreased significantly across age decade, with median scores declining from 9 to 5 (p for trend < 0.0001) and 5 to 3 (p for trend < 0.0001), respectively (Table 1). Median serum levels for estradiol and testosterone did not change significantly across age decade in this cohort, but a significant decrease in the serum level of bioavailable testosterone across age was evident, with medians declining from 67.0 to 47.0 ng/dl (Table 1; p for trend < 0.0001).

Erectile function and sex drive domains were modestly correlated with testosterone and bioavailable testosterone serum sex hormone levels (Table 2). Bioavailable testosterone had the strongest correlations with erectile function and sex drive domains (unadjusted $r = 0.16$; $p = 0.01$, and $r = 0.20$; $p = 0.001$), respectively. After adjusting for age, the associations between bioavailable testosterone and both the erectile function and sex drive domains weakened and lost statistical significance ($r = 0.04$; $p = 0.54$ and $r = 0.09$; $p = 0.15$), respectively. Testosterone was only significantly correlated with the erectile function domain ($r = 0.14$; $p = 0.02$) and remained significant after age-adjustment ($r = 0.12$; $p = 0.04$). After adjusting for age, diabetes, hypertension, coronary heart disease, mental health status, and smoking history, the association between testosterone and the erectile function domain was slightly attenuated and lost significance ($r = 0.11$; $p = 0.06$). Estradiol was not associated with either the sex drive or erectile function domains.

Categorical comparisons (Table 3) of associations between serum sex hormones and low sex drive indicated that low testosterone serum hormone levels were associated with low sex drive (age-adjusted odds ratio (OR) = 1.87; 95% confidence interval (CI) = 1.02, 3.45). A similar, non-significant association was also seen between lower serum testosterone and decreased erectile function (age-adjusted OR= 1.67; 95% CI = 0.87, 3.19). Adjustment for age, diabetes, hypertension, coronary heart disease, mental health status, and smoking history did not significantly change results between the adjusted and unadjusted models.

DISCUSSION

In this study, higher total testosterone and bioavailable testosterone levels were associated with an increased erectile function domain score, with higher bioavailable testosterone also associated with an increased sex drive score. Adjustment for age abolished associations between bioavailable testosterone and sexual function measures, but not between total testosterone and erectile function. Finally, adjustment for several comorbid conditions (known risk factors for sexual dysfunction) did not affect associations between androgen levels and sexual function measures.

Our study offered a unique opportunity to examine sex hormone levels, sex drive, and erectile function in a community-based population of Caucasian men, 40-70+ years of age. The inclusion of serum sex hormone levels, including both serum testosterone and bioavailable testosterone levels, while adjusting for age and comorbidities, strengthens our findings by allowing examination of the roles these hormones play in both erectile function and sex drive. With questions from the Brief Male Sexual Function Inventory, we were able to assess erectile function and sex drive in this community-based population, and correlate erectile function and sex drive scores with the serum sex hormone levels. Interestingly, comparison of our community-based study results with those of a Norwegian community-based study showed no clinically relevant differences in the Brief Male Sexual Function Inventory domains between the two populations of men [27].

It is believed that sex hormones play a predominantly modulating role by their effect on sex drive and sexual behavior [28]. Although animal models show that testosterone has a direct effect on erectile function, the role of testosterone in human erectile function is less clear [29]. As Morales and Heaton [30] point out, endocrine abnormalities may account for anywhere from 2 to 23% of erectile dysfunction issues, but the current rudimentary understanding of the erectile mechanism seldom permits the assignment of one etiologic factor; often comorbidities need to be considered. However, adjustment for comorbidities in our study did not affect the association between testosterone, erectile function, and sex drive, suggesting that low testosterone levels may impact sexual function independently of the effects of comorbid medical conditions.

Results from our study also suggest that a complex relationship exists between age, sex hormone levels, erectile function, and sex drive. We found that increasing age was strongly associated with both declining bioavailable testosterone and declining sexual function, and, after adjusting for age, correlations between bioavailable testosterone and sexual function scores were sharply attenuated. Age may therefore be viewed as a strong confounder of the relationship between bioavailable testosterone levels and sexual function. Alternatively, however, declining bioavailable testosterone may also be viewed as part of an age-related etiologic pathway leading to decline in sexual function. If age leads to declining bioavailable testosterone through specific biologic mechanisms, and declining bioavailable testosterone levels lead in time to decreased sexual function, adjusting our associations for age actually results in over-adjustment, potentially obscuring a biologic pathway that leads to sexual dysfunction. Interestingly, age was not associated with total testosterone level, and adjustment

for age, therefore, did not substantially influence the association between total testosterone level and erectile function. This suggests that age-related mechanisms may have an effect on the levels of bioavailable testosterone rather than total testosterone.

Mental health may also have an effect modification on sex drive and erectile function [31]. Previously our study has shown that compared to men without impaired mental health, men with impaired mental health have an inverse association between penile pain and sexual drive or sexual function [32]. These results imply that mental health may decrease sexual activity resulting in a decreased likelihood of reporting impaired sexual function even when present. Furthermore, impaired mental health may also decrease the cognition of any impairment with sexual function [32]. When adjusting for mental health status, smoking, diabetes, hypertension, and coronary artery disease, the age-adjusted association between testosterone and the erectile function domain, was slightly attenuated and marginally significant ($r = 0.11$; $p = 0.06$).

Other studies have examined the association between erectile function, sex drive, and sex hormones. Ahn et al. [33] found total testosterone levels showed no significant correlation with any of the five domains of the International Index of Erectile Function questionnaire and that decreasing free testosterone correlated with increasing age and had the strongest correlation with erectile function. Ansong and Punwaney [34] found differences among mean levels of total testosterone and free testosterone that were not statistically significant among men with low, moderate, and high sex drive. Similarly, the Massachuesetts Male Aging study found no associations among total testosterone and bioavailable testosterone and erectile dysfunction. However, in men with an increased lutenizing hormone levels, testosterone levels were associated with an increased risk of erectile dysfunction [35]. Tsujimura et al. [36] found significant unadjusted correlations between increasing bioavailable testosterone and increases in the International Index of Erectile Function-5 score for erectile function and between decreases in bioavailable testosterone and increasing age.

These studies paint a complicated and sometimes conflicting picture of the association between various forms of testosterone, age, erectile function, and sex drive. Our study showed that total testosterone and erectile function were significantly correlated even after adjustment for age. However, total testosterone was not significantly correlated with sex drive. Bioavailable testosterone was significantly correlated with both erectile function and sex drive, but these associations disappeared after age-adjustment. Taken together, these results suggest that the age-related decline in sexual function may be due to age-related declines in levels of bioavailable testosterone rather than total testosterone levels.

There are some potential limitations to this study that should be considered. Due to the cross-sectional nature of this study, causal inferences can not be made from the associations between serum hormone levels, erectile function, and sex drive. Because we do not know the temporal sequence of events, causality can not be established, i.e. serum hormone levels change then erectile function and/or sex drive changes. In a cross-sectional analysis it is difficult to know which came first, the risk factor or the disease, therefore, causality can not be established [37]. The potential for non-participation bias exists due to the low participation rate at baseline (55% response rate) for the entire cohort. Previously, we had documented modest differences in baseline participants with regards to age, home location, and prior history of urologic conditions compared with non-participants [21]. We did observe greater drop-out in men who reported having erectile dysfunction and men who reported existing comorbidities at baseline [38]. If lower hormone levels affecting erectile dysfunction resulted in differential attrition, our results could be biased, as men with erectile dysfunction were more likely to drop-out of the study, therefore this may have resulted in underreporting of the condition in our cohort. Comorbidities such as diabetes and hypertension were based on self-report of medical diagnosis at baseline. Some studies have shown a lack of concordance between self-report and

medical records [39]. However, most studies show a strong concordance between self-report of chronic medical conditions such as hypertension and diabetes [40,41]. In addition, generalizability may be limited, as all participants in this cohort study were Caucasian and were 50-85 years of age. Therefore, these findings may not be applicable to other ethnic populations and age groups. However, we currently have no reason to believe that the physiological mechanism relating androgens to sexual function differs between race and ethnic groups. Additionally, only one venipuncture sample was drawn for each measurement. While multiple measurements would allow adjustment for day to day variation in hormone levels, this isn't practical for our large longitudinal study. We did strive for morning blood draws (n = 286, 97%) in this study after observing greater diurnal variation in our sub-sample.

These cross-sectional results suggest the relationship between aging, sex hormones, erectile function, and sex drive is complex. Adjusting for comorbidities did not attenuate correlations between hormone levels and sexual function, suggesting that these androgen levels may exert an influence on sexual function apart from established risk factors for sexual dysfunction. Additionally, adjustment for age attenuated associations between bioavailable testosterone and sexual function measures, but not between total testosterone and erectile dysfunction. This suggests that the age-related decline in sexual function may be due to age-related declines in levels of bioavailable testosterone rather than total testosterone levels.

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Table 1

Distribution of erectile function score, sex drive score, and serum sex hormones in the study cohort, Olmsted County, Minnesota, USA

	Total Cohort		Age 40-59		Age 60-69		Age 70+		r	p-value*
Variable	**N = 294**		**N = 104**		**N = 133**		**N = 57**			
	Med	**(Q1, Q3)**	**Med**	**(Q1, Q3)**	**Med**	**(Q1, Q3)**	**Med**	**(Q1, Q3)**		
Erectile Function Domain	8.0	(5.0, 10.0)	9.0	(7.0, 11.0)	8.0	(5.0, 10.0)	5.0	(2.0, 8.0)	**-0.34**	<0.0001
Sex Drive Domain	4.0	(3.0, 5.0)	5.0	(4.0, 6.0)	4.0	(3.0, 5.0)	3.0	(2.0, 4.0)	**-0.35**	<0.0001
Estradiol, pg/ml	25.0	(20.0, 31.0)	26.0	(20.0, 33.0)	24.5	(19.0, 30.0)	25.5	(19.0, 32.5)	-0.02	0.77
Testosterone, ng/dl	339.0	(277.0, 434.0)	352.5	(284.0, 441.0)	330.0	(265.0, 428.0)	339.0	(273.0, 426.0)	-0.07	0.22
Bioavailable Testosterone, ng/dl	56.8	(44.9, 77.2)	67.0	(54.4, 86.1)	54.2	(44.9, 71.0)	47.0	(36.8, 56.8)	**-0.36**	<0.0001

* Test for trend, Spearman correlation

Table 2

Spearman correlations between sex hormones, erectile function, and sex drive domains, Olmsted County, Minnesota, USA

	Serum Hormones					
	Estradiol		Testosterone		Bioavailable Testosterone	
	r	p-value	r	p-value	r	p-value
Erectile Function Domain[‡]						
Unadjusted	-0.01	0.92	**0.14**	0.02	**0.16**	0.01
Age-Adjusted	-0.01	0.81	**0.12**	0.04	0.04	0.54
Adjusted[*]	-0.03	0.66	0.11	0.06	0.06	0.34
Sex Drive Domain[‡]						
Unadjusted	0.06	0.30	0.10	0.09	**0.20**	0.001
Age-Adjusted	0.06	0.32	0.08	0.17	0.09	0.15
Adjusted[*]	0.07	0.27	0.08	0.18	0.09	0.14

[‡]Erectile Function and Sex Drive Domains - Questions on sexual function were from the Brief Male Sexual Function Inventory. The domains were calculated by summing the responses to specified questions.

[*]Adjusted for age, diabetes, hypertension, coronary heart disease, mental health status, and smoking history

Table 3

Associations between serum sex hormones and sexual dysfunction in the study cohort, Olmsted County, Minnesota, USA

		Estradiol < Median			Testosterone < Median			Bioavailable Testosterone < Median		
		OR[§]	95% CI[*]		OR	95% CI		OR	95% CI	
Erectile Dysfunction										
	Unadjusted	0.86	0.45	1.63	1.70	0.90	3.19	1.23	0.66	2.30
	Age-adjusted	0.89	0.46	1.71	1.67	0.87	3.19	0.83	0.42	1.62
	Adjusted[ǂ]	0.91	0.44	1.88	1.57	0.79	3.14	0.77	0.37	1.58
Low Sex Drive										
	Unadjusted	1.24	0.68	2.28	1.87	1.02	3.40	1.20	0.66	2.18
	Age-adjusted	1.33	0.72	2.47	1.87	1.02	3.45	0.93	0.49	1.76
	Adjusted[ǂ]	1.36	0.71	2.57	2.01	1.07	3.77	0.92	0.48	1.76

[§] Odds Ratio

[*] 95% Confidence Interval

[ǂ] Adjusted for age, diabetes, hypertension, coronary heart disease, mental health status, and smoking history