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Racial Differences in Hypogonadal Improvement and Prostate-Specific Antigen Levels in Hypogonadal Men Treated With Testosterone Replacement Therapy

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ABSTRACT

Purpose: To observe hypogonadal men undergoing testosterone replacement therapy (TRT) and assess racial differences in hypogonadal improvement and prostate-specific antigen (PSA) levels.
Materials and Methods: In a retrospective analysis, 75 hypogonadal men were followed for an average 34 months after initiating TRT. Total testosterone and PSA levels were assessed every 6 months, and patients diagnosed with prostatitis or prostate cancer during treatment were excluded.
Results: For 16 African American men, the average age at diagnosis of hypogonadism was 53.5 years, compared with 57.8 years in 59 Caucasian men (p = NS). Pre- and post-treatment testosterone was 219 ng/dL and 310 ng/dL in African American men, and 247 ng/dL and 497 ng/dL in Caucasian men (p = NS). Symptomatic response was 81% in African American men and 93% in Caucasian men (p = NS). Baseline PSA level was 1.32 ng/mL in African American men and 1.27 ng/mL in Caucasian men, and there was no significant difference in PSA between racial groups at 6-month intervals, although there was a small decreasing trend in the PSA of African Americans compared with Caucasians.
Conclusions: Hypogonadal African American men have a similar normalization of testosterone and symptomatic response as hypogonadal Caucasian men, and PSA levels remain stable over time in both groups. In this hypogonadal cohort, in contrast to studies of eugonadal men, higher PSA levels in African Americans were not observed.

Key words: *prostate-specific antigen; hypogonadism; testosterone; continental population groups*
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INTRODUCTION

Testosterone deficiency syndrome (TDS) is a condition characterized by serum androgen deficiency that adversely affects the function of multiple organ systems and negatively impacts quality of life. The clinical symptoms include sexual dysfunction such as erectile dysfunction and decreased libido, as well as fatigue, depressed mood, impaired cognition, and decreased muscle mass (1). Although the majority of cases of TDS occur in aging men, for which the syndrome is commonly referred to as late-onset hypogonadism or andropause, TDS can also occur in younger men. Treatment of TDS with testosterone replacement therapy (TRT) is appropriate when the testosterone level is below the lower limit of normal, generally accepted to be 300 ng/dL (2).

An extrapolation from the Massachusetts Male Aging Study found a prevalence of TDS of almost half a million new cases per year in men in

their fifth, sixth and seventh decades of life, and as a result of the expanding population of the elderly, the incidence of TDS is on the rise (3). Racial differences of the prevalence and incidence of TDS are unknown because epidemiologic series on the subject have been primarily comprised of Caucasian men.

The beneficial effects of TRT in the treatment of TDS are well characterized. As levels of serum testosterone are normalized, the desired improvements in sexual function, mood, cognition, and muscle mass can be achieved. The question of how TRT affects racial groups differently has not been addressed in previous studies. It is unknown if different racial groups normalize testosterone levels with the same vigor, or if the same symptomatic response can be achieved.

Racial differences of androgen levels of eugonadal men have been previously examined, although the results of many studies are discordant. While several previous studies have shown African American men to have higher baseline testosterone levels than Caucasian men (4-7), others have shown no differences (8-12). One of the largest prospective studies of racial differences of serum androgen levels in eugonadal men found no significant differences in total testosterone, bioavailable testosterone, or sex-hormone binding globulin levels in 538 African American, 651 Hispanic, and 710 Caucasian men (13).

The average prostate-specific antigen (PSA) level of African American men has been shown in multiple studies to be higher than the average PSA level of Caucasian men, both in eugonadal men with a new diagnosis of prostate cancer (14), as well as in eugonadal men without prostate cancer (15-17). Moul and colleagues examined the PSA level of 541 men with newly diagnosed prostate cancer and reported that after adjusting for stage, grade, and age, the mean PSA value for 133 African American men was 14.00 ng/mL compared with 8.29 ng/mL for 408 Caucasian men ($p < 0.001$) (14). To study racial differences in PSA level and PSA density in men without prostate cancer, a retrospective study of 826 consecutive men who underwent prostate biopsy was performed. Of the 498 men with negative biopsies, serum PSA levels (7.97 ng/mL versus 4.30 ng/mL, $p < 0.0001$) and calculated PSA density (0.19 versus 0.11, $p < 0.0001$) were significantly higher in African American men than in Caucasian men (15).

This difference in PSA has been shown to not be the result of racial differences in prostate size. In a study of 11,011 men who underwent prostatectomy, race and serum PSA values were correlated to prostate weight, and although serum PSA was 15% higher in African American men there were no significant associations between race and prostate size (17). As described above, racial differences of androgen levels have not been definitely proven to be higher in African Americans even though this potential difference may partially explain the difference in PSA levels given the strong positive association between prostate size and serum PSA value (18). Racial differences in hormones such as estrogen, insulin, and insulin-like-growth factor that also regulate prostate size may augment or even negate the potential androgenic difference. Other theories that have been investigated to explain the racial difference in PSA include genetic polymorphisms. African Americans are more likely to possess polymorphisms favoring increased androgen activity, including shorter CAG trinucleotide repeats in the androgen receptor gene and a less active CYP3A4 gene which is involved with the deactivation of testosterone (19,20).

Both short-term and long-term changes in the PSA levels of hypogonadal men undergoing TRT have been reported. A review of 18 short-term TRT trials found an average initial increase in PSA level of 0.3 ng/mL, and the same authors reported that in six studies of short-term TRT in slightly older men with TDS, there was a higher average increase in PSA level of 0.43 ng/mL (21). Rhoden and Morgentaler reported that 579 hypogonadal men on TRT from nine different studies, with a duration of treatment of about one year, had a mean PSA level increase of 0.46 ng/mL (22). Wang et al. reported that in 163 hypogonadal men on TRT for 3 years, after a small initial increase in PSA level of 0.26 ng/mL at 6 months, there were no further PSA level increases with continued TRT over the following 3 years (23). In another study of 187 hypogonadal men on TRT, there were no significant differences in PSA after one year (24). With the longest follow-up data available, a recent study of 81 hypogonadal men on TRT found that PSA levels remain stable after normalization of testosterone for at

least 5 years (25). The racial differences in PSA levels of hypogonadal men undergoing TRT are unknown.

The aim of the present study was to retrospectively review patients undergoing TRT for TDS to evaluate the racial differences in hypogonadal improvement and PSA levels. We hypothesized that the normalization of testosterone levels, as well as the symptomatic responses, will be similar among hypogonadal Caucasian and African American men undergoing TRT. Based on previous studies of race and PSA, we also hypothesized that the PSA levels of African American men with TDS will be higher than the PSA levels of Caucasian men.

MATERIALS AND METHODS

The medical records of all men evaluated in the Urology Clinic at our institution from January 2000 through June 2006 were queried for a diagnosis of hypogonadism by International Center for Diseases-9 (ICD-9) code 257.2, yielding 267 men initially. In order to be diagnosed with hypogonadism, the patient must have reported symptoms in addition to having had a serum testosterone level below 300 ng/dL. Men then must have been seen in our clinic at least two or more times with the diagnosis.

For inclusion in the study, full demographic information must have been available, and each patient must have had an initial testosterone and PSA level. The patients must have been started on TRT and then had at least one subsequent testosterone level and PSA level measured within one year of initiating TRT. All men included in the study had a normal baseline PSA level prior to initiating TRT and underwent routine digital rectal examinations during treatment. Patients with a biopsy-proven diagnosis or recent history of prostatitis prior to treatment were excluded from the study. Four men were diagnosed with prostate cancer while on TRT and were excluded. The decision to perform prostate biopsy during TRT was made at the discretion of the clinician (CCC) without strict criteria, but all four men with diagnosed cancer had an abnormally increased PSA velocity with two consecutive PSA elevations. Further details of the men diagnosed with prostate cancer have been previously published (25). One Asian male, and one male with race listed as "other," were excluded secondary to insufficient numbers. After applying these criteria, 75 men with TDS were selected for a complete chart review.

Each patient's age at the time of diagnosis, and race, were identified as demographic data. The patient's symptomatic response to treatment was determined subjectively by the patient in follow-up clinic visits as either a positive response or no response. Comorbid conditions including benign prostatic hyperplasia (BPH), coronary artery disease, diabetes mellitus type 2, hypertension, hyperlipidemia, and obstructive sleep apnea were also assessed. BPH was specifically assessed by the clinician prior to initiating TRT by querying for lower urinary tract symptoms and by digital rectal examination. The other comorbid conditions were identified through chart review rather than ICD-9 coding, and were not defined by strict criteria.

Testosterone and PSA levels were drawn during a morning clinic, generally between 9 a.m. and 12 p.m., although the exact time varied and was not recorded. The PSA level was performed by UNC McLendon Laboratories (Chapel Hill, NC), and the total and free testosterone levels were performed by Mayo Medical Laboratories (Rochester, MN). The free testosterone was calculated with a direct radioimmunoassay. The form of TRT was selected by patient preference, and both the form and dose were not consistently available. The target testosterone level was a eugonadal level (> 300 ng/dL) with symptomatic improvement, and the dose was titrated accordingly by the clinician.

The patients were evaluated in regular six-month intervals, and rarely if the treatment dates were not exactly at 6 months they were rounded to the closest six-month interval. Basic statistical data was obtained at each 6-month interval for all variables. The data were compared using a Student's-t-test, with $p < 0.05$ considered statistically significant.

RESULTS

Patient characteristics are available in Table-1. For 16 African American men, the average age at diagnosis of TDS was 53.5 years (range 41-56), com-

Table 1 – *Patient characteristics.*

	Caucasian Men	African American Men
Number of patients	59	16
Age (years)	57.8	53.5
Follow-up (months)	36.9	23.3
BMI (kg/m2)	31.3	32.7
Comorbidities (%)		
BPH	44.1	12.5*
Hypertension	47.4	56.3
Coronary artery disease	23.7	25.0
Diabetes mellitus	22.0	56.3*
Hyperlipidemia	33.9	56.3
Obstructive sleep apnea	10.2	0
Baseline PSA (ng/mL)	1.27	1.32

**p < 0.05 BMI = body mass index; BPH = benign prostatic hyperplasia; PSA =prostate-specific antigen.*

pared with 57.8 years (range 25-82) in 59 Caucasian men (p = NS). The mean follow-up for Caucasian men was 36.9 months compared with 23.3 months for African American men (p = NS). Among comorbid conditions, Caucasian men had more BPH (44.1% versus 12.5%, p < 0.05), and African American men had a higher prevalence of diabetes mellitus type 2 (56.3% versus 22%, p < 0.05).

Pre- and post-treatment (after 1 year) total testosterone levels were 247 ng/dL and 497 ng/dL in Caucasian men (p < 0.05), and 219 ng/dL and 310 ng/dL in African American men (p < 0.05). When the pre-treatment total testosterone level of 247 ng/dL for the Caucasian cohort was compared with the pre-treatment level of 219 ng/dL in African Americans, there was no significant difference (p = NS). Similarly, the post-treatment total testosterone levels were not statistically different when the two racial cohorts were compared, 497 ng/dL in Caucasian men versus 310 ng/dL in African American men (p = NS). Total testosterone levels remained eugonadal at 3 years after initiating TRT, with 355.3 ng/dL in Caucasian men and 326.3 ng/dL in African American men. Free testosterone levels were 7.68 ng/dL and 9.14

Table 2 – *Racial differences in biochemical and symptomatic responses to TRT.*

	Caucasian Men	African American Men
Total testosterone (ng/dL)		
Baseline	246.6	218.9
1 year	496.6	310.1
3 years	355.3	326.3
Free testosterone (ng/dL)		
Baseline	7.68	9.14
1 year	15.63	9.97
3 years	13.23	8.95
Symptomatic Response (%)	93.2	81.3

**p = NS; TRT = testosterone replacement therapy.*

Table 3 *– Racial differences in PSA level.*

	Caucasian Men PSA Level (ng/mL) ± SD	**African American Men** PSA Level (ng/mL) ± SD
Baseline	1.27 ± 1.04	1.32 ± 0.78
6 months	1.39 ± 0.98	1.24 ± 0.64
12 months	1.61 ± 1.47	1.19 ± 0.64
18 months	1.44 ± 1.43	1.00 ± 0.53
24 months	1.38 ± 1.04	1.28 ± 0.49

**p = NS; PSA = prostate-specific antigen; SD = standard deviation.*

ng/dL in Caucasian men and African American men, respectively. At one year, free testosterone after TRT increased to 15.63 ng/dL in Caucasians and 9.97 ng/dL in African Americans, and these values were consistent at 3 years, with 13.23 ng/dL for Caucasians and 8.95 ng/dL in African Americans. The symptomatic response was 81% in African American men and 93% in Caucasian men, although this was not statistically different. The racial differences in the biochemical and symptomatic response are listed in Table-2.

The baseline PSA level was 1.32 ng/mL in African American men and 1.27 ng/mL in Caucasian men. The changes in PSA levels in 6-month intervals are listed in Table-3 and are displayed in Figure-1. At 6-month intervals, there was a small decreasing trend in the PSA level of African American men over 2 years of treatment compared with Caucasian men. However, none of the differences in PSA levels between the two racial cohorts at each time point were statistically significant, and the PSA levels remained stable over the 2 year period in all men.

COMMENTS

In hypogonadal men treated with TRT, racial differences in hypogonadal improvement have not been previously reported. In the present study, symptomatic hypogonadal African American men had comparable baseline testosterone levels as Caucasian men. Additionally, the symptomatic and biochemical responses of total testosterone achieved at 1 year and at 3 years were similar between the two cohorts. The free testosterone levels of African American men did not respond to TRT with the same vigor as the total testosterone. Sex hormone binding globulin levels were unavailable in this study, and therefore the discrepancy between total and free testosterone cannot be further explained. These data suggest that there are no racial differences in hypogonadal improvement among hypogonadal Caucasian and African American men undergoing TRT. This is consistent with eugonadal men, as studies vary as to whether a racial difference in androgen levels exists (4-12).

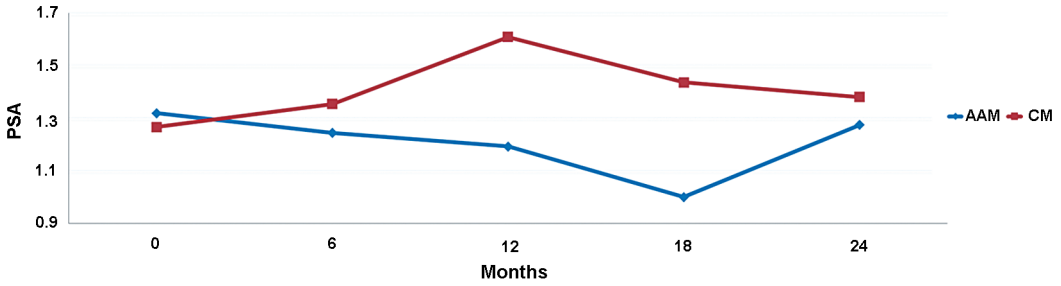

Figure 1 *– Comparing prostate-specific antigen (PSA) change of African American men (AAM) versus Caucasian men (CM) treated with testosterone replacement therapy in 6-month intervals.*

Population-based studies have shown that African American men have higher PSA levels than Caucasian men (14-17). The racial differences in PSA levels of hypogonadal men, and how the PSA changes during TRT among different races, have not been published before this study. Several previous studies have reported that PSA either remains stable, or has a small initial increase that stabilizes over time (21-25). In the small cohort of hypogonadal men in the present study, the baseline PSA was not different between the racial groups, with 1.32 ng/mL in African American men and 1.27 ng/mL in Caucasian men ($p = NS$). After initiation of TRT, the PSA was followed every 6 months for a two year period, and there was a small decreasing trend without statistical significance in the PSA levels of African American men over 2 years of treatment compared with Caucasian men, although the PSA remained stable over time in all men. The higher mean PSA level of eugonadal African American men that has been previously reported was not observed in our cohort of hypogonadal men. Furthermore, after two years of TRT resulting in a corrected, eugonadal total testosterone level, the PSA did not increase in 6-month intervals. These data suggest that androgens are less likely to play a role in the higher baseline PSA levels of eugonadal African American men; however, further research is necessary to explain the observed racial differences in the PSA levels of eugonadal men.

This study has several important limitations. All of the standard limitations inherent to a retrospective chart review apply to this study. The sample size was small with 75 men, and the two racial groups were not well matched, with only 16 African American men compared with 59 Caucasian men. It can be argued that with only 16 African American men that the study is underpowered to identify a true racial difference if there indeed is one. This discrepancy can lead to selection bias that can adversely affect the results. The follow-up period for the Caucasian men was longer with a mean 36.9 months versus 23.3 months for the African Americans. The reason for the different follow-up period is simply that the African American men were lost to follow-up earlier, and this is a limitation of a retrospective study. It is unclear whether the discrepancy in follow-up time affects the results, although ideally the follow-up period would be equal between the two cohorts. The doses of testosterone and delivery system were not consistently available and therefore were not reportable, and these data would be useful correlative data to the biochemical and symptomatic response data. The assessment of a symptomatic response was only quantified in this study by either a positive response or no response, and ideally a validated questionnaire to assess the response would be preferred, although to our knowledge one does not exist. The prevalence of BPH was higher in the Caucasian group, 44.1% versus 12.5% ($p < 0.05$), and because of the positive association between prostate size and serum PSA value, these differences in BPH could affect the baseline PSA level (18). Additionally, diabetes mellitus occurs in a higher incidence in the African American group at 56.3% versus 22.0% in the Caucasian group ($p < 0.05$). Because hypogonadism is a component of metabolic syndrome and can be associated with insulin resistance and diabetes mellitus, the racial difference in the prevalence of diabetes mellitus may confound the analysis (26). There are too few subjects to adjust for the difference in diabetes mellitus, but it can explain the difference of the baseline testosterone level and ultimately the PSA.

CONCLUSIONS

With these limitations in mind, and understanding that this is a small, retrospective study, we can make several useful conclusions based on the fact that this is the first study to report the racial differences in hypogonadal improvement and PSA changes in men undergoing TRT. Hypogonadal African American men had a similar normalization of total testosterone and symptomatic response as Caucasian men undergoing TRT. PSA levels over time trended slightly lower in hypogonadal African American men on TRT compared with Caucasian men, although the PSA remained stable in all men. In this hypogonadal cohort, in contrast to other studies of eugonadal men, higher PSA levels in African Americans were not observed. Larger, prospective studies are necessary to confirm these findings.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In the current article the authors evaluated the effects of testosterone replacement therapy (TRT) assessing racial differences regarding symptomatic response and prostate specific antigen (PSA) variation.

Regarding symptomatic response it is interesting to observe that satisfactory clinical response was reported by 81 and 93% ($p > 0.05$) of African American and Caucasian men, respectively. Even with a potential selected bias related to a higher number of Caucasian men (59 vs. 16) when compared with African American individuals as well as a numerically, but not significantly, period of follow-up in the Caucasian Group (36.9 vs. 23.3 months, respectively). This is a very high rate of clinical response and may reflect strict inclusion criteria, specially related to the levels of baseline testosterone (218 and 246 ng/dL). An important limitation of the current study is the fact that the authors considered only subjective evaluation to characterize clinical response. This aspect limits major considerations regarding clinical response evaluation. Certainly, the major improvements were related to patient sexual concerns. However, appropriate objective evaluation is recommended and there are several tools available in the literature for this purpose. A high rate of clinical response (overall 70%) to TRT could also be observed in a recent study, Rhoden and Morgentaler (1). Even with a shorter follow-up in this

study the first 3 months response was a pivotal issue in maintaining men on TRT.

Another aspect analyzed in the current study was the influence of TRT on PSA levels regarding race. It is well recognized that African America men are of greater risk for developing prostate cancer and that PSA is the most important marker for early diagnosis. There was no significant increase in PSA levels before and after initiating TRT independently of the race group. In a review of the literature of 579 hypogonadal men under TRT the mean increase in PSA levels was 0.46 ng/mL (2). Some authors observed in their series that after a small initial increase (mean 0.26 ng/mL), no further increases in general was observed (3). Also other authors (2) demonstrated, that in a selected population free of prostate cancer, based in a prior biopsy before starting TRT, that PSA decreased in 21%, unchanged in 22%, and increased in 57% cases. All of this information supports the fact of the limited influence of testosterone levels and PSA levels (4). One of the possible explanations regarding this issue is the fact that exogenous testosterone does not raise intraprostatic concentrations of testosterone or dihydrotestosterone, suggesting a saturation model. Based on this concept androgens exert their prostatic effects primarily via binding to the androgen receptor (AR), and maximal androgen-AR binding is achieved at serum testosterone concentrations well below the physiologic range. Finally, prostate function is exquisitely sensitive to variations in androgen concentrations at very low concentrations, but becomes insensitive to changes in androgen concentrations at higher levels (5). Based on this concept the current study demonstrates that testosterone levels have a limited effect on changes in PSA levels independently of race when hypogonadal (non-castrated) are submitted to TRT restoring testosterone levels to an eugonadal status.

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EDITORIAL COMMENT

The diminution in serum androgen levels in aged men has been extensively studied. The mechanisms of this phenomenon have not been fully illustrated, and are probably multifactorial, involving the hypothalamic-pituitary-testicular axis. The greatest concerns regarding testosterone replacement therapy is the fear of causing or promoting prostate cancer. A decline in testicular function with a consequent decline in testosterone level is recognized as a common occurrence in older men (1). Androgens regulate the

function and growth of the prostate and may contribute to the development of prostate cancer and benign prostatic hypertrophy (2).

The effect of parenteral testosterone replacement therapy on prostatic specific antigen (PSA) level or the development or growth of prostate cancer is unclear. This has prompted many investigators to investigate the effect of this treatment on serum PSA levels in hypogonadal men with erectile dysfunction. Previous studies have shown no significant differences between the baseline levels of mean, median, and range of PSA and categories of PSA level (normal, borderline, high) at one year post-testosterone therapy (3). In the present study, the authors elegantly demonstrated that Hypogonadal African American men have a similar normalization of testosterone and symptomatic response as hypogonadal Caucasian men, and PSA levels remained stable over time in both groups. However, more long-term studies are warranted to further investigate the relationship between testosterone replacement and PSA level and to better clarify the effects of parenteral testosterone replacement therapy on the development or growth of prostate cancer.

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