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DOI:10.4158/EP-2017-0203

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EP-2017-0203

Original Article

**ESTROGEN LEVELS DO NOT RISE WITH TESTOSTERONE TREATMENT FOR
TRANSGENDER MEN**

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Running title: Estrogen Levels in Transgender Men, *Endocr Pract.* 2018;24(No. 4)

Submitted for publication **date?**

Accepted for publication January 14, 2018

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Published as a Rapid Electronic Article in Press at <http://www.endocrinepractice.org> on **date?**.

DOI: 10.4158/EP-2017-0203.

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ABSTRACT

Objective: Existing transgender treatment guidelines suggest that for transmasculine treatment, there is a possible need for estrogen-lowering strategies adjunct to testosterone therapy. Further, guidelines advocate consideration of prophylactic female reproductive tissue surgeries for transgender men to avoid the possibility of estrogen-related health risks. Despite the paucity of objective data, some transgender men seek conversion inhibitors. We sought to determine estradiol levels in transgender men treated with testosterone therapy and the change in those levels with treatment, if any.

Methods: Estradiol levels were extracted from the electronic medical records of 34 anonymized transgender men treated with testosterone therapy at the Endocrinology Clinic at Boston Medical Center.

Results: With increased testosterone levels in transgender men, a significant decrease in estradiol levels was noted. There was a significant negative correlation between testosterone levels and body mass index, which may serve to explain part of the mechanism for the fall in estradiol levels. Even though the fall in estradiol levels was significant statistically, the actual levels remained within the normal male range, even with 6 years of follow-up.

Conclusion: These data suggest that when exogenous testosterone is used to achieve normal serum male testosterone levels for transgender men, it is converted to normal male levels of estradiol, with some decline in those estradiol levels that might be attributable to a fall in fat mass. There appears to be no role for aromatase conversion inhibitors or other estrogen-reducing strategies in transgender men. (**Endocr Pract. 2018;24:xxx-xxx**)

Keywords: transgender health, estradiol, hormone replacement therapy

Abbreviation:**BMI** = body mass index**INTRODUCTION**

Transgender individuals are those with gender identity different from external sexual anatomy at birth. Studies show that 0.6% of the adult population in the United States identify as transgender (1). Many, but not all, transgender individuals undergo hormone therapy. The standard transmasculine regimen includes exogenous androgens to virilize the individual. Current evidence suggests that hormone therapy for transgender adults is relatively safe, without the risk of significant adverse effects (2). However, the efficacy of treatment has not been assessed for many regimens, including treatment with testosterone therapy alone.

There are a lack of data on testosterone treatment in transgender men, both in regard to effect on estradiol levels and overall treatment efficacy. In nontransgender populations, there is reported concern for undesirable estrogenic effects in male-bodied individuals administered exogenous testosterone. Reports have also associated increased serum estradiol levels with risk of gynecomastia in males in general (4).

The concerns regarding aromatization of testosterone and consequent supraphysiologic levels of estradiol have extended to the treatment of transgender men. Indeed, the 2017 Endocrine Society clinical practice guidelines for transgender individuals recommend intentional decrease of endogenous estradiol (4), and the 2012 Standards of Care–7 from the World Professional Association for Transgender Health suggest oncology consultation for certain at-risk transgender men (5). The guidelines report an absence of data for female reproductive tract malignancy in trans men but still suggest consideration of total hysterectomy and oophorectomy

in transgender men to lower risks of female reproductive tract disease. A proposed mechanism for female reproductive tract disease in transgender men is aromatization of testosterone to estradiol, with the suggestion that exogenous testosterone causes heightened levels of estradiol, posing a risk factor for endometrial cancer (6). Thus, concerns are raised for transgender men that testosterone treatment may result in undesired estrogenic effects (menstrual cycle, pelvic pain) and compromised treatment via aromatase conversion of androgens to supraphysiologic levels of estradiol (7).

In contrast to the concerns for supraphysiologic estrogen levels, a 1-year study by the European Network for the Investigation of Gender Incongruence found that in transgender men on testosterone treatment, estradiol levels decreased significantly over a 6-month period (8). Deutsch et al (9) also found a decrease in estradiol levels over a 6-month period. Both studies suggested that the testosterone treatment suppresses the hypothalamic pituitary axis, with a resulting reduction in endogenous estradiol (6).

An associated consideration in noting potential changes in estradiol level in transgender men is the observation of body mass index (BMI), a measure of adiposity. It is generally accepted that in nontransgender men, higher BMI relates to increased adipose tissue, the site of testosterone aromatization to estradiol which affects serum estradiol levels. However, Rolf et al (10) observed no change in the BMI and estradiol levels of hypogonadal men treated with testosterone. This observation contrasted with a secular trend for increasing BMI and estradiol over the same time interval among their control cohort of eugonadal men (10,11). Thus, the primary impact of testosterone treatment for hypogonadal men might be increased muscle mass with increased measured BMI but no increase in estradiol. Such a phenomenon may be the primary observation in transgender men treated with testosterone as well. The current study

sought to investigate the impact of a longer period of testosterone therapy on estradiol levels in transgender men.

METHODS

Inclusion Criteria and Data Collection

In 2015 and 2016, we asked all transgender men who visited the Endocrinology Clinic at Boston Medical Center and were treated with testosterone for consent for a retrospective anonymous chart review. Of the 36 men, 34 agreed (94%).

The medical records of the identified 34 transgender men were retrospectively examined and data extracted in a de-identified fashion compliant with the Internal Review Board at the Boston University Medical Campus. Data in the charts were sufficient to review 6 years of treatment with testosterone therapy.

Because of the significant heterogeneity among metabolic responses in people, we used each individual as his own control, following the change in the evaluated parameters both over time and relative to the testosterone levels achieved.

Patient Treatment and Sex Hormone Assay

At Boston Medical Center, the standard transmasculine hormone treatment approach includes testosterone, typically through a weekly intramuscular or subcutaneous injection. Testosterone cypionate and testosterone enanthate are used interchangeably, with the choice typically depending on local stock. Doses are titrated up to a typical maximum of 125 mg weekly. Peak testosterone levels are measured for routine monitoring, and trough levels are checked at larger intervals. Peak levels are measured 24 to 48 hours after the weekly testosterone injection, and trough levels are measured immediately before. The goal is to achieve serum

testosterone levels that are within the normal range for nontransgender men, with trough levels at 1 week kept above 300 ng/dL. No estrogen blockers were used in the treatment of transgender men.

Serum testosterone levels reported are peak levels (measured 24 to 48 hours after an injection) and were total testosterone samples assayed at Quest Diagnostics (Chantilly, VA) using liquid chromatography–tandem mass spectrometry (LC/MS/MS). Serum estradiol levels reported were based on samples assayed at Quest Diagnostics (San Juan Capistrano, CA) using Quest’s ultrasensitive estradiol assay with LC/MS/MS methodology.

Data Analysis

Data used in the study included the testosterone, estradiol, and hematocrit levels along with BMI of each patient at each visit to the clinic. Patients were followed at 3-month intervals for the first year and 6-month intervals thereafter; however, not all patients had recorded laboratory values for all measures in each visit.

Laboratory levels covering the period for each patient from initiation of therapy through 6 years of treatment (15 clinic visits) were graphed. Bivariate analyses were conducted on estradiol versus testosterone, estradiol versus BMI, testosterone versus BMI, and testosterone versus hematocrit to determine relationships among these variables.

Among our cohort, 22 patients started testosterone at time 0, and 12 started testosterone prior to time 0. We analyzed our data for each group separately. We only used the new start cohort to define the baseline. We found no difference between the subcohorts in either the direction or significance of changes observed for all other endpoints.

RESULTS

Age of Transgender Individuals Studied

On average, transgender men were 33 years old. The range was 18 to 68 years old, with a median of 31 years old (Table 1).

[Insert Table 1 near here]

Testosterone Levels Increased With Treatment

Testosterone levels rose significantly between baseline (35 ng/dL) and several months after the initiation of treatment ($P<.0001$). However, once steady-state doses were achieved after approximately 9 months, peak testosterone levels did not significantly change and were maintained at an average of 650 ng/dL (Fig. 1).

[Insert Figure 1 near here]

Estradiol Levels Decreased With Increasing Testosterone Levels in Transgender Men

A regression analysis of serum estradiol with respect to serum testosterone revealed that there was a significant decrease in estradiol levels with increasing testosterone ($P<.02$; Fig. 2 A).

At Steady-State, Estradiol Levels Did Not Decrease Over Time

A regression analysis of serum estradiol with respect to time revealed the appearance of a declining trend in estradiol levels from a baseline average of 81 pg/mL to an average of 54

pg/mL upon initiation of testosterone therapy, but the change was not statistically significant. At steady-state, there was no change in estradiol levels over 6 years ($P = .2$; Fig. 2 B).

[Insert Figure 2 near here]

BMI Decreased With Increased Serum Testosterone Level

Transgender men had a starting average BMI of 31 kg/m², and mean BMI achieved at steady state was 29 kg/m². A regression analysis of testosterone with respect to BMI revealed a statistically significant decrease in BMI with increasing serum testosterone levels ($P < .05$; Fig. 3).

Increased BMI Was Not Associated With Change in Estradiol Levels

Estradiol levels in transgender men remained stable even when BMI was greater. Regression of estradiol with respect to BMI showed no significant correlation between the two ($P = .96$; Fig. 4).

[Insert Figure 3 near here]

Hematocrit Increased With Increased Serum Testosterone Level

Consistent with previous reports by others (10), regression analysis showed a statistically significant increase in hematocrit with increased serum testosterone ($P < .05$). However, the hematocrit levels measured remained within normal range, at an average of 45%.

[Insert Figure 4 near here]

DISCUSSION

While there has been much concern about the potential harm from transgender medical intervention (13), reports on the efficacy of specific treatment regimens are lacking. Fear of harmful androgen impact on female reproductive tissue (2) has resulted in some guidelines advocating for transgender men to undergo hysterectomy to avoid that risk. A proposed mechanism for the harmful effect is conversion of exogenous testosterone to estradiol with resulting supraphysiologic estradiol levels (5).

This is the first report to demonstrate the response of estradiol to testosterone treatment in transgender men over an extended period of time. Previous authors have reported a decrease in estradiol levels over shorter follow-up periods, suggesting that testosterone treatment can suppress the hypothalamic-pituitary axis with a resulting reduction in endogenous sex steroids, including estradiol. We found that there was a significant decrease in estradiol levels with increasing testosterone treatment. Although exogenous testosterone may suppress the hypothalamic-pituitary axis, some testosterone aromatizes to estradiol, and physiologic levels are maintained. While the change in estradiol level relative to testosterone was significant, when analyzed over time, the change was not significant in our cohort, despite a trend toward decreasing estrogen upon initiation of testosterone therapy. Thus, a larger sample size might confirm the absence of change or might demonstrate a statistically significant decrease.

Our data suggest that the estrogen levels among the transgender men may have been slightly lower when the source was peripheral aromatization of exogenous testosterone relative to the estradiol levels in the same individuals when the source was their own ovaries. However,

the key finding from our data is that it is extremely unlikely that there was an unappreciated rise in serum estradiol levels secondary to aromatization from exogenous testosterone.

Although our data did not address intracellular aromatization of testosterone to estrogen, the decrease in serum estradiol levels provides some support for more recent proposals that there is no extra risk to female reproductive tissues, such as endometrium, cervix, and breast tissue, from androgen exposure at normal male levels (2). Further, the maintenance of serum estradiol levels in the normal range throughout the range of serum testosterone levels and across many years was reassuring that bone mineral density should be secure vis-à-vis sex steroid impact in testosterone-treated transgender men (14).

In contrast to reports among nontransgender men, estradiol levels were not higher with higher BMI in our cohort of transgender men (15). A BMI increase in our cohort could reasonably have been expected in response to exogenous testosterone resulting in more muscle mass as opposed to adipose tissue. Thus, even in the setting of a rise in BMI, the actual fat content would have been stable or even decreasing for these individuals, with decreased subsequent estradiol production (2). Elbers et al (16) reported that in transgender men, testosterone treatment impacts body fat distribution by decreasing subcutaneous fat composition. Such a decrease would have minimal impact on estradiol levels, because subcutaneous fat is known to have a lower rate of estradiol production compared to visceral fat (17). Still, the net impact may be the observed decrease in serum estradiol levels.

Therefore, in our cohort, we believe the lack of increase in estradiol even in the setting of greater BMI during testosterone treatment may be attributed to a change in the fat mass with its off-setting impact on aromatase conversion.

In general, among our patients, increasing testosterone levels resulted in a significant drop in BMI. Variations on these findings have been observed among nontrans male populations. Future studies should investigate the mechanism of the observed decrease in BMI. The increased muscle mass from testosterone treatment may mean that there is an even larger loss of fat mass than might have been predicted.

Our cohort saw a significant increase in hematocrit, although still within the normal range. Although not significant, a report by Jacobeit et al (18) is representative of others in that they found a modest upward trend in hematocrit over 36 months, with a range of $41 \pm 4\%$ to $46 \pm 4\%$. Perhaps the greater significance in our data can be attributed to the longer duration of our study and larger sample size.

Our study suffered from a modest-sized cohort. Therefore, some of the trends we observed for other endpoints might prove significant with a larger sample. In addition, our study was limited to total testosterone levels because they are the most consistently measured and have been so over the interval of the study. Still, confounding related to binding proteins cannot be addressed with these data.

CONCLUSION

Estradiol levels remain within the normal range in medically treated transgender men and do not rise. Thus, there is no evidence for elevated estradiol levels that may need to be mitigated with aromatase inhibitors. Further, we found no evidence of serum estradiol rise acting as added risk to female reproductive tissues in transgender men, although these data do not address intracellular aromatization of testosterone to estrogen.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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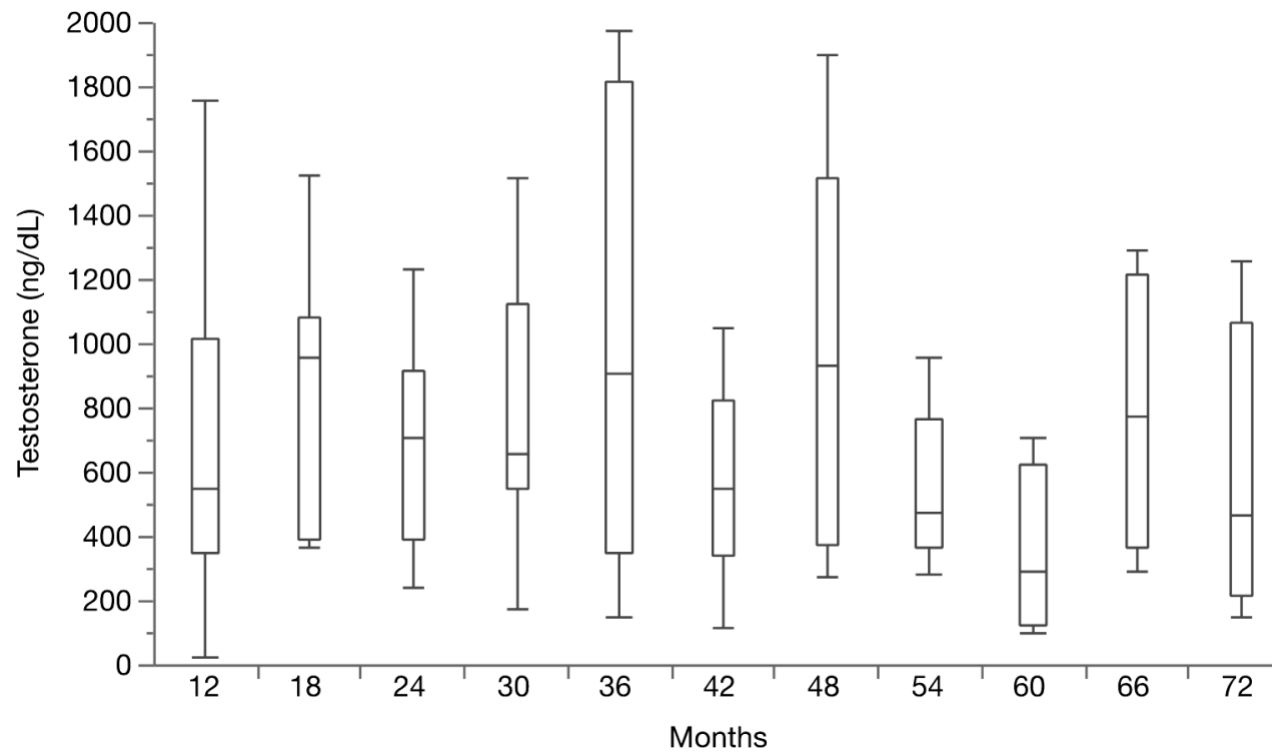
FIGURES & TABLES

Fig. 1. There was no significant change in testosterone levels among treated transgender men once steady-state levels were achieved ($P>.05$).

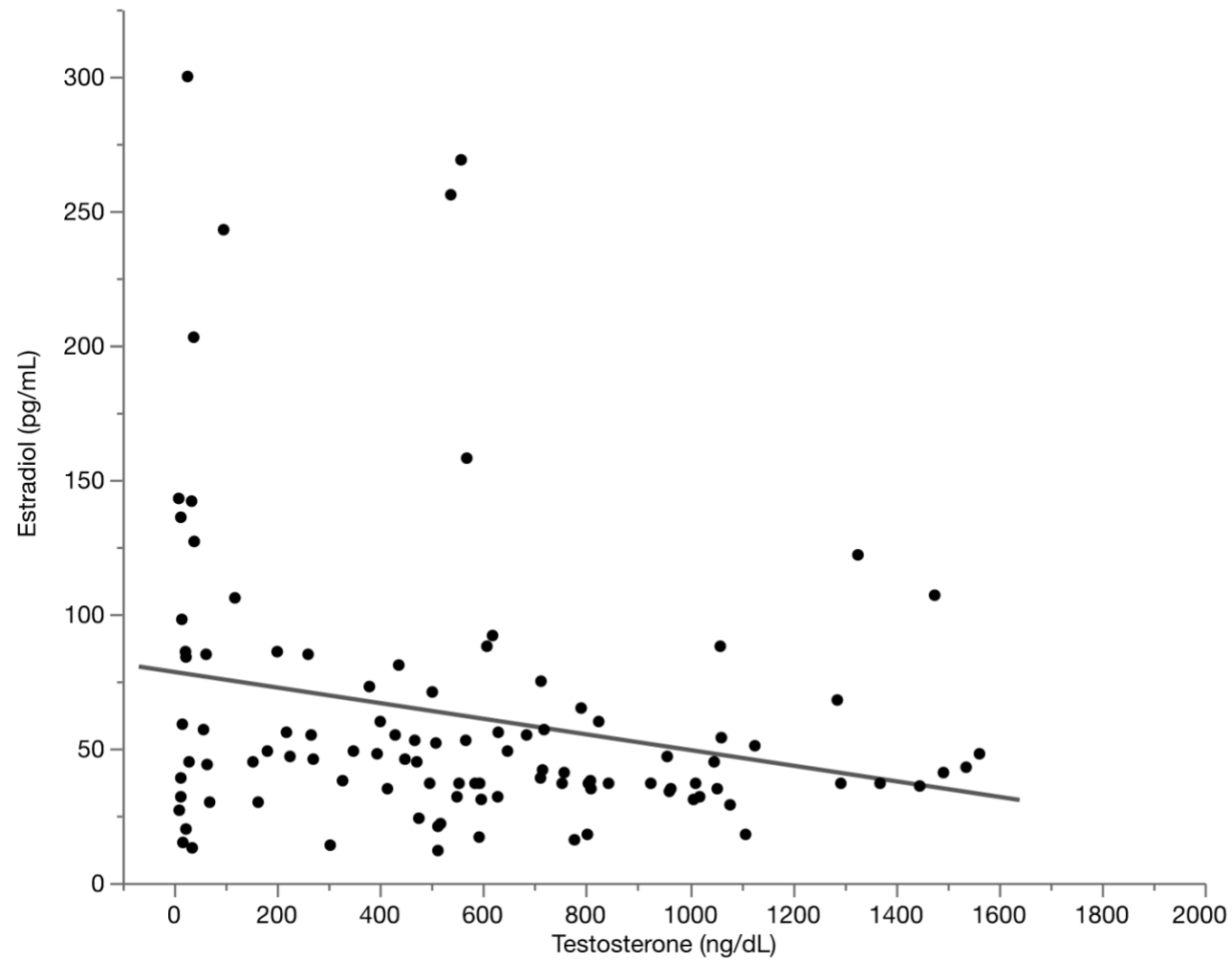
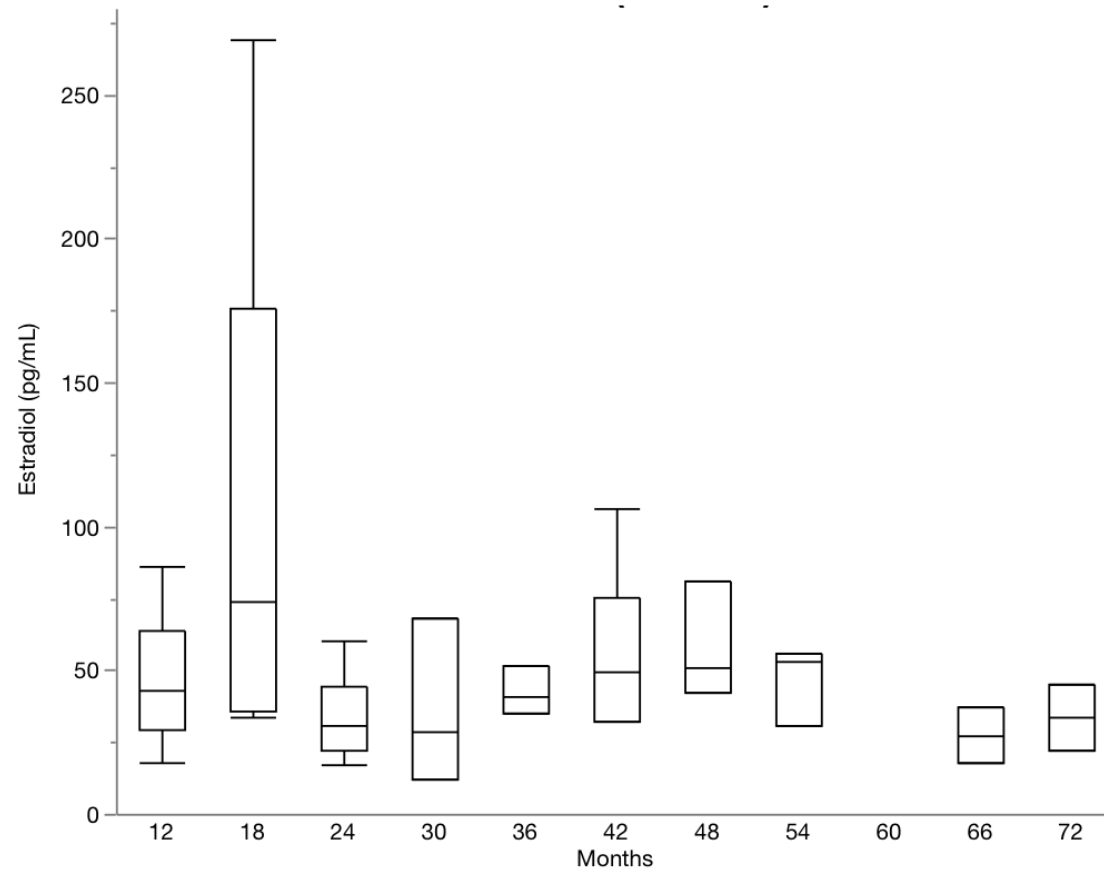


Fig. 2. (A) There was a significant decrease in estradiol levels with increasing testosterone ($P < .02$).



(B) At steady-state, there was no significant change in estradiol levels over time ($P = .2$).

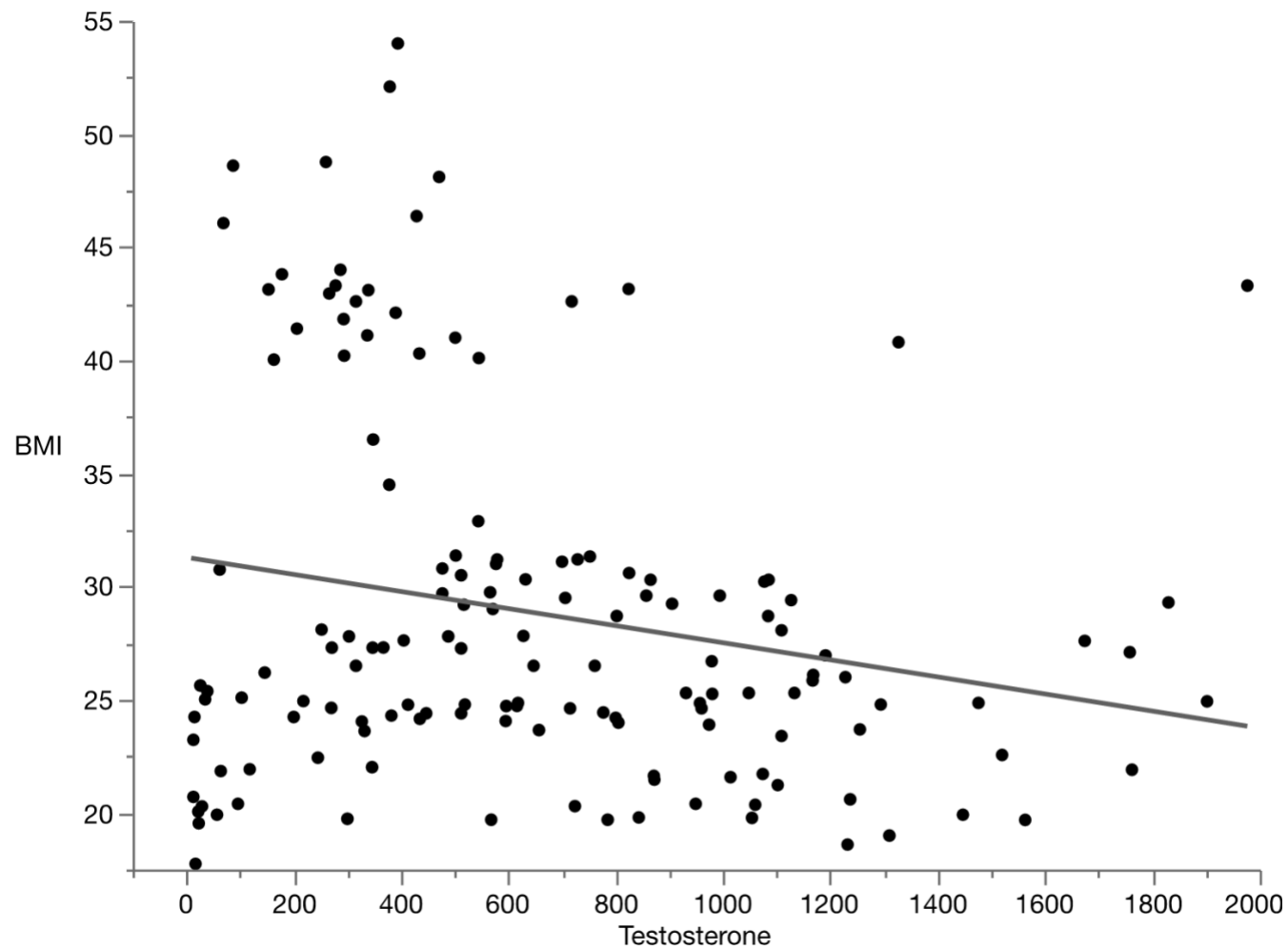


Fig. 3. There was a significant decrease in body mass index (BMI) with increasing testosterone ($P = .01$).

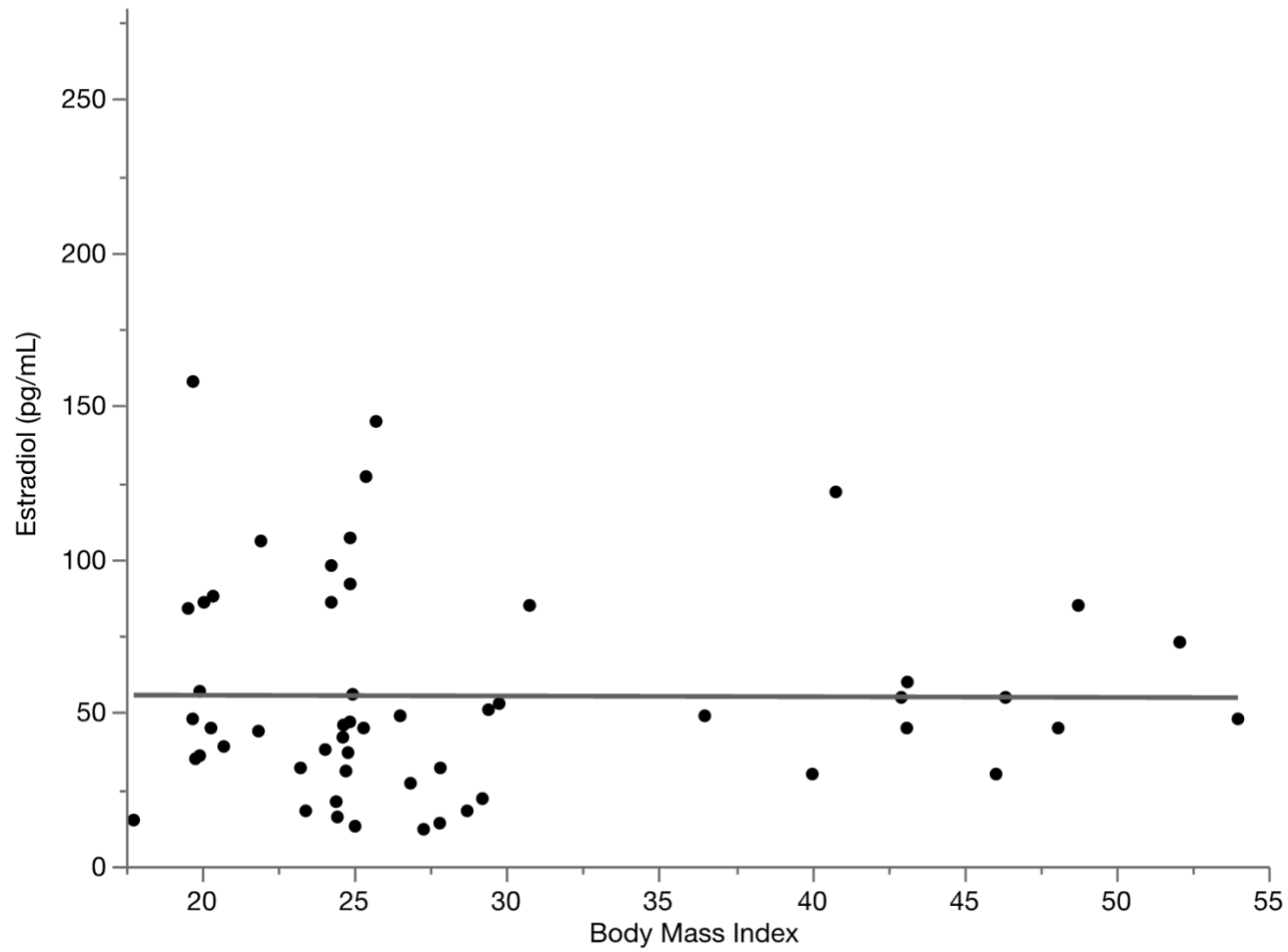


Fig. 4. There was no significant change in estradiol level with increasing body mass index ($P = .96$).

Table 1
Demographics of Patients Included in the Study^a

	Mean	Median	Range
Age at first visit (years)	33	31	18-68
Average BMI (kg/m ²) over visits	28.9	26.5	18.5-44.2
Testosterone dosage (mg)	80.3	75	25-200

Abbreviation: BMI = body mass index.

^aTestosterone was given weekly and administered parenterally (either intramuscularly or subcutaneously). The range reflects peak levels at 24 to 48 hours after a weekly injection. Trough levels were ascertained on occasion for all patients to confirm their being above the lower limit of the normal male range.