Original Contribution

Associations Between Longitudinal Changes in Serum Estrogen, Testosterone, and Bioavailable Testosterone and Changes in Benign Urologic Outcomes

Jennifer L. St. Sauver*, Debra J. Jacobson, Michaela E. McGree, Cynthia J. Girman, George G. Klee, Michael M. Lieber, and Steven J. Jacobsen

* Correspondence to Dr. Jennifer L. St. Sauver, Division of Epidemiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (email: stsaucer.jennifer@mayo.edu).

Initially submitted June 24, 2010; accepted for publication November 18, 2010.

Some men have rapid increases in benign prostatic enlargement and lower urinary tract symptoms (LUTS), and it is not clear how sex steroid hormones contribute to the rates of change in these urologic outcomes. Therefore, the authors conducted a population-based cohort study of 648 men residing in Olmsted County, Minnesota, from 1990 to 2007, to examine associations between baseline sex steroid hormones, the rate of change in these hormones, and the rates of change in LUTS, maximum urinary flow rate, and prostate volume. Annual changes in hormone levels and urologic outcomes were calculated using mixed-effects regression models. Associations between hormone variables and rates of change in urologic outcomes were assessed with linear regression models. Higher baseline estradiol levels and rapid declines in estradiol over time were associated with rapid increases in LUTS and rapid decreases in maximum flow rate. Lower baseline bioavailable testosterone levels and more rapid declines in bioavailable testosterone were associated with more rapid increases in prostate volume. These results suggest that both absolute sex steroid hormone levels and the rates at which the levels change may be important in the development of urologic conditions in aging men.

estradiol; prostatic hyperplasia; testosterone

Abbreviations: AUASI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; DHT, dihydrotestosterone; LUTS, lower urinary tract symptoms.

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) are common in aging men. The factors that lead to the development of these conditions have not been clearly defined; however, the development of BPH is known to be sex steroid hormone-dependent (1, 2). Testosterone is converted to dihydrotestosterone (DHT) by the 5α-reductase enzyme, and higher DHT levels are associated with prostate enlargement (3). Additionally, 5α-reductase inhibitors have been shown to be effective for reducing prostate volume, thereby demonstrating the importance of testosterone in prostate growth (4, 5). Animal model data also suggest that other sex steroid hormones, including estradiol, may contribute to LUTS through effects on the urethra and bladder (6–8).

Despite these data, studies in which associations between serum sex steroid hormone levels and prostate enlargement and LUTS have been examined showed modest or no correlations between hormone levels and these outcomes (9–13). Data examining longitudinal associations between sex steroid hormone levels and benign urologic outcomes are more limited. However, higher estradiol levels have been associated with a decreased risk of later receiving surgery for BPH (14). Additionally, higher estradiol and testosterone levels, as well as a higher testosterone:17β-diol-glucuronide ratio, were associated with a lower risk of developing symptomatic BPH (15). Kristal et al. (15) suggested that higher serum estradiol and testosterone levels might be markers for decreased 5α-reductase activity, as inhibitors targeting this enzyme have been associated with higher serum levels of these hormones.

In summary, cross-sectional associations between sex steroid serum hormone levels and BPH and LUTS are modest,
but longitudinal studies suggest that higher serum levels of estradiol and testosterone may be associated with a decreased risk of later developing benign urologic outcomes. However, few data are available regarding changes in hormones and changes in urologic outcomes over time. The rates at which prostates enlarge or LUTS develop vary significantly among men (16–18). Sex steroid hormone levels also change with increasing age (19–22), but it is not clear how these levels or the rates of change in these levels contribute to the rates of change in prostate volume or LUTS. To address these questions, we determined whether baseline levels of serum sex steroid hormones were associated with the rates at which LUTS, maximum urinary flow rate, or prostate volume changed over time. We also determined whether the rates of change in these hormones were associated with the rates of change in these urologic outcomes.

MATERIALS AND METHODS

Study population

Details related to the development of the study cohort have been previously published (23, 24). Briefly, a randomly sampled, population-based group of white men between 40 and 79 years of age residing in Olmsted County, Minnesota, in 1990 was identified through the Rochester Epidemiology Project. The Rochester Epidemiology Project is an ideal population-based sampling frame, as it captures virtually the entire population of Olmsted County, Minnesota (25). For men between 40 and 79 years of age in 1990, the Rochester Epidemiology Project identified 96% of the men in this age range predicted to reside in this county by the 1990 US Census. We used the complete list of these men as our sampling frame and chose a random sample of 5,135 of these men to participate in the study in 1990. The medical records of participants and nonparticipants indicated few differences except for a slightly greater prevalence of benign urologic conditions among participants (26). Participants completed a baseline questionnaire that assessed comorbidities, biosocial risk factors, and the presence of LUTS using questions similar to those from the American Urological Association Symptom Index (AUASI). All participants also voided into a portable urometer to measure maximum urinary flow rates. In 1990, a random subsample of 537 men (25.4%) was invited to participate in a detailed clinical urologic examination that included transrectal ultrasound to determine prostate volume, and those participants also provided a morning blood sample. Overall, 476 (89%) men agreed to participate in this more intensive examination.

The cohort was actively followed on a biennial basis for 16 years. During the second and third rounds, men who did not participate in the follow-up were replaced by men randomly selected from the community (n = 332). Of the replacement men, 158 were added to the clinic subset. Since that time, the study has been maintained as a closed cohort, but 133 men who participated in only the questionnaire portion of the study were added to the in-clinic portion of the study in round 8 (Figure 1). A total of 767 men have participated in at least 1 in-clinic examination. Of these men, 648 (84%) had hormone levels available for evaluation. Men who dropped out of the study were more likely to be older and to have suffered a stroke than were men who remained in the study. The presence of LUTS was not associated with dropout (27). The study was reviewed and approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center.

Measurement of LUTS, prostate volume, and maximum flow rate

Methods for measuring each outcome have been previously described. Briefly, LUTS were measured by using a previously validated questionnaire with questions similar to those in the AUASI (28, 29). Prostate volume was measured by transrectal ultrasound (Briel & Kjær type 8551
(7.0 MHz) endosonic multiplane transducer, Nærum, Denmark). Maximum urinary flow rates were measured electronically using a Dantec 1000 urometer (Dantec Medical, Santa Clara, California) (30).

Measurement of serum sex steroid hormone levels

**Estradiol.** A high-sensitivity double antibody radioimmunoassay was used to measure estradiol levels (Diagnostic Products Corp., Los Angeles, California) in samples collected during rounds 5 and 7. Estradiol assays were run twice for each individual, and the mean of the 2 values was used in the analysis (10, 31). Estradiol levels in samples collected during rounds 8 and 9 were assayed using a competitive binding immunoenzymatic assay (Beckman Coulter Unicel Dxi 800, Brea, California). Intraassay coefficients of variation for estradiol were 18.3%, 3.8%, and 7.2% at 3.6, 40.1, and 297 pg/mL, respectively. Interassay coefficients of variation for estradiol were 10.7%, 8.9%, and 7.3% at 21.1, 53.98, and 133 pg/mL, respectively.

**Total testosterone.** A competitive chemiluminescent immunoassay on the ACS-180 automated immunoassay system (Bayer Diagnostics Corp., Tarrytown, New York) was used to measure total testosterone in serum samples collected during rounds 2 and 3. Testosterone levels in samples collected during rounds 5, 7, 8, and 9 were assayed using a competitive binding immunoenzymatic assay (Beckman Coulter Unicel Dxi 800). Intraassay coefficients of variation for testosterone were 8.0%, 4.1%, and 3.2% for the levels of 98, 442, and 984 ng/dL, respectively. Interassay coefficients of variation for testosterone were 9.3%, 9.0%, and 8.8% at 114, 438, and 848 ng/dL, respectively.

**Bioavailable testosterone.** Serum albumin levels were measured by binding albumin to brom cresol green at a pH of 4 and were measured photometrically at 600 nm by using a Roche/Hitachi 912 chemistry analyzer (Roche Diagnostics, Basel, Switzerland). Sex hormone-binding globulin was measured using the Immulite 2000 two-site chemiluminescent immunoassay (Diagnostic Products Corp., Los Angeles, California). Bioavailable testosterone was then calculated from total testosterone, albumin, and sex hormone-binding globulin concentrations with an equation system adapted from Sødergård et al. (32; reviewed in reference 33).

Statistical analyses

**Standardization of sex steroid hormone measures.** Changes in assays or the stability of the sex steroid hormones in frozen serum may have led to changes in hormone levels over time independent of biologic factors. Therefore, we assessed the relations between hormone measurements for each round and age and adjusted to ensure that measurements for a given age were consistent between rounds. Samples collected during round 2 had consistently higher testosterone levels by age than did samples collected during the other rounds of follow-up (Figure 2A). However, slopes across age were consistent; therefore, an offset was applied so that all hormone levels were standardized to round 9 levels. This standardization ensured that hormone levels for a given age were comparable across all rounds (Figure 2B). This method is similar to that reported by Harman et al. (19), in which testosterone levels measured and stored at multiple points in time were standardized to a common date. As round 2 measures were consistently the highest, data were standardized both including and excluding round 2 measures. Results were consistent whether or not round 2 measures were included; therefore, final standardizations included round 2 measures.

**Estimation of changes in sex steroid hormones and urologic outcomes.** Linear mixed-effects regression models were used to estimate annual longitudinal changes in each hormone measure by regressing each measure on the time from initial measure and 10-year age groups. An interaction term was included to allow for different slopes across age groups. An overall annual change for each man was determined by combining the average longitudinal changes (fixed effects) with the individual changes (random effects). Similarly, both fixed and random effects allowed determination of an overall baseline intercept for each age decade and allowed for offsets for each individual. Measurements were obtained after prostate cancer diagnosis and use of herbal medications for BPH, 5α-reductase inhibitors, testosterone replacement therapy, and leuprolide acetate. Linear mixed-effects models were used to estimate annual longitudinal changes in each urologic measure (AUASI score, maximum flow rate, and prostate volume). Measurements of prostate volume, AUASI score, and maximum flow rate were censored after development of prostate and bladder cancers, BPH surgeries and procedures, and use of any medications for treatment of BPH.

As the first sex steroid hormone measures were from serum collected in 1992 (round 2 of follow-up), the corresponding 1992 urologic measures were used as the baseline outcomes. Because of skewed distributions, a natural log transformation was applied to hormone measurements, maximum flow rate, and total prostate volume measurements. The slopes therefore represent the percentage of change per year assuming an exponential growth curve. AUASI score slopes represent the absolute change per year in score. The maximum likelihood methodology used in mixed model analysis implicitly averages over the predictive distribution for missing data, so no further imputing was performed.

**Estimating correlations between baseline sex steroid hormones and rates of change in hormone levels and rates of change in urologic outcomes.** Spearman rank correlation coefficients were used to estimate relations between baseline sex steroid hormone levels and annual changes in hormone measures with annual changes in urologic measures (AUASI score, maximum flow rate, and prostate volume). Multiple linear regression models were used to assess relations of annual changes in urologic measures (slopes) with baseline urologic measures (intercepts), baseline hormone levels (intercepts), and annual changes in hormone levels (slopes). Models were constructed in 2 ways. The first set of models included baseline urologic measures, baseline sex steroid hormone measures, and rates of change in hormone measures. The second set of models considered the same variables and used forward selection regression. As results from both sets of models were virtually identical, the models including all
variables are presented. Models were individually adjusted for baseline age, body mass index, alcohol use, and smoking status. Because only age was significant in the multivariable models and because addition of the other covariates did not alter either the $R^2$ value or the point estimates of the other variables, only the age-adjusted models are presented.

RESULTS

Data from 648 (84.5%) men were included in this study. The median follow-up for events occurring after a testosterone measure was 8.0 years (25th, 75th percentiles: 2.7, 12.2), whereas the median follow-up for events after an estradiol measure was 7.0 years (25th, 75th percentiles: 2.7, 8.0).

Baseline median and mean levels of sex steroid hormones and urologic outcomes are presented in Table 1 and Figure 3A. Baseline bioavailable testosterone levels were lowest among the oldest men compared with the youngest men in the study ($P < 0.001$). Baseline estradiol and testosterone did not differ by age ($P_{\text{trend}} = 0.86$ and 0.63, respectively).

Figure 2. A) Natural log-transformed testosterone levels by age at the time of the measurement (rounds 2 through 9), Olmsted County, Minnesota, 1990–2007. B) Natural log-transformed testosterone levels by age at the time of the measurement (rounds 2 through 9) with all measures standardized to round 9 hormone levels.
Table 1. Characteristics of the Study Population, Olmsted County, Minnesota, 1990–2007

<table>
<thead>
<tr>
<th>Age Range, Years</th>
<th>Overall</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>≥70</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>25th Percentile</td>
<td>75th Percentile</td>
<td>Median</td>
<td>25th Percentile</td>
<td>75th Percentile</td>
</tr>
<tr>
<td>Baseline value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol, pg/mL</td>
<td>24.02</td>
<td>21.83</td>
<td>32.12</td>
<td>22.38</td>
<td>21.83</td>
<td>30.57</td>
</tr>
<tr>
<td>Testosterone, ng/dL</td>
<td>338</td>
<td>260</td>
<td>436</td>
<td>351</td>
<td>256</td>
<td>436</td>
</tr>
<tr>
<td>Bioavailable testosterone, ng/dL</td>
<td>92.72</td>
<td>67.46</td>
<td>123.32</td>
<td>120.78</td>
<td>92.89</td>
<td>160.87</td>
</tr>
<tr>
<td>AUASI score</td>
<td>5</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Maximum flow rate, mL/second</td>
<td>19.70</td>
<td>14.20</td>
<td>26.00</td>
<td>20.75</td>
<td>16.20</td>
<td>28.20</td>
</tr>
<tr>
<td>Prostate volume, mL</td>
<td>26.93</td>
<td>21.75</td>
<td>34.16</td>
<td>22.72</td>
<td>18.95</td>
<td>26.79</td>
</tr>
<tr>
<td>Rate of change, % change/year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.13</td>
<td>-0.32</td>
<td>0.64</td>
<td>-0.45</td>
<td>-0.73</td>
<td>0.18</td>
</tr>
<tr>
<td>Testosterone</td>
<td>-0.19</td>
<td>-0.49</td>
<td>0.11</td>
<td>0.25</td>
<td>0.11</td>
<td>0.45</td>
</tr>
<tr>
<td>Bioavailable testosterone</td>
<td>-1.66</td>
<td>-1.92</td>
<td>-1.46</td>
<td>-2.04</td>
<td>-2.18</td>
<td>-1.90</td>
</tr>
<tr>
<td>AUASI scoreb</td>
<td>0.25</td>
<td>0.12</td>
<td>0.40</td>
<td>0.17</td>
<td>0.08</td>
<td>0.29</td>
</tr>
<tr>
<td>Maximum flow rate</td>
<td>-1.66</td>
<td>-2.21</td>
<td>-1.19</td>
<td>-1.18</td>
<td>-1.51</td>
<td>-0.89</td>
</tr>
<tr>
<td>Prostate volume</td>
<td>2.24</td>
<td>1.73</td>
<td>2.82</td>
<td>2.34</td>
<td>1.80</td>
<td>2.79</td>
</tr>
</tbody>
</table>

Abbreviation: AUASI, American Urological Association Symptom Index.

a Test for trend across age groups.
b AUASI score is raw change per year.
The rates at which hormones and urologic outcomes changed over time are shown in Table 1 and Figure 3B. The rate at which testosterone levels declined was highest among the men in the oldest age group (−0.98% per year among those ≥70 years of age vs. 0.25% per year among those 40–49 years of age; \( P_{\text{trend}} < 0.001 \)). However, declines in bioavailable testosterone levels were the lowest among men in the oldest age group (−1.37% per year among those ≥70 years of age vs. −2.04% per year among those 40–49 years of age; \( P_{\text{trend}} < 0.001 \)). The rate at which estradiol levels changed was associated nonlinearly with baseline age of the men in the study (\( P = 0.03; \) Table 1 and Figure 3B).

In univariable models, rapid changes in AUASI score were correlated with baseline AUASI score, baseline bioavailable
testosterone levels, and the rates of change in both testosterone and bioavailable testosterone levels (Table 2). Similar associations were seen when rate of change in maximum flow rate was examined as the outcome (Table 2). A different pattern was seen when rate of change in prostate volume was examined as the outcome, as baseline estradiol and rate of change in estradiol were associated with prostate volume (Table 2).

In multivariable models, a higher baseline AUASI score and higher baseline estradiol but a more rapid decline in estradiol was associated with a more rapid increase in AUASI score ($R^2 = 0.20, P < 0.001$; Table 3). Similarly, a lower baseline maximum flow rate and a higher baseline estradiol level were associated with a more rapid decline in maximum flow rate ($R^2 = 0.37, P < 0.001$; Table 3). Finally, a higher baseline prostate volume, a lower baseline bioavailable testosterone level, and a more rapid decline in bioavailable testosterone were associated with more rapid increases in prostate volume ($R^2 = 0.42, P < 0.001$; Table 3).

### Table 2. Correlations Between Hormone and Urologic Outcome Intercept Values, Rates of Change in Hormone Levels, and Rates of Change in Urologic Outcomesa, Olmsted County, Minnesota, 1990–2007

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>AUASI Score, Change/Year</th>
<th>Maximum Flow Rate, % Change/Year</th>
<th>Prostate Volume, % Change/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman R</td>
<td>P Value</td>
<td>Spearman R</td>
</tr>
<tr>
<td>Baseline (intercept) value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.02</td>
<td>0.74</td>
<td>-0.10</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.06</td>
<td>0.16</td>
<td>-0.01</td>
</tr>
<tr>
<td>Bioavailable testosterone</td>
<td>-0.19</td>
<td>&lt;0.001</td>
<td>0.48</td>
</tr>
<tr>
<td>AUASI score</td>
<td>0.51</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Maximum flow rate</td>
<td></td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of change (% change/year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>-0.02</td>
<td>0.59</td>
<td>-0.08</td>
</tr>
<tr>
<td>Testosterone</td>
<td>-0.28</td>
<td>&lt;0.001</td>
<td>0.56</td>
</tr>
<tr>
<td>Bioavailable testosterone</td>
<td>0.19</td>
<td>&lt;0.001</td>
<td>-0.46</td>
</tr>
</tbody>
</table>

Abbreviation: AUASI, American Urological Association Symptom Index.

a Slopes and intercepts were obtained from models of natural log-transformed hormone measures, maximum flow rate, and prostate volume.

### Table 3. Proportion of Variance Explained by Multivariable Longitudinal Regression Modelsa Predicting Rate of Change in AUASI Score, Maximum Flow Rate, and Prostate Volumeb, Olmsted County, Minnesota, 1990–2007

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>AUASI Score, Change/Year</th>
<th>Maximum Flow Rate, % Change/Yearc</th>
<th>Prostate Volume, % Change/Yearc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\hat{b}$</td>
<td>$P$ Value</td>
<td>$\hat{b}$</td>
</tr>
<tr>
<td>Baseline age</td>
<td>0.003</td>
<td>0.18</td>
<td>-0.0002</td>
</tr>
<tr>
<td>Intercept (AUASI score, maximum flow rate, or prostate volume)</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Estradiol intercept</td>
<td>0.44</td>
<td>0.03</td>
<td>-0.01</td>
</tr>
<tr>
<td>Change in estradiol</td>
<td>-7.79</td>
<td>0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>Testosterone intercept</td>
<td>0.01</td>
<td>0.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in testosterone</td>
<td>-2.95</td>
<td>0.50</td>
<td>0.19</td>
</tr>
<tr>
<td>Bioavailable testosterone intercept</td>
<td>0.23</td>
<td>0.18</td>
<td>0.002</td>
</tr>
<tr>
<td>Change in bioavailable testosterone</td>
<td>14.95</td>
<td>0.29</td>
<td>0.21</td>
</tr>
<tr>
<td>$R^2$, F-test $P$ value</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>0.37</td>
</tr>
<tr>
<td>Multiple correlation (R)</td>
<td>0.45</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AUASI, American Urological Association Symptom Index.

a Models include all predictor variables shown in this table.

b Slopes and intercepts were obtained from models of natural log-transformed hormone measures, maximum flow rate, and prostate volume.

c Betas represent natural log-transformed values.
DISCUSSION

We found that both baseline hormone levels and rates of change in hormone levels were associated with the rates of change in AUASI score, maximum urinary flow rate, and prostate volume over time. Additionally, we found that the baseline value of each of these outcomes was strongly associated with the rate of change in the same urologic outcome over time.

In multivariable models, we found that higher baseline estradiol levels were correlated with more rapid worsening of AUASI score and maximum flow rate. However, more rapid declines in estradiol were associated with more rapid increases in AUASI score. It is not clear why a higher baseline level of estradiol but a more rapid decline in estradiol would be associated with more rapid worsening of urologic symptoms. We conducted a secondary analysis to determine if the longitudinal decline in estradiol levels was consistent across both high and low baseline levels (data not shown). The decline was consistent; therefore, an interaction between baseline estradiol level and change in estradiol level does not seem to explain our findings. In women, estrogen replacement therapy has been associated with improvement of overactive bladder symptoms (34). Additionally, previous animal studies indicated that estradiol has positive effects on the female bladder (35–39). However, the effects of estradiol on the male urologic system may be more complicated. Valeri et al. (37) found that the male urinary rat bladder was more susceptible to ischemic damage that occurred during obstructed micturition and was not protected by estradiol to the same degree as female rat bladders. Streng et al. (40) have also found that high levels of estrogens triggered bladder outlet obstruction in castrated male mice, but low levels of estrogens improved urologic function in these mice. Further studies are therefore necessary to better understand the role of estrogens in male urologic function.

Results of a few small trials have shown that testosterone replacement therapy is useful in relieving LUTS in hypogonadal men (41, 42). These trials have been small and limited to men with established hypogonadism. However, if these data and our data are correct, one possible mechanism through which testosterone might alleviate LUTS could be through conversion to estradiol and subsequent positive effects of estradiol on the bladder. For this reason, measuring estradiol levels as well as testosterone levels in future trials would be useful in sorting out the effects of testosterone on LUTS.

In contrast to the rate of change in AUASI score and maximum flow rate models, estradiol and changes in estradiol were not associated with rate of change in prostate volume. Instead, men who had the lowest baseline bioavailable testosterone and the most rapid declines in bioavailable testosterone also had the most rapid increases in prostate volume. Testosterone is converted to DHT, and higher testosterone also had the most rapid increases in prostate volume over time. Additionally, we found that the baseline value of each of these outcomes was strongly associated with the rate of change in the same urologic outcome over time.

Testosterone levels may reflect increased 5α-reductase activity, which could contribute to higher DHT levels and subsequent increases in prostate volume. Unfortunately, we were not able to assess either serum or intraprostatic DHT levels in this population, and such measures are necessary to determine whether this is a plausible hypothesis.

Finally, the rate of change in each outcome was strongly associated with the baseline level of each outcome. For example, men with higher baseline AUASI scores had the most rapid increases in AUASI score over time. These associations persisted after adjusting for age and sex steroid hormone measures, suggesting that men with worse urologic measures at baseline are the ones who are most likely to deteriorate more rapidly. Worse AUASI scores, lower maximum flow rates, and larger prostate volumes may reflect biologic processes acting within men that result in the adverse urologic outcomes observed at baseline. Importantly, these results also suggest that future longitudinal studies of urologic or BPH outcomes should account for baseline urologic conditions.

There are a number of additional factors to consider when interpreting these data. First, the method we used for standardizing hormone levels across multiple rounds of follow-up assumed that measurements of hormone levels for a given age were consistent from year to year. Therefore, standardizing the hormone levels to the last round would have eliminated a cohort effect if one existed. Higher sex hormone-binding globulin and testosterone levels have been observed among Danish men born in the early 1920s than in those born decades later (45). Other investigators have also found an age-independent decline in serum testosterone that could be due to birth cohort differences (46).

In the present study, we found that testosterone levels were highest in samples collected during rounds 2 and 3 of the study, but there were virtually no differences in levels collected in later rounds (Figure 2A). As the time frame between the study rounds was short, it seems unlikely that the higher levels observed in the 2 earliest rounds were due to a cohort effect. Additionally, the assay used to obtain testosterone levels changed between rounds 3 and 5, suggesting that assay differences most likely account for the higher levels in rounds 2 and 3 compared with later rounds.

Second, the current state-of-the-art technology for measuring hormone levels is mass spectroscopy. Unfortunately, measurement of hormone levels in these specimens occurred at different points throughout the 20-year follow-up period, using the best available technology at the time. Because of financial constraints, we were not able to remeasure all hormone levels in the available serum specimens by using other technologies. Therefore, the absolute levels of hormones obtained from the technologies described in the methods section may differ from the levels that would be obtained using mass spectroscopy. However, the ranks of the hormone levels (and the rates of change in the levels) should not change (47). Therefore, the inferences should remain consistent regardless of how the hormone levels were initially measured.

The results of the analyses in multivariable models differed from the results of univariable analyses. In univariable models, bioavailable testosterone levels and changes in bioavailable testosterone levels were associated with changes in AUASI score. However, after adjusting for all baseline hormone levels and changes in hormone levels simultaneously, we found that estradiol and changes in estradiol levels, but not testosterone levels, were associated with
changes in AUASI score. The interrelations among hormone levels are correlated and complex. For example, estradiol is synthesized from testosterone (48); therefore, higher levels of testosterone could lead to increased levels of estradiol. Our results suggest that it might be inappropriate to examine hormone variables individually when assessing their contribution to urologic outcomes.

Finally, our study population consisted only of white men. There are reports of sex steroid hormonal differences among men of different races (49–51), and if the mechanisms by which hormones contribute to urologic outcomes in these men differ, our results may not be generalizable to men of other races or ethnicities.

In summary, both sex steroid hormone levels and the rate of change in sex steroid levels were associated with the rate of change in urologic outcomes among aging men. Additionally, the strongest associations observed in our study were between worse baseline levels of each outcome and rapid declines in each outcome. Clinically, our results suggest that men who present with poor baseline urologic measures are at higher risk for more rapid deterioration in each of these measures.

ACKNOWLEDGMENTS

Author affiliations: Division of Epidemiology, Mayo Clinic College of Medicine, Rochester, Minnesota (Jennifer L. St. Sauver, Steven J. Jacobsen); Division of Biomedical Statistics and Informatics, Mayo Clinic College of Medicine, Rochester, Minnesota (Debra J. Jacobson, Michaela E. McGree); Merck & Co., North Wales, Pennsylvania (Cynthia J. Girman); Department of Health Sciences Research, Department of Lab Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota (George G. Klee); Department of Urology, Mayo Clinic College of Medicine, Rochester, Minnesota; and Department of Research and Evaluation (Michael M. Lieber), Southern California Permanente Medical Group, Pasadena, California (Steven J. Jacobsen).

The original cohort was established through funding from Merck Research Laboratories. This work was supported by the National Institutes of Health (grant numbers DK58859, AR30582, and RR24150).

The authors thank the Mayo Clinic Immunochemical Core Laboratory for assay support. The authors also thank the study personnel and Sondra Buehler for her assistance in preparation of this manuscript.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the funding institutes or the National Institutes of Health. The funding agencies did not influence the study design, analysis, or interpretation of the results.

Conflict of interest: Dr. Cynthia Girman is an employee of and owns stock in Merck Co., Inc. Dr. Steven J. Jacobsen is an employee of Kaiser Permanente.

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