Treatment of Symptomatic Androgen Deficiency

Results From the Boston Area Community Health Survey

Susan A. Hall, PhD; Andre B. Araujo, PhD; Gretchen R. Esche, MS; Rachel E. Williams, PhD; Richard V. Clark, MD, PhD; Thomas G. Travison, PhD; John B. McKinlay, PhD

Background: Despite the aging of the US population and increasing sales of prescription testosterone, treatment patterns for androgen deficiency (AD) are poorly understood. We describe patterns and correlates of testosterone treatment in community-dwelling men.

Methods: The Boston Area Community Health Survey is an observational study of a population-based random sample of racially and ethnically diverse men representative of Boston, Massachusetts. Data collected by in-person interview from April 2002 to June 2005 included health status, socioeconomic status, access to medical care, and use of prescription medications. A venous blood sample was collected. The operational definition of untreated AD was serum total testosterone level less than 300 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) and free testosterone level less than 5 ng/dL, and the presence of at least 1 specific symptom (low libido, erectile dysfunction, or osteoporosis) or 2 or more less-specific symptoms (sleep disturbance, depressed mood, lethargy, or diminished physical performance) and not using prescription testosterone. Any man who was using testosterone was considered to have treated AD.

Results: Data were available for 1486 Boston Area Community Health Survey participants (mean age, 46.4 years; age range, 30-79 years). A total of 5.5% (95% confidence interval, 3.5-8.5) men met the criteria for having untreated, symptomatic AD, and 0.8% (95% confidence interval, 0.4-1.4) met the criteria for having treated AD. Considering all cases, the proportion treated was 12.2%. Men with untreated AD seemed to have adequate access to care.

Conclusions: Under our assumptions, a large majority (87.8%) of 97 men in our groups with AD were not receiving treatment despite adequate access to care. The reasons for this are unknown but could be due to unrecognized AD or unwillingness to prescribe testosterone therapy.

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timate the percentage of men receiving treatment for AD and to describe how treated and untreated men differed with respect to care-seeking behaviors and potential barriers to health care.

STUDY DESIGN AND DATA COLLECTION

The BACH Survey is a population-based, cross-sectional observational study of male and female residents of Boston, Massachusetts. Details of the BACH study design and procedures are described elsewhere.6 A 2-stage, stratified cluster sampling design was used for the purposes of recruiting equal numbers of participants to prespecified age groups (30–39 years, 40–49 years, 50–59 years, and 60–79 years), racial/ethnic groups (black, white, and Hispanic), and sex. Interviews were completed for 63.3% of eligible subjects, with a resulting study population of 2301 men and 3205 women including 1770 black participants, 1859 white participants, and 1877 Hispanic participants. After written informed consent was obtained, data were collected between April 2002 and June 2005 during a 2-hour interview conducted by a trained, bilingual interviewer, usually in the participants’ homes. A venous blood sample (20 mL) was also collected as close to awakening as possible (median time since awakening for men was 3 hours 38 minutes).7

Medication information including prescription TTh was collected as follows. Participants were asked to gather all over-the-counter and prescription medications used in the last 4 weeks for recording of the label information. In addition, participants were asked specifically if they were using male hormones or medications for specific indications (eg, diabetes). Medications gathered or reported were coded using the Slone Drug Dictionary,8 whose coding process identifies drug components and classifies them using a modified form of the American Hospital Formulary System Drug Information, 2007, Pharmacologic-Therapeutic Classification System.9 All protocols and informed consent procedures were approved by the institutional review board of New England Research Institutes.

The measurement of testosterone in the BACH Survey has been reported previously.7 In brief, the level of testosterone was measured using a competitive electrochemiluminescence immunoassay (Elecsys 2010 autoanalyzer; Roche Diagnostics, Indianapolis, Indiana). The lower limit of detection for testosterone was 2 ng/dL (to convert to nanomoles per liter, multiply by 0.0347), and the day-to-day imprecision values at concentrations of 0.24, 2.73, and 7.01 ng/mL were 7.4%, 2.2%, and 1.7%, respectively; within-run values at the same concentrations were 4.6%, 1.4%, and 1.1%. Free testosterone was calculated using the mass action equations described by Södergärd et al,10 with association constants for testosterone from Vermeulen et al.11 These calculations take into account the concentrations of serum total testosterone and sex hormone–binding globulin. The possible binding of other steroids to sex hormone–binding globulin was disregarded. A fixed albumin concentration of 4.3 g/dL (to convert to grams per liter, multiply by 10) was assumed. The association constant of sex hormone–binding globulin for testosterone was 1.0 × 10^10/mmol, and of albumin for testosterone was 3.6 × 10^10/mmol.11 All assays used in the study have been approved by the Food and Drug Administration for clinical use. Testosterone values obtained in the study have been approved by the Food and Drug Administration for clinical use. Testosterone values obtained in the study have been approved by the Food and Drug Administration for clinical use. Testosterone values obtained in the study have been approved by the Food and Drug Administration for clinical use. Testosterone values obtained in the study have been approved by the Food and Drug Administration for clinical use. Testosterone values obtained in the study have been approved by the Food and Drug Administration for clinical use.

OPERATIONAL DEFINITION OF TREATED AND UNTREATED AD

As in a previous analysis, the operational definition for AD included both symptoms and serum testosterone levels, as recommended by the Clinical Guidelines Subcommittee of the Endocrine Society for evaluation of AD in adult men (Figure 1).5,16 Data were available in the BACH Survey for 2 groups of symptoms considered specific for AD (low libido, erectile dysfunction [ED], or osteoporosis), and less specific for AD (depressed mood, lethargy, sleep disturbance, or diminished physical performance). Specific symptoms were assessed as follows: men who reported that their level (degree) of sexual desire or interest during the last 4 weeks was low or very low were considered to have low libido; men with a score of 17 or less on the International Index of Erectile Function were considered to have ED;17 and men having a health care provider diagnosis of osteoporosis or fracture of the hip, wrist, or spine after age 50 years were considered to have osteoporosis. For nonspecific symptoms, depressed mood and sleep disturbance during the last week were assessed using yes-no questions of “I felt depressed” and “My sleep was restless” in the abridged 8-item Center for Epidemiologic Studies–Depression scale.18 The presence of lethargy was defined as a “Sometimes” or “Often” reply to the query “Did you have a lot of energy??” considering the past 4 weeks. Low physical performance was considered present if the physical component score of the 12-item Short-Form Health Survey was in the lowest quintile.19 Total symptom score (possible range, 0–17) and mean symptom score were defined as the sum and arithmetic mean of number of symptoms, respectively.

Men with at least 1 specific symptom or 2 or more nonspecific symptoms were considered to be symptomatic. Among these, participants were considered to have AD if their total testosterone level was less than 300 ng/dL and free testosterone level was less than 5 ng/dL. Men who met the operational definition using symptom criteria and testosterone levels and who had no prescription data for TTh were assumed to have untreated AD. Because there are limited indications for TTh (ED, Klinefelter syndrome, hypogonadism, delayed puberty, and corticosteroid-induced hypogo-
of health insurance (private, public, or none), marital status, and race/ethnicity (black, white, or Hispanic) were self-reported and used in this analysis for the purpose of measuring health disparities. Additional categorical variables were type of health insurance (private, public, or none), marital status, current smoker (yes/no), and socioeconomic status constructed as a function of standardized income and educational achievement variables for the northeastern United States and classified as low, medium, and high. Comorbidities were considered present if a participant responded yes to the question “Have you ever been told by a health care provider that you have or had [hypertension], [diabetes, type I or II], or [cardiovascular disease]?”. Six variables related to access to care or care seeking were created from the queries “How many times in the last year did you go see a health care provider for any reason?” “Do you go for regular care?” (yes-no and type of facility); “Are you having trouble paying for health or medical care, or medications?” (yes-no); “How important to you would noticing a decline in your interest in sex or reduced sex drive (libido) be for you to seek medical care?” and “How important to you would difficulty obtaining or maintaining an erection be for you to seek medical care?” (extremely important or important vs neither unimportant nor important or unimportant or extremely unimportant).

RESULTS

The overall mean (SE) age of the 1486 men in our analysis sample was 46.4 (0.5) years (age range, 30-79 years). A total of 815 men from the BACH Survey were excluded because of missing data or medication exclusions; these excluded men were not different from the analysis sample for age, smoking status, body mass index, self-reported health status, and the presence of diabetes mellitus (all P > .45). Ninety-seven men from our analysis sample met the operational definition of untreated AD (n=86) or were prescribed TTh (n=11). The prevalence of TTh among these 97 men was 12.2% (95% confidence interval, 5.6-24.5). Figure 2 shows the concept of the illness iceberg applied to these data; the portion of the iceberg appearing above the water’s surface represents those men who are being treated, and the portion below the surface represents men with symptomatic disease not being treated. A total of 5.5% (95% confidence interval, 3.5-8.5) of men had untreated, symptomatic AD. The overall prevalence of TTh was 0.8% (95% confidence interval, 0.4-1.4). Men were using the following: testosterone gel (n=1), testosterone patch (n=3), testosterone cream (n=1), testosterone cypionate (n=1), or unspecified formulations of testosterone (n=5). All of the unspecified forms of testosterone used were self-reported as administered in intervals defined in weeks, which suggests that these were injectable formulations.

Compared with men without AD, men with treated or untreated AD (meeting the operational definition of AD and not receiving TTh) were older (P = .07); the percentage of white men was similar across the 3 groups (Table 1). Regardless of treatment status, men with AD had a significantly higher prevalence of cardiovascular disease (P < .01) and elevated blood pressure (P = .01). Men with treated or untreated AD had significantly higher body mass index on average than men without AD (P = .03). Men with untreated AD had a mean body mass index of 35.0 compared with 29.3 for those receiving treatment and 28.4 for those without AD.

Similar percentages of men with untreated and treated AD reported difficulty paying for health care (Table 2).

Figure 2. Iceberg concept of androgen deficiency (adapted from Last). Weighted prevalence of men treated and untreated for androgen deficiency in the Boston Area Community Health Survey (n=97). Percentages are weighted by the inverse of the possibility of being selected; thus, they do not equal arithmetic calculations. Eleven men prescribed testosterone therapy were assumed to have treated androgen deficiency. Untreated androgen deficiency was defined as the presence of at least 1 specific symptom (low libido, erectile dysfunction, or osteoporosis) or 2 nonspecific symptoms or more (depressed mood, lethargy, sleep disturbance, or diminished physical performance) plus total testosterone level less than 300 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) and free testosterone level less than 1 ng/dL, plus no record of prescribed testosterone therapy.

Analytic Sample and Statistical Analysis

There were 2301 men in the BACH study. Excluded from the analysis were 412 men with missing information on hormone variables, 12 men with hormone values 4 SD from the mean that were considered implausible outliers, and 19 men who were taking medications known to affect androgen levels such as antiandrogen therapy or over-the-counter dehydroepiandrosterone. An additional 372 men were excluded because of missing data on symptoms related to AD. Consequently, data for 1486 men were available for analysis. Because of a small frequency in our group with treated AD (n=11), statistical testing of this group was not emphasized. However, when comparisons were made between a combined group of men with treated or untreated AD compared with men with no AD, a χ² test was performed for categorical covariates and a Wald-type F test for continuous variables. To account for the sampling design, all reported prevalence percentages and sample means were weighted by the inverse of the probability of selection using survey data analysis statistical software (SUDAAN version 9.0.0; RTI International, Research Triangle Park, North Carolina). This ensures that estimates provided may be interpreted as representative of the community-dwelling population in Boston.

Covariates

Body mass index (calculated as weight in kilograms divided by height in meters squared) was grouped into 3 categories (≤25, 25.0-29.9, and ≥30), with weight and height measured by the interviewer. Race/ethnicity (black, white, or Hispanic) was self-reported and used in this analysis for the purpose of measuring health disparities. Additional categorical variables were type of health insurance (private, public, or none), marital status,
Men with untreated AD were the most likely of the 3 groups to have low socioeconomic status, to have no health insurance, and to receive primary care in an emergency department or hospital outpatient clinic. However, all men with AD, regardless of treatment status, were more likely than men without AD to report receiving regular care (P = .08) and had a higher mean number of annual health care provider visits (P < .01). Men meeting our definition of untreated AD reported a mean (median) of 15.1 (8.0) visits per year for health care compared with 6.7 (2.8) visits per year among those without AD and 12.0 (6.7) visits among those with treated AD. Regarding care seeking because of a decline in libido, most men with untreated AD (75.7%) believed care seeking was worthy. Importance of care seeking for an erection problem was similar among treated (75.1%) and untreated men (75.9%).

We examined the distribution of symptoms considered specific and nonspecific for AD by the Clinical Guidelines Subcommittee of the Endocrine Society according to treatment status (Table 3). Although numbers were too low to statistically test differences, we observed that men receiving TTh had fewer symptoms associated with AD (mean, 2.1) compared with those with untreated AD (mean, 3.2), and men who did not meet our definition of AD reported, on average, nearly 1 symptom (mean, 0.9). Because symptoms were part of our operational definition, it was expected that the mean would be higher in the group with untreated AD. Nearly half reported low libido or ED, whereas sleep disturbance and low physical performance were the most common nonspecific symptoms. Among men who did not meet the definition of treated or untreated AD, 40.1% had 1 or 2 symptoms. Sleep disturbance was the most prevalent symptom (30.6%), followed by low physical performance, ED, and depressed mood (approximately 15% each). Mean total and free testosterone levels were lowest in the group with untreated AD, which was expected because a clinically low testosterone level was a requirement for our operational definition. Among men who received TTh, 55.6% had clinically low total or free testosterone levels, whereas nearly 20% of men without AD had clinically low total testosterone levels and 5% had clinically low free testosterone levels. Four of 11 men (40%) receiving TTh would have met
our operational definition on the basis of the presence of symptoms and clinically low testosterone levels.

Table 2. Health Insurance Status, SES, and Care-Seeking Behaviors in 1486 Men From the BACH Survey With Treated, Untreated, and No AD

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Treated AD (n = 11)</th>
<th>Untreated AD (n = 86)</th>
<th>No AD (n = 1389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health insurance, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>8 (72.7)</td>
<td>34 (45.5)</td>
<td>782 (70.7)</td>
</tr>
<tr>
<td>Public</td>
<td>2 (16.5)</td>
<td>42 (58.1)</td>
<td>311 (24.9)</td>
</tr>
<tr>
<td>None</td>
<td>1 (8.5)</td>
<td>12 (16.2)</td>
<td>294 (24.3)</td>
</tr>
<tr>
<td>SES, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2 (16.5)</td>
<td>10 (12.2)</td>
<td>298 (21.1)</td>
</tr>
<tr>
<td>Medium</td>
<td>6 (50.8)</td>
<td>28 (33.3)</td>
<td>509 (58.4)</td>
</tr>
<tr>
<td>High</td>
<td>3 (23.8)</td>
<td>9 (10.8)</td>
<td>282 (16.6)</td>
</tr>
<tr>
<td>Care-seeking behavior, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular care</td>
<td>9 (81.8)</td>
<td>78 (90.5)</td>
<td>1041 (75.8)</td>
</tr>
<tr>
<td>Site of regular carea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient clinic or physician office</td>
<td>8 (88.9)</td>
<td>53 (62.8)</td>
<td>766 (55.2)</td>
</tr>
<tr>
<td>HMO</td>
<td>2 (20.8)</td>
<td>10 (11.8)</td>
<td>262 (18.7)</td>
</tr>
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<td>Hospital emergency department</td>
<td>1 (10.0)</td>
<td>9 (10.5)</td>
<td>79 (5.7)</td>
</tr>
<tr>
<td>Hospital outpatient clinic</td>
<td>2 (20.9)</td>
<td>41 (47.7)</td>
<td>408 (29.7)</td>
</tr>
<tr>
<td>Annual health care provider visits, mean No. (SE)</td>
<td>12.0 (3.3)</td>
<td>15.1 (2.3)</td>
<td>6.7 (0.5)</td>
</tr>
<tr>
<td>Having difficulty paying for health care</td>
<td>4 (36.4)</td>
<td>28 (32.6)</td>
<td>271 (19.0)</td>
</tr>
<tr>
<td>Reports it is important or extremely important to seek care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline in libido</td>
<td>8 (72.7)</td>
<td>61 (71.4)</td>
<td>1100 (73.6)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>9 (81.8)</td>
<td>25 (29.1)</td>
<td>1226 (86.7)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, androgen deficiency; BACH, Boston Area Community Health; HMO, health maintenance organization; SES, socioeconomic status.

a Men with prescribed testosterone therapy were assumed to have treated AD. Untreated AD was defined as the presence of at least 1 specific symptom (low libido, erectile dysfunction, or osteoporosis) or 2 or more nonspecific symptoms (depressed mood, lethargy, sleep disturbance, or diminished physical performance) plus total testosterone level less than 300 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) and free testosterone level less than 5 ng/dL, plus no record of prescribed testosterone therapy. For categorical variables, percentages are weighted percents of column totals, enabling comparison of each covariate by AD status. All analyses are weighted by the inverse of the probability of being selected; thus, percentages do not equal arithmetic calculations.

b The number of missing values for covariates was as follows: health insurance, 2; SES, 61; regular care, 19; site of primary care: outpatient clinic or physician office, 3; HMO, 6; hospital emergency department, 3; hospital outpatient clinic, 3; annual health care provider visits, 1; having difficulty paying for health care, 1; care seeking because of decline in libido, 2; or erectile problem, 9. Variables in bold were significantly different considering treated AD plus untreated AD vs no AD groups, using a P-value of < .10 for a χ² test (categorical variables) or Wald-type F test (continuous variables).

c Patients reported more than 1 source of regular care; thus, percentages sum to higher than 100%.

To our knowledge, this is the first study to estimate treatment patterns for AD in a population-based, US random sample. The Hypogonadism in Males (HIM) Study, which included 2165 men aged 45 years and older visiting 95 primary care practices in the United States, estimated that 3.7% of that sample was receiving treatment for AD, compared with 0.8% in our sample.3 The HIM participants were considerably older than those in the BACH Survey (mean age, 60.5 vs 46.4 years, respectively), and the prevalence of AD estimated in the HIM Study was 38.7%, compared with 5.5% in our analysis. About 10% of men with AD in the HIM Study were being treated, compared with 12.2% in the BACH Survey; thus, the treated estimates are similar. The HIM investigators did not present characteristics by treatment status permitting further comparison. We observed that men receiving TTh had fewer symptoms than those with AD not receiving TTh, but 40% still met the operational definition for AD. We are unable to draw any conclusions about the efficacy of TTh in this nonclinical study. In addition to the small number of men in the treatment group, we had no information on the presence or severity of symptoms before treatment was initiated.

Our definition of untreated AD was based on the guidelines suggested by the Clinical Guidelines Subcommittee of the Endocrine Society,16 but not all symptoms were
available in the BACH Survey and our definition has not been independently validated in other data sets. A full description of age-specific prevalence and the distribution of symptoms and testosterone levels in the BACH Survey is available elsewhere. We made an assumption that the use of testosterone was for treatment of AD, as indication was not collected for all medications. Testosterone may have been prescribed for previously diagnosed, disease-based forms of hypogonadism. Men may have underreported testosterone injections received in medical care, and, therefore, we may have underestimated treatment prevalence because these medications would not have been physically collected by the interviewer in the home. Other limitations in our medication data are that adherence to therapy, duration of use, and date of initiation of therapy were not captured.

Although the rarity of AD and its treatment led to small numbers and limited our ability to make statistical comparisons between treated and untreated men, our study population was generally well-suited to capture treatment patterns and barriers to care for AD. Subjects were randomly selected from the community and were not necessarily seeking medical care. This enabled us to better capture undiagnosed and untreated AD. In addition, the generalizability of the BACH Survey to the US population is known. Men participating in the BACH Survey were less likely to be employed, more likely to receive Medicare, and more likely to have seen a health care provider in the last 6 months compared with men participating in the National Health and Nutrition Examination Survey, National Health Interview Survey, or Behavioral Risk Factor Surveillance Survey. Medicare coverage and health insurance status were similar to those in the national surveys, as were the distributions of common comorbidities (except for asthma, which was more common in the BACH Survey).

In conclusion, in this population-based study, we found that most men with symptomatic AD were untreated and are not likely to be explained by underutilization of medical care among men in Boston. However, whether Boston is representative of national testosterone prescription patterns is unknown.

An iceberg conceptualization of disease implies that the symptomatic untreated group should be treated; however, it cannot be known from this nonclinical study whether it would be medically appropriate and beneficial to give TTh to those men identified as having untreated AD in this study. However, given the 2006 publication of the Clinical Guidelines Subcommittee of the Endocrine Society outlining treatment, increasing sales of testosterone products, and uncertainty about the safety of TTh, treatment patterns for AD in the population should continue to be monitored for change. Treatment considerations would be better informed with well-designed clinical studies to evaluate the benefit-risk ratio of TTh for AD.

In conclusion, in this population-based study, we found that most men with symptomatic AD were not receiving TTh. The reasons for this are unknown but do not seem to be fully explained by barriers to health care access or differences in health care–seeking behaviors.

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Correspondence: Susan A. Hall, PhD, New England Research Institutes, Nine Galen Street, Watertown, MA 02474 (shall@neriscience.com).
Author Contributions: Dr Hall had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hall, Araujo, Williams, Clark, and McKinlay. Acquisition of data: McKinlay. Analysis and interpretation of data: Hall, Araujo, Esche, Williams, Clark, Travison, and McKinlay. Drafting of the manuscript: Hall, Araujo, Esche, Williams, Clark, Travison, and McKinlay. Critical revision of the manuscript for important intellectual content: Hall, Araujo, Esche, Williams, Clark, Travison, and McKinlay. Statistical analysis: Hall, Araujo, Esche, and McKinlay. Obtained funding: Williams, Clark, and McKinlay. Administrative, technical, and material support: McKinlay. Study supervision: McKinlay. Epidemiologic expertise: Hall, Araujo, Williams, and McKinlay.

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REFERENCES