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ORIGINAL ARTICLE

Effect of testosterone therapy on the female voice

R. Glaser[a], A. York[b] and C. Dimitrakakis[c]

[a]Millennium Wellness Center, Dayton and Wright State University Boonshoft School of Medicine, Department of Surgery, Dayton, Ohio, USA; [b]York Data Analysis, Seattle, WA, USA; [c]1st Department of Ob-Gyn, Athens University Medical School, Athens, Greece and National Institutes of Health, NICHD, Bethesda, MD, USA

ABSTRACT

Objectives This prospective study was designed to investigate the effect of testosterone, delivered by subcutaneous implants, on the female voice.

Methods Ten women who had opted for testosterone therapy were recruited for voice analysis. Voices were recorded prior to treatment and at 3 months, 6 months, and 12 months while on testosterone therapy. Acoustic samples were collected with subjects reading a sentence, reading a paragraph, and participating in a conversation. Significant changes in the voice over time were investigated using a repeated-measures analysis of variance with the fundamental frequency (F_0) as a response variable. Demographic variables associated with characteristics of the voice were assessed.

Results There were no significant differences in average F_0 related to smoking history, menopausal status, weight, or body mass index. There was no difference in average fundamental speaking frequency (sentence, paragraph, conversation) between the pre-treatment group and any post-treatment group at 3 and 12 months. There was an increase in sentence speech F_0 at 6 months. Two of three patients with lower than expected F_0 at baseline improved on testosterone therapy.

Conclusion Therapeutic levels of testosterone, delivered by subcutaneous implant, had no adverse affect on the female voice including lowering or deepening of the voice.

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Testosterone; implant; women; menopause; voice; fundamental frequency; aging

Introduction

Hormones, including estrogens, androgens and progesterone, affect the female voice throughout the lifespan and accordingly, hormone deficiency influences fundamental speaking frequency[1–3]. The female voice deepens with age, menopause and smoking[4,5]. Testosterone has been claimed to be associated with lower female voice[2]. However, despite case reports and questionnaire studies reporting subjective changes associated with high-dose androgenic therapy, there remains a lack of prospective objective data supporting these claims, particularly in regards to female replacement dosages of (human identical) testosterone[6–8]. Even with supra-physiologic doses of androgens used in female gender reassignment, which should be sufficient to induce vocal change, the results are not always consistent[9,10].

Testosterone declines with age in both men and women and testosterone therapy is being increasingly used to treat symptoms of hormone deficiency in women including breast cancer survivors[11–13]. To date, no studies have documented the potential positive or negative effects of pharmacologic (clinically effective) replacement doses of subcutaneous testosterone implants on the female voice.

Fundamental speaking frequency, F_0, often expressed in hertz (Hz), is a measure of how high (increased F_0) or low (decreased F_0) a person's voice sounds. Factors influencing F_0 include laryngeal size, effective vocal cord length (the part that vibrates), the amount of fluid in the vocal cord and inflammation[14]. Furthermore, there are many common etiologies of hoarseness and voice changes, which make a causal relationship of testosterone difficult to elucidate[15].

This prospective pilot study was designed to investigate the effect of testosterone therapy, delivered by subcutaneous implant, on the female voice and vocal cord function, i.e. fundamental speaking frequency.

Methods

Ten female patients who opted for testosterone implant therapy were recruited to participate in this pilot study.

CONTACT Dr R. L. Glaser rglaser@woh.rr.com 228 E. Spring Valley Drive, Dayton, Ohio 45458, USA
Supplemental data for this article can be accessed here.

All patients were part of a prospective IRB study looking at the incidence of breast cancer in women treated with testosterone implants for symptoms of hormone deficiency. All patients were counseled and signed an informed consent.

Patient demographics are listed in Table 1. The mean age at accrual was 51.3 ± 6.8 years. Four patients were postmenopausal and six were pre/perimenopausal. Three of ten patients were current smokers. Testosterone dosing is weight-based[11]. The mean patient weight was 66.1 ± 11.8 kg and the mean testosterone dose was 138 ± 22.7 mg. Implants were inserted at 3-month intervals on average. Serum testosterone levels were measured at baseline and on therapy.

Data was collected at four intervals: pre-implantation of testosterone, 3 months into treatment, 6 months into treatment and 1 year into treatment. Acoustic samples were recorded in a quiet room using an Olympus digital recorder located 10 cm from the subjects. Samples consisted of the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) sentences, the Rainbow passage and conversational speech. The CAPE-V sentences comprise a standardized protocol developed for evaluation of vocal quality[16]. The Rainbow passage contains a mixture of consonants proportional to those found in everyday speech and is used to assess differences among English dialects[17,18]. The conversational sample was prompted by the request to describe how to make a peanut butter sandwich. Acoustic samples were segmented by task and analyzed via Real Time spectrum analyzer with the fundamental speaking frequency of each sample determined[19].

The R software program[20] was used for all statistical computations. Changes in the voice over time were investigated using a repeated-measures analysis of variance with F_0 as a response variable: parameters were estimated using the lme4 package[21]. We also compared these results to those from Friedman's non-parametric repeated measures test for the eight subjects with no missing data. Demographic variables possibly associated with characteristics of the voice, such as menopausal status, smoking history, and body mass index (BMI) were assessed using the analysis of variance.

Table 1. Patient demographic variables.

Continuous variables	*n*	*Mean ± standard deviation*	*Minimum*	*Maximum*
Age (years)	10	51.3 ± 6.8	35.3	59.9
Weight (kg)	10	66.1 ± 11.8	51.7	86.1
Body mass index (kg/m^2)	10	23.7 ± 4.5	18.7	33.8
Mean testosterone dose (mg)	10	138.0 ± 22.7	113.0	183.0
Baseline testosterone level (ng/dl)	10	17.2 ± 9.8	5.0	31.0
Therapeutic testosterone level (ng/dl)	9	471.6 ± 148.1	293.0	690.0
Categorical variables	*Level*		*n (%)*	
Smoking history (%)	never		5 (50.0)	
	past		2 (20.0)	
	present		3 (30.0)	
Menopausal status (%)	post		4 (40.0)	
	pre		6 (60.0)	

Results

Data for fundamental speaking frequency can be found in Figure 1. There are two missing data points. The pretreatment measure for subject 5 is missing due to file deletion during hard drive failure. The 6-month follow-up data for subject 9 is missing due to lack of follow-up by the subject.

At the time of initial implant, there were no significant differences in average F_0 related to smoking history ($p = 0.34$), age ($p = 0.80$), menopausal status ($p = 0.96$), weight ($p = 0.11$), or BMI ($p = 0.09$). This remained the case at each testing interval ($p > 0.29$ in all cases). The within-speaker coefficient of variation (CV) for the average F_0 across dates ranged between 3 and 10%. The inter-subject CV for the average F_0 within date was greater, ranging between 9 and 11%.

Despite therapeutic serum levels of testosterone (471.6 ± 148.1 ng/dl) well above endogenous ranges for over 1 year (Table 1), there was no significant change in median fundamental speaking frequency (sentence, paragraph, conversation) between the pre-treatment group and any post-treatment group at any interval, i.e. 3 months, 6 months or 12 months ($p > 0.54$ in all cases) (Figure 2). Based on the repeated measures analysis of variance for all subjects, the average mean F_0 was *higher* at 6 months ($p < 0.01$), but not significantly different from baseline at 3 and 12 months (Table 2). This difference was explained by a large increase in F_0 for sentence speech, which at 6 months was significantly higher from baseline. In contrast, the F_0 in the conversation and paragraph modes was not different ($p > 0.25$ in both cases). Analysis of variance demonstrated no significant change in the mean F_0 (sentence, paragraph, conversation) between the initial tests and after 12 months on testosterone therapy ($p = 0.52$) (see Supplementary data to be found online at http://informahealthcare.com/doi/abs/10.3109/13697137.2016.1136925). Friedman's non-parametric test showed that, for the eight subjects with complete observations, there were no significant differences in mean F_0 over the four time-periods ($\chi^2 = 2.85$, d.f. = 3, $p = 0.42$). Fundamental speaking frequency for two of three patients (subjects 8 and 10, Figure 1) with lower than expected F_0 at baseline, *increased* while on testosterone therapy. These two subjects also had the highest testosterone levels on therapy (690 and 671 ng/dl).

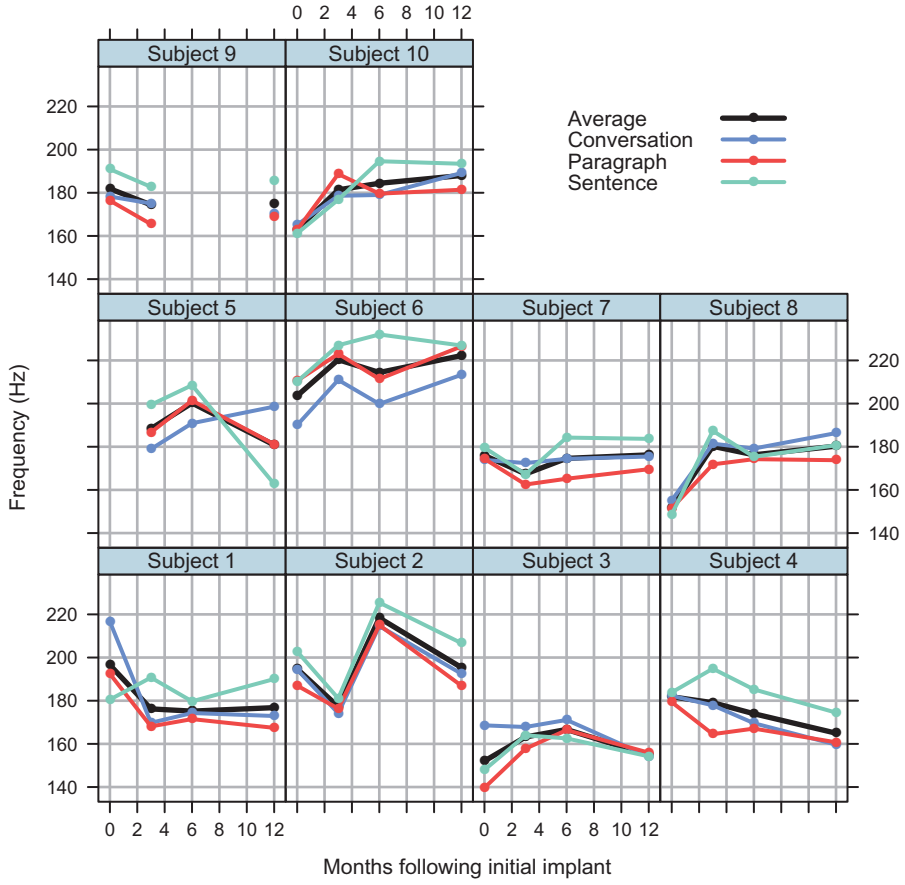

Figure 1. Fundamental frequencies (F_0) of voice measured in ten subjects treated with testosterone implants over a 12-month period. The measurements were made for reading a sentence, reading a paragraph and engaging in conversation. The average F_0 for each patient at each testing interval is also shown. Subjects 1, 2, 4, 5, 8 and 10 were pre/perimenopausal (Pre). Subjects 2, 8 and 9 were current smokers (S).

Discussion

We did not see a difference in F_0 between subjects based on smoking, age, BMI, or menopausal status. This can be explained by the small sample size and within-speaker variability in F_0. Factors such as emotional state (depressed or excited), posture, vocal effort, menstrual cycle, inflammation, medications and other factors affect intrapersonal fundamental speaking frequency[14,22–24], which will make small changes in F_0 difficult to detect.

Results from this 1-year pilot study demonstrated that clinically effective doses of testosterone, delivered by subcutaneous implant, had no measurable adverse effect on the female voice despite therapeutic levels of testosterone well above ranges for endogenous production[25]. Our results are in contrast to Talaat's frequently cited report of 'irreversible changes', data extrapolated from 2-month-old female mice treated with 150–200 times the human male dose of anabolic steroids[26] and case reports on high-dose androgenic agents used in female gender reassignment patients[9,10]. This is not surprising as the beneficial effects as well as side-effects (e.g. voice changes) of androgenic therapy depend on the structure of the molecule, the route of administration and obviously the dose[11,25].

In females, the amount of testosterone released from the subcutaneous implant is approximately 1.4 mg/day, based on average dose and duration of therapy, compared to 400–800 mg/day of oral danazol, a synthetic steroid that binds to the androgen receptor. Even with the high doses of danazol used to treat endometriosis, questionnaire study results are mixed, with the largest study on 452 subjects reporting a 3% incidence of self-reported voice change[8,27]. Although caution should be used in comparing non-equivalent studies or extracting data to non-equivalent groups, our results do support previous prospective findings by Nordenskjöld who concluded 'no significant vocal changes in 23 patients that could be attributed to the androgenic properties of danazol therapy (600 mg/day) at 3 and 6 months'[6]. Pattie's subsequent objective study on ten patients treated with danazol found similar

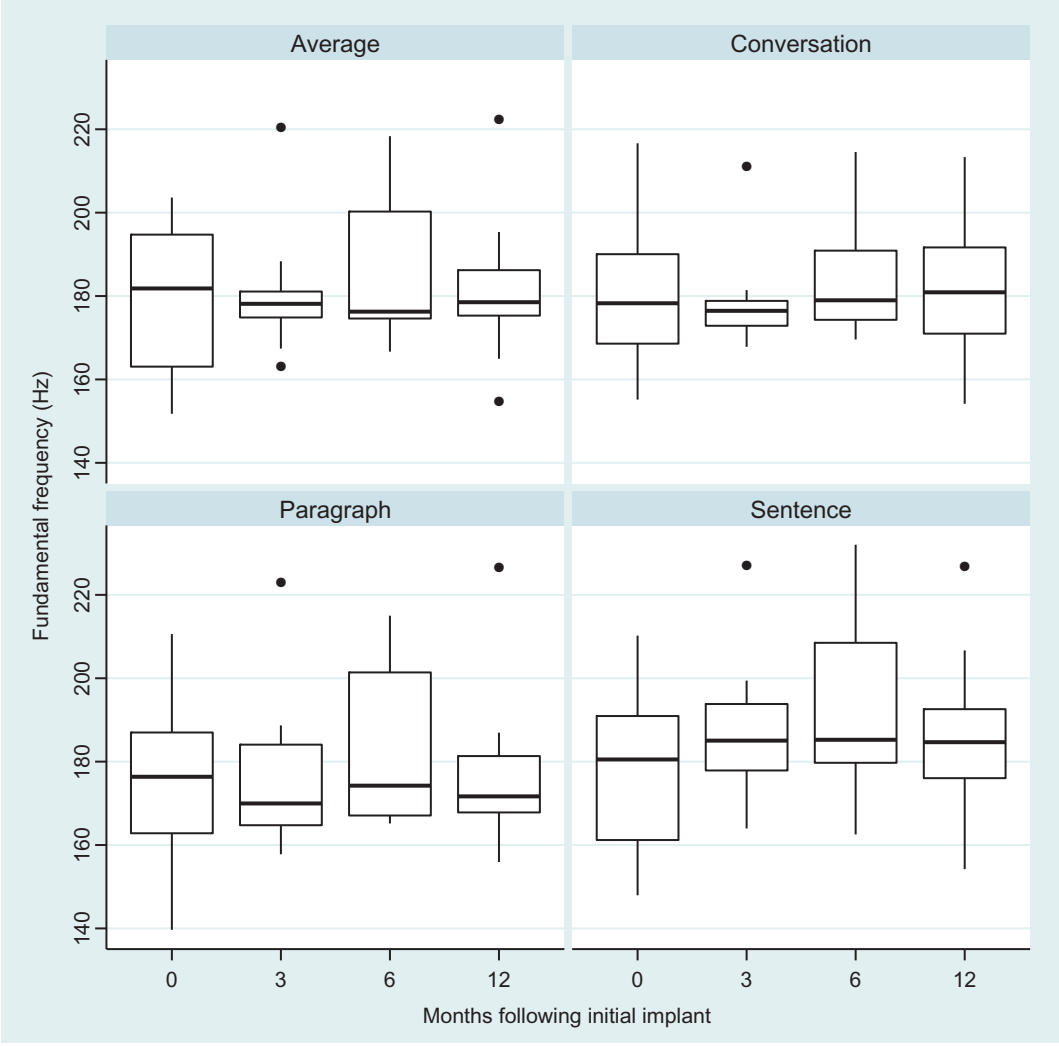

Figure 2. Box-whisker plot of fundamental frequency (F_0) of all subjects at baseline, 3 months, 6 months and 12 months during subcutaneous testosterone therapy by context (Average, Conversation, Paragraph, and Sentence); the mid-line is the median, the boxes enclose data from the 25th percentile to the 75th percentile.

Table 2. Mean fundamental frequency (F_0) expressed in hertz (Hz) at baseline, 3 months, 6 months and 12 months. There was no significant difference in mean F_0 between baseline and 12 months ($p = 0.55$). From the repeated measures analysis of variance at 6 months, mean F_0 was significantly *higher* than baseline, but not at 3 and 12 months.

F_0 (Hz)	*n*	*Mean ± standard deviation*	*Minimum*	*Maximum*
0 months	9	177.9 ± 19.0	151.8	203.6
3 months	10	180.8 ± 15.6	163.2	220.3
6 months	9	187.1 ± 19.1	166.7	218.3
12 months	10	181.4 ± 18.2	154.8	222.2

results, cautioning against reliance on perceptual descriptions of voice changes[7].

Two of three patients with lower than normal F_0 at baseline improved on testosterone therapy, which could be coincidental. However, if casual, an increase in F_0 could be explained by testosterone's immune-modulating (anti-inflammatory) properties[28], and its beneficial effect on muscle strength, bone density, pulmonary function and connective tissue health, all of which worsen with aging and testosterone decline. There was also an unexpected increase in mean F_0 in sentence speech at 6 months, which did not persist at 12 months. Again, this could be due to the small sample size and normal within-speaker variance. Most notably, a *decrease* in mean F_0, i.e. lowering/deepening of the voice, was not noted in any speech mode at any time period during testosterone replacement therapy.

These prospective objective findings are important, as subjective 'voice changes' during androgenic therapy are occasionally reported. Although none of our ten subjects complained of voice changes on therapy, hoarseness is a common complaint with a lifetime incidence up to 47%, and a point prevalence of 6.6% in

persons under 65 years of age[15]. This is significant, as some women on testosterone therapy will experience 'hoarseness' or 'voice changes' at some point during treatment and many will assume that testosterone is causative, as will their physician. However, there are many common factors known to cause hoarseness/voice changes including inflammation, infection, acid reflux, allergies, vocal cord polyps, trauma to the vocal cords, thyroid issues, tumors and various medications including thrombolytics, bisphosphonates, angiotensin-converting enzyme inhibitors, antihistamines, diuretics, anticholinergics, antipsychotics, and inhaled steroids[14,15,22]. Hoarseness is more prevalent in women than men and testosterone deficiency is recognized as a cause of hoarseness[15]. In light of existing data, in women who experience voice changes or hoarseness on testosterone therapy, other etiologies should be investigated and ruled out before testosterone is assumed to be causative.

This is the first prospective study examining the effect of testosterone replacement therapy on the female voice. Limitations of this study include the small number of subjects, the diverse population and two of 40 missing data points. Strengths include objective measurements of fundamental speaking frequency, the 1-year length of follow-up with four testing intervals, documented treatment compliance, i.e. subcutaneous implant, and the measurement of serum testosterone levels.

Conclusion

Despite 'reports' in the literature, and urban legends on the Internet, there is a lack of quality evidence supporting that testosterone replacement therapy negatively affects the female voice. The results from our 12-month prospective study found no adverse effects from therapeutic levels of testosterone on the female voice consistent with previous prospective findings on even higher (non-transgender) doses of androgenic agents. Further studies should be done on the potential positive and negative effects of testosterone replacement therapy on the aging female voice including subpopulations of women who rely on voice such as singers.

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