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Testosterone pellet implants and migraine headaches: A pilot study

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ABSTRACT

The purpose of this prospective pilot study was to determine the therapeutic effect of continuous testosterone, delivered as a subcutaneous implant, on the severity of migraine headaches in pre- and post-menopausal patients. Twenty-seven women with a history of documented migraine headache were asked to rate their headache severity using a five-point scale at baseline (prior to therapy); and again, 3 months following treatment with testosterone implants. Improvement in headache severity was noted by 92% of patients and the mean level of improvement was statistically significant (3.3 on a 5 point scale). In addition, there was no difference in the level of improvement between pre- and post-menopausal cohorts. Seventy-four percent of patients reported a headache severity score of '0' (none) on testosterone implant therapy for the 3-month treatment period. Continuous testosterone was effective therapy in reducing the severity of migraine headaches in both pre- and post-menopausal women.

1. Introduction

Migraine headaches are associated with hormonal changes in females. This pilot study was designed to determine the effect of continuous testosterone, delivered by subcutaneous implant, on migraine headache severity in pre- and post-menopausal women.

Testosterone replacement is usually equated to males with gonadal disorders resulting in low testosterone. However, testosterone has wide ranging biological effects in pre- and post-menopausal women, in part because of widespread androgen receptors found in brain, spinal cord, nerves, breast, bone, muscles, cardio-vascular system, lungs, GI tract, bladder, vaginal tissue, uterus, skin, hair follicles and adipose tissue. Testosterone can also exert its effect indirectly via aromatization to estrogen in these organs, ovary and adrenal gland.

Androgen production in women declines gradually throughout the reproductive years [1]. A woman of 40 has approximately half the testosterone of a 21 year old [2]. Recent studies have focused on testosterone therapy in both pre- and post-menopausal women with symptoms of relative androgen deficiency including; diminished sense of well-being, dysphoric mood (sadness, depression, anxiety, irritability), fatigue, decreased libido, insomnia, hot flashes, bone loss, decreased muscle strength, changes in cognition and memory, pain, vaginal dryness and incontinence [3,4]. Continuous testosterone delivered by subcutaneous implant has been safely used in women since 1938 and until recently, was the only licensed form of testosterone for women in England.

Migraine headaches occur in 18% of the female population with their peak prevalence occurring during 35–45 years of age [5]. Forty to seventy percent of women have menstrual migraine, which are migraines that occur during perimenstrual time-period (2 days before to 3 days after the onset of menstruation). It has been demonstrated that declining serum levels of estrogen trigger attacks of menstrual migraine. Therefore, there is ample data to suggest that fluctuations in ovarian hormones are responsible for the provocation of migraine headache in susceptible women [6].

There is sparse data suggesting that androgens are effective in the prevention of migraine and other headache disorders. Lichten and colleagues reported that administration of danazol

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to premenopausal women was associated with a decrease in the frequency of migraine headache [7]. Another study reported that migraine headaches improved with constant, adequate dosages of estrogen-androgen combinations as well as testosterone alone in post-menopausal women; also, that hormone delivery by pellet implantation gave superior results compared to oral or other parenteral routes of administration [8]. A recent study reports that testosterone replacement in patients with cluster headaches and low testosterone levels resulted in complete relief of headaches [9].

We aimed to study the effects of subcutaneous testosterone implants on the severity of migraine headaches in pre- and post-menopausal patients self-referred or referred by their physician for symptoms of androgen deficiency including: hot flashes, sleep disturbances, depressive mood, anxiety, irritability, physical fatigue, impaired memory, chronic pain, urinary problems and vaginal dryness.

2. Materials and methods

2.1. Study group

In an ongoing 10-year IRB approved trial on breast cancer occurrence and subcutaneous testosterone implant therapy,[1] it was observed that patients often reported relief of their headaches with therapy. Patients also reported that their headache would recur prior to (re)-insertion of subsequent testosterone implant, often as the first or foremost symptom associated with declining testosterone levels. Because of this observation, it was decided to perform a pilot study that prospectively evaluated the effect of testosterone implants on headaches in pre- and post-menopausal women treated for symptoms of androgen deficiency.

Criteria for inclusion in the prospective study included a documented history of migraine headache with previous workup with CT, MRI or other testing for headaches, diagnosis of migraine headache by primary care physician, visit to a neurologist for headache, and/or prior use of medication prescribed for migraine headache. In addition, all patients included in the study had experienced a migraine headache within 4 weeks of their initial visit to the clinic. All patients signed a consent form.

2.2. Data collection and statistical analysis

Female patients presenting to the clinic (RG) with symptoms of androgen deficiency and a chief complaint of migraine headache, were asked to rate their headaches on a 5-point scale developed for this pilot trial. The 5-point rating scale permitted the patient to describe the perceived severity of their headache: none 0, mild 1, moderate 2, severe 3, or extremely severe 4. The initial (baseline) survey was completed at the patient's first office visit, prior to testosterone implant therapy. Approximately 3 months later, at their next appointment for testosterone (re)-implantation, patients were asked to rate the severity of their migraines while on therapy. The mean scores were calculated at baseline (prior to therapy) and 3 months later (on average), following testosterone therapy, in the entire cohort as well as pre- and post-menopausal groups individually. A paired Student's *t*-test was used to determine if the perceived severity of migraines changed significantly after treatment. Student's *t*-tests were also used to determine if the severity was different for pre- vs. post-menopausal patients.

2.3. Therapy

Patients were treated with 130 ± 19.7 mg (range 100–160 mg) of testosterone, delivered subcutaneously in a sustained release pellet implant. Subcutaneous testosterone dosing is weight-based and effect is dose dependent [4]. Published data confirms efficacy as well as safety in doses of 75–225 mg in up to 3 decades of therapy [4,8,10–16]. Under local anesthesia, the 3.1 mm (diameter) pellets were advanced into the subcutaneous tissue in the upper gluteal area using a small trocar placed through a 5 mm incision, which was then closed with a steri-strip. There were no complications related to the procedure.

3. Results

3.1. Patient demographics

Twenty-seven patients, previously diagnosed with 'migraine headache', were enrolled in the study and received their first testosterone pellet insert between June 2009 and March 2010. Sixteen (59%) were pre-menopausal and 11 (41%) were post-menopausal, either spontaneous or surgical. The mean age of the combined cohort was 47.4 ± 9.6 years (range 31–79); 41.8 ± 5.5 years (range 31–52) for pre-menopausal patients, 55.5 ± 8.7 years (range 45–79) for post-menopausal patients.

3.2. Severity scoring and response to therapy

Mean severity scores for intensity of headaches at baseline (pre-treatment) and at follow-up (on testosterone therapy) are listed in Table 1. Significant improvement in migraine headache severity was demonstrated in the entire group as well as in pre- and post-menopausal cohorts treated with testosterone implant therapy. The perceived severity score after treatment was significantly less than before treatment ($t = 14.3$, df = 26, $P < 0.0001$). There was no difference in pre-treatment severity ($t = 1.0$, df = 25, $P = 0.32$) or post-treatment severity ($t = 1.5$, df = 25, $P = 0.14$) by menopausal status. In addition, there was no difference in the absolute change in pre- and post-treatment severity by menopausal status ($t = 0.8$, df = 25, $P = 0.39$).

Self reported medication use prior to testosterone therapy, frequency of headaches, pre-therapy severity scoring, and post-therapy severity scoring for each patient is listed in Table 2. The

Table 1
Mean ± SE age, baseline headache severity score, severity score on testosterone therapy, and absolute change in severity score; combined cohort, pre-menopausal and post-menopausal patients.

	Combined cohort $N = 27$	Pre-menopausal $N = 16$	Post-menopausal $N = 11$
Mean age	47.4 ± 9.6 years	41.8 ± 5.5 years	55.5 ± 8.7 years
Mean severity score[a] at baseline	3.63 ± 0.55	3.72 ± 0.52	3.5 ± 0.59
Mean severity score[a] on therapy	0.37 ± 1.08	0.63 ± 1.36	0[b] ± 0
Absolute change[c] in severity score	3.26 ± 1.19	3.1 ± 1.46	3.5 ± 0.59
	$P < 0.001$	$P < 0.001$	$P < 0.001$

[a] 5-Point rating scale, perceived severity of headache (none 0, mild 1, moderate 2, severe 3, or extremely severe 4).
[b] One patient continued prescription medication daily and one patient had complete relief (none 0) for a limited time only (3 weeks).
[c] The difference between baseline scores and scores on testosterone therapy.

[1] Glaser, R (PI) and Dimitrakakis, C (PI). Testosterone Implants and the Incidence of Breast Cancer: TI BCaP 0108 (Testosterone Implant Breast Cancer Prevention Trial 0108), IRB Approved 21 March 2008. Atrium Medical Center, Premier Health Partners, One Medical Center Drive, Middletown, Ohio 45005. Atrium Medical Center IRB is registered through the Office for Human Research Protections (OHRP).

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Table 2
Individual patient data; age, menopausal status, medication use, headache frequency, pre-therapy severity score and post-therapy severity score and notes.

Age (menopausal status)	Medication usage for HA prior to therapy	Reported headache frequency	Severity score prior	Severity score on therapy	Notes Unless otherwise noted, no headache/no medication for HA on TE therapy
52 (post)	Triptan prn	2–3/month	4	0	
45 (post)	Triptan/BB prn	3 days/month	4	0	No HA first 2 months, then moderate
50 (post)	APAP/ASA/CF qd	Daily	4	0	
56 (post)	Triptan qd	Daily	4	0*, 1–2	*No HA 2 weeks, then less frequent, less severe, Triptan prn
59 (post)	Unknown	1/month	4	0	
54 (post)	Triptan prn	1–2/week	4	0	
53 (post)	APAP/ASA/CF qd	Daily	2.5	0	
79 (post)	BB, IB prn	Daily	3	0	
55 (post)	Triptan qd	Daily	3	0	No HA on daily Triptan
57 (post)	SL medication prn	1/month	3	0	
51 (post)	Triptan/BB prn	1/month	4	0	
37 (pre)	OCP APAP/ASA/CF prn	*q* month/cycle	4	0	D/C OCP
44 (pre)	IB prn	*q* month/cycle	2.5	0	
31 (pre)	Triptan prn	2/month	3	0	
46 (pre)	APAP/ASA/CF prn	1/month	3	3	Less frequent, 1/3 months
49 (pre)	Propo-N APAP prn	1/month	3	0	
40 (pre)	Triptan qd	1/month	4	0	
52 (pre)	Triptan prn	10 days/month	4	4	No change freq/severity
47 (pre)	Propo-N APAP, IB prn	*q* month/cycle	4	0	No HA 9 weeks, then severe
41 (pre)	APAP/ASA/CF prn	1/month	4	0	
38 (pre)	APAP/ASA/CF prn	*q* month/cycle	4	0	
38 (pre)	APAP/ASA/CF prn	daily	4	0	
48 (pre)	Triptan prn	7–9/month	4	0**, 3	** No HA 3 weeks only, then less frequent (3/month), less severe
37 (pre)	Triptan/midrin prn	7–10/month	4	0	
41 (pre)	OCP, Triptan prn	*q* month/cycle	4	3	Same frequency, less severe, D/C OCP
41 (pre)	Triptan prn	3/month	4	0	
39 (pre)	Triptan, IB prn	3/month	4	0	

Abbreviations; HA, headache; D/C, discontinued; APAP/ASA/CF, acetaminophen aspirin caffeine; IB, ibuprofen; BB, beta-blocker; Triptan, selective seratonin receptor agonist; Propo-N APAP, acetaminophen propoxyphene; OCP, oral contraceptive pill.

majority of patients reported no headaches and no use of medications (for headaches) during testosterone implant therapy (Table 2).

Twenty-five of the 27 patients returned for a second pellet implant, on average, 3 months later. Of the 2 patients that did not return, one reported no improvement, and one reported improvement in headache, but did not return for therapy (both patients were contacted by phone). All 25 patients that returned for therapy completed the follow-up questionnaire.

Of the 25 women who returned for a second pellet (re)-insertion, 20 (74%) reported a score of '0' (no migraine headache) with testosterone therapy alone for ten or more weeks following implantation. Two (7%) patients improved for 2–3 weeks only. Of the three remaining patients; one had less migraine occurrence (frequency), but same severity (Score 3 to 3), one had complete relief of migraine (0) but with continued daily, prescription 'preventative' medication (i.e. Triptan) and one went from extremely severe (4) requiring hospitalization to severe (3) and no longer required hospitalization (Table 2). No adverse reactions to testosterone pellet therapy were reported.

3.3. Additional/prior hormone therapy

Two pre-menopausal patients on oral contraception for migraine headache control, discontinued them after their first testosterone pellet implant. A third patient remained on oral contraception for birth control. A fourth pre-menopausal patient was able to discontinue her 0.0375 mg transdermal estradiol patch that had been prescribed for hot flashes, insomnia, fatigue, vaginal dryness and urinary symptoms. A fifth patient discontinued her topical progesterone cream, which had also been prescribed for hot flashes. No hormone therapy was prescribed in addition to the testosterone implant.

4. Discussion

Our prospective pilot study has shown that continuous testosterone, delivered by subcutaneous implant, was effective in decreasing the severity of migraine headaches in pre- and post-menopausal women. All patients in this study presented to the clinic with symptoms of relative androgen deficiency (RAD) and a poorer quality of life as measured by the validated, Menopause Rating Scale, which further strengthens the relationship of hormone imbalance to migraine headache. We have previously shown that continuous testosterone, delivered by subcutaneous implant, was equally effective in both pre- and post-menopausal patients for relief of symptoms [4].

Interestingly, the prevalence of migraine headaches in females (age 35–40) coincides with testosterone decline [1,2,5] and the onset of symptoms of RAD. In this study, we have shown that subcutaneous testosterone therapy had a beneficial effect on migraine headaches, in addition to the documented beneficial effects on symptoms of RAD. Previous studies have shown that estrogens play an important role in migraine headaches [6]. Continuous delivery of testosterone by the implant and binding to the androgen receptor may counteract, or balance, the affects of excess or fluctuating estradiol. In clinical practice, we also see an improvement in breast pain, anxiety, PMS, dysfunctional uterine bleeding and other symptoms of estrogen excess with testosterone therapy. In addition, subsequent to the collection of this data, we have found that many pre-menopausal patients have superior headache relief (intensity and duration) with the addition of anastrozole (an aromatase inhibitor that reduces estrogen) delivered in combination with testosterone, further emphasizing the role of estrogen in migraine headaches.

The mechanism through which testosterone modulates migraine headaches is unknown, but might involve suppression of cortical spreading depression (CSD), which is thought to occur

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during the aura phase of migraine headache. Eikermann-Haeter and colleagues demonstrated that the frequency of CSD was reduced after administration of testosterone in orchiectomized male mice that possessed the FHM1 R192Q mutation for familial hemiplegic migraine [17]. Testosterone is a neuroactive steroid and has been shown to increase serotontin, which may also play a role in prevention of headaches [8,18]. The effect of testosterone as a vasodilator [19], although controversial in the etiology of migraine headaches, may play a role in relief of headaches by stabilizing cerebral blood flow. Furthermore, testosterone has been shown to be both anti-inflammatory [20] and neuro-protective [21]. Thus, there are several possible mechanisms by which continuous testosterone may protect against migraine headaches.

Although there is significant inter-individual variation and intra-individual circadian variation, we have previously documented mean therapeutic total testosterone levels of 299.36 ± 107.34 ng/dl, 4 weeks following pellet implantation. In addition, symptoms recur with serum testosterone levels two to three times the upper limits of normal for endogenous production (data not shown). We have found that these levels of testosterone in serum are required to deliver adequate (i.e. biologically relevant) amounts of testosterone to the androgen receptor for a therapeutic effect. Unlike estradiol, there are no reports of tachyphylaxis with subcutaneous testosterone therapy. Furthermore, in our practice (RG) of over 12,000 testosterone insertions in over 4000 women-years of therapy, there has been no evidence of tachyphylaxis or decrease in response to subcutaneous testosterone therapy.

A major weakness of this 'proof of idea' trial was the use of a non-validated scale to measure severity of migraine symptoms, along with the inability of this scale to clearly differentiate between intensity and frequency of headaches. In addition, there was no control group, so we were unable to quantify a 'placebo effect', which can be as high as 50% for headache prevention. However, the fact that the majority of patients reported 'no headache' and 'no medication use' until, on average, 3 months after implantation, speaks against placebo.

5. Conclusion

This pilot study has shown that sustained release of testosterone, provided by the subcutaneous implant, was effective therapy for migraine headaches in pre- and post-menopausal patients. Further studies using a validated scale are needed to confirm the beneficial effect of continuous testosterone therapy in controlling difficult migraine headaches in women.

Contributors

RG and CD contributed equally to the research, design of the study, analyzing the data, writing and editing the ms. RG recruited participants. NT participated in writing. VM contributed to writing and editing the ms. All authors approved the final manuscript.

Competing interest

None declared.

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