Author's Accepted Manuscript

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PII: S0022-5347(14)03024-9
DOI: 10.1016/j.juro.2014.03.089
Reference: JURO 11351

To appear in: *The Journal of Urology*
Accepted Date: 13 March 2014

Please cite this article as: Ramasamy R, Scovell JM, Kovac JR, Lipshultz LI, Testosterone Supplementation Versus Clomiphene Citrate: An Age Matched Comparison Of Satisfaction And Efficacy, *The Journal of Urology*® (2014), doi: 10.1016/j.juro.2014.03.089.

TESTOSTERONE SUPPLEMENTATION VERSUS CLOMIPHENE CITRATE: AN AGE MATCHED COMPARISON OF SATISFACTION AND EFFICACY.

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Key words: hypogonadism, symptoms, ADAM, qADAM, gels, injections.

Word count:

Abstract=250

Manuscript = 1722

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ABSTRACT

Purpose: To compare satisfaction and treatment efficacy in men with symptomatic hypogonadism receiving clomiphene citrate (CC) or testosterone supplementation therapy (TST).

Materials and Methods: Men receiving CC, testosterone injections (T injections) or testosterone gels (T gels) for symptomatic hypogonadism (total testosterone < 300 ng/dL) reported satisfaction with their current treatment regimen using the quantitative androgen deficiency in aging male (qADAM) questionnaire.

Results: A total of 93 men on T injections, T gels, or CC (**n=31 in each group**), were age matched from a retrospective cohort of 1150 men on TST. **We compared the men who received TST to 31 men who were not on1 TST (controls)**. Median serum testosterone (T) levels increased from pre-treatment levels in all men, regardless of therapy type (CC=247 to 504 ng/dL, T injections=224 to 1104 ng/dL, T gels=230 to 412 ng/dL, $p<0.05$). The final median serum total T levels in men on CC (504 ng/dL) was lower ($p<0.01$) than men taking T injections (1014 ng/dL), but similar to men on T gels (412 ng/dL, $p=0.31$). Despite different serum T levels, men on all three therapies reported similar satisfaction levels (qADAM=35 (CC), 39 (T injections), 36 (T gels), 34 (controls) were similar ($p>0.05$). Men on T injections reported a greater libido then men on CC (4 vs. 3, $p=0.04$), T gels (4 vs. 3, $p=0.04$), controls (4 vs. 3, $p<0.01$).

Conclusions: Testosterone supplementation regimens and CC are efficacious in improving serum total testosterone levels. No difference in overall hypogonadal symptoms exists between men on any TST. Despite lower serum total T levels, men taking CC and T gels report similar levels of satisfaction compared to men taking T injections.

INTRODUCTION

Idiopathic age related hypogonadism affects nearly 40% of men age 45 years or older[1], and is a current health epidemic. Typically, hypogonadism presents with persistent non-specific symptoms of diminished libido, fatigue, poor concentration, erectile dysfunction, lack of concentration, and depressed mood in the presence of low serum testosterone levels [2-4]. These low serum testosterone levels have multiple negative systemic effects including increased rates of cardiovascular disease, dyslipidemia, diabetes, metabolic syndrome, and osteoporosis, as well as all-cause mortality[5, 6]. **Testosterone in the bloodstream is bound mostly to SHBG and to a lesser extent albumin and corticosteroid-binding globulin. Only a very small fraction (~1-2%) is unbound, or "free," and thus biologically active. SHBG increases with age and inhibits the function of testosterone.** Indeed, numerous studies exist showing testosterone supplementation therapy (TST) to be effective in increasing serum testosterone levels[7-11] with a correlated clinical improvement in quality of life, weight, and waist circumference[12, 13].

The androgen decline in the aging male (ADAM)[14], and more recently the quantitative ADAM (qADAM)[15] questionnaires are used to asses the subjective symptoms of hypogonadism. Yamaguchi et al. showed that patients treated at least 6 months with TST had improvement in their ADAM scores[16] and a study by Taylor and Levine showed improvement of ADAM scores for hypogonadal men being treated with clomiphene citrate[17].

Clomiphene citrate (CC) is a selective estrogen receptor modulator that has been shown to be an effective treatment for male hypogonadism by indirectly increasing serum testosterone levels, and increasing the testosterone/estradiol ratio[18, 19]. **While CC is not FDA approved for hypogonadism, it has been used off-label for many years. Side effects are typically minor**

and may include nausea, dizziness, weight gain and fluid retention. Improvement in serum testosterone is achieved by inhibition of the negative feedback of estradiol to the hypothalamic-pituitary-gonadal axis (HPGA) at the level of the hypothalamus. The subsequent release of LH and FSH from the anterior pituitary results in greater stimulation of Leydig cells which produce the anabolic hormone testosterone[20]. Recent evidence suggests that clomiphene citrate may be an appropriate alternative treatment for male hypogonadism because it is safe[21], affordable, and effective [22, 23] at improving serum testosterone levels[17].

Testosterone injections have been used for many years; however, this modality often generates serum testosterone levels with peak and trough values above and below the normal range – with unclear effects of how these fluctuations affect satisfaction. Preparations such as T gels provide a more stable level of serum testosterone. We performed a cross-sectional **retrospective** comparison of hypogonadal symptoms in men using clomiphene citrate, testosterone gels, injections **and in men not on TST**. We hypothesized that men taking clomiphene citrate for symptomatic hypogonadism were just as satisfied (represented by qADAM scores), with their therapy than those on testosterone gels or injections - despite varying serum total testosterone levels.

MATERIALS AND METHODS

Following approval by the Institutional Review Board (IRB) at Baylor College of Medicine (Houston, Texas), qADAM questionnaires[14, 15] were given to all patients presenting with symptoms of hypogonadism. **The qADAM questionnaire consists of the 10 questions of the original ADAM[14], with 'yes' and 'no' replaced by a Likert scale of 1–5, in which 5 represented the absence of a given symptom and 1 represented maximal symptoms. The**

qADAM was devised to better quantify improvement in hypogonadal symptoms when full symptom resolution is not achieved. The scores for qADAM range from 10-50, and a lower score indicates more severe hypogonadal symptoms. **All questions were weighted equally and there is no threshold score to that has been shown to accurately diagnose hypogonadism.**

We analyzed data based on different treatment regimens: clomiphene citrate, testosterone gel, testosterone injections, and **eugonadal men not on TST (controls) in a retrospective cross-sectional design.** Treatment regimens included CC (25mg orally once a day), T gels (Testim 1% or Androgel 1.62%, 2-4 pumps/day), and T injections (testosterone cypionate 100-200mg once a week intramuscularly[7]) for men being treated for symptomatic hypogonadism (defined as total testosterone <300 ng/dL and ≥3 positive symptoms on the androgen deficiency in aging male (ADAM) questionnaire[14, 15]. **All men who had a testosterone level on treatment and completed the ADAM questionnaire were included in the analysis.**

Treatment efficacy was evaluated with pre- and post-treatment serum testosterone levels. Post-treatment serum testosterone values were taken on the same visit that the qADAM questionnaires were completed. Testosterone and estradiol measurements were performed using the radio-immuno assay with Beckman Access II platform (Beckman Coulter, Fullerton, CA, USA). Testosterone levels were drawn before 10 AM for men younger than 40, and between 9 AM and 5 PM for men older than 40. Since the variability in serum testosterone of men on T injections makes the timing of blood draws difficult; samples were collected during the patient's scheduled follow-up visit with no special concern for the timing of the last injection. The variability in levels was obviated by the random nature of the draw and the amount of patients surveyed.An equal number of men in each treatment regimen were age-matched to eliminate the confounding effect of age on hypogonadal symptoms. Data was analyzed using

Microsoft Excel (Microsoft, Redmond, WA) and Minitab16 (Minitab Inc.). All values were reported as median ± inter-quartile range (IQR), and a Mann-Whitney test was used to evaluate a difference in medians between groups. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

The charts of 1150 men on TST men were reviewed and a total of 93 men were age-matched with an equal number of men (n=31) on CC, T injections, or T gels (Table 1). Additionally, we age-matched another 31 men not on TST. There was no difference in median age between men on CC (40.9 y), T injections (40.5 y), T gels (43.9 y) and men not on TST (40.5), p>0.05). **Median** testosterone levels increased from pre-treatment levels in all men regardless of therapy type (CC = 247 to 504 ng/dL, T injections = 224 to 1104 ng/dL, T gels 230 to **412** ng/dL p<0.05). The largest increase was seen in men on T injections (956 ng/dL) with a more modest increase in men on CC (272 ng/dL) or T gels (243 ng/dL). The final mean serum total T levels in men on CC (525 ng/dL) was lower (p<0.01) than men taking T injections (1014 ng/dL) but similar to men on T gels (412 ng/dL, p=0.31). As expected, testosterone levels in men not receiving TST (310 ng/dL) were significantly lower (p<0.05) than men on TST. Serum estradiol was greater in men on T injections (6.0 ng/dL) than in men on CC (2.0 ng/dL, p<0.01), T gels (2.0 ng/dL, p<0.01), or in men not on TST (2.0, p<0.01). Similarly, the testosterone to estradiol ratio (T/E) was greater in men on T injections (200, p<0.01) and men on CC (181, p=0.03) when compared to men not on TST (145).

Despite different serum T levels, men on all three therapies, as well as men not taking TST, reported similar levels of hypogonadal symptoms. Quantitative ADAM scores (35, 39, 36, and 34) were similar (p>0.05) for the men on CC, T injections, T gels, and no TST respectively

(Figure 1). Based on the results of the qADAM, men on T injections compared to men on CC, T gels, and no TST reported a greater libido (4 vs. 3 vs. 3 vs. 3, p=0.047, 0.04, <0.01). The remaining symptoms of hypogonadism on qADAM questionnaire were similar between men on CC and TST.

DISCUSSION

In this study, we demonstrated no differences between hypogonadal symptoms between men on clomiphene citrate, testosterone injectables, and testosterone gels - despite the highly elevated serum testosterone levels in the men using testosterone injectables. This suggests that supra-physiologic levels of testosterone are not directly correlated with decreases in hypogonadal symptomology. Indeed, symptom resolution may be a better guide than serum testosterone values for evaluating the efficacy of TST in an individual patient.

Most patients are treated with either T gels or injections for symptomatic hypogonadism. Currently, fewer men, are given CC as an alternative treatment modality for hypogonadism. On the whole, in the current study, men taking CC reported equal rates of resolution of their hypogonadal symptoms (via the qADAM) compared to men prescribed T injections or gels. This evidence suggests that there may be a larger role for CC as a treatment for symptomatic hypogonadism as an alternative to testosterone gels or injections especially in younger men who are interested in fertility preservation. **Of concern, up to 20% of urologists could prescribe exogenous testosterone, a medication known for its contraceptive potential, to men with infertility.**[24]

The findings from this study dispel the notion that a pure linear relationship exists between serum T and satisfaction levels[4]. In a recent study Yeap et al., the authors demonstrated

a U-shaped association between testosterone levels and cardiovascular mortality[25]. Men with serum T levels in the highest quartile had a higher risk of mortality than men in the middle quartiles. With studies pointing to an association between serum T and cardiovascular risk, practitioners should target symptom improvement rather than simply a rise in T levels as the end goal.

Interestingly, when components of the qADAM questionnaire were analyzed separately, men on T injections reported a higher libido compared to men taking CC and T gels. Furthermore, serum estradiol levels were found to be higher in men on T injections versus men on CC or T gels. These associations between elevated serum estradiol levels and higher libido corroborates the recent study by Finkelstein *et al.* that documented an important role for estrogen in the regulation of sexual function in men on T gels [26].

The current study has both strengths and limitations. The ability to capture men on the same day that serum hormones are evaluated allows accurate comparisons to be drawn between serum hormone levels and perceived symptomology. In addition, the age-matched design removes age as a confounding variable – especially important given that younger men report increased satisfaction with TST [27]. **In addition, CC was prescribed to typically young men with infertility and age matching would potentially eliminate this bias.** We sought to identify the question of what, if any, differences may be found between TST modality by evaluating the symptoms from the patient's perspective. The use of a control group of eugonadal men not on TST and a standardized, validated questionnaire (qADAM) to evaluate satisfaction and hypogonadal symptoms also adds further strength to our findings. The study is limited by its retrospective and cross-sectional design and the fact that **pre-treatment qADAM values were not available**. A limitation of the qADAM questionnaire is its poor specificity. The lack of

specificity is not only due to the fact that many positive responses in the questionnaire may be indicative of other conditions such as depression, but also because scores derived from these questionnaires do not predict or correlate well with measured free and total testosterone[28]. Moreover, while we could not control the timing of the T injection (**could have confounded the results**), the fact that our average testosterone levels were significantly elevated compared to the CC and T gels suggests that the majority of patients were captured within 3-4 days post-injection. **In addition, only one serum testosterone level was included in the analysis since we wanted to evaluate the relationship between qADAM score and serum testosterone.**

CONCLUSION

Men taking CC for symptomatic hypogonadism reported similar hypogonadal symptoms compared to age-matched men on T injections and gels. These comparable hypogonadal symptoms amongst the different treatment regimens suggest that CC could be just as effective in treating hypogonadism as other well-established treatment modalities. Given that CC has fewer potential side effects compared to either T injections or gels, and is more affordable, there may be a larger role for its use to treat men with symptomatic hypogonadism.

Legends:

Figure 1: Comparison of serum total testosterone and quantitative ADAM scores among men on different testosterone supplementation therapies.

Table 1: Age matched-pair comparison of men on testosterone supplementation therapy (testosterone injections, testosterone gels, and clomiphene citrate). Data are reported as medians +/- IQR. * P-value calculated using Mann-Whitney U test.

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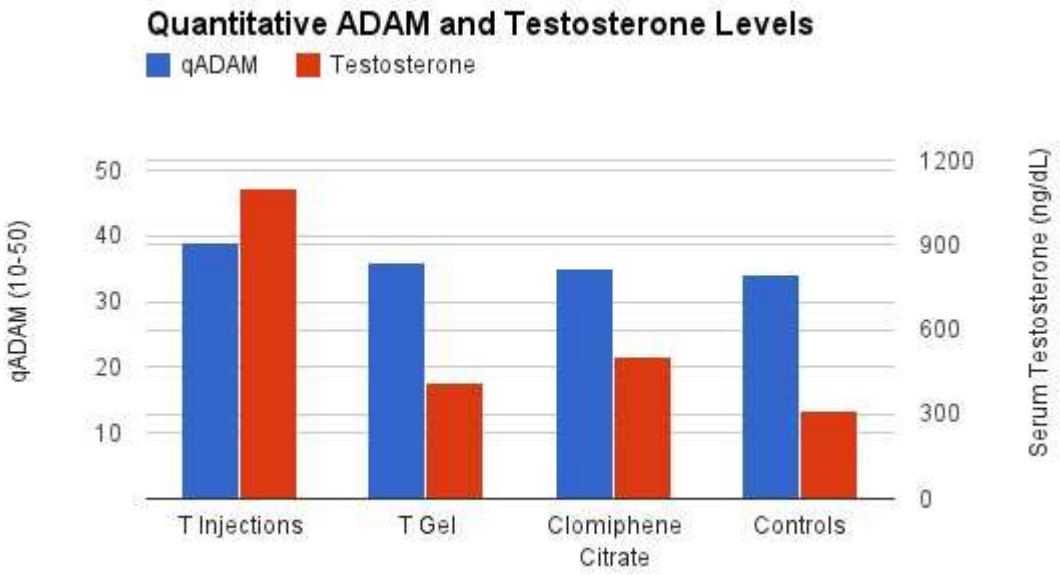

Table: Age matched-pair comparison of men on testosterone supplementation therapy (testosterone injections, testosterone gels, and clomiphene citrate). Data are reported as medians +/- IQR. * P-value calculated using Mann-Whitney U test.

	Testosterone injections (1)	**Testosterone gels (2)**	**Clomiphene citrate (3)**	**No TST (4)**	**p-value (1 v 2)**	**p-value (1 v 3)**	**p-value (1 v 4)**	**p-value (2 v 3)**	**p-value (2 v 4)**	**p-value (3 v 4)**
Age (years)	40.5 ± 9.2	43.9 ± 13.7	40.9 ± 9.4	40.5 ± 10.4	0.23	0.83	0.90	0.17	0.27	0.69
Pre-treatment T (ng/dL)	223.5 ± 182.5	230.0 ± 151.0	247.0 ± 66.5	-	0.65	0.71	-	0.78	-	-
Post-treatment T (ng/dL)	1104.0 ± 866.5	412.0 ± 339.0	503.5 ± 306.8	310.0 ± 136.0	**<0. 01**	**<0.01**	**<0.01**	0.31	0.064	**<0.01**
Delta T (ng/dL)	956 ± 879	243.0 ± 375.5	271.5 ± 325.8	-	**<0.01**	**<0.01**	-	0.60	-	-
Estradiol (ng/dL)	6.0 ± 5.8	2.0 ± 1.0	2.0 ± 1.0	2.0 ± 0.0	**<0.01**	**<0.01**	**<0.01**	0.52	0.18	0.58
T/E ratio	200.0 ± 116.4	175.0 ± 114.5	181.0 ± 119.5	144.5 ± 91.2	0.15	0.36	**<0.01**	0.50	0.19	**0.03**
qADAM (range 10 – 50)	39 ± 8	36 ± 9	35 ± 8	34 ± 9	0.53	0.45	0.16	1.00	0.30	0.27
Libido (range 1-5)	4.0 ± 1.0	3.0 ± 2.0	3.0 ± 2.0	3.0 ± 1.5	**0.04**	**0.04**	**<0.01**	0.68	0.36	0.14

Abbreviations:

Clomiphene citrate (CC)

Testosterone gel (T gel)

Testosterone injections (T injections)

Testosterone supplementation therapy (TST)

Quantitative androgen decline in the aging male (qADAM)