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ORIGINAL ARTICLE

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Direct conversion from long-acting testosterone replacement therapy to Natesto allows for spermatogenesis resumption: Proof of concept

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Abstract

Long-acting testosterone replacement therapy (TRT) suppresses spermatogenesis. A short-acting TRT, Natesto, maintains spermatogenesis in some men. This study evaluated hormonal and semen parameters converting men from long-acting TRT to Natesto. Baseline hormones, again on long-acting TRT and 1 month after converting to Natesto, as well as semen parameters 3 months after converting to Natesto were assessed. Twenty-seven men were directly converted from long-acting forms of TRT to Natesto. Mean duration on long-acting TRT was 24.3 ± 19 months. Testosterone levels were similar on long-acting forms of TRT and Natesto, however; E2 levels were significantly lower on Natesto. Ten men had semen analyses demonstrating azoospermia while on long-acting TRT, the remainder were presumed to be azoospermic or severely oligospermic which has been well established as an effect of long-acting TRT. All 27 men had resumption of spermatogenesis with a mean sperm concentration of 50.7 million/ml after converting to Natesto, considered within the fertile range. One couple achieved a pregnancy 4 months after converting to Natesto. Hypogonadal men on long-acting TRT interested in resumption of spermatogenesis may convert directly to Natesto for an opportunity to do so while remaining on a form of TRT and achieving lower E2 levels.

KEYWORDS
estradiol, hypogonadism, semen analysis, sperm, testosterone

1 | INTRODUCTION

The pituitary gland secretes gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH) in a pulsatile fashion which signal the testicles for spermatogenesis and testosterone production, respectively. Gonadotropins are suppressed with long-acting traditional modalities of testosterone replacement therapy (TRT) such as transdermal gels, intramuscular injections, and subcutaneous pellets, and therefore decrease intratesticular testosterone levels which results in suppression of spermatogenesis (Anderson & Baird, 2002; Crosnoe et al., 2013; MacIndoe et al., 1997). Traditionally, clomiphene citrate (CC) has been used off-label for its mechanism of inhibiting

estradiol (E2) negative feedback to the hypothalamus and thereby ultimately increasing LH secretion to stimulate the Leydig cells of the testicles which, in turn, increase testosterone production in a spermatogenesis preserving manner for hypogonadal men desiring to maintain fertility potential (Krzastek et al., 2019). The majority of men treated with CC achieve eugonadal serum testosterone levels; however, E2 levels tend to rise, and hypogonadal symptom response to CC has been reported to be less optimal than on TRT, particularly libido (Dadhich et al., 2017; Kavoussi et al., 2021). Low libido poses a challenge for conception. Natesto, a short-acting intranasal TRT, allows for maintenance of FSH and LH within normal ranges in most men despite some suppression from baseline levels, thereby allowing for maintenance of spermatogenesis when given to TRT naïve patients or after a washout period from other TRT modalities in most men, as well as in most men converting from CC to Natesto (Kavoussi, 2021; Kavoussi et al., 2021; Ramasamy et al., 2020).

2 | MATERIALS AND METHODS

After the data in the three publications revealing most men treated with Natesto may maintain spermatogenesis (Kavoussi, 2021; Kavoussi et al., 2021; Ramasamy et al., 2020) was discussed with 27 men on forms of long-acting TRT who were interested in regaining spermatogenesis but not wanting to discontinue TRT for fear of symptomatic repercussions, they were counselled on the option of directly converting from their long-acting form of TRT to Natesto, understanding the spermatogenic outcome of such a manoeuvre was unknown to date. These men were initially diagnosed with hypogonadism after presenting with hypogonadal symptoms and having two morning serum testosterone levels of less than 300 ng/dl. Between August 5th, 2021, and November 22nd, 2021, 27 men receiving care at a reproductive urology practice were converted from treatment with a long-acting TRT directly to Natesto with no washout period and serum testosterone, FSH, LH and E2 were obtained 1 month after converting to Natesto, 1 h after administration of the morning dose of Natesto, and a semen analysis was obtained 3 months after converting to Natesto. All semen analyses were performed at a single high complexity andrology laboratory. All men were initiated on Natesto 11 mg twice daily intranasal administration, and if they did not achieve eugonadal levels obtained 1 h after administration of Natesto 1 month after initiation of treatment, the dose was titrated up to three times daily. Only 1/27 (3.7%) of the men required up titration to three times daily dosing. The results reported on Natesto were on the treatment regimen that achieved eugonadal levels.

After St. David's Healthcare institutional review board exemption was obtained (1841964-1) due to the de-identified nature of the data collected, a retrospective chart review was performed of the electronic health record to assess the hormonal and semen parameter value responses from converting from long-acting TRT to Natesto. Student's *t* test was used for statistical analysis with a *p* value of <0.05 considered statistically significant. Results are expressed as means ± standard deviations.

3 | RESULTS

Twenty-seven men were directly converted from long-acting forms of TRT to Natesto. The forms of long-acting TRT included 5 men on transdermal gels, 20 men on intramuscular testosterone cypionate injections, and 2 men on subcutaneous pellets. The mean age of these 27 men was 39 ± 8 years. The men were on long-acting TRT for a mean duration of 24.3 ± 19 months prior to conversion to Natesto. Mean baseline testosterone, FSH, LH, and E2 prior to any treatment, as well as mean testosterone and E2 on long-acting TRT are shown in Table 1. The serum levels were obtained 4 h after application of transdermal gels, trough levels on intramuscular injections, and peak levels on subcutaneous pellets. Ten of the 27 men had semen analyses obtained while on long-acting TRT, all of which revealed azoospermia at the time as expected. The other 17 men did not have semen analyses obtained on long-acting TRT as they were not interested in fertility potential at the time that they initiated TRT. The mean hormonal levels 1 month after converting from long-acting TRT to Natesto as well as semen parameter values 3 months after converting to Natesto are shown in Table 1. There was no difference in FSH and LH levels when compared at baseline to 1 month after conversion to Natesto. Serum testosterone levels were similar on long-acting forms of TRT in comparison to Natesto, however; the E2 levels were significantly lower on Natesto than on forms of long-acting TRT. All 27 men had resumption of spermatogenesis with a mean sperm concentration of 50.7 million/ml, clinically considered well within the fertile range. One couple achieved a pregnancy 4 months after converting to Natesto.

4 | DISCUSSION

It has been demonstrated that spermatogenesis may be maintained in many men initiating the short-acting intranasal testosterone gel Natesto for men naïve to treatment or after a washout period from long-acting forms of TRT (Ramasamy et al., 2020). It has also been demonstrated that the majority of men converting from CC to Natesto can maintain spermatogenesis, maintain lower E2 levels, and have improved libido (Kavoussi, 2021; Kavoussi et al., 2021). In this study, it has now been demonstrated for the first time, that men on long-acting forms of TRT can convert directly to Natesto and normalize gonadotropins and resume spermatogenesis. This option may be of great interest to hypogonadal men who want to continue to maintain optimal symptomatic response to treatment by remaining on TRT, rather than converting to CC, by simply changing from a long-acting form of TRT to a short-acting form of TRT in Natesto, with an opportunity for gonadotropins to resume to stimulate resumption of spermatogenesis. The men's fertility status at baseline prior to being diagnosed with symptomatic hypogonadism and starting long-acting TRT prior to expressing interest in fertility potential was unknown. The men were counselled on the impact of long-acting TRT but were not planning on future fertility at that time. However, they showed a response to resume spermatogenesis to what are considered normal sperm concentrations after direct conversion from long-acting TRT to Natesto after changing their minds

TABLE 1 Hormonal parameters at baseline, on long-acting testosterone replacement modalities (topical gels, intramuscular injection, and subcutaneous pellets), and on Natesto for men with hypogonadism ($n = 27$)

	Baseline	Long-acting testosterone	Natesto	*p* value
Testosterone (ng/dl)	234.2 ± 53	761 ± 278	643.9 ± 170	0.0675
Estradiol (pg/ml)	23.7 ± 10	39.6 ± 19	21.5 ± 8	**0.0001**
Follicle stimulating hormone (mIU/ml)	4.5 ± 5		3.7 ± 4	0.519
Luteinizing hormone (mIU/ml)	4.6 ± 4		4.6 ± 5	1.0
Semen volume (ml)			2.6 ± 1	
Sperm concentration (mil/ml)			50.7 ± 36	
Total motility (%)			56.2 ± 18	
Forward progressive motility (%)			28.6 ± 13	
Normal morphology (%)			4.9 ± 4	
Total motile sperm count (mil)			69.1 ± 65	

Note: Semen parameters on Natesto. Results are expressed as means ± standard deviations. *p* values for testosterone and estradiol levels are comparing men on long-acting forms of testosterone replacement versus Natesto. *p* values for follicle stimulating hormone and luteinizing hormone levels are comparing baseline levels prior to any treatment to treatment with Natesto. Bold value indicates statistical significance.

and expressing interest in fertility. Although only 10 of the 27 had proven azoospermia on long-acting forms of TRT, it is widely accepted that men on long-acting forms of TRT are expected to be azoospermic or severely oligospermic, which has been demonstrated extensively in past studies. The mean duration of men on long-acting TRT with semen analyses proving azoospermia while on the long-acting therapy was 32.9 ± 17.9 months, which is a longer mean duration than the entire studies cohort. There was only one patient with a duration of less than 1 year at 3 months which actually skewed the mean and the standard deviation. The remainder of these men had durations on long-acting TRT of 24, 26, 37, 60, 14, 37, 60, 32, and 36 months. In the men who were proven to be azoospermic by semen analyses while on long-acting TRT, the mean sperm concentration 3 months after converting to Natesto was 41.0 ± 27.4 million/ml, indicating a robust resumption of spermatogenesis. Interestingly, gonadotropins in the entire cohort in the study normalized as early as 1 month after converting from long-acting forms of TRT to Natesto and all the men in this cohort had resumption of spermatogenesis, demonstrated by semen analyses, as early as 3 months after making this change in medication. This conversion from long-acting to short-acting TRT not only allowed for normalization of the hypothalamic–pituitary–gonadal axis and resumption of spermatogenesis but had the added benefit of a statistically significant mean lower E2 level. This data is not suggesting that Natesto is stimulating spermatogenesis any more effectively than just discontinuing long-acting TRT would but is suggestive of this as an option for some men to be able to remain on a different form of TRT, with a short-acting nature allowing resumption of spermatogenesis rather than continued suppression of spermatogenesis on a long-term TRT and allowing for continued symptomatic relief on TRT. Although this data set has not been carried out for a very long duration thus far for pregnancy data, one couple achieved a pregnancy 4 months after converting from long-acting TRT to Natesto.

Limitations to this study include a short follow up duration and a relatively small sample size. This study is not powered to confirm that all men regardless of duration on long-acting TRT converting to Natesto can reinitiate the hypothalamic–pituitary–gonadal axis and resume spermatogenesis, but it is a proof of concept that some men are able to achieve these outcomes. A power calculation was not performed, but this is a proof of concept study, further study with larger populations with a power calculation is warranted based on this proof of concept. Another limitation is not having baseline semen analyses on the men prior to initiation of long-acting TRT, which there would not have been a reason to obtain clinically in these hypogonadal men not interested in fertility when they first initiated long-acting TRT for a symptomatic response, but then changed their minds about fertility potential. As this is a retrospective chart review of clinical outcomes in these men, semen analysis results pre-treatment with a long-acting TRT are not available. There is a need for further study on this with a prospective study. However, the current data still reveals that resumption to robust semen parameters is possible after converting from long-acting TRT directly to Natesto. A limitation to this data that requires caution is the question of whether men on long-acting TRT for longer durations prior to converting to Natesto would have as favourable of a response to converting to Natesto. Further study is needed to answer this question. Another potential limitation may be that men on long-acting TRT modalities were grouped together under a single category, despite using three different formulations of long-acting TRT. Although all forms of long-acting TRT act similarly in their mechanism to suppress the hypothalamic–pituitary–gonadal axis, inter-formulation variation and the quality of compliance may be a consideration for consistency of use.

5 | CONCLUSIONS

Some hypogonadal men on long-acting forms of TRT who are interested in resumption of spermatogenesis may convert from long-acting TRT directly to Natesto for an opportunity to do so while remaining on a form of TRT and achieving lower E2 levels.

AUTHOR CONTRIBUTIONS

Parviz K. Kavoussi: Substantial contributions to research design, acquisition, analysis, and interpretation of data; drafting and revising the manuscript critically; and approval of the final version. **Graham L. Machen**: Substantial contributions to acquisition of data; drafting and revising the manuscript critically; and approval of the final version. **Shu-Hung Chen**: Substantial contributions to acquisition of data; drafting and revising the manuscript critically; and approval of the final version. **Melissa S. Gilkey**: Substantial contributions to acquisition of data; drafting and revising the manuscript critically; and approval of the final version. **Justin Chen**: Substantial contributions to acquisition of data; drafting and revising the manuscript critically; and approval of the final version. **Yazan Hamzeh**: Substantial contributions to acquisition of data; drafting and revising the manuscript critically; and approval of the final version. Kenneth I. Aston: Substantial contributions to acquisition of data; drafting and revising the manuscript critically; and approval of the final version. **Shahryar K. Kavoussi**: Substantial contributions to acquisition of data; drafting and revising the manuscript critically; and approval of the final version.

CONFLICT OF INTEREST

Parviz K. Kavoussi: Speaker bureau: Acerus pharmaceuticals, Antares pharmaceuticals, Clarus pharmaceuticals. Graham L. Machen, Shu-Hung Chen, Melissa S. Gilkey, Justin Chen, Yazan Hamzeh, and Kenneth I. Aston: none. Shahryar K. Kavoussi: Speaker bureau: Abbvie.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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