SEXUAL MEDICINE REVIEWS REVIEWS

The Effect of Longer-Acting vs Shorter-Acting Testosterone Therapy on Follicle Stimulating Hormone and Luteinizing Hormone

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Abstract

Introduction: Testosterone (T) replacement therapy causes suppression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) that can lead to decrease in semen parameters and possible infertility. Different T formulations may have varying suppression on FSH and LH.

Objective: To study whether shorter-acting T (multiple daily dosing) has less suppression on FSH and LH serum levels compared with longer-acting T (transdermal gel, injectable).

Methods: A systematic literature search was conducted by following the protocol based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols. We comprehensively reviewed the literature by systematically searching manuscripts indexed in PubMed from 1995 to March 13, 2019 to identify studies reporting changes in FSH and LH in hypogonadal men treated with exogenous T which evaluated the effect of exogenous T on FSH and LH.

Results: A total of 8 studies reported the effect of T on FSH and LH in 793 hypogonadal men: 2 used long-acting injectables (enanthate or undecanoate) in a total of 16 men, 5 used intermediate-acting daily topical gels or patches in a total of 471 men, and 1 used short-acting intranasal T (125 μL/nostril, twice a day or three times a day) in 306 men. Long-acting injectables decreased FSH by 86.3%, intermediate-acting daily gels/patches decreased FSH by 60.2%, and short-acting intranasal gel decreased FSH by 37.8%. Long-acting injectables decreased LH by 71.8%, intermediate-acting daily gels/patches decreased LH by 59.2%, and short-acting intranasal gel decreased LH by 47.3%.

Conclusions: Our findings suggest that short-acting T preparations do not decrease serum FSH or LH to the same extent as longer-acting transdermal gels and injectables. However, further clinical trial data are necessary to determine whether the effect of short-acting TRT on gonadotropins translates into similar changes in semen parameters and fertility. **Masterson TA, Turner D, Vo D, et al. The Effect of Longer-Acting vs Shorter-Acting Testosterone Therapy on Follicle Stimulating Hormone and Luteinizing Hormone. Sex Med Rev 2020;XX:XXX–XXX.**

Key Words: Testosterone; Luteinizing Hormone; Follicle-Stimulating Hormone; Gonadotropins

INTRODUCTION

Low testosterone (low T) affects 35% of men older than the age of 45 years.[1] Treatment generally consists of T replacement therapy (TRT) using exogenous forms of T: long-lasting pellets, injections, transdermal gels and patches, and intranasal gel.[2] Direct-to-consumer marketing has increased awareness of low T leading to increased number of prescriptions for TRT.[3] What is concerning is that, about 12% of TRT prescriptions are prescribed to men of reproductive age.[4] Some of the side effects of TRT is decreased intratesticular T levels, infertility, azoospermia, and testicular atrophy[2] — all of which can be detrimental to men of reproductive age. In fact, up to 65% of normal men become azoospermic after 6 months of TRT (weekly intramuscular injections of 200 mg T enanthate) and testis volume can decrease by 23%.[5,6] Current strategies for increasing T without affecting fertility or testis volume are off-label prescriptions of estrogen receptor modulators (eg, clomiphene citrate), aromatase inhibitors (eg, anastrozole), and human chorionic gonadotropin.[2] The main reason that human chorionic gonadotropin and

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clomiphene citrate are able to preserve spermatogenesis is thought to be because of preservation of intratesticular T. Previous studies showed the utility of 17-hydroxyprogesterone as a biomarker of intratesticular T and demonstrated that 17-hydroxyprogesterone was undetectable in men receiving exogenous T, in contrast to those in the control group (men with serum T $\geq$ 300 mg/dL not receiving any treatment) and men treated with human chorionic gonadotropin and/or clomiphene citrate ($P < .05$).[7] Because these medications are off label for the symptomatic treatment of hypogonadal men, and most not Food and Drug Administration approved for use in men, identifying strategies to increase T that may lessen side effect are critical.

Azoospermia and testicular atrophy result from exogenous T suppression of the hypothalamic–pituitary–gonadal axis via a negative feedback mechanism. In our prior work, a short-acting nasal gel T (Natesto, Food and Drug Administration approved, May 2014) was shown to increase serum T, maintain gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH), within normal range, and not significantly affect semen parameters.[8] Unlike the dosing of other forms of exogenous T (subdermal pellets, injections, and transdermal gels) that provide steady delivery for 24 hours or more, nasal gel is delivered either 2 or 3 times a day, providing discrete peaks (or pulses) in serum T levels with a return to baseline T levels between peaks. Pulsatile dosing, and more importantly, the existence of daily troughs between doses, may allow for reinitialization of pulsatile release of gonadotropin-releasing hormone (GnRH) and therefore maintaining the production of LH and FSH. Because GnRH release cannot be directly measured in humans, FSH and LH are used as surrogates.[9] We therefore hypothesized that short-acting T has a lesser effect on serum levels of gonadotropins (LH and FSH) than long-acting exogenous T.

Objectives and Research Question

We sought to determine whether shorter-acting T (multiple daily dosing) has less suppression on serum FSH and LH levels compared with longer-acting T (transdermal gel, injectable). Therefore, the aim of this systematic review was to determine the changes in serum FSH and LH levels in hypogonadal men treated with short- and long-acting exogenous T.

METHODS

A systematic literature search was conducted by following the protocol based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols. It was prospectively registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) as record PROSPERO CRD42019138191.

We comprehensively reviewed the literature by systematically searching manuscripts indexed in PubMed from 1995 to March 13, 2019, to identify studies reporting changes in FSH and LH in hypogonadal men treated with exogenous T. The search terms selected were incorporated in the following Boolean expression: testosterone AND (FSH OR follicle stimulating hormone OR gonadotropin). We chose to include FSH as a search term to limit the number of article results because this hormone is not as frequently measured in studies on TRT. FHS measurements, as opposed to LH, are not included in the workup or follow-up of TRT in the American Urological Association or Endocrine Society guidelines.[2] Our search was limited to with human, adult male subjects, published in English. The primary search was undertaken on 13 March 2019.

Study Selection

Our primary study question was whether short-acting T (multiple daily dosing) has less suppression of serum FSH and LH compared with long-acting T (transdermal delivery or injectable) in hypogonadal men. A study was included if it (i) reported an increase of mean serum T into eugonadal range in a population of adult hypogonadal men, (ii) reported FSH and LH at baseline and after T therapy, (iii) contained original data, and (iv) used a T currently approved by the Food and Drug Administration. A study was excluded if it was intended to develop a male contraceptive because these studies often use multiple simultaneous interventions and increase T into the upper limits of normal. When a manuscripts' method appeared to meet criteria but did not provide complete information for our analysis, investigators were contacted via e-mail. Although we considered all study designs eligible, we did not find any randomized controlled trials comparing T therapies that reported changes in FSH and LH, so we therefore included only observational studies.

Data Collection

In a first phase, the studies were independently reviewed by 3 authors (TM, DT, DV) using the title and abstract. In a second phase, full-text articles were independently reviewed by the same authors (TM, DT, DV). Full-text articles were selected using the inclusion criteria previously mentioned. Disagreement on article exclusion or inclusion was settled by the senior author (RR). Data of baseline and final serum T, FSH, and LH were extracted and added into an Excel spreadsheet and analyzed as per the type of exogenous T therapy used (Table 1). Results were reported as the mean ± SD, with serum T levels reported in units of nmol/L and FSH and LH levels reported in units of IU/L. When data from articles were only available in the form of a plot or figure, WebPlotDigitizer (https://apps.automeris.io/wpd/) was used to facilitate the extraction of data values.

Data Analysis

Statistical analysis was performed using SAS, version 9.04.01, for Mac. The differences between the mean final hormone levels and the mean baseline levels were divided by the mean baseline levels to calculate the percentage change in FSH and LH,

Table 1. Studies included in analysis grouped by duration of action

Mean % change in gonadotropins		
	FSH	LH
Long acting	−86.3	−71.8
Intermediate acting	−60.2	−59.2
Short acting	−37.8	−47.3

FSH = follicle-stimulating hormone; LH = luteinizing hormone.

respectively. Mean percent change in FSH were grouped as per type of T: injection, transdermal gels/patches, and short-acting intranasal gels. To graphically represent the population effect of each study, circles with area proportional to the study's sample size were generated on Excel, with the center of each circle located at the percentage change in the mean hormone level. We then grouped results based on long-acting (injections), intermediate-acting (gels and patches), and short-acting (nasal gel) and performed an analysis of variance weighted for sample sizes of the studies included to investigate statistically significant differences in mean changes of LH and FSH for each mode of TRT.

RESULTS

The primary search identified 673 records from PubMed. After removing duplicates, there were 55 records to screen for titles and abstracts, plus 1 additional article identified through Google Scholar for a total of 56. After the first phase, 643 articles were excluded, and the full texts of the remaining 31 articles were checked for eligibility. After the second phase, 23 articles were excluded, giving a total of 8 studies that met the inclusion criteria and were included in this review (Figure 1). We defined long-acting Ts as those dosed less frequently than once a day, intermediate-acting as those dosed daily, and short-

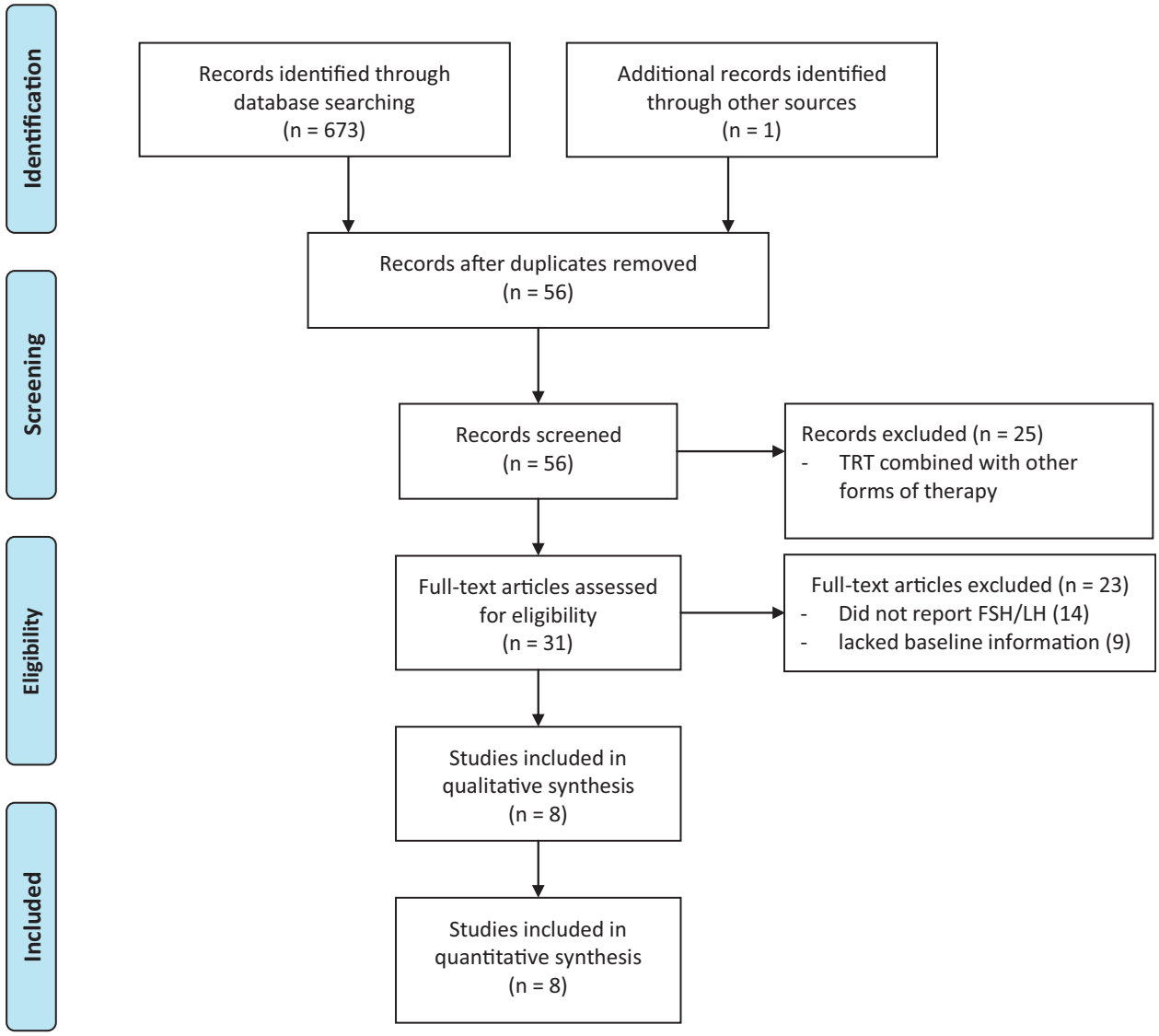

Figure 1. PRISMA flow diagram of inclusion criteria. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Figure 1 is available in color online at www.smr.jsexmed.org.

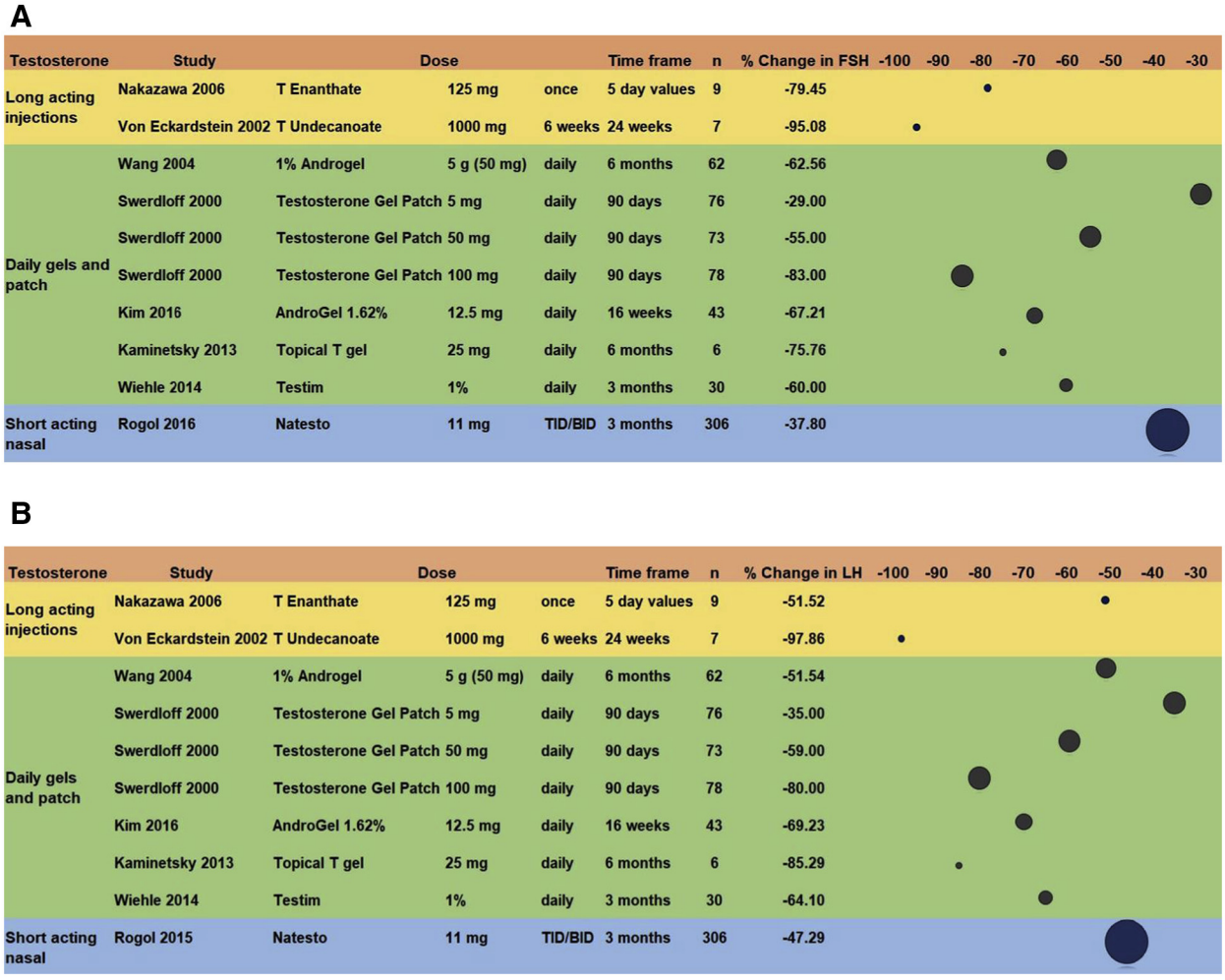

Figure 2. (A) Scatterplot showing the percent change in mean FSH for individual studies. The center of the circle lines up with percent change in mean FSH and the area of the circle represents the number of patients in each study. (B) Scatterplot showing the percent change in mean LH for individual studies. The center of the circle lines up with percent change in mean LH and the area of the circle represents the number of patients in each study. FSH = follicle-stimulating hormone; LH = luteinizing hormone. Figure 2 is available in color online at www.smr.jsexmed.org.

acting as those dosed multiple times per day. The included 8 studies reported the effect of T on FSH and LH in 793 hypogonadal men: 2 used long-acting injectables (enanthate or undecanoate) in a total of 16 men,[10,11] 5 used intermediate-acting daily topical gels or patches in a total of 471 men,[12–16] and 1 used short-acting intranasal T (125 μL/nostril, twice a day or three times a day) in 306 men.[17] Long-acting injectables decreased FSH by 86.3%, intermediate-acting daily gels/patches decreased FSH by 60.2%, and short-acting intranasal gel decreased FSH by 37.8% (Figure 2A). Long-acting injectables decreased LH by 71.8%, intermediate-acting daily gels/patches decreased LH by 59.2%, and short-acting intranasal gel decreased LH by 47.3% (Figure 2B). In all studies, the mean T levels after TRT were within normal range (300−1,000 ng/dL). There was no statistically significant difference between groups (long acting, intermediate acting,

Table 2. Analysis of variance (ANOVA) test between groups (long acting, intermediate acting, and short acting) as determined by one-way ANOVA weighted for sample size for either percent change in LH (F [2,7] = 1.18, $P = .36$) or FSH (F [2,7] = 0.76, $P = .50$)

Therapy group	Sum of weights	Mean % change in FSH (95% CI)	Mean % change in LH (95% CI)
Short acting	306	−37.8 (–, –)	−47.3 (–, –)
Intermediate acting	368	−24.9 (−55.8, 6.0)	−23.7 (−53.7, 6.2)
Long acting	16	−86.3 (−184.8, 12.2)	−71.8 (−363.9, 220.3)

FSH = follicle-stimulating hormone; LH = luteinizing hormone.
Sum of weights represents the total sample size within each group.

short acting) as determined by one-way analysis of variance weighted for sample size for either % change in LH (F [2,7] = 1.18, $P = .36$) or FSH (F [2,7] = 0.76, $P = .50$).

DISCUSSION

To date, there has never been a comparison of the effect of exogenous T on gonadotropins. In this systematic review, we intended to determine if short-acting T (multiple daily dosing) has less suppression of FSH and LH production compared with longer-acting T (transdermal delivery or injectables). The results from studies included in this systematic review demonstrate that short-acting T increased serum T levels into normal range, while having less suppression of FSH and LH production compared with intermediate-acting Ts (gels and patches) and long-acting Ts (injectables).[10−17]

Secretion of gonadotropins, LH and FSH, is stimulated by GnRH release from the hypothalamus onto the pituitary.[18] The mechanism of how 1 hormone, GnRH, can stimulate the release of 2 distinct gonadotropins can be explained by the frequency of its release. When GnRH is released in fast pulses, approximately every 1−2 hours, the pituitary favors release of LH and stimulates the production of T from the testicle. In contrast, for FSH secretion, the pituitary needs to receive a pulse of GnRH every 4−6 hours.[19,20] In our study, we saw suppression of both LH and FSH with all forms of T; however, the suppression was less pronounced with short-acting T.[17] Interestingly, less suppression of FSH compared with that of LH was noted in the short-acting T (Table 2). Although serum GnRH is unable to be measured, LH has been used as an indirect measure of GnRH secretion. This preservation of LH in the serum with short-acting T formulations suggests that the shorter-acting T formulations may have less suppression on the hypothalamic−pituitary−gonadal axis and GnRH pulsatility.

The gonadotropins FSH and LH stimulate testicular function. The physiological role of LH is stimulation of T synthesis from Leydig cells. FSH stimulates Sertoli cells that supports spermatogonial differentiation and maturation and the production of androgen-binding proteins that are essential in maintaining the high intratesticular T levels.[21] More than 95% of the testicular volume is dedicated to spermatogenesis, and without LH and FSH, the synthetic functions of the testes come to a halt, leading to atrophy and infertility. Therefore, short-acting T, through maintenance of LH and FSH release, may preserve testicular function, including spermatogenesis and endogenous T production; however, prospective studies evaluating the effects of short-acting T are needed.

American Urological Association guidelines on TRT state that response is measured through clinical symptom improvement and subsequent measurement of serum T levels[2]; however, T measurement alone does not provide a complete picture of biological response to therapy. In normal men, T levels follow a diurnal variation with high levels in the morning and troughs in the afternoon. Currently, no T treatment perfectly mimics the normal physiology of T secretion.[22] Long-acting TRT provides a steady state, whereas short-acting TRT provides multiple peaks and troughs throughout the day. We know that men maintained in the upper limit of normal serum T have a higher incidence of polycythemia and other unwanted side effects.[23] At the other end of the spectrum, short-acting T has therapeutic spikes followed by troughs leading some to believe this form of TRT is less effective. However, a recent study found that despite periodically being in the hypogonadal range, men report symptom improvement using short-acting nasal T gel.[24,25] In an effort to maximize the homogeneity of the study cohort, we excluded studies that did not put subjects into the eugonadal range − both to eliminate those who were put into supratherapeutic ranges and those not receiving an efficacious dosing of T.

Strengths of this study are its novelty in the literature and thorough search. No other systematic review has compared the effect of short- vs long-acting TRT on gonadotropins. Limitations of this review are the relatively small numbers of studies in each T therapy group, and therefore, we performed a systematic review rather than a comprehensive meta-analysis. Surprisingly, we were unable to identify studies assessing gonadotropin changes that used T pellets, the epitome of long-acting TRT. In addition, we do not have detailed information of the study populations, specifically the number of men with primary vs secondary hypogonadism in each study. This limitation is potentially important as men with primary hypogonadism are expected to have much higher LH and FSH values than men with secondary hypogonadism. We attempted to report the number of men whose FSH became undetectable on therapy, which would show complete suppression of the hypothalamic−pituitary−gonadal axis; however, this value was not available for most studies. Nevertheless, the impact of this is minimized because baseline vs end of treatment LH and FSH values were compared and each subject served as their own internal control.

CONCLUSION

Our analyses support that long-acting Ts may have greater suppression of FSH and LH than shorter-acting formulations. However, further clinical trial data are necessary to determine whether the effect of short-acting TRT on gonadotropins translates into differences inside effects, such as fertility and testis volume.

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STATEMENT OF AUTHORSHIP

Thomas A Masterson: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Darren Turner: Investigation, Resources, Writing - Review & Editing; Ruben Blachman-Braun: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Jordan C Best: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Gerwin Westfield: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Nathan Bryson: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Ranjith Ramasamy: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition.

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