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Review

The evidence for seasonal variations of testosterone in men

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ABSTRACT

Ample evidence exists to support the concept of diurnal variations in testosterone levels; however, substantiation for seasonal fluctuations is sparse and inconsistent. Since circadian disparities exist, laboratory screening for hypogonadism has traditionally been conducted using serum testosterone levels obtained in the early morning. Should circannual variability of testosterone be confirmed, it would make the monitoring of testosterone levels more difficult while forcing the development of seasonal reference standards to allow for comparison. Moreover, decisions to begin treatment and adjustment of practice patterns would likely follow. This review thoroughly explores all of the available evidence concerning seasonal variations in testosterone levels. The impacts of melatonin, vitamin D, sleep–wake cycles, light exposure, physical activity, BMI, and waist circumference are also discussed. Current research suggests that while some evidence exists to support the notion of seasonal testosterone variations, the discussed inconsistencies preclude the incorporation of this concept into current clinical standards.

Contents

1. Introduction

Testosterone (T) contributes significantly to male development, reproduction, and aging. Due to an improved understanding of the links between hypogonadism and men's health, the symptoms surrounding age-related declines in T have become increasingly well-recognized. Indeed, the office evaluation of the aging male now requires a thorough understanding of the relationships between male sexual function, hypogonadism, and cardiovascular risk. The association of hypogonadism with metabolic syndrome, visceral adiposity, erectile dysfunction, and insulin resistance requires the treating physician to be astute concerning patient follow-up, management and treatment related side effects [1].

Currently, testing for T requires clinicians to be aware of the diurnal variations that exist, since improperly ordered laboratory values can impact treatment decisions. It is well established that diurnal variations in T levels exist with levels stable throughout the morning and early afternoon followed by modest declines in the evenings [2–4]. It has been hypothesized that these variations are influenced by a constellation of factors including melatonin, age, sleep–wake cycles, and circadian rhythms [5].

Given the substantial evidence for diurnal T variations, the Endocrine Society, in its clinical practice guidelines, recommended that adult men screened for androgen deficiency syndromes have their initial T levels drawn in the morning [6]. It is tempting to speculate that similar variations could exist where seasonal

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patterns of photic input, sunlight exposure, and activity levels impact circadian and hormonal rhythms [7]. Similarly, if confirmed, predictable seasonal variations in T would require the establishment of seasonal reference standards. Currently, studies on seasonal T variations have yielded significant heterogeneity with no recognized consensus. In this review, the current status of the literature is summarized and recommendations made as to the impact of seasonal variations on the current clinical standards.

2. Seasonal variations in testosterone: the evidence

In one of the earliest manuscripts on the topic, Reinberg et al. [8] demonstrated circannual variation in plasma T in five Parisian males with peak plasma levels and sexual activity occurring in the month of October. Shortly thereafter, Smals et al. [9] examined a group of 15 healthy male subjects and found statistically significant seasonal patterns in T levels. The authors recorded peaks in the summer and early autumn and a nadir in the winter and early spring [9]. Since that time, seasonal variation has been confirmed in several cross-sectional studies of ethnically, socially, and geographically varied populations of men [10–16]. Others however, have not shown similar circannual variations [17–20]. Inconsistent variations have also been identified in a number of longitudinal studies on seasonal patterns of T [9,15,21–23].

Svartberg et al. [24] cross-sectionally examined the seasonal variations in total and free testosterone (TT and FT), luteinizing hormone (LH), and sex hormone binding globulin (SHBG) levels amongst 1548 men living in northern Norway. A population selected based on its exposure to a wide seasonal variation in both temperature and daylight. Among these men, TT showed bimodal seasonal variation with peak values in October–November and a nadir in June. Similar results were seen in patterns of FT demonstrating peaks in December and a nadir in August. Notably, the lowest T levels occurred in months with the highest temperatures and longest hours of daylight. The variations in hormone levels were large, with a 19% and 31% difference between the lowest and highest monthly mean levels of TT and FT respectively. The authors hypothesized that these fluctuations could be explained by the variation in daylight exposure and temperature [24].

While the study had a significant confounder in that a large length of time (i.e. 0800–1600) was deemed suitable for the laboratory T collection, a substantial seasonal effect on T was still highlighted [24]. A follow-up cross-sectional study [7] was conducted on men exposed to less extreme seasonal changes in sunlight and temperature (San Diego, California) to determine whether seasonal variations of T persisted in this population. In the 915 men studied, neither TT nor bioavailable T (BT) varied by season [7]. These results were independent of age as well as anthropometric measurements and no association with air temperature or duration of sunlight exposure was documented [7]. The conflicting results obtained in the study set in California and the original Norwegian study were postulated to be due to differences in climate and sleep patterns [7,24].

In a population with a similar photoperiod and climate (Denmark), Andersson et al. [25], obtained monthly blood samples on 27 men during a 17-month period. Measurements of inhibin B, follicle stimulating hormone (FSH), LH, TT, and estradiol (E2) levels were recorded. The authors found seasonal variation in LH and T levels, but not in the levels of other sex hormones. The seasonal variation in TT paralleled the variation seen in LH with peak levels in the summer (June–July) and nadirs in the winter and early spring [25]. This data reported by Andersson et al. [25] is in contrast to the Svartberg study [24], which showed peaks in the fall and a nadir in the summer. The lack of concordant seasonal changes in hormone patterns in these two geographically similar populations calls into question the clinical significance of these findings.

Whereas the aforementioned studies had limited study populations, Moskovic et al. examined serum TT, E2, SHBG, FSH, LH and dehydroepiandrosterone (DHEA) in 11,000 men in the southwestern United States [26]. Given the previous finding by Crawford et al. [4] which suggested that diurnal variation diminished after age 60, men in the Moskovic study were divided into cohorts of less than 60 years of age and those greater than 60 years of age. This division was to control for potential physiologic differences in age-related hormonal regulation. Moskovic et al. [26] subsequently found statistically significant differences in E2, testosterone: estrogen ratio (T:E), FSH, and SHBG between seasons. The magnitude of these differences was only significant in the younger cohort of patients, although the younger cohort was also larger ($N = 9669$ versus 1954). Peak to trough variations were 16.5% for T: E ratio, with a peak in the spring and nadir in the fall. The difference between T:E ratio in the two cohorts was hypothesized to be due in part to increased physical activity in the younger cohort and evidence to suggest that the HPG axis is more sensitive in younger men [27]. Whereas no significant change in TT was observed, a 10% change was noted in FT between peak (summer) and trough (fall) values; however, this was not clinically significant.

Despite its sample size, the Moskovic study [26] still failed to show statistically significant differences in TT, LH, FT and DHEA in either cohort. This study was also limited in that samples were collected between 0900 and 1900 and was based on initial, single patient observations as opposed to longitudinal data [26]. Along with the prior Svartberg study in San Diego [7], this represented the second investigation in the southwestern United States which failed to show significant seasonal TT variation. This suggests that the prior Scandinavian studies were demonstrating a regional effect. Further research in dissimilar climates and populations is required to replicate the variability in these prior studies and substantiate their findings.

One such study by Brambilla et al. [20] was based in Boston, Massachusetts and therefore contrasts with the prior Moskovic study [26] in the potential regional effects of climate and epidemiology. The authors examined seasonal fluctuations in androgens, including serum TT, FT, BT, dihydrotestosterone (DHT), SHBG, LH, DHEA, dehydroepiandrosterone sulfate (DHEA-S), E2, and cortisol. One hundred and twenty-one men, aged 30–79, completed six morning blood draws at 0, 3, and 6 months [20]. Time of enrollment was random in order to capture data from all twelve months. Aside from cortisol, there was no evidence of seasonal variation in hormone levels [20]. Peak levels were within 4% of the mean level for all hormones examined. The authors found that intra-individual variation was greater for each hormone evaluated when compared with seasonal variation. Brambilla et al. [20] concluded, therefore, that seasonal effects are likely not an important source of significant variation clinically.

Whereas regional influences may account for some of the observed patterns of seasonal variation, age within the study population also has the potential to confound these results. For instance, Moskovic et al. [26] found more significant seasonal variation in T:E ratio in younger men whereas Svartberg [7] found neither TT nor BT varied by season and these results were independent of age. Similarly, Tancredi et al. [19], in a study of 5028 men aged 50 and over, showed that monthly variations in serum FT values did not show significant seasonal variation (<15%) [19]. Dai et al., in an epidemiologic study, demonstrated that age and obesity correlated with T levels in 243 men; however, while diurnal variation was noted, seasonal variation of T was not [17].

Based on the substantial heterogeneity within these studies, the evidence for seasonal variation of androgens can only be characterized as inconsistent at this time.

3. Seasonal variations in testosterone: influence of light exposure, melatonin and sleep–wake cycles

Seasonal changes in the duration of the light–dark cycle are known to cause variations in the activity of human neuroendocrine systems. Light exposure and its potential impact on reproductive hormone variability was recently evaluted in a series of men from the Arctic Circle. Ruhayel et al. [28] examined how extremes of temperature and light–dark cycles might influence these hormone fluctuations. The authors reported on two cohorts of Norwegian men divided by those living north (Tromsø) and south (Oslo) of the Arctic circle to maximize variations in photoperiod and temperature. These 205 men underwent serial blood measurements over a 12-month period including during the study period daylight maximum and minimum. Serum concentrations of FSH, LH, TT, E2, SHBG, and urinary excretion of the major melatonin metabolite, 6-sulfatoxymelatonin (aMT6s) were assessed. aMT6s levels were evaluated based on the association of melatonin with sleep–wake cycles and circadian rhythm [28].

Both locations demonstrated declining LH levels during the early winter; however, seasonal variation of LH was only significant in Tromsø. The seasonal variation of TT concentrations was significant in Oslo, but not in Tromsø, and neither location showed significant seasonal variation of FT levels [28]. One would have expected that seasonal patterns in sex hormones, if influenced by photoperiod and temperature, would have been most apparent in this population where climatic influences are significantly divergent. However, aside from LH, patterns of change in other sex steroids were non-seasonal, possibly due to confounding factors such as lifestyle and variation in genetic backgrounds [28].

As a correlate to fluctuations in photoperiod, Svartberg et al. [7,24] hypothesized that changes in sleep patterns could also have influenced the discrepancy between the presence of androgen variation in their original Norwegian study in comparison to their San Diego study. Phase shifts in hormone secretion have been shown to be causally related to concomitant shifts in the onset of sleep; however, in the study by Ruhayel et al., which did not show significant variation in T, the recorded sleep duration did not differ between summer and winter amongst the groups [28]. The authors could not exclude its influence, however.

Given the central regulation of melatonin and its effect on light–dark cycles and sleep, Svartberg, Ruhayel and others have postulated that melatonin may likewise influence the hypothalamic–pituitary–testicular (HPT) axis [7,23,28,29]. Melatonin secretion and subsequent urinary excretion of aMT6s has been shown to correspond to changes in the light–dark cycle and sleep patterns [28,30]. In the prior study by Ruhayel et al. [28], seasonal changes in T concentration exhibited significant correlation with the changes in excretion of aMT6s, a melatonin by-product; however, this correlation was only seen in the Oslo population. Conversely, seasonal changes in LH concentration demonstrated significant correlation with the changes in aMT6s in Tromsø alone. Urinary aMT6s concentrations were lowest during early summer in both locations indicating possible suppression due to longer daylight exposure. The correlations between changes in T and LH and excretion of aMT6s, although significant, differed in the two locations indicating this relationship was likely circumstantial [28].

Martikainen and Huhtaniemi [23,30] similarly examined the associations between melatonin and gonadotropins in a population of 24 men. The participants were followed over a period of 13 months in northern Finland, where day length is 22 h in the summer and 3.5 h in the winter. Serum melatonin levels showed two annual peaks in December and May with a nadir in August. The melatonin peak in May was associated with significant increases in LH. The authors found no significant differences in FSH, LH, or T levels between individual months leading them to conclude that extreme seasonal changes in daylight do not play an obvious role in the regulation of testicular androgens [23,31]. The lack of consistent variation in the levels of T and LH in these studies weakens the argument for a substantial relationship between melatonin secretion, sleep, and variations in sex hormones.

4. Seasonal variations in testosterone: the role of the hypothalamic–pituitary–testicular axis and vitamin D

Several investigators have sought to determine the interrelationship between hormones of the HPT axis, vitamin D, and seasonality. A recent, randomized, placebo-controlled trial by Pilz et al. suggested that vitamin D may increase the production of T in men [32]. Additional studies have previously given scientific support to the relationship between vitamin D and reproductive hormones [33,34]. In the European Male Aging Study, a cross-sectional survey of 3369 men was performed with T, E2, DHT, LH, FSH, SHBG, and vitamin D levels assayed [35]. FT levels were lower and LH levels were higher in men with vitamin D deficiency. Vitamin D was positively associated with TT and FT and negatively with E2 and LH. After adjustments were made for potential health and lifestyle confounders, no statistically significant associations were found between vitamin D and individual sex hormones. Notably, seasonal variation was seen only for Vitamin D [35]. Despite a lack of a correlation in seasonal patterns, reinforcement of a relationship between vitamin D and androgens has important clinical implications as both vitamin D deficiency and hypogonadism have been associated with morbidity and mortality [36,37].

A cross-sectional study by Wehr et al. examined vitamin D, T, and SHBG levels in 2299 men referred for coronary angiography [38]. Men with sufficient vitamin D levels had statistically significant higher levels of T compared with vitamin D deficient men. When adjusting for confounders, a significant association remained between vitamin D and T. In contrast to the study by Lee [35], T showed a seasonal pattern with a nadir in March and a peak in August. Wehr et al. concluded that androgen levels and vitamin D levels are associated in men and reveal concordant seasonal variation. The population examined, however, was restricted to older men with atherosclerosis and, therefore, the data could not be generalized [38].

A population-based study was therefore needed to confirm the seasonal patterns in vitamin D and T seen in the Wehr study. Nimptsch and colleagues investigated a population of 1362 men, aged 40–75, from the Health Professionals Follow-up Study [39]. This included assays of Vitamin D, T, and FT. Vitamin D was positively associated with TT and FT levels; however, unlike for vitamin D, the authors did not observe any seasonal variation of T concentrations [39]. While the association of vitamin D with T levels appears founded, these studies lend further uncertainty as to the evidence for seasonal patterns of T.

5. Seasonal variations in testosterone: lifestyle influences?

The potential exists that seasonal changes in androgens may be due to other factors that vary during the year. For instance, physical activity increases significantly during the summer months [40,41], and exercise has been shown to be a potent stimulus for the production of T [42]. A study examining seasonal variation in waist circumference and BMI found both to be greater in winter than in summer months [43]. One may postulate that seasonal changes in

serum hormone levels could be attributed to alterations in habitus and subsequent aromatization. Likewise, changes in physical activity may account for some of the seasonal variations seen in prior investigations. In their study of 915 men in San Diego, Svartberg et al. found that physical activity reliably varied by season, with a peak in August; however, adjusting for physical activity did not change the lack of seasonal variation seen in T [7].

The Svartberg studies similarly evaluated the associations between seasonal variations in T, waist circumference, and waist to hip ratio [14,24]. The authors found a significant age-adjusted, negative correlation between waist circumference and TT and FT. These hormone associations were stronger for waist circumference than for waist–hip ratio or BMI, suggesting that waist circumference may be the anthropometric measurement most reflective of endogenous T levels. Adjustments for BMI and lifestyle factors diminished but did not remove these associations [14,24]. Waist to hip ratio followed changes in daylight and temperature, with peak values during the summer. The lowest T levels occurred in months with the highest temperatures and longest hours of daylight, an inverse relationship with waist to hip ratio [14,24].

6. Conclusions

The studies reviewed in this manuscript illustrate the heterogeneity present within the literature in regards to seasonal variations of T. Limitations of these works include: differing environments with wide-ranging temperatures and day–night patterns; variable protocols for timing of blood draws; and inconsistency in accounting for potential modifiers such as BMI. Whereas some studies relied upon longitudinal data, others were only obtained from single observations.

If significant seasonal variability of androgens exists, then it follows that screening and laboratory assessment of potentially hypogonadal men and subsequent treatment decisions would be affected. At this time, recommendations regarding timing of T assessment based on seasonal variations remain in question. Contrary to the substantial evidence for diurnal variation of T, reproducible data demonstrating seasonal patterns of T has been more elusive. While some studies suggest its effects, others have failed to replicate these results. The discussed inconsistencies preclude incorporation of circannual patterns of T into current practice guidelines. It can be concluded, therefore, that seasonal variations of T, if present, cannot yet be deemed clinically significant.

Contributors

Ryan P. Smith M.D.: Data acquisition through literature review, Analysis and interpretation of data, Drafting of manuscript.

Robert M. Coward M.D. and Jason R. Kovac M.D., Ph.D.: Drafting of manuscript, Revisions for scientific and factual content.

Larry I. Lipshultz M.D.: Design and outline of review, Drafting of manuscript, Revisions for scientific and factual content, Supervision.

Competing interests

The following authors: 'Ryan P. Smith, Robert M. Coward, Jason R. Kovac and Larry I. Lipshultz' declare no conflict of interest.

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