The Interplay Between Adult-Onset Hypogonadism and Prostate Cancer: A Literature Review

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ABSTRACT

The interplay between endogenous testosterone (Te) and prostate cancer (PCa) has long been recognized, with androgen deprivation therapy (ADT) being a cornerstone of advanced and metastatic PCa management. However, the association between Te levels and PCa risk remains complex and not fully understood.

This review delves into the complex relationship between adult-onset hypogonadism (AOH) and PCa, shedding light on the complexities surrounding PCa risk and disease aggressiveness. Despite the significant prevalence of PCa among men, particularly as they age, and the emergence of AOH as a prevalent health concern, data regarding their association remains heterogeneous and inconsistently documented. While some studies suggest a potential correlation between low Te levels and decreased PCa detection rates, others indicate a higher risk of aggressive pathological features, primarily observed in prostatectomy cohorts. It's noteworthy that there's evidence indicating hypogonadal men might face an increased risk of reclassification during active surveillance (AS) of low-risk disease. This is supported by the observation of elevated rates of disease upgrading in historical cohorts of low-risk prostatectomies. These contradictory findings are poorly reflected in treatment guidelines. Further research is imperative to comprehensively understand the clinical and associative correlations between AOH and PCa risk and biology, thereby informing more effective management strategies in the future.

KEYWORDS: Testosterone; Prostate cancer; Hypogonadism; Tumor Grade; Risk

INTRODUCTION

Prostate cancer (PCa) stands as the most prevalent cancer among men, with around one in eight men facing a diagnosis in their lifetime. In the United States (US) alone, approximately 300,000 new cases of PCa are estimated in 2024, resulting in about 35,250 deaths from the disease.[1] The average age at diagnosis stands at 66, with most cases diagnosed in the localized stage.[2] Besides advancing age, where the risk markedly escalates after 50, other risk factors for PCa encompass family history, African American ethnicity, and specific genetic mutations, such as BReast CAncer (BRCA)1 and BRCA2, and HOXB13 variants, although these mutations – often linked with more aggressive behavior – likely contribute to only a fraction of PCa occurrences.[3]

Concurrently, adult-onset hypogonadism (AOH) emerges as a prevalent health concern affecting millions of men globally.[4] The incidence of low testosterone (Te) and symptomatic hypogonadism, according to clinical definitions, among men aged 40–79 years ranges from 2% to 6%,[4] whereas the prevalence based on biochemical criteria, reflecting lower-than-normal total Te levels (often <250–300 ng/dl) in comparison to young men, is notably higher.[5]

The significance of Te in PCa was initially highlighted by Huggins and Hodges in 1941.[6] Their pivotal study proposed a direct correlation between circulating Te levels and the progression of PCa, elucidating that both disease advancement and regression might be related to Te serum levels.[6]

Androgen deprivation therapy (ADT) is a cornerstone treatment in advanced and metastatic PCa management due to the overexpression of androgen receptors in metastatic disease.[7] However, high Te levels have not been definitively associated with an increased risk of PCa,[8] although some data have previously suggested evidence on this link.[9-11] Interestingly, studies have been shedding light on the association between AOH and the risk of developing PCa,[12,13] as well as its potential effects on the cancer's biological aggressiveness.[14,15]

This review aims to consolidate and discuss the existing knowledge regarding the interplay between AOH and PCa risk and aggressiveness.

HYPOGONADISM

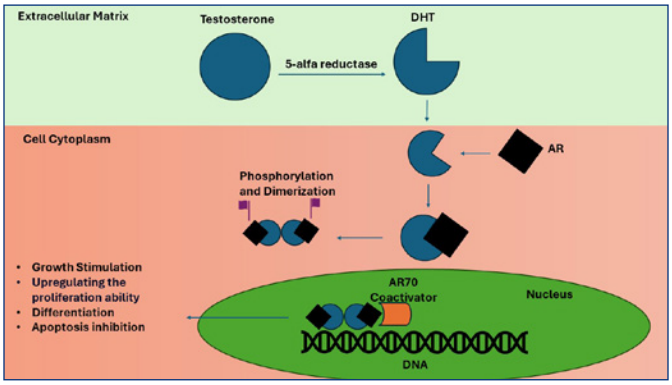
Te and DHT

The primary male hormone, Te is predominantly produced by the Leydig cells in the testes following luteinizing hormone (LH) secretion from the pituitary gland. Within target tissues such as the prostate gland, skin, and hair follicles, Te is converted to dihydrotestosterone (DHT) by 5-alpha reductase (5aR), (**Figure 1**).[16] DHT is a more potent androgen due to its higher affinity for androgen receptors in target tissues. Te and DHT are crucial for various physiological processes, including the development of male genitalia during fetal

Figure 1. DHT and the Prostate gland

Figure 1 illustrates the androgen action within prostate cells which involves the local conversion of Te to DHT. DHT then binds to AR, prompting its migration from the cytoplasm to the nucleus. Within the nucleus, the DHT-AR complex binds to androgen-responsive elements, triggering specific gene expression.[61]

DHT = Dihydrotestosterone; AR = Androgen Receptor; Te = Testosterone



development, spermatogenesis, maintenance of erectile function, and libido. Additionally, androgens play a critical role in stimulating muscle growth and maintaining bone density.[16]

The androgenic Te pathway is a key target for treating urological conditions such as benign prostatic hyperplasia (BPH) with 5aR inhibitors (5aRI) like finasteride and dutasteride. These inhibitors have shown impressive reductions in prostatic volume, which are largely responsible for the troubling urinary symptoms arising from an enlarged prostate gland.[17] This approach was proven to reduce risks of BPH progression in terms of acute urinary retention and need for surgical intervention.[18] Secondly, ADT (also known as biochemical castration) is the mainstay treatment in cases of advanced and metastatic PCa, and finally exogenous testosterone therapy is employed in cases of symptomatic AOH.[19]

Adult Onset Hypogonadism

Hypogonadism is categorized into two subtypes: primary (or hypergonadotropic) hypogonadism and secondary (or hypogonadotropic) hypogonadism.

Primary hypogonadism, also referred to as primary testicular failure, occurs due to dysfunction of the testes themselves, with various potential causes including genetic diseases (such as Klinefelter syndrome), trauma, and infections. Biochemically, it is characterized by compensatory elevated levels of gonadotropins (LH and Follicle-stimulating hormone [FSH]) because of testicular failure, along with low Te levels.

On the other hand, secondary hypogonadism results from dysfunction of the hypothalamic-pituitary-gonadal (HPA) axis, leading to inadequate stimulation of the testes. In this scenario, LH levels are low, which consequently reduces the triggering of Leydig cells for Te production.[20]

AOH, also known as "andropause," is typically characterized by mixed testicular and hypothalamic-pituitary dysfunction.[21] In Greek, "Andras" signifies human male, while "pause" denotes a cessation. Therefore, "andropause" can be defined as a syndrome linked to reduced sexual satisfaction or a decline in overall well-being due to low Te levels in older men.[22]

The Sexual Medicine Society of North America defines AOH as "a clinical and biochemical syndrome characterized by a deficiency of Te with symptoms and signs that can be caused by testicular and/or hypothalamic-pituitary dysfunction." While AOH is characterized by testosterone deficiency and the failure to mount an adequate compensatory pituitary response to low testosterone levels, with gonadotropin levels being low or within the normal range, this condition is clinically distinct from classical primary and secondary hypogonadism.[23] Common manifestations of AOH include sexual dysfunction, such as reduced libido and erectile dysfunction, as well as decreased muscle mass and strength, increased deposition of body fat (particularly visceral adiposity), decreased bone density (osteoporosis), and diminished muscle tone. Additionally, AOH may lead to psychological and cognitive effects, including mood changes and decreased energy levels. Furthermore, decreased Te levels are associated with metabolic syndrome, insulin resistance, and an increased risk of cardiovascular disease.[24,25] Indeed, the criteria for diagnosing AOH include lower than normal total Te on repeated measurements (<300ng/dL) with at least two clinical symptoms.

Interplay Between Hypogonadism and PCa

Under normal physiological conditions, around 70% of Te binds tightly to sex-hormone-binding-globulin (SHBG), approximately 20–30% weakly binds to albumin, and the remaining 1–2% exists in its free form – the most bioavailable.[26] In males, pubertal surges in serum Te reach their peak around the age of 20 and typically remain stable until the eighth decade of life.[27] These levels decrease with the onset of concomitant co-morbidities.[23]

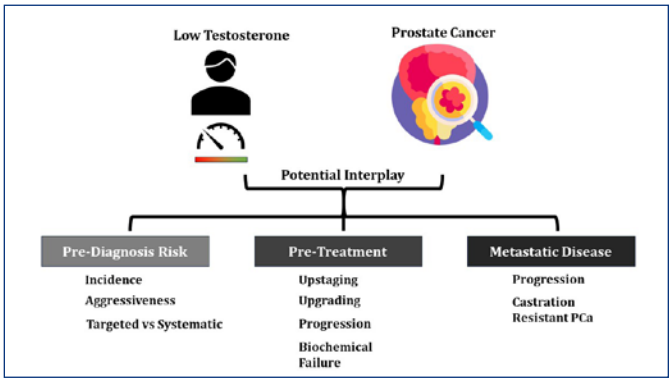
During the second trimester of gestation, fetal Te plays a pivotal role in stimulating the development of the epididymis, vas deferens, and seminal vesicles. Simultaneously, DHT facilitates the development of the prostate, urethra, and external genitalia. The post-pubertal surge in Te further results in up to a 10-fold increase in prostate volume compared to its pre-pubertal size.[28]

The physiological link between Te and potential PCa development remains incompletely understood. In 1941, Huggins and Hodges proposed that PCa growth was driven by androgens, based on observations of the benefits of castration in PCa patients.[6] Previous laboratory studies showed a response of well-differentiated PCa cell lines to androgen exposure, in addition to programmed cell death upon androgen withdrawal.[29,30] However, conflicting findings such as

Figure 2. The Interplay between AOH and PCa

Figure 2 illustrates the potential interplay between adult-onset hypogonadism and prostate cancer risk and aggressiveness on pre-diagnosis, pre-treatment, and metastatic disease effects.

AOH = Adult-Onset Hypogonadism; PCa = Prostate Cancer



were seen in Bladou et al's (1996) study showed that PCa regrew after castration,[31] thus challenging that accepted role of endogenous Te in the *de novo* pathogenesis of human PCa. The diverse findings across numerous studies, which are primarily retrospective and employ varied criteria for defining "low Te" have led to uncertainty regarding the effects of hypogonadism PCa risk and its aggressiveness.[8] Interestingly, this confusion might be the reason why current guidelines do not address this clinically significant question in the field.[32–34]

The subsequent sections simplify the available data on the effects of low endogenous Te on PCa risk of development and aggressiveness in the (1) pre-diagnosis; (2) pre-treatment; and (3) metastatic state (**Figure 2**). **Tables 1** and **2** systematically illustrate the studies discussed in the following sections.

PRE-DIAGNOSIS

Negative Correlation

Several studies in the field failed to demonstrate a correlation between pre-biopsy Te level and prostate biopsy results.

Morote et al (2010) conducted a prospective study involving 478 patients undergoing transrectal ultrasound (TRUS)-guided prostate biopsy, with 16.7% identified as hypogonadal.[35] Despite a 45.2% incidence of PCa within the cohort, no significant differences in total or free Te levels were found between PCa and non-PCa groups. Similarly, Mo Koo et al (2010) analyzed 120 patients with baseline PSA >10 undergoing TRUS biopsy, finding no differences in PCa detection rates or disease aggressiveness among hypogonadal and eugonadal men.[36] Two pivotal studies, including Muller et al (2012) and a meta-analysis by Roddam et al (2008), found no correlation between Te levels and PCa risk.[37,38] Muller's study, examining the placebo arm of the

Table 1. Pre-Diagnosis Studies

Study	Participants (low Te)	Study Design	Findings
Increased risk			
Morgentaler et al. (2006)	345 untreated hypogonadal men	Prospective cohort study	PCa detected in 21% of men with testosterone levels ≤250 ng/dL compared to 12% with levels >250 ng/dL (OR 2.02).
Shin et al. (2010)	568 (283)	Retrospective study	Higher rates of PCa in the lower Te group (OR=1.99). No high odds of high-risk disease.
Yano et al. (2007)	420 (118)	Serum Te as PCa Predictor	Patients with PCa had lower Te levels than those with benign pathology, especially with higher Gleason scores and poorly differentiated cancer.
Decreased risk			
Watts et al. (2018)	6933 PCa cases, 12088 controls	Collaborative analysis of 20 prospective studies	Men in the lowest tenth of free Te levels had a 23% reduced risk of PCa compared to men in the 8th to 10th tenth group. Non-significantly higher risk of high-grade disease.
Negative Correlation			
Morote et al. (2009)	478 (80)	Prospective study	No significant difference in total or free Te levels between PCa and non-PCa groups. Detection rate slightly lower in hypogonadal group but not statistically significant. Serum Te levels not associated with PCa risk or aggressiveness.
Mo Koo et al. (2010)	120 (24) patients with baseline PSA > 10	Prospective study	No differences observed in PSAD, PSA, or disease aggressiveness between hypogonadal and eugonadal men.
Muller et al. (2012)	Placebo arm of REDUCE trial	Meta-analysis	No correlation between low/high Te levels and PCa detection rates.
Roddam et al. (2008)	3,886 PCa patients, 6,438 controls	Meta-analysis	No significant difference in PCa detection rates between the highest and lowest tertiles of Te. Variation in free Te concentrations within the normal range may not impact prostate biology.

PCa = Prostate Cancer; Te= Testosterone; OR: Odds Ratio; PSA=Prostate Specific Antigen PSAD = Prostate Specific Antigen Density

Table 2. Post-Diagnosis Studies

Author	N (low Te)	Trial Protocol	Pathological Staging Features	Pathological Grading Features	Biochemical Failure
Isom-Batz et al. (2005)	326	Retrospective	NA	Lower Te correlated with adverse pathological stage	PSA progression free: 66% vs 84% (5 years), statistically insignificant
Yamamoto et al. (2007)	272 (49)	Retrospective	NA	NA	Five-year biochemical failure free rate significantly worse for low Te (67.8% vs 84.9%)
Lane et al. (2008)	455 (21)	Prospective	-	Low Te had greater prevalence of Gleason 4–5 pattern	No association with biochemical progression within 10 years
Xylinas et al. (2011)	107 (21)	Prospective	NA	Low Te was an independent risk factor for high Gleason score (³7) and locally advanced stage	No difference in biochemical recurrence or progression
Bo Dai et al. (2012)	110 (38)	Prospective	No differences in pathological T stage were noted in relation to Te levels.	Low Te correlated with higher incidence of Gleason 8–10 pattern in histology	NA
Garcia-Cruz et al. (2012)	137	Prospective	Low Te was associated with higher PSA, clinical staging, tumor burden, and bilaterality	Low Te was associated with higher Gleason score >7	NA
Pichon et al. (2015)	937 (139)	Prospective	NA	Upgrading was higher in low Te group: overall 45.3% vs 40.9%, and from Gleason 3 to 4 (20.1% vs 11.6%)	NA
Llukani et al. (2017)	502 (102)	Retrospective	Higher portion of positive lymph nodes (11.5 vs 1.5 %) in low Te group	Higher proportion of Gleason 8–10 19.2% vs. 5.1%, P = 0.012) In men under 65	—

N = Number; NA = Not applicable; PSA = Prostate Specific Antigen

Reduction by Dutasteride of PCa Events (REDUCE) trial, reported comparable PCa detection rates between low and high Te groups. The meta-analysis pooled data from 18 trials, revealing no significant differences in PCa detection rates across Te tertiles.

Of note, variation across the normal range of circulating free Te concentrations may not lead to changes in prostate biology, unless circulating concentrations are low.

Evidence of Risk Increase

Several series pointed to a curious phenomenon, with patients with endogenous low Te exhibiting adverse prognostic PCa.

Morgentaler et al (2006) examined a cohort of 345 untreated hypogonadal men with PSA <4.0 ng/ml. They found that PCa was detected in 21% of men with Te levels ≤250 ng/dL compared to 12% with levels >250 ng/dL (P = 0.04), indicating a relationship between low Te and PCa (OR 2.02, 95% CI 1.10–3.72).[39]

Yano et al (2007) evaluated the potential of serum Te as a predictor of PCa. They found that among patients with PSA <10 ng/ml, patients diagnosed with PCa had lower levels of Te compared to those with a benign pathology. Interestingly, patients with a Gleason score over 7 or moderately to poorly differentiated cancer tended to have a lower Te level, supporting that high-risk PCa is associated with lower Te levels.[12] Finally Shin et al (2010) compared the PCa incidence upon biopsy of two groups of men based on a cutoff of Te 385 ng/dl and showed higher rates (OR of 1.99) of PCa in the lower T group, but no high odds of high-risk disease.[40]

Evidence of Risk Reduction

Watts et al (2018) conducted a collaborative analysis of 20 prospective studies to examine if men with lower Te levels had a reduced chance of PCa. Data was collected for 6,933 PCa cases and 12,088 controls for which there was information of Te levels pre-diagnosis. Men who were at the bottom 10th percentile of free Te had a lower risk of PCa than the remaining men. When comparing men in the lowest 10th percentile to men in the 8th to 10th percentile group the reduction in risk was 23% – mostly affected by low risk PCa incidence. Interestingly, their findings, although non-significant, suggest that there may be a trend towards higher risk of high-grade disease in patients with higher levels of Te (OR = 1.51, 95% CI 0.952.57).[13]

These results might be explained by a non-linear association between low Te levels and PCa. The variation in Te will not necessarily influence prostate growth or stimulation if the intraprostatic DHT concentrations remain stable and the androgen receptors become saturated.[13] Morgentaler and

Traish found that beyond a certain serum Te concentration, androgens have a limited ability to stimulate PCa growth. Subsequent increases in serum Te levels beyond that concentration did not stimulate the prostate because the binding capacity of the intra-prostatic androgen receptors had been saturated.[41] The association of low DHT Te levels with PCa was examined in two large trials: the PCa Prevention Trial (PCPT) and the REDUCE trials. These trials investigated the effect of 5aRI which reduce the intraprostatic DHT concentration by up to 90%. Both trials concluded a 23–25% risk reduction in developing PCa in patients treated by 5aRI. Yet those who were diagnosed with cancer tended to suffer from a higher-grade disease (27% in PCPT and 58% in the REDUCE trial).

This may explain why very low levels of Te seem to be associated with a lower risk of PCa yet above a certain threshold the risk is not influenced.

Difference in mpMRI Fusion Biopsies

Prostate biopsies went from blind finger-guided transrectal needle biopsies, to ultrasound guided, and are now increasingly relying on the use of MRI studies to identify regions of interest prior to biopsy. These MRI studies of the prostate are superimposed on images produced during real-time ultrasound guided biopsy. The aim is to allow targeting of the region of interest specifically. Lesions on MRI are classified using the Prostate Imaging Reporting and Data System (PIRADS) system, ranging from 1 to 5, where 1 and 2 denote benign findings, 3 suggests low to intermediate suspicion, 4 implies high suspicion, and 5 indicates very high suspicion. As PIRADS scores increase, so does the risk for clinically significant prostate cancer (csPCa).[42,43] The utilization of pre-biopsy MRI improves the precision compared to the previous systematic blind sampling approach. Currently, alternative strategies are under evaluation, such as integrating MRI into screening protocols,[44] which may potentially obviate the need for biopsy entirely in cases of suspected low cancer risk. In addition, studies are looking at the possibility of omitting systematic for targeted only when prior systematic biopsies yielded negative results.[33,45] Of note, MRI studies in men under AS is of great interest to prevent oversampling and unnecessary biopsies.

Recent evidence from the era of mpMRI fusion biopsy suggests an association between hypogonadism and the detection rates of PCa and csPCa. Sugano et al (2020) compared PCa detection rates between systematic biopsy (SB) and targeted biopsy (TB) in hypogonadal versus eugonadal patients. Out of 522 patients, the hypogonadal cohort included 49 individuals (9.4%), with a median Te level of 148 ng/dl compared to 304 ng/dl in the eugonadal cohort.

In the hypogonadal cohort, TB detected 12.2% more csPCa compared to SB (40.8% vs. 28.6%), while in the eugonadal cohort, it detected only 5.9% more (43% vs. 37%). Although the increase in PCa detection with TB was twice as high in the hypogonadal cohort compared to the eugonadal cohort, this difference was not statistically significant. However, hypogonadism was identified as an independent predictor of decreased detection of csPCa on systematic biopsy. These findings support the idea that targeted biopsy is of higher yield in hypogonadal men too.[46]

POST-DIAGNOSIS: LOCALIZED DISEASE

Treated by Radical prostatectomy

It has been demonstrated in several studies that pretreatment serum Te levels are associated with adverse pathological features and the progression of localized PCa patients undergoing radical prostatectomy (RP).[41-43] In these studies, lower preoperative Te levels were linked to increased pathology upgrading and higher Gleason scores, suggesting a potential role in predicting more aggressive disease phenotypes.

Isom-Batz et al retrospectively analyzed the association between Te and disease outcome in 326 patients undergoing RP. They found that lower testosterone correlated with adverse pathological and clinical stage, biopsy grade and PSA. However, they did not find a relationship between low Te and biochemical recurrence.[47] Yamamoto et al (2007) similarly analyzed 272 patients, yet in their review testosterone did not correlate with any pathologic outcome but was found to be an independent predictor of biochemical recurrence. In their study, five-year biochemical failure free rate of the patients with preoperative low Te was significantly worse than that with normal levels.[48]

Similar findings were observed as associations between low Te levels and a greater prevalence of high-grade Gleason patterns, albeit without direct links to biochemical progression.[44,45] Low Te levels continue to be correlated with adverse prognostic factors both before and after treatment, including higher PSA levels, advanced clinical staging, increased tumor burden, and elevated post-treatment progression risk.[14,49] These collective findings highlight the potential significance of pretreatment serum Te levels in risk stratification and treatment decision-making for localized PCa, although further research is warranted to clarify underlying mechanisms and clinical implications comprehensively.

The variability in both data quality and findings within this field makes it challenging to draw definitive conclusions. Current guidelines do not provide specific recommendations for screening, treatment, or follow-up decisions in hypogonadal men, possibly due to the difficulty in establishing clear-cut guidance, highlighting a gap in current recommendations.[33,34,50]

Treated by Radiotherapy

Fewer studies have been performed in men who have received radiation therapy. Usera et al (2020) investigated how pretreatment Te levels correlate with biochemical progression free survival (BPFS), metastasis-free survival (MFS),

and overall survival (OS) in patients undergoing definitive radiotherapy treatment for PCa. They found no significant correlation between pretreatment Te level and BPFS, MFS or OS.[51]

Taira et al (2009) examined if men with low Te who were treated with brachytherapy and ADT had a worse outcome than men with normal levels of Te. They followed 1,916 patients with a median follow-up of 7.2 years; 26% of the patients received ADT. Prostate specific mortality at 10 years was 0.8% and overall mortality was 22%. Low pretreatment Te levels did not independently impact disease recurrence or OS. However, patients with low baseline Te who also received ADT showed a tendency towards decreased overall survival.[52] These findings challenge the rhetoric that low Te is protecting and is, in effect, a contradictory finding. In men with low pretreatment Te which did not impact survival outcomes, further manipulating the androgenic pathways with ADT demonstrated negative outcomes. ADT, as was mentioned earlier, is a cornerstone of advanced PCa care and is desirable for its ability to cause senescence of Te dependent PCa cells.[53]

METASTATIC PCA

In the settings where ADT is the mainstay of treatment, are pretreatment levels of Te important to consider? This question was answered by Ribeiro et al (1997) who assessed 144 metastatic patients treated with ADT and analyzed various pretreatment parameters. Serum Te was found to have a significant influence on OS indicating lower levels of Te inferred a more aggressive disease.[54] These findings were published 12 years prior to Taira et al (2009) but seem to echo the same hypothesis. In a HPG axis that is already unbalanced, further manipulation with ADT may portend negative outcomes.

Perachino et al (2010) retrospectively reviewed 129 patients diagnosed with bone only metastatic PCa and previously untreated with ADT. While maintaining low levels of Te after treatment initialization was associated with increased overall survival, pretreatment Te levels did not predict survival.[55] Considering that Ribeiro evaluated other sites besides bone, there appears to be site-dependent variability in the behavior of the prostate cancer cells and distribution of androgen receptors.

TE TREATMENT AND PCA

Patients suffering from AOH would benefit from Te treatment, yet the cancer-related risks of this treatment have not yet been fully elucidated. Calof et al (2005) performed a meta-analysis of 19 placebo-controlled studies analyzing the adverse events of Te treatment. The combined rate of all prostate events (PCa, elevated PSA, and prostate biopsies) was significantly greater in testosterone-treated men than in placebo-treated men (OR = 1.78, 95% confidence interval [CI], 1.07–2.95).[56] As for men with an established diagnosis of PCa, whether on active surveillance or after definitive treatment for localized disease, the evidence is weaker. Pastuszak et al (2013) retrospectively evaluated patients who received Te treatment after radical prostatectomy and did not find an increased risk for recurrence in treated individuals.[57]

Morgentaler et al (2011) followed 13 patients under active surveillance and treated with Te. They found no local progression or distant disease upon a median 2.5 years follow-up.[58]

Current AUA guidelines on the Evaluation and Management of Te Deficiency (last updated on Feb. 2018) provide the following statements in this regard: (1) "PSA should be measured in men over 40 years of age prior to the commencement of Te therapy to exclude a PCa diagnosis" (clinical principle). (2) "Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of PCa" (strong recommendation; evidence level: Grade B). (3) "Patients with Te deficiency and a history of PCa should be informed that there is inadequate evidence to quantify the risk-benefit ratio of Te therapy." (expert opinion).[59]

The highest quality data to date addressing the question "Does exogenous Te treatment increase the incidence of PCa risk in men with AOH?" comes from the Te Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) study. This randomized controlled study enrolled 5,204 men (aged 45-80 years) with hypogonadism, PSA ≤3, and negative DRE. Participants were randomized to receive either exogenous Te or a placebo. After a mean follow-up of 33 months (SD=12), no observed increased risk in either overall PCa occurrence (12 [0.46%] vs. 11 [0.42%], p=0.8), nor high-grade PCa specifically (5 [0.2%] vs. 3 [0.12%], p=0.51) for the Te vs. placebo groups, respectively.[60]

CONCLUSIONS

The interplay between serum Te and PCa is complex and significant, particularly evident in the chronological correlation between PCa risk and AOH with aging. Te and DHT interact directly with prostate glandular and stromal cells, and castration treatment impacts PCa cell division and progression. Data in this field is very heterogeneous and inconsistently documented, making the question whether AOH is associated with elevated risk of PCa hard to answer. While low Te levels may correlate with PCa detection, there's a higher risk of aggressive features, especially in prostatectomy cohorts. Pathological upgrading from Gleason 3 to 4 prompts consideration of whether hypogonadal men are at higher risk for reclassification during AS. Finally, data in the field has shown no evidence linking exogenous Te treatment for men with symptomatic AOH to the development, progression, or recurrence of PCa.

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[Email corresponding author for complete reference list]

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