Original Article

Effects of Androgen Deprivation Therapy on Pain Perception, Quality of Life, and Depression in Men With Prostate Cancer

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Abstract

Context. Previous animal and human research suggests that testosterone has antinociceptive properties. Castration in male rodents increases pain perception which is reversed by testosterone replacement. Pain perception also improves in hypogonadal men with testosterone therapy. However, it remains unclear whether androgen deprivation therapy (ADT) in men with prostate cancer (PCa) is associated with an increase in pain perception.

Objectives. To evaluate the effects of ADT on pain perception, depression and quality of life (QOL) in men with PCa.

Methods. Thirty-seven men with PCa about to undergo ADT with leuprolide acetate (ADT group) were followed prospectively for six months to evaluate changes in clinical and experimental pain. Forty men who had previously undergone prostatectomy for localized PCa and were in remission served as controls (non-ADT group). All participants were eugonadal at study entry. Primary outcomes were changes in clinical pain (assessed with Brief Pain Inventory questionnaire) and experimental pain (assessed with quantitative sensory testing). Secondary outcomes included evaluation of depression, anxiety levels, and quality of life.

Results. Serum testosterone levels significantly decreased in the ADT group but remained unchanged in the non-ADT group. There were no significant changes in pain thresholds, ratings, or other responses to quantitative sensory tests over the 6-month course of the study. Clinical pain did not differ between the two groups, and no changes from baseline were observed in either group. Men undergoing ADT did experience worsening of depression (0.93; 95% CI = 0.04–1.82; $P = 0.042$) and QOL related to physical role limitation (−18.28; 95% CI = −30.18 to −6.37; $P = 0.003$).

Conclusion. ADT in men with PCa is associated with worsening of depression scores and QOL but is not associated with changes in clinical pain or pain sensitivity. J Pain Symptom Manage 2018;55:307–317.

Key Words

Prostate cancer, GnRH agonists, testosterone, quantitative sensory testing, pain perception, pain tolerance, quality of life, depression

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Introduction

Substantial body of animal research across a number of species has shown that testosterone has antinociceptive properties and that it modulates sensitivity to pain.[1,2] Castration of male rodents is associated with increased sensitivity to pain while testosterone administration in these castrated animals provides greater analgesia in response to noxious stimuli.[3] This improvement in analgesia is across a variety of noxious stimuli, including thermal, mechanical, and pressure stimuli. There is also abundant evidence that women and men do not experience pain equally.[4] Large-scale epidemiological studies find that both acute and chronic pain conditions are reported more frequently by women than men.[5–7] Women are also at a greater risk for developing chronic widespread pain, which is estimated to affect 10%–15% of the population.[8] In addition to reporting clinical pain, women also exhibit greater sensitivity to experimental pain and perceive standardized painful stimuli as more intense than men including mechanical, electrical, thermal, and chemical stimuli across body sites.[9] These data suggest that testosterone enhances the potency of endogenous opioids in men.

In addition to these clinical reports, functional neuroimaging studies further confirm differential nociceptive processing among men and women.[10] Imaging studies reveal that endogenous serum testosterone levels are positively correlated with the activation of the rostral ventromedial medullary area which enhances the activity of descending pain inhibitory pathways.[11] Furthermore, randomized placebo-controlled clinical trials in hypogonadal men with chronic pain show that testosterone replacement is associated with improvement in clinical pain, experimental pain, and health-related quality of life (QOL),[12] further confirming that testosterone has antinociceptive properties.

Prostate cancer (PCa) is the most common solid cancer in American men.[13,14] As prostate is an androgen-dependent tissue, androgen deprivation therapy (ADT) is used in men with locally advanced, recurrent and metastatic disease.[15–17] The goal of ADT is to suppress testosterone production, lowering it into the castrate range (<50 ng/dL).[18] As a result, men undergoing ADT experience profound androgen deficiency which is associated with a number of adverse effects that include sexual dysfunction, osteoporosis, vasomotor symptoms, metabolic syndrome, and reduced QOL.[19–21] Since sex steroids play an important role in pain physiology, the profound androgen deficiency that occurs as a result of ADT might also have a detrimental impact on pain perception in these patients. This is particularly relevant as patients with cancer have a high prevalence of pain even in the absence of metastatic disease.[22–24] Furthermore, evaluation of men undergoing ADT provides an ideal opportunity to determine the antinociceptive role of testosterone.

The Androgen Deprivation Therapy and Pain Perception Study was a prospective observational cohort study that evaluated clinical and experimental pain in men with nonmetastatic PCa undergoing ADT and compared them to men with localized PCa who had previously undergone prostatectomy and were in remission.

Methods

Study Design and Participants

The ADT and Pain Study was a prospective observational cohort study to evaluate changes in pain perception and tolerance in men undergoing ADT for PCa. Thirty-seven men about to undergo medical ADT with GnRH agonist (22.5 mg of leuprolide acetate [Lupron depot; TAP Pharmaceuticals, Lake Forest, IL]) every three months with a planned intervention of at least six months were enrolled from the Dana-Farber Cancer Institute (ADT group). These men also received an androgen receptor antagonist (bicalutamide) during the first month of treatment to prevent tumor flare. Additionally, 40 men with PCa who had undergone prostatectomy and/or radiation therapy for organ-confined PCa at least six months prior to enrollment and were in remission were also enrolled and served as the control group and were recruited from the Brigham and Women's Hospital (non-ADT group). All men had normal serum total testosterone concentrations at the time of enrollment and did not have any chronic pain condition. Other exclusion criteria included surgical ADT, skeletal metastasis, use of opioid analgesics, peripheral neuropathy, painful inflammatory conditions, use of glucocorticoids, diabetes, and moderate-to-severe depression as assessed by the Patient Health Questionnaire (PHQ-9).[25]

The study protocol was approved by the Institutional Review Board at the Dana–Farber Cancer Institute, Boston, Massachusetts. Enrollment took place between July 2013 and April 2016; the last participant completed the study in November 2016. All participants provided written informed consent.

Primary Outcomes

The primary outcomes were the change in self-reported pain as assessed by the Brief Pain Inventory (BPI) questionnaire and experimental pain as assessed by quantitative sensory testing (QST). All assessments were performed at baseline and then 6 weeks, 3 months, and 6 months into ADT (ADT group). For the non-ADT group, assessments were performed at