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Relationship between Androgen Deprivation Therapy and Normal-Tension Glaucoma in Patients with Prostate Cancer: A Nationwide Cohort Study

Jee Soo Ha[1], Hye Sun Lee[2], Ju-Young Park[3], Jinhyung Jeon[1], Do Kyung Kim[4], Min Kim[5], Ho Sik Hwang[6], Tae Hyo Kim[7], Hyun Kyu Ahn[8], and Kang Su Cho[1,9]

[1]Department of Urology, Prostate Cancer Center, Gangnam Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, Seoul;
[2]Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul;
[3]Department of Statistics and Data Science, Yonsei University, Seoul;
[4]Department of Urology, Soonchunhyang University Hospital, Soonchunhyang University College of Medicine, Seoul;
[5]Department of Ophthalmology, Institute of Vision Research, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;
[6]Department of Ophthalmology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul;
[7]Department of Urology, Dong-A University Hospital, Busan;
[8]Department of Urology, College of Medicine, Ewha Womans University, Seoul;
[9]Center of Evidence Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, Korea.

Purpose: This study assessed the relationship between newly developed normal-tension glaucoma (NTG) and androgen deprivation therapy (ADT) in patients with prostate cancer.

Materials and Methods: A retrospective population-based cohort study was performed. During the period between 2008 and 2017, a total of 218203 prostate cancer patients were identified in a nationwide claims database in the Republic of Korea. The final analysis included 170874 patients (42909 in the ADT group, 127965 in the control group) after applying the inclusion and exclusion criteria. The incidences of NTG according to ADT duration were compared with controls. Exact matching was conducted to adjust comorbidities between cohorts. Cox proportional hazard regression models were performed after controlling for latent confounding factors, and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of NTG according to ADT were obtained.

Results: In the matched cohort, the ADT group was associated with a significantly reduced risk of NTG in multivariable analysis compared to the control group. The risk of NTG decreased in patients who underwent ADT for less than 2 years (HR=0.824; 95% CI, 0.682–0.995; p=0.0440) and in those using ADT over 2 years (HR=0.796; 95% CI, 0.678–0.934; p=0.0051), compared to the controls.

Conclusion: Medical castrations for patients with prostate cancer results in a lower incidence of newly diagnosed NTG compared to no ADT. These findings suggest that testosterone may be involved in the pathogenesis of NTG.

Key Words: Glaucoma, prostate neoplasms, testosterone

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Corresponding author: Kang Su Cho, MD, PhD, Department of Urology, Prostate Cancer Center, Gangnam Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
Tel: 82-2-2019-3471, Fax: 82-2-3462-8887, E-mail: kscho99@yuhs.ac

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INTRODUCTION

Prostate cancer is an androgen-dependent disease.[1] Androgen deprivation therapy (ADT) has played an essential role in the treatment of patients with locally advanced, recurrent, and metastatic disease. Meng, et al.[2] reported that almost half of patients with prostate cancer undergo ADT at some point after their diagnosis. ADT has shown remarkable effects in reducing the burden of prostate cancer; however, several side effects are well-known. These include hot flashes, insulin resis-

tance, cardiovascular diseases, osteoporosis, and fractures, causing the patient to have a diminished quality of life and requiring further interventions.[3] Therapeutic castration can be achieved either surgically or medically: indeed, both strategies are equivalent in suppressing serum testosterone. Currently, medical ADT with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is the mainstay of treatment in prostate cancer.[4]

Glaucoma refers to a group of optic neuropathies that involves a progressive loss of retinal ganglion cells and constriction of the visual field. Glaucoma affects more than 70 million people worldwide, with approximately 10% blinded bilaterally, making it the leading cause of irreversible blindness.[5,6] Primary open-angle glaucoma (POAG) is the most commonly reported type of glaucoma in population-based prevalence studies.[7] Recent meta-analyses have shown that POAG has male predominance, indicating that sex hormones may be involved in the development of POAG.[8,9] Following their thorough review of experimental and clinical studies, Patel, et al.[10] concluded that sex hormones, such as estrogen and testosterone, may affect ocular blood flow and intraocular pressure (IOP). In our previous research, the use of ADT was associated with a decreased risk of POAG in patients with prostate cancer, suggesting that testosterone may be involved in the pathophysiology of POAG.[11]

Normal-tension glaucoma (NTG), also known as low-tension glaucoma, has a similar optic neuropathy to POAG, but the IOP is within the normal range of 21 mm Hg or less.[12,13] Although there is controversy regarding whether NTG is a part of POAG or a distinctive disease entity, NTG does have distinctive features compared to POAG.[13] According to a recent review, NTG occurs in approximately 30%–40% of patients with POAG in Caucasian populations, but comprises a higher proportion (over 70%) of POAG in Asian populations.[7] Therefore, we postulated that hormonal changes following ADT may affect ocular health in patients with prostate cancer. Herein, we investigated the risk of newly developed NTG according to ADT in men with prostate cancer using a nationwide health insurance claims database in the Korean population.

MATERIALS AND METHODS

Ethics

This study was performed in accordance with all applicable laws and regulations, good clinical practices, and ethical principles, as described in the Declaration of Helsinki. The Institutional Review Board of Gangnam Severance Hospital approved the study protocol (approval number: 3-2019-0339). Patient-identifying information was not accessible from the Health Insurance Review and Assessment Service (HIRA) database.

Database

The National Health Insurance System in the Republic of Korea is a universal public health coverage system. This system includes more than 95% of Korean residents. The HIRA collects claims data submitted by healthcare providers for reimbursement. HIRA contains data on healthcare services for approximately 50 million beneficiaries each year.[14]

Study cohorts

The 10th revision of the International Classification of Diseases (ICD-10) codes was used to identify eligible patients for enrollment in this study. A total of 218203 patients who visited medical institutions for prostate cancer (ICD-10 code C61.0) were identified from January 1, 2008 to December 31, 2017. Among them, patients who had records of being treated with prostate cancer before 2008 (n=22895) were excluded. Since the proportion of surgical castration in Korea is extremely smaller than that of medical castration, we excluded patients who underwent bilateral orchiectomy (n=1112) to focus on the relationship between medical ADT and NTG. Patients who had previously been treated for any type of glaucoma or diagnosed with NTG within 3 months from the index date were also excluded (n=23322). Finally, a total of 170874 patients were included for analysis (Fig. 1).

Definition of groups, outcomes, and covariates

The study cohort was divided into the ADT group and the controls. The ADT group was defined as those who received at least one dose of GnRH agonist or antagonist since being diagnosed with prostate cancer. On the other hand, patients who were diagnosed with prostate cancer but had never received GnRH agonist or antagonist were classified as the controls. The summation of the action periods for GnRH agonist or antagonist was defined as the cumulative dose of ADT. The study outcome was newly developed NTG. Considering the known risk factors for glaucoma, adjustment covariates included patient's age, history of hypertension, diabetes, dyslipidemia, cardiovascular disease, cerebrovascular disease, migraine, chronic liver disease, and rheumatoid arthritis. These comorbidities were identified by ICD-10 diagnostic codes (Supplementary Table 1, only online). Medication history, including GnRH agonist or antagonist and anti-androgens, was identified using the billing codes in the HIRA database (Supplementary Table 1, only online). Index date was defined as the date of first ADT usage for the ADT group and the date of prostate cancer diagnosis for the control group.

Statistical analysis

We defined the end of the follow-up period as the date at which an event occurred or the date of the last valid inpatient or outpatient record. We used exact matching to adjust for comorbidities between the ADT group and the control group (Table 1), and propensity score matching was performed to adjust covariates between anti-androgen users and non-users in the ADT group (Supplementary Table 2, only online). Student's t-test for

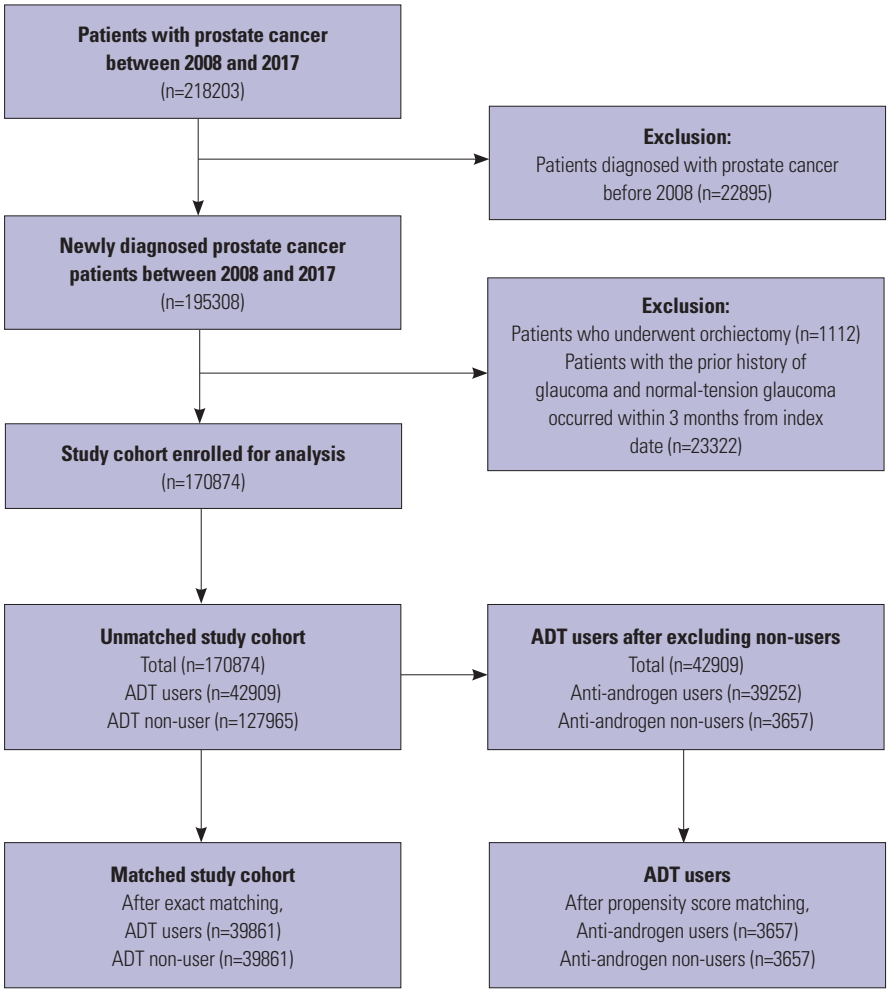

Fig. 1. Flow diagram of the study cohort. ADT, androgen deprivation therapy.

continuous variables and Pearson's chi-squared test for categorical variables were used. Univariable and multivariable Cox proportional hazard regression models were used to obtain adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of events. The Kaplan-Meier method was used to estimate the cumulative incidence of events. Since there was a difference in the definition of index date between the two groups, we performed supplementary analyses after adjusting for the follow-up duration. The median time to ADT use from the time of prostate cancer diagnosis was 24 days in the ADT group; thus, the adjusted index date for the control group was defined as 24 days after the date of prostate cancer diagnosis.[15] We conducted clustered Cox regression analysis and stratified Cox regression analysis as sensitivity analyses for each of the matched datasets. *P*-values<0.05 were deemed statistically significant, and all statistical tests were two-sided. All statistical analyses in this study were performed with SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

ADT and the risk of normal-tension glaucoma in the entire cohort

From the initial study cohort (n=170874), the ADT group and controls comprised 42909 and 127965 men, respectively. After exact matching, 39861 patients were selected from each group. Among the baseline characteristics, the follow-up duration was the only significantly different covariate between the two groups (3.58±2.49 years in the ADT group vs. 3.98±2.75 years in the control; $p<0.0001$) (Table 1). In multivariable analysis, the ADT group showed a significantly lower risk of NTG compared to the controls. The risk of NTG decreased in patients with a cumulative dose of ADT for less than 2 years (HR=0.824; 95% CI, 0.682–0.995; $p=0.0440$) and over 2 years (HR=0.796; 95% CI, 0.678–0.934; $p=0.0051$), compared to the controls. Meanwhile, the patient's baseline history of hypertension, diabetes, dyslipidemia, and chronic liver disease was a risk factor for newly diagnosed NTG (Table 2, Fig. 2).

To rule out the effect of discrepancies in the definitions of the index date between the two groups, an adjusted index date

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Table 1. Baseline Characteristics of the Entire Study Cohort

Variables	Before matching			After exact matching		
	ADT (n=42909)	Non-ADT (n=127965)	*p* value	ADT (n=39861)	Non-ADT (n=39861)	*p* value
Age, yr	72.72±8.02	64.86±10.26	<0.0001	72.10±7.80	72.10±7.80	>0.9999
Follow-up, yr	3.52±2.47	4.31±2.82	<0.0001	3.58±2.49	3.98±2.75	<0.0001
ADT						
No	0 (0.00)	127965 (100)		0 (0.00)	39861 (100)	
<2 yr	24620 (57.38)	0 (0.00)		22717 (56.99)	0 (0.00)	
≥2 yr	18289 (42.62)	0 (0.00)		17144 (43.01)	0 (0.00)	
Hypertension	18175 (42.36)	43828 (34.25)	<0.0001	16370 (41.07)	16370 (41.07)	>0.9999
Diabetes mellitus	15809 (36.84)	42349 (33.09)	<0.0001	14529 (36.45)	14529 (36.45)	>0.9999
Dyslipidemia	17050 (39.74)	52973 (41.40)	<0.0001	15672 (39.32)	15672 (39.32)	>0.9999
Cardiovascular disease	8876 (20.69)	24760 (19.35)	<0.0001	7897 (19.81)	7897 (19.81)	>0.9999
Cerebrovascular disease	6527 (15.21)	14210 (11.10)	<0.0001	5501 (13.80)	5501 (13.80)	>0.9999
Migraine	3314 (7.72)	10186 (7.96)	0.1158	2600 (6.52)	2600 (6.52)	>0.9999
Chronic liver disease	4484 (10.45)	16235 (12.69)	<0.0001	3862 (9.69)	3862 (9.69)	>0.9999
Rheumatoid arthritis	2735 (6.37)	8269 (6.46)	0.5206	2092 (5.25)	2092 (5.25)	>0.9999
Normal-tension glaucoma	386 (0.90)	1516 (1.18)	<0.0001	356 (0.89)	500 (1.25)	<0.0001

ADT, androgen deprivation therapy.
Data presented as mean±standard deviation or n (%).

Table 2. Univariable and Multivariable Cox Regression Analyses for Normal-Tension Glaucoma in the Matched Study Cohort

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CIs)	*p* value	HR (95% CIs)	*p* value
Age, yr	1.009 (1.000–1.018)	0.0477	1.009 (1.000–1.018)	0.0507
ADT				
No	Ref.		Ref.	
<2 yr	0.845 (0.700–1.020)	0.0802	0.824 (0.682–0.995)	0.0440
≥2 yr	0.802 (0.683–0.941)	0.0068	0.796 (0.678–0.934)	0.0051
Hypertension (Yes vs. No)	1.398 (1.202–1.627)	<0.0001	1.252 (1.069–1.466)	0.0053
Diabetes mellitus (Yes vs. No)	1.321 (1.150–1.516)	<0.0001	1.196 (1.037–1.380)	0.0142
Dyslipidemia (Yes vs. No)	1.431 (1.247–1.642)	<0.0001	1.317 (1.137–1.526)	0.0002
Cardiovascular diseases (Yes vs. No)	1.049 (0.881–1.249)	0.5915	0.910 (0.760–1.088)	0.3011
Cerebrovascular diseases (Yes vs. No)	1.173 (0.963–1.429)	0.1130	1.055 (0.863–1.290)	0.5999
Migraine (Yes vs. No)	1.243 (0.946–1.635)	0.1185	1.182 (0.898–1.555)	0.2330
Chronic liver disease (Yes vs. No)	1.351 (1.090–1.674)	0.0060	1.275 (1.027–1.583)	0.0279
Rheumatoid arthritis (Yes vs. No)	1.275 (0.947–1.716)	0.1096	1.194 (0.886–1.608)	0.2439

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio.

was introduced for the controls. The statistical outcomes did not differ from the prior results (Table 3). Clustered Cox regression analysis and stratified Cox regression analysis confirmed the statistical findings without significant difference in the sensitivity analyses for each of the matched datasets (data not shown).

Anti-androgen agents and the risk of normal-tension glaucoma in the ADT group

In the ADT group (n=42909), anti-androgens were prescribed concurrently with GnRH agonists and antagonists in most patients (n=39252, 91.5%). The effect of anti-androgens was not included in the main analysis due to the existing multicollinearity between ADT and anti-androgen agents. Subgroup analysis was performed to assess the effect of anti-androgens on the incidence of NTG. Anti-androgen users and non-users were selected by 1:1 propensity-score matching according to age and ADT duration from the ADT group. Each of the 3657 patients from the two groups were included in the subgroup analysis (Supplementary Table 2, only online). Between anti-androgen users and non-users, there was no difference in the risk of NTG in multivariable Cox regression analysis (Supplementary Table 3, only online).

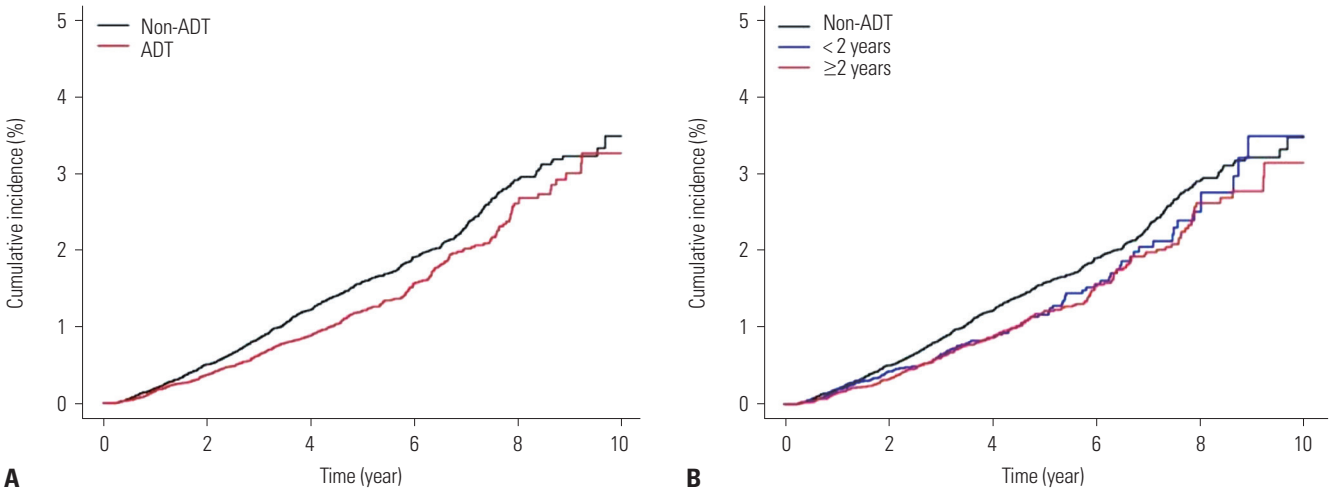

Fig. 2. Cumulative incidence of normal-tension glaucoma according to the use of ADT (A) and the cumulative dose of ADT (B). ADT, androgen deprivation therapy.

Table 3. Univariable and Multivariable Cox Regression Analyses for Normal-Tension Glaucoma in the Matched Study Cohort after Adjusting for Follow-Up Duration of Non-ADT Group

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CIs)	*p*-value	HR (95% CIs)	*p*-value
Age, yr	1.009 (1.000–1.018)	0.0484	1.009 (1.000–1.018)	0.0504
ADT				
No	Ref.		Ref.	
<2 yr	0.825 (0.683–0.997)	0.0463	0.803 (0.665–0.970)	0.0229
≥2 yr	0.789 (0.672–0.925)	0.0036	0.782 (0.666–0.917)	0.0025
Hypertension (Yes vs. No)	1.397 (1.201–1.626)	<0.0001	1.253 (1.069–1.467)	0.0052
Diabetes mellitus (Yes vs. No)	1.320 (1.150–1.516)	<0.0001	1.196 (1.037–1.380)	0.0142
Dyslipidemia (Yes vs. No)	1.430 (1.246–1.642)	<0.0001	1.318 (1.138–1.526)	0.0002
Cardiovascular diseases (Yes vs. No)	1.049 (0.881–1.249)	0.5931	0.910 (0.760–1.089)	0.3018
Cerebrovascular diseases (Yes vs. No)	1.173 (0.963–1.429)	0.1139	1.055 (0.863–1.290)	0.6014
Migraine (Yes vs. No)	1.243 (0.946–1.635)	0.1185	1.182 (0.899–1.555)	0.2319
Chronic liver disease (Yes vs. No)	1.350 (1.090–1.673)	0.0060	1.275 (1.027–1.583)	0.0278
Rheumatoid arthritis (Yes vs. No)	1.274 (0.947–1.716)	0.1098	1.194 (0.886–1.609)	0.2431

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio.

DISCUSSION

This large population-based study demonstrated a tendency for the prevalence of NTG to decrease in patients who are medically castrated. The ADT group showed a lower cumulative incidence of NTG compared to controls in the matched cohort. Even if the cumulative dose of ADT was limited to less than 2 years, the incidence of NTG was still lower than that in the controls; however, the concurrent use of anti-androgen agents did not affect the incidence of NTG. To the best of our knowledge, no prior studies have explored the relationship between ADT and the risk of NTG. The present study suggests that serum testosterone might be associated with the pathophysiology of NTG.

A number of previous studies have established the effect of sex hormones, such as estrogen, androgen, and progesterone, on glaucoma. Although some studies have shown that sex hormones play a role in optic neuropathies, evidence with which to draw more solid conclusions is still lacking. Studies on women before and after menopause have shown an effect of estrogen on glaucoma. Estrogen is associated with an increase in ocular blood flow, a decrease in IOP, and enhanced neuroprotective properties.[10] On the other hand, testosterone may have the opposite effect from estrogen on ocular blood flow. Indeed, one study showed that higher testosterone levels in postmenopausal women were associated with an increased POAG risk and higher IOP.[16] Most of studies investigating the association between sex hormones and glaucoma have included female study participants. In females, the production of female sex hormones suddenly decreases to the bottom after menopause. Meanwhile, in males, decreases in male sex hormones happen much more gradually, and they do not completely decrease.

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For this reason, the influence of testosterone on risk factors and pathophysiological processes of the eye has been difficult to measure in clinical research. ADT is a non-physiological treatment that abruptly reduces testosterone as a medical necessity; thus, assessing the role of testosterone on ocular health in patients who have undergone ADT is a promising and interesting approach.

Not much is known about the effects of testosterone on glaucoma, but male predominance has been reported in some epidemiological studies. Tham, et al.[8] demonstrated male predominance of POAG in a Bayesian meta-regression model (odds ratio, 1.36; 95% credible interval, 1.23–1.52). Rudnicka, et al.[17] reported that the overall prevalence of POAG in men was 1.37 times higher than that in women (95% credible interval, 1.22–1.53) after adjusting for age, race, publication year, and survey methods. Therefore, treatments that cause loss of testosterone can be assumed to have protective effects against POAG development. Despite these studies, the way testosterone affect ocular health still remains uncertain. This study may spur ideas required for further research to determine how testosterone influences optic nerve damage.

Several population-based epidemiological studies have shown that the prevalence and dominant subtypes of glaucoma vary among races and countries, but the exact mechanism has not yet been elucidated. The prevalence of POAG and the proportion of NTG can vary according to ethnicity. In the United States, the prevalence of POAG is estimated to be six times as high in certain age groups among African American individuals than in Caucasian individuals.[18] The prevalence of POAG is the highest in Africans (6.23±2.42%), followed by Asians (2.20± 0.92%), and the lowest in Caucasians (1.89±0.66%).[7] Indeed, NTG comprises the majority of POAG cases in Asians (approximately 50%–90%) and Africans (57.1%), and a lower proportion in Caucasians (30%–38.9%).[7,13,19] Similarly, prostate cancer has racial differences: African Americans experience a disproportionately higher incidence of, and mortality from, prostate cancer, compared to Caucasians. Studies have explored racial differences in prostate cancer mortality by looking at the androgen axis, which included using serum testosterone levels, racial polymorphisms within the 5alpha-reductase enzyme, and racial differences in polyglycine and polyglutamine repeat lengths within the androgen receptor.[20] Despite the lack of evidence on the relationship between NTG and the androgen axis, we can assume that racial differences might be associated with varying prevalence of NTG, as demonstrated in prostate cancer research. Our observations, which show a relationship between ADT and the risk of NTG, also favor such a theoretical assumption.

This study had some limitations. The use of systemic medications known to affect glaucoma, such as corticosteroids, antihistamines, H2-blocking agents, and antipsychotics with anticholinergic properties, was not considered. Our large-population database comprised ICD-10 codes entered by physicians in South Korea. Serum testosterone levels, detailed data on IOP, and results of optic nerve examination of individuals were not provided in this database. In addition, relevant lifestyle factors, such as smoking, obesity, or other clinical data, including blood pressure and other laboratory values, were not available in the HIRA database. It is well-known that ADT worsens various metabolic diseases,[21] and we cannot rule out the possibility that metabolic diseases exacerbated by ADT may have had some effect on NTG. Mediation analysis will be helpful to elucidate the indirect effects of ADT on NTG. However, this would require additional operational definitions to define the "worsening of metabolic diseases," which might compromise the interpretation of our study. In order to statistically identify the indirect effects of ADT, an additional study based on a well-constructed database that provides information on other clinical parameters, such as laboratory values and blood pressure, will be needed.

Despite some limitations, this study confirms the trend that medical castration decreases the incidence of NTG. This study lends to further research in prostate cancer patients undergoing ADT. Prospective research may be possible if patients commencing ADT could undergo ophthalmologic examination. Our study design could serve as a cornerstone for novel approaches to elucidate the relationship between testosterone and ocular health.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jee Soo Ha and Kang Su Cho. Data curation: Hye Sun Lee and Ju-Young Park. Formal analysis: Hye Sun Lee and Ju-Young Park. Funding acquisition: Tae Hyo Kim, Do Kyung Kim, and Kang Su Cho. Investigation: Jee Soo Ha, Tae Hyo Kim, Hyun Kyu Ahn, and Do Kyung Kim. Methodology: Jee Soo Ha, Tae Hyo Kim, and Kang Su Cho. Project administration: Jee Soo Ha, Jinhyung Jeon, Tae Hyo Kim, Hyun Kyu Ahn, and Do Kyung Kim. Resources: Do Kyung Kim and Kang Su Cho. Software: Hye Sun Lee and Ju-Young Park. Supervision: Kang Su Cho. Validation: Min Kim, Ho Sik Hwang, and Kang Su Cho. Visualization: Jee Soo Ha and Ju-Young Park. Writing—original draft: Jee Soo Ha and Jinhyung Jeon. Writing—review & editing: Jee Soo Ha and Kang Su Cho. Approval of final manuscript: all authors.

ORCID iDs

Jee Soo Ha https://orcid.org/0000-0002-3923-4619
Hye Sun Lee https://orcid.org/0000-0001-6328-6948
Ju-Young Park https://orcid.org/0000-0003-0782-614X
Jinhyung Jeon https://orcid.org/0000-0001-8663-1310
Do Kyung Kim https://orcid.org/0000-0002-3696-8756
Min Kim https://orcid.org/0000-0003-1873-6959
Ho Sik Hwang https://orcid.org/0000-0003-4794-4001

Tae Hyo Kim https://orcid.org/0000-0002-5994-7878
Hyun Kyu Ahn https://orcid.org/0000-0002-1996-6249
Kang Su Cho https://orcid.org/0000-0002-3500-8833

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