Diabetes and Androgen-Deprivation Therapy-Related Diabetes in Prostate Carcinogenesis

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Abstract

Regarding diabetes-related carcinogenesis and androgen deprivation therapy-related metabolic disease, respectively, prostate cancer and ADT are linked to diabetes. This study's objective is to thoroughly review the pertinent literature. In the US, it is projected that 218,000 men receive a new prostate cancer diagnosis each year. 10% of them are still discovered to have metastases, while 30% of patients with nonmetastatic prostate cancer had recently undergone ADT in addition to them. Contrary to other cancers, type 2 diabetes has been linked to a decreased incidence of prostate cancer, according to population-based studies. However, more recent large cohort studies have found a link between diabetes and advanced, high-grade prostate cancer. The greater likelihood of advanced illness at diagnosis can be attributed to the lower serum testosterone and PSA levels in diabetic men, even if it is still unclear why these men have a lower prevalence of prostate cancer. Meanwhile, 3 months after the start of ADT, 25–60% of patients already exhibit insulin resistance, and long-term ADT increases the risk of developing diabetes (reported hazard ratio of 1.28–1.44). Although it has been proposed that cytokines like Il-6 and TNF- may be relevant to diabetes brought on by ADT, its mechanism is not well known.

Keywords: Prostate cancer; Androgen deprivation therapy; ADT; miRNA markers; Castration-resistant prostate cancer; Therapy effectiveness.

Introduction

Regarding diabetes-related carcinogenesis and androgen deprivation therapy-related metabolic disease, respectively, prostate cancer and the hormonal therapy for it (ADT) have been linked to diabetes. In both epidemiological and etiological methods, the current research systematically introduces prostate carcinogenesis in association with diabetes and ADT-related diabetes/insulin resistance.

The following search terms for diabetes-associated prostate carcinogenesis were used in PubMed and MEDLINE searches for articles published between January 1991 and November 2011: prostate cancer AND insulin resistance, hyperglycaemia, cancer risk, and diabetes. The keywords androgen deprivation therapy OR hormone therapy AND diabetes, insulin resistance, hyperglycaemia, and metabolic syndrome were used to search the literature on ADT-related diabetes. Similar search techniques were used to find pertinent publications on androgen metabolism, growth hormone (GH), insulin-like growth factor (IGF)-1, and other topics. Review papers were not included, with the exception of studies involving statistics, meta-analysis, or reanalysis. All full papers supporting them that were based on evidence levels 1 and 2 and level 3 were retrieved from our institution's library, donated by other universities, or purchased, and pertinent articles on experimental

In the United States, it is estimated that 32,000 men lose their lives to prostate cancer each year and 218,000 men worldwide receive a new diagnosis, making prostate cancer one of the most frequent malignancies. According to patient characteristics including age and comorbidities, disease-specific risk, and therapeutic alternatives for prostate cancer are chosen with informed consent. About 10% of patients are still found to have metastatic disease at diagnosis, despite the fact that the prostate-specific antigen (PSA) test has caused a stage migration with an increase in low- to intermediate-risk localised illness. Additionally, based on high histopathological grade (Gleason score of 8–10) or high PSA level (serum PSA higher than 20 ng/mL), 20–35% of the patients are classified as having locally progressed illness or localised high-risk malignancy.

Men with type 2 diabetes have lower PSA levels than men without the disease, according to the findings of recent population-based cohort studies. Is exposure to PSA screening linked to a lower risk of prostate cancer in men with diabetes, given the evidence of lower PSA levels in diabetic men? Kasper et al. showed an increased risk of prostate cancer in men with diabetes compared to those without diabetes in a longitudinal observational study that included 4,511 men with newly diagnosed prostate cancer between 1986 and 2004. However, the odds ratio was still modest in the PSA era (0.86). In a recent population-based study carried out in Taiwan, 985,815 study participants were followed up between 1998 and 2009, including 104,343 diabetes patients identified in 1997. The unadjusted and adjusted risk ratios in diabetes men for incident prostate cancer were 6.97 (5.34-9.10) and 1.56 (1.19-2.04) respectively. Uncertainty existed over the frequency of PSA screening in this cohort.

Therefore, diabetes raises the prevalence of poor-risk prostate cancer in the screening-based cohort or regional cancer registration and is linked to a lower PSA level in the general population. The latter is consistent with findings from earlier studies on prostate cancer biology; low testosterone environment in vivo is associated with high Gleason score, advanced disease stages, and a poor prognosis. It can be explained by the frequent reduced testosterone levels in men with increased insulin resistance or type 2 diabetes. All of these investigations have revealed a connection between cancer cells' high viability and malignant potential and their adaptability to low-testosterone environments. Most recently, Bottom and colleagues revealed that males with prostate cancer have a high incidence of predominant Gleason pattern 4 (histologically high-grade pattern) and low serum testosterone. On 452 males who undergone radical prostatectomy, a prospective study was conducted; the final study group included 431 eligible patients. In surgical specimens, 132 patients (31%) showed Gleason pattern 4 predominance, and their serum total testosterone level was lower (4.00 versus 4.50 ng/mL) than that of the 299 patients with predominance of lower histological grade. Interestingly, the history of diabetes was detected more frequently in individuals with the predominant Gleason pattern 4 (8.4% vs. 2.7). Accordingly, diabetes contributes to the occurrence of high-grade/advanced prostate cancer most likely by allowing more malignant potential to develop in an environment with low testosterone.

It is still not understood why diabetes is linked to decreased PSA levels, making it difficult to explain the mechanism underlying lower PSA levels in diabetic males. Serum testosterone levels in males with type 2 diabetes are likely to

be lower, as previously mentioned. However, their median deviation from the level of normo-gonadotropic testosterone is about 30%. It is yet uncertain whether a significant drop in testosterone levels affects serum PSA levels. There is a limit to the capacity of testosterone to induce androgenic activities, including the proliferation of the prostate epithelium, according to a notion promoted by Morgentaler that can explain the discrepancy between androgen and PSA levels. A surplus of testosterone and its intracellular prostatic metabolite, dihydrotestosterone, are present in physiologic concentrations of testosterone, maintaining optimal prostatic growth. The Saturation Point is a key concentration threshold for testosterone below which prostate tissue begins to grow androgen-dependently in the intracellular environment. Thus, it does not appear that the minor decline in testosterone in diabetic males explains why their serum PSA levels are lower.

The possibility that a greater insulin level is linked to a higher risk of prostate cancer is also of interest. 392 men with prostate cancer and 392 matched controls were the subjects of prospective conditional logistic regression analysis by Stocks and colleagues. The researchers found that the prostate cancer group had lower levels of homeostatic model assessment of insulin resistance (HOMA-IR) than the control group (versus), and that an increase in HOMA-IR was linked to a lower risk of prostate cancer (odds ratio = 0.60, 95% confidence interval [CI], 0.38–0.94). Insulin levels had no effect on the incidence of incident prostate cancer in a different case-control study that included 174 men in both the case and control groups. Contrarily, a recent cohort study by Hammerstein and colleagues with a 9-year follow-up period revealed that the PR diagnostic insulin level was higher in men with incident prostate cancer than in men without the disease (fasting serum insulin, 12.0 versus 9.0 mU/l), despite the fact that the study only included a small number of prostate cancer patients and the insulin level's hazard ratio was not clear. These varying outcomes can be influenced by the observation period's length and study methodology. Increased insulin levels were linked to higher risks of prostate cancer, according to a recent case-cohort investigation on a sizable registered cohort (OR = 1.50–2.55 among comparable insulin quartiles). Similar findings from a prior population-based investigation were published.

Most recently, an experimental study reported intracellular de novo steroidogenesis promoted by insulin in prostate cancer. It also demonstrated that insulin upregulated the transcription of androgen-metabolizing enzymes like CYP17A1 and 5-reductase in prostate cancer cells LNCaP and 22RV1, which express androgen receptor, in a dose-dependent manner. In their investigation, the intracellular levels of dehydroepiandrosterone and testosterone increased by insulin 18-fold and 60-fold, respectively, (in both), and the protein level of CYP17A1 in LNCaP also increased dramatically with insulin. These findings imply that insulin may actively encourage the growth of prostate cancer cells. However, these findings are based on research examining the impact of insulin on prostate tumorigenesis in the early stages or a castration-resistant prostate cancer experimental model.

Materials and Methods

The study sample included 20 age-matched male controls (years old) who had not had ADT and 30 male prostate cancer patients (years old) who were undergoing long-term ADT. Patients with prostate cancer received ADT for an average of 15.06 months (range 3-60 months). Prostate cancer patients receiving ADT was the only requirement for inclusion in the ADT group. Infectious keratitis or conjunctivitis, ongoing use of eye drops, a history of eye surgery, and severe systemic illnesses were prohibited. Between June 2018 and December 2019, all participants were sourced from Zhenjiang First People's Hospital.

Discussion

Sebaceous glands are known to proliferate and differentiate in all parts of the body when androgens are present. Androgens are also crucial for the development of the meibomian glands, which are enormous sebaceous glands that express androgen receptors. ADT, on the other hand, decreases androgen levels over the long term, which can slow or stop prostate cancer growth, but this results in physiological alterations to the ocular surface. The current study looked at how ADT-treated prostate cancer patients' ocular surface structure and function changed. In comparison to age-matched controls, these individuals had more tear film debris, uneven eyelid margins, meibomian gland atrophy and orifice metaplasia, and a pronounced decline in the quality of meibomian gland secretions.

Demodex mites may contribute to MGD. Since the rate of ocular demodex infestation was much greater in the symptomatic ADT group (9/9, 100.00%) than in the asymptomatic ADT group, it may be concluded that prostate cancer patients' complaints of eye discomfort were caused by ocular demodex infestation. reported that ocular pain patients had a high prevalence of demodex. Furthermore, the results demonstrated a correlation between the OSDI score and the degree of ocular irritation and the quantity of demodex mites. All of the data point to the possibility that demodex infestation can worsen the subjective signs of ocular surface injury. Demodex elimination may therefore be helpful in reducing MGD-related ocular surface irritation.

Age, gender, and hormonal considerations are just a few of the underlying causes of MGD. Aging may affect the quality of meibomian gland secretions by causing the acini epithelial cells in the meibomian gland to atrophy. Age-related declines in sex hormone levels, particularly androgens, may be a factor in meibomian gland loss, which can result in thicker meibum, hyperkeratinisation of the orifices, and obstruction of the meibomian glands. MGD caused by androgen insufficiency has been seen in prostate cancer patients on ADT, but no studies have yet found a link between the length of ADT and changes to the ocular surface. In the current study, the length of ADT was negatively correlated with the NI-BUT but favourably correlated with the meibomian gland dropout score in the ADT group.

This suggests that poorer tear function and a greater meibomian gland dropout area were related to a longer duration of ADT. Similar to this, lower serum testosterone levels and atrophy of acinar cells are both associated with decreased sebaceous gland function and output. Age tends to cause meibomian gland atrophy, and an infrared minibiography study found a strong relationship between age and the reduction of meibomian gland area. In other words, changes to the meibomian gland are linked to androgen levels. Therefore, we made the assumption that androgens might promote meibomian gland activity, improving tear film stability and reducing tear film evaporation and thereby alleviating symptoms of dry eyes. The risk of MGD can significantly rise with a longer ADT period.

To the best of our knowledge, this is the first study to look into how long-term ADT affects a person's chance of developing MGD in an Asian population. Our investigation into the connection between androgens and the ocular surface revealed that a lack of androgen was associated with eyelid margin abnormalities, meibomian gland loss, and pain in the eyes. We have shown that prolonged ADT increases the risk of MGD in men with prostate cancer. Demodex infection may also make ocular surface irritation worse. Patients with prostate cancer who are taking ADT must closely monitor their ocular surface health and take demodex medication.

Conclusion

In the general population, diabetes is linked to lower PSA levels, whereas in the prostate cancer registration-based cohort, it is linked to a higher incidence of advanced prostate cancer. Although the cause of the first link is uncertain, the second can be explained by lower testosterone levels in men who have type 2 diabetes or higher insulin resistance. Early on after the start of ADT, insulin resistance is frequently seen, and long-term ADT use is linked to an increased risk of developing diabetes. A regulating link between proinflammatory cytokines and sex hormones is conceivably involved in ADT-related diabetes, albeit the exact mechanism is still unknown.

Conflict of Interests

None

Acknowledgment

None

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