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PROSTATE CANCER AND DIABETES: BIOLOGY OR DETECTION BIAS?

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ABSTRACT

Prostate cancer and diabetes are the two highly prevalent health problems in men worldwide and have a high mortality rates but their association is quite complex and contradictory. This review reported several population based studies which tried to establish a possible association and explains the mechanism by which diabetes exhibits its effect on prostate cancer progression. It also explores the literature around the expression of various receptors and genes which enlightens the possible molecular basis of association and the effect of current antidiabetic drugs like metformin and insulin on the growth and advancement of prostate cancer in diabetic men. Masking of early tumor detection by diabetes might be the possible explanation for the reported inverse association with worse prognosis and shorter survival rate in diabetic prostate cancer patients.

KEYWORDS: Prostate Cancer, Type 2 Diabetes Mellitus, Androgen Receptor, Insulin Receptor, IGF-1 Receptor, Antidiabetic Drugs

INTRODUCTION

Prostate cancer (PCa) and diabetes mellitus type 2(T2DM) are the two highly prevalent health problems affecting men worldwide (1). PCa is the second most commonly diagnosed malignancy in adult men around the globe and the fifth leading cause of demise from cancer in developed countries (2,3). T2DM, have been linked to increased risk of development of malignancies and related mortality including PCa in some studies but the protective role of T2DM on PCa is yet to be confirmed as there is conflicting literature present on it (4,5). Studies performed in western countries on association of T2DM with PCa mostly confirm a decreased risk whereas Asian studies reported an increased risk of PCa among the diabetic population. These variation in results might be due to lifestyle, ethnicity or genetic differences (6).

Although strong epidemiological evidences links PCa and T2DM, yet the underlying pathophysiological and molecular mechanism of T2DM with PCa is not clearly understood in detail. However changes in serum androgens, insulin, Insulin-like Growth factors (IGFs) levels and genetic susceptibility in diabetics can at least serve as partial etiology (7). Recently conducted Genome-wide association studies (GWAS) have identified some common Single Nucleotide Polymorphisms (SNPs) that are associated to PCa but their function and interaction with other genetic and non-genetic aspects are largely unknown. It is of particular interest to study interactions between PCa SNPs and diabetes as several SNPs like *JAZf1* and *HNF1B/TCF2* has been stated to be connected with both the diseases (8).

PROSTATE CANCER AND DIABETES ASSOCIATION: EVIDENCE FROM POPULATION BASED STUDIES

Some population based studies investigating the possible association between T2DM and PCa reported inconsistent findings. Some studies reported reduced risk (Table 1) while some reported elevated risk (Table 2). One meta-analysis reported a significant increased risk of developing PCa in diabetic Asian men in both case-control (unadjusted Relative Risk (RR)= 1.65, 95% CI 1.09–2.48, P < 0.001; adjusted RR= 1.44, 95% Confidence Interval (CI) 1.15–1.81, P = 0.001) and cohort studies (unadjusted RR= 3.71, 95% CI 2.19–6.27, P < 0.001; adjusted RR= 1.26, 95% CI 1.01–1.57, P = 0.001) (9) while a non-significant elevated risk of PCa with diabetes was reported by another meta-analysis (HR, 1.51; 95% CI, 0.94-2.43) (10).

Meta-analysis for observational studies between 1971 to 2011 by Bansal D *et al* compared PCa risk in diabetic and non-diabetic subjects and reported overall significant reduced risk (14%) of PCa in diabetic patients (pooled RR 0.86; 95% CI 0.80-0.92).

Subgroup analysis of cohort alone (pooled RR 0.87; 95% CI 0.80-0.94) and case-control studies alone (pooled RR 0.85, 95% CI 0.74-0.96) also reported reduced risk among diabetics (11). These findings correlates with the meta-analysis by Kasper JS who reported negative association of T2DM with PCa (RR 0.84; 95% CI 0.76-0.93) (12). A hospital based case-control study between 1991 and 2002 on Italian population reported no association between the two diseases (13). National Health and Nutritional Examination Survey (NHANES) II reported 21.6% decrease in mean Prostate Specific Antigen (PSA) level in diabetic men compared to non-diabetic with increasing difference in the mean levels with increase in years since diagnosis of diabetes. This might cause a diagnostic bias as fewer diabetic patients might proceed to diagnostic prostate biopsy and decreases the ratio for PCa in diabetic men (14). Pre-existing diabetes, either type-1 or type-2 compromised the health related quality of life of PCa patients and increases the risk of all-cause mortality (15,16) as reported by Chen Y *et al*., diabetes significantly increase death risk from any cancer, including prostate (HR 1.41; 95% CI 1.09, 1.82) (17). More aggressive PCa with higher gleason scores and increased incidences of lymph node metastasis were detected in men with diabetes than in non-diabetic patients independent of age and body weight (18-20). However most recent study examining the relationship between PCa and T2DM at two different time periods following different screening guidelines reported incidence of smaller, less aggressive PCa in diabetic men (21). Association between PCa and T2DM may also be driven by obesity which is confirmed by some observational studies but due to detection bias, PCa is usually underdiagnosed which explains the reduced risk of non-aggressive and elevated risk aggressive PCa in obese men (1). Choi JB *et al*. reported low incidence of PCa in low BMI group diabetic patients whereas high incidence is reported high BMI groups that emphasizes the necessity of different BMI control strategies to prevent incidence of PCa in diabetics (7).

Author	Study Design	Study population	Main findings
Chen CB *et al.* 2018 (6)	Retrospective cohort study from British Columbia, Canada between 1994 to 2012	Among 160566 participants, 80001 had diabetes.	Decreased risk of PCa in Chinese and Indian ethnicity with co-incidental diabetes. Incidence rate of PCa was lower in diabetics (1.717-183.4) as compared to non-diabetics (209.7-225.5) per 1000 person-year (Adjusted HR 0.82, 95% CI 0.78-0.86). Chinese men (Adjusted HR 0.54, 95% CI 0.46-0.63) Indian men (Adjusted HR 0.66, 95% CI 0.49-0.89)
Fall K *et al* 2013 (4)	Case- control study between 2002 and 2006	44,352 men with PCa 221,495 age-matched controls	Lower risk of PCa among men with T2DM than men without T2DM (OR, 0.80; 95% CI, 0.76–0.85)
Pierce BL & Ahsan H 2010 (82)	Case- control study	1,171 non- Hispanic white, PCa cases and 1,101 matched controls	Increasing T2DM genetic susceptibility is associated with reduced PCa risk ($p < 0.01$), highest quartile of the T2DM allele count (>20 risk alleles) being associated with reduced PCa risk (OR = 0.77; CI: 0.60–0.99) compared to the lowest category (< 17 risk alleles).
Kasper JS *et al.* 2008 (53)	Prospective cohort study from 1986–2004	4,511 new PCa cases were identified between 1986-2004 (237 cases were diabetic)	Men with diabetes had reduced PCa risk compared to non-diabetics (HR 0.83 (95% CI: 0.74-0.94). Reduced PCa risk with increased time since diabetes diagnosis. First year (HR: 1.30, CI: 0.97-1.72), 1–6 years (HR: 0.82, CI: 0.66, 1.02), 6–15 (HR: 0.75, CI: 0.61, 0.93) and >15 years (HR: 0.78, CI: 0.63, 0.96).
Waters KM *et al*. 2008 (83)	Prospective Cohort study of 12 years between 1993-2005	Among 86,303 men, 5,941 were identified with prostate cancer.	Diabetics had significant lower risk of PCa than non-diabetics (RR 0.81; 95% CI 0.74-0.87).

Table 1: Population based Studies Reporting Reduced Risk of Prostate Cancer in Diabetics.

PROSTATE CANCER AND DIABETES: POSSIBLE BIOCHEMICAL MECHANISM OF ASSOCIATION

There is quite a complex link between PCa and diabetes (Figure-1). Diabetes, on one hand seems to reduce PCa risk as men with T2DM have decreased serum androgen levels which is directly linked with PCa risk, while on the other hand T2DM is characterized with higher serum insulin levels and demand in pre and early diabetic states, which leads to decrease in the serum Insulin-like Growth Factor-1 Binding protein (IGFBP-1) levels and consequently to elevated IGF-1. All these factors being possibly linked with PCa risk (13). Some studies reported shorter survival time after diagnosis of PCa in diabetic men compared to men without diabetes. Early-onset diabetes might elevate PCa risk, higher risk observed between 1-3 years and then progressively declines after 5-10 years of diagnosis, therefore long-standing diabetes might be the reason for reduced of PCa risk (22). The possible justification for the decreased risk of PCa in long-term diabetes may be reduced serum levels of Insulin due to β-cell depletion, reduced serum testosterone, IGF-1 and IGF-1 signalling over time after the diagnosis of diabetes and also involvement of type 2 diabetes related factors such as diabetic complications and medications (23,24).

PROSTATE CANCER AND DIABETES: MOLECULAR ASSOCIATION

GENE POLYMORPHISMS

A convincing genetic link between PCa and diabetes was derived from findings of various studies. Lindstorm S. *et al*. observed significant interaction between diabetes and *JAZF1* SNP rs10486567 (p=0.04) and reported a strong link between T2DM and PCa risk (OR: 0.73, 95% CI: 0.64-0.83) (25). However Stevens V.L. *et al.* reported association of *JAZF1* SNPs rs10486567 and rs6968704 with reduced PCa risk but not diabetes. Also, *HNF1B* SNPs, rs11649743, rs4430796 and rs7501939 were associated with decreased PCa and increased diabetes risk (26). Gudmundsson J. *et al*. reported another *HNF1B* gene SNP (rs7501939 and rs3760511) with increased PCa risk and decreased diabetes risk (27). Ten unique SNPs on *HNF1B* and an SNP on intron 2 of *JAZF1* gene were reported to be significantly related to the risk of developing PCa. Further GWAS has shown that SNPs in these regions are also associated with T2DM, so the possibility of diabetes mediated prostate cancer-SNP relationship must be considered (8). Information from these genotype studies concludes that the allele for PCa risk protects against T2DM (9).

Exon 1 of Androgen Receptor (AR) gene contains CAG and GGN repeats polymorphism encoding polyglutamine and polyglycine stretch respectively (28) whose length inversely correlates with the transcriptional activity of AR, smaller CAG repeats have higher transcriptional activity (29). Malavige LS *et al*. studied AR CAG polymorphism and reported it to be insignificantly associated with presence of diabetes, insulin resistance, Fasting Blood Sugar (FBS) or HBA1C which might be due to the effect of diabetic treatment to maintain parameters within normal range (30). However a 14 years follow-up study reported association of greater number of CAG repeats at the testosterone receptor gene with future BMI and increased HBA1c (31)

ANDROGEN RECEPTOR SIGNALING AND NON-ANDROGEN DEPENDENT ACTIVATION OF ANDROGEN RECEPTOR

Testosterone and dihydrotestosterone (DHT) is responsible for biological differentiation, development and normal functioning of the prostate through AR signaling that plays a vital role in the development and advancement of PCa and is the main target for intervention in PCa (2) that gives way to Androgen deprivation therapy (ADT) as one standard treatment for metastatic PCa. ADT results in significant reduction in number of prostate secretory cells through apoptosis (32) and yields a 5 years survival rates (33). However, the evidence that low levels of androgen do not exclude prostate carcinoma suggests that other than androgens, growth factors also mediate the prostate cell growth and carcinogenesis (2, 34) as most patients relapse with Castration-Resistance Prostate Cancer (CRPC) after ADT (33). Use of ADT in diabetic men was also associated with elevated risk of diabetes complications as men spend a significant part of their lives in a testosterone deficient environment to increase longevity that causes several unfavorable alterations in the body composition such as increase in the total and visceral fat, insulin resistance and loss of muscle mass which itself acts as an independent risk factor for T2DM (1, 35) and further worsened diabetes control (36). Androgen-independent activation of AR signaling confers castration resistance in PCa. Ligand-binding domain of AR have high proportion of mutations as observed in both hormone-refractory and metastatic PCa which could possibly activate AR by other growth factors, steroid hormones and cytokine receptor pathways (33).

ANDROGEN RECEPTOR OVEREXPRESSION IN PROSTATE CANCER WITH DIABETES

Initially, loss of AR mRNA and protein expression was suggested to cause androgen-independent

Author	Study design	Study population	Main findings
Murtola TJ *et al.* 2018 (84)	Prospective cohort study of 14.7 years follow-up	Among 17,860 men included, 1,663 were diagnosed with prostate cancer (808/8,481 in normoglycemic group, 454/5,812 in pre-diabetic group and 401/3,567 in diabetic group)	Diabetic men had increased risk of PCa compared to normoglycemic men (HR 1.52, 95% CI 1.31-1.75)
Yaturu H *et al.* 2017 (85)	Retrospective data base study between 2010- 2012	497 (46%) PCa patients among 6777 subjects with T2DM	Higher frequency of PCa in diabetics compared to other cancers.
Park J *et al.* 2014 (86)	Single-center, retrospective medical data base study between 2008-2013	Among 1363 men included in the study, 338 were diabetic and 393 were prostate cancer cases. Population was divided into three groups: A no diabetes group (DM-), good glycemic control group (DM+GC) and poor glycemic control group (DM+PC)	Main finding: Elevated risk of PCa including high grade tumors in poor glycemic diabetes control. Significant higher rate of overall PCa detection in DM+PC group compared to DM- group (OR= 2.313, P=0.001).
Tseng CH *et al.* 2011 (87)	Prospective cohort study between 2003 to 2005	494630 men for all ages and 204741 men ≥40 years without PCa randomly selected from National Health Insurance in 2005 and the subject's reimbursement data bases retrieved back to 1996 and followed from 2003-2005	A positive link between T2DM and PCa with a remarkable increase in the youngest age of 40-64. The risk ratio (95% CI) for all ages and age between 40-64, 65-74 and ≥75 was 5.83 (5.10-6.66), 2.09 (1.60-2.74), 1.35 (1.07-1.71) and 1.39 (1.12-1.71) respectively
Murad AS *et al.* 2010 (88)	Population-based, case-control study between June 2002 and November 2006	1,551 PCa cases and 2,993 controls were genotyped for SNP in the glucokinase gene, rs1799884	Positive association between the AA variant rs1799884 and PCa (ORAA v GG= 1.40, 95% CI= 0.95 to 2.07) indicating importance of hyperglycemia in mediating relationship between diabetes and PCa.

Table 2: Population based Studies Reporting Increased Risk of Prostate Cancer in Diabetics

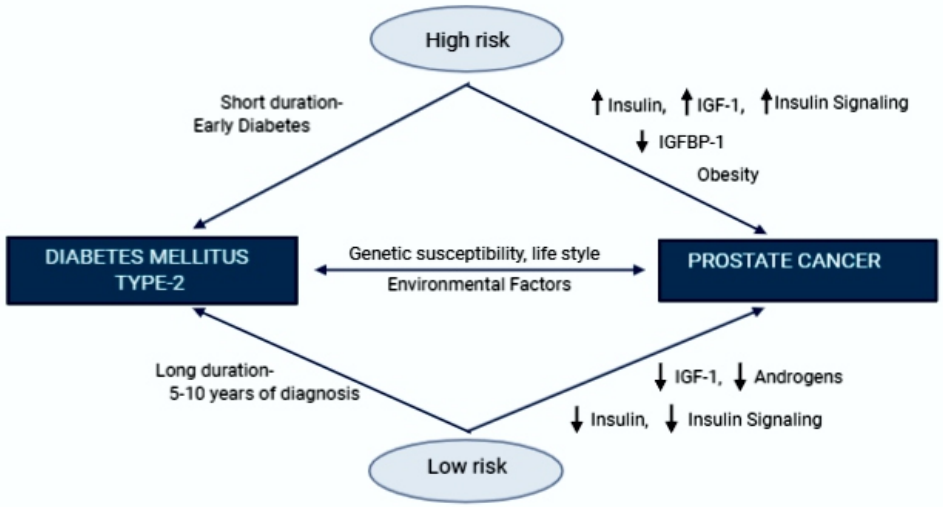

Fig. 1: Mechanism of association of prostate cancer and diabetes. Early diabetes have high risk and long duration diabetes have low risk of PCa development. IGF-1: Insulin-like Growth Factor, IGFBP-1- Insulin-like Growth Factor-1 Binding Protein.

proliferation of PCa as AR is not expressed in highly aggressive or metastatic cell line model of rodent and human but contrary to this belief, however, AR amplification is observed in primary PCa as well as in advancement to hormone sensitive and hormone refractory cancers (32,37). AR gene amplification is contained by one-third of the locally recurrent hormone refractory cancers, which leads to overexpression of the AR mRNA, AR protein and androgen regulated gene, suggesting that amplification of the AR gene permits the regrowth of cancer cells by reactivating AR transcriptional activity during androgen deprivation (38,39). AR is the most common mutated gene and advanced genomic studies revealed that CRPC patients harbor AR gene overexpression (33). Alteration in the AR cistrome of CRPC patients was discovered compared to normal prostate tissue such as enrichment of tumor-specific HoxB13 and FoxA1 motifs near AR binding sites (40).

Insulin/IGF-I signaling up regulates AR in presence of T2DM. Lutz S.Z. *et al.* in his case-control study reported enhanced AR expression and signaling in tumor tissue of diabetic PCa patients. AR expression was also highly associated with Ki-67 which is a higher T-stage cell proliferation marker (34). However, Barbosa-Desongles A. *et al*. reported down regulation of AR mRNA and protein levels with increasing glucose concentration through NF-κB activation which retarded tumor growth and protect against PCa in *in vivo* and *in vitro* experiment using PAC120 mouse model and LNCaP Cell lines respectively (41).

PROSTATE SPECIFIC ANTIGEN EXPRESSION

PSA (also known as Kallikrein-related peptidase 3) is normally secreted by prostate cells as well as by most PCa and major site of PSA gene expression is the prostate. Subsequently expression of PSA gene has become the most widely used sensitive biomarker for the screening, detection and prognosis of PCa (42). However, it shows low accuracy due to high rate of false-negative and false-positive results (43).

Androgens regulates PSA gene expression mediated by AR, through three androgen responsive element (ARE) located in the proximal 6kb of the PSA promoter that contains enhancer elements (32,44). Transcription of PSA gene is enhanced upon binding of AR complex to ARE as it regulates the gene transcription of the specific promoter regions of the PSA gene (45). Low PSA levels were associated with more severe diabetes which may explain the reason behind reduced reported risk of PCa in diabetic men (46). In contrast**,** the raised expression of *KLK3* which is an AR downstream target gene and encodes PSA, was reported with increased tumor content in diabetic men compared to men without diabetes (34).

IGF-1 AND IGF-1R GENE EXPRESSION AND SIGNALING

Experimental studies have reported transformation and proliferation of tumor cells with alterations in IGF functions. Wide range of human cancers, including breast, lung, thyroid, and prostate etc. have overexpressed *IGF-1*, *IGF-2*, and *IGF-1R* genes. Several epidemiological studies also suggested the association of breast, prostate, and colorectal cancer risk with genetic variation in *IGF-1, IGF-1R* and *IGFBP-3* (47). *IGF-1* promotes non-ligand activation of *AR* and AR signalling pathway in patients those are given ADT and contributes to the androgen-independent progression of PCa (2,48). However, the mechanisms through which *IGF1* and other growth factors promotes AR-mediated transcription of PCa cells remain unclear (49). Higher levels of plasma *IGF-1* are linked to higher rates of prostate gland malignancy (50) but no association has been established with androgen refractory prostate cancer (51).

Insulin and IGF's family reactivates AR signaling in androgen deprived environment via Insulin receptor (IR) and IGF1R signaling (2,34). Serum IGFs, like IGF-1 and IGF-2 (to lesser extent) causes proliferation of normal and transformed prostatic cells by stimulating cell cycle progression thorough its mitotic and anti-apoptotic effects mediated by IGF1R (52). IGF-I expression in prostate epithelium of transgenic mice leads to IGFIR activation and spontaneous tumor development in the prostate. Also *in vitro* studies reported promotion of AR transcriptional activity via IGF-I in absence of androgens, suggesting the role of IGF-I in PCa progression from hormone sensitive to hormone refractory stage (51). In contrast, Heni M *et al.* reported significantly low level of IGF-1R in patients with T2DM (22). Cohen D.H. *et al.* demonstrated the presence of type IGF1R but no IGF-II receptors on normal prostate epithelial cells using (125 I)-IGF-I binding studies (53). Ouban A. *et al*. reported strong expression of IGF-1R in 6 out of 11 human cancer tissues (54). The IGF1R appears to be overexpressed in most PCa cell lines but several studies have reported significantly reduced levels as the disease becomes androgen-independent (55).

INSULIN AND INSULIN RECEPTOR GENE EXPRESSION

The direct effect of the IR on prostate tumour tissue has only recently been studied because of the structural and regulatory similarity with the IGF system. However, the role of IGF-1 in development and

progression of cancer has been studied for over 20 years (56,56). A correlation of higher incidence of PCa with raised serum insulin levels and insulin resistance is reported by some recent studies but the understanding of mechanism by which insulin signalling mediates regulation of AR function is lacking (58). Alteration in the level of insulin contributes to the development of tumor as it has strong mitogenic and growth-stimulatory effect on the prostate and other tissues Production of IGFBP-1 and possibly IGFBP-2 is reduced by high circulating insulin levels which further increases the availability of circulating free, bioactive IGF-1 and in addition, increases the production of advance glycation end products, which promotes carcinogenesis (59).

Insulin signalling is associated with PCa as Insulin Receptor Substrate (IRS) -2 is found to be overexpressed in PCa as compared to IRS-1. IRS-1 and IRS-2 was identified as suppressor and positive regulator of metastasis in breast cancer respectively. As insulin, a ligand for IR is evidently raised in T2DM, findings of increased IRS-2 (downstream to IR) in PCa suggests high metastasis risk in diabetic men which further leads to shorter survival time after diagnosis of PCa in patients with T2DM compared to non-diabetics (22). Lutz SZ *et al*. also correlated altered composition of IR or IGF-1R with elevated expression of AR in PCa in diabetic men that also favour the mitogenic isoform (20). Study done by Venkateswaran V. *et al.* on mice model carrying human PCa xenografts showed association of high refined carbohydrates diet with increased tumor development and signalling pathways activation downstream to the IR. LNCaP human PCa cells were injected subcutaneously in athymic mice and were randomly assigned to high carbohydrate – high fat or low carbohydrate – high fat diets (n=20 per group). Mice on the high carbohydrate – high fat diet had increased tumor growth (95% CI = 608-822 mm3; P <.001), significantly increased serum insulin, serum IGF-1 levels and modestly higher IR levels (60).

MASKING OF PROSTATE CANCER BY DIABETES: DETECTION BIAS

The exact mechanism that leads to low PSA levels and thus masking prostate cancer detection is not yet defined as the cause is likely multifactorial. The regulation of cellular production of PSA, standard biomarker for the detection of PCa is also not yet fully

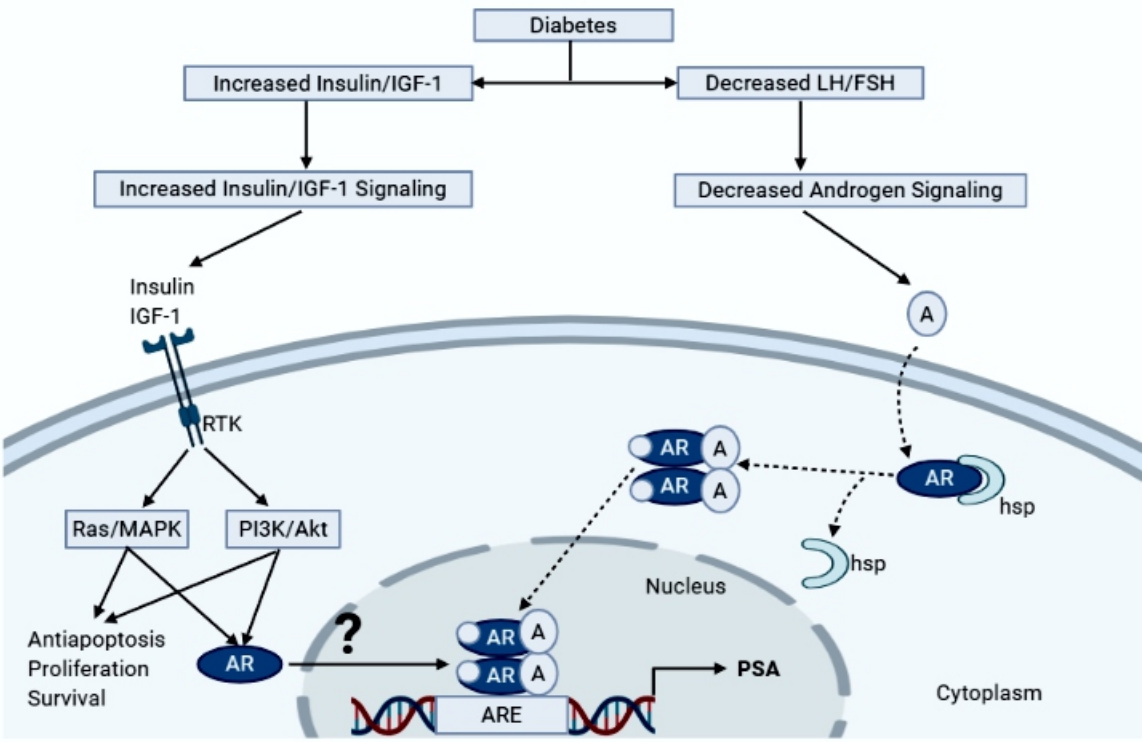

Fig.2 Diabetes leads to hypogonadism due to decrease in LH/FSH secretion which causes decrease testosterone secretion that further leads to decrease AR activation and signaling. However insulin/IGF-1 levels are elevated in diabetics leading to increased RTK signaling which causes activation of AR probably through phosphorylation of AR but the exact mechanism is not elucidated yet. PSA gene expression is mediated by androgens and AR through AREs present in the promoter region of PSA. Decreased androgen levels and AR signaling leads to low PSA levels in diabetics which might cause masking of early detection of PCa as serum PSA level is the standard biomarker for PCa diagnosis. Low PSA levels leads to fewer biopsies. Dotted lines show decreased signaling.

understood. However a possible mechanism is suggested (Figure 2), which consists of conversion of testosterone to DTH, binding to the AR and interacting with ARE located in the promoter region of PSA gene which is also supported by multiple studies reporting decrease PSA levels in men with Benign Prostatic Hyperplasia (BPH) and PCa following ADT (61).

In recent years, studies confirmed that male patients with T2DM are more prone to develop hypogonadism (62). T2DM causes decrease in LH secretions that results in decreased testosterone secretion from the Leydig cells (63). Decrease in the PSA levels was reported with severe forms of diabetes (48) which might be due to low testosterone levels in diabetics leading to low AR signaling and consequently low PSA gene and protein expression, consequently leading to fewer biopsies and causing detection bias by masking of PCa. However an inverse association of PSA with testosterone levels is reported in a a recent study (64). Despite low circulating testosterone levels, AR signalling is maintained by multiple mechanisms that activates AR such as amplification or overexpression by growth factor signalling resulting in increased protein expression but the mechanism is not yet clearly understood (65).

ANTI-DIABETIC DRUGS AND PROSTATE CANCER GROWTH

Several anti-diabetic drugs are responsible for the elevated or reduced risk of PCa in diabetic men (66). Some therapeutic strategies used in diabetes treatment leads to elevated serum insulin levels which includes all insulin-dependent glucose lowering therapies and sulfonylureas, Therefore, glucose lowering therapies independent of insulin might prove to be an improved treatment option for PCa patients to ensure better prognosis (35). One population based cohort study done on association of various anti-diabetic drugs with PSA levels, frequency of PSA testing and detection of PCa showed that inverse association between PCa and diabetes is not mediated by lowering of PSA level by anti-diabetic drugs and thus masking tumor detection but due to detection bias as men on anti-diabetic medication receive fewer biopsies (67).

METFORMIN

Metformin (1,1-dimethylbiguanide), an insulin sensitizer is a cheap and widely used first-line oral medication for treating T2DM. Multiple evidences and epidemiological studies reported reduced cancer risk including PCa and improve cancer prognosis and survival with metformin treatment due to its characteristic property of reducing plasma glucose and insulin concentrations (68). Besides regulating cancer cell proliferation and apoptosis, metformin prevent PCa growth by targeting *c-MYC* oncogene and also significantly inhibited PCa cell migration in vitro as well as in vivo which is a major step in cancer metastasis. Metformin activates AMP activated protein kinase (AMPK) in the liver that in turn represses mammalian target of rapamycin (mTOR) and AR signalling pathways, thus inhibiting PCa growth. However, anticancer properties of metformin and its molecular mechanism of inhibition of PCa cell migration is still unclear. Yu T *et al*. reported reduced levels of SUV39H1, a histone methyltransferase of H3 Lys9, in PCa cells treated with metformin which inhibits their migration by disturbing the integrin-FAK signalling (66,69). Chen X also reported upregulation of pigment epithelium-derived factor (PEDF) expression that inhibits PCa cell proliferation and migration (70).

One retrospective study reported better prognosis and fewer biochemical recurrences (15% vs 8%), metastasis (5% vs 0%) and death (23% vs 10%) in diabetic PCa patients with adjuvant metformin therapy compared to controls not on metformin (71). However a randomized, placebo-controlled study reported no correlation of metformin use with reduced PCa risk. Therefore, the reported reduced risk of PCa in men on metformin might be due to the effect of diabetes and not metformin (72).

INSULIN AND INSULIN SECRETAGOGUES

Evidences from epidemiological studies showed that higher insulin levels may lead to cancer development. Use of insulin and insulin secretagogues might have a vital role in elevating the risk of cancer development in several individuals. Compared to diabetic patients on metformin treatment alone, sulfonylureas and insulin increases cancer development and related mortality risk (5). Zaorsky NG *et al* reported worse outcome and toxicities in prostate cancer patients on Insulin or with unmanaged diabetes (73). In contrast, A cohort study assessing PCa risk with anti-diabetic medication reported decreased risk in men on insulin (89%) or sulfonylurea (11%) compared to diabetic men not on any anti-diabetic medication and no decrease risk in men on metformin (74). Similar findings were also reported in another prospective cohort study with decreased risk of PCa in Insulin users overall (HR 0.49, 95% CI 0.26–0.92) and insulin users with diabetic complications (HR 0.36, 95% CI 0.15–0.87), compared to non-diabetic men (75). Feng X reported no significant association of Insulin use with PCa risk in diabetic patients (HR: 0.80, 95% CI: 0.58–1.12) (76).

THIAZOLIDINEDIONES

Thiazolidinediones (TZDs) or glitazones are insulin-sensitizing peroxisome proliferator–activated receptor (PPARγ) agonists and possess several anticancer activities, such as growth inhibition,

apoptosis induction and cell differentiation due to which they are currently considered a potential target for both chemoprevention and cancer therapy. TZDs do not increase insulin secretion directly or cause hypoglycemia when used alone (77). One cohort study by He XX *et al* reported improved survival of diabetic PCa patients on THZs (HR:0.454, 95% CI:0.213–0.965) (78)

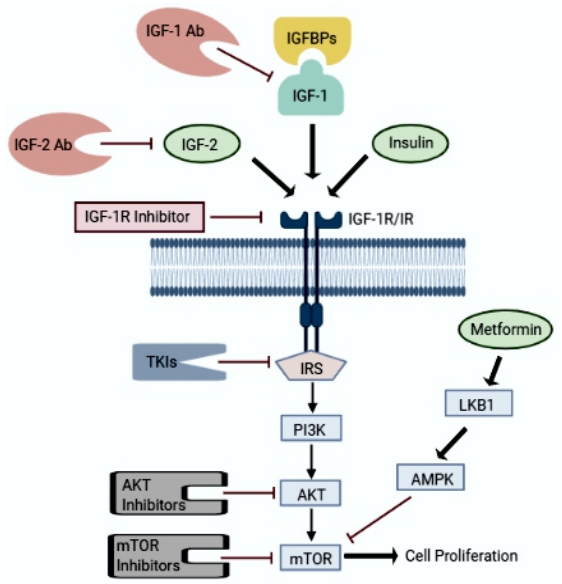

Fig. 3 Anti-cancer therapeutic strategies targeting Insulin and IGF-1 signaling. Monoclonal antibodies directed against IGF-1 and IGF-2 prevents them to bind to IGF-1R. Monoclonal antibodies against IGF-1R prevents interaction of IGF-1R to insulin and IGF-1. Insulin can also bind to IGF-1R and promotes cell proliferation. Inhibitor of tyrosine kinase (TKI) inhibits the activation of receptor and downstream signaling pathway. Metformin also have direct inhibitory effect on cancer cell development and proliferation. It inhibits mTOR by activating AMPK.

PROMISING CANCER THERAPIES

IGF-1 RECEPTOR TARGETED THERAPY

Data from various laboratory, clinical and population based studies suggested the role of IGFs family in different cancers that leads to the development of novel anticancer therapies targeted against IGF signalling pathway (Figure-3). Activity of IGF-1R and its downstream signalling pathway can be inhibited by using different inhibitors which can bind at different steps of the signalling pathway like inhibitors of ligand binding to IGF-1R, inhibitors of IGF-1R expression, inhibitors of tyrosine kinase (TKIs) activity and AKT or mTOR inhibitors (2). Several *in vivo* and *in vitro* studies reported inhibition of PCa cell growth by reducing IGF-1R expression that blocks IGF-1 signalling (52). Various IGF-1R TKIs like Linsitinib, Picropodophyllin, Masoprocol, nordihydroguaiaretic acid showed pre-clinical efficacy but showed disappointing results in clinical trials as they also inhibits metabolic insulin signalling which leads to hyperinsulinemia and dose-limiting hyperglycemia. Pharma companies have also terminated IGF-1R monoclonal antibody programs and only success of Teprotumumab is showing promising outcome. Research are going on to identify predictive biomarkers which proof effectiveness of any targeted therapy (79).

METFORMIN THERAPY

Several studies reported use of metformin in cancer treatment and suggest its role in enhancing the effectiveness of PCa therapies (ADT). Some reported significant reduced PCa cell growth with combined metformin and bicalutamide than either metformin or bicalutamide alone (80). A Multicentre Phase 2 Trial (NCT 01243385) evaluated the effect of metformin treatment on progression-free survival and PSA doubling time in patients with castration-resistant PCa (CRPC) and reported safe use of metformin in non-diabetic patients. Disease stabilization and PSA doubling time prolongation was also found in some patients. Favourable toxicity profile, and positive effect of metformin on metabolic parameters in PCa, recommends the role of metformin as cancer therapeutic (81).

CONCLUSION

There is widespread conflicting literature on association of PCa with T2DM. It is debatable whether T2DM is associated with protection or risk of PCa. Majority of population based studies reported low risk of prostate cancer among diabetics and only few reported increased risk while some studies does not found any significant association between these two diseases. Reports from several biochemical and molecular studies are also controversial as some reported a positive association while some reported negative association.

Possible explanation behind this inverse association is the lower PSA level in diabetic and obese men which leads to fewer biopsies due to potential detection bias and consequently less diagnosis of prostate cancer at an early stage as majority of these studies were published in the PSA era. Activation and overexpression of AR by insulin/IGF-1 signaling, detection of more aggressive tumors, lymph node metastasis and masking of early tumor detection by diabetes may explain the worse prognosis and shorter survival rate in diabetic men suggesting a positive link between PCa and T2DM.

FUTURE RESEARCH DIRECTIONS

- Further larger sample size human studies on association of PCa with diabetes are needed to be done that support increased risk of cancer in diabetics and its mechanism of association.
- Studies examining association of diabetes and obesity with varying grades and stages of PCa are needed to explain the possible link between these diseases and the severity of PCa with co-incidental diabetes which would justify the reason behind the poor outcome of PCa with shorter survival time when diabetes is present.
- Long term follow-up study of influence of various anti-diabetic drugs on cancer risk and their role as cancer therapeutic is needed to better understand their association. Therefore, further investigations is of interest.
- Also studies on biomarkers for early detection of PCa in diabetics is needed.

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