DOI:10.24041/ejmr2019.145

PROSTATE CANCER AND DIABETES LINK: ROLE OF INSULIN AND INSULIN LIKE GROWTH FACTORS

Afreen Khan, Anu Chandra, Abbas Ali Mahdi*, S.N. Sankhwar**

Department of Biochemistry

Era's Lucknow Medical College & Hospital, Sarfarazganj Lucknow, U.P., India-226003

Department of Biochemistry, Department of Urology***

King George's Medical University, Lucknow, U.P., India-226003

Received on : 28-08-2019
Accepted on : 24-10-2019

Address for correspondence
Dr. Anu Chandra
Department of Biochemistry
Era's Lucknow Medical College & Hospital, Lucknow-226003
Email: anuchandra24@gmail.com
Contact no: +91-8172857543

ABSTRACT

Prostate cancer (PCa) and Diabetes are two major, growing health problems that affect millions of men worldwide. PCa is the second most frequently diagnosed malignancy worldwide, especially in developed countries and fifth leading cause of death from cancer in men. The relation between diabetes and prostate cancer risk is complex.T2DM is associated with increased risk of several cancer like cancer of pancreas, colo-rectum, liver, breast and endometrium but protective effect of diabetes mellitus on prostate is yet to be confirmed.Data from previous studies done on association of diabetes with prostate cancer shows conflicting results. Some studies reported a positive association where as some reported negative association between diabetes and prostate cancer.The time risk between PCa and T2DM is uncertain as few studies reported increased risk in the early short term followed by a reduced risk after 5-10 years of diagnosis of diabetes. Diabetes is associated with changes in insulin levels and demand, which tend to be higher in pre- and early diabetic states. These lead to decreased insulin-like growth factor-I (IGF-I) binding protein levels and, consequently, to higher IGF-I, all factors possibly associated with the risk of prostate cancer. Reduced risk of prostate cancer in long-term diabetes may be due to the reduction in Insulin, Insulin-like growth factor-1 (IGF-1) and testosterone levels over time after the diagnosis of diabetes.

KEYWORDS: Prostate cancer, Diabetes Mellitus, Insulin, Insulin-like growth factor-1.

INTRODUCTION

Prostate cancer (PCa) and Diabetes are two major, growing health problems that affect millions of men worldwide (1). PCa is the second most frequently diagnosed malignancy worldwide (2), especially in developed countries (3) and fifth leading cause of death from cancer in men (4). Diabetes, especially Type-2 is also a growing epidemic worldwide and is characterized by insulin resistance, hyperglycemia, hyperinsulinemia and hyperlipidemia (5). Several studies have shown that Type 2- diabetes mellitus (T2DM) significantly associated with increased risk of several cancers and the association between them is of clear importance (6). T2DM is associated with increased risk of several cancer like cancer of pancreas, breast, liver, biliary tract, kidney, esophagus (7-8), colo-rectum and endometrium but T2DM is associated with protection from prostate is yet to be confirmedas there is extensive but conflicting literature on protective effect of T2DM on Pca (9-10).

EPIDEMIOLOGY

Incidence and mortality estimates for PCa are retrived from the GLOBOCANdatabase in 2018reported that there will be almost 1.3 million new casesof prostate cancer and 359,000 associated deaths worldwide in 2018. It is the most frequently diagnosed malignancy among menin over one-half (105 of 185) of the countries of the world**,** remarkably in the Americas, Northern and Western Europe, Australia/New Zealand, and much of Sub-SaharanAfrica. It is the leading cause of cancer death among menin 46 countries, mostly in Sub-Saharan Africa andthe Caribbean (4). As compared to the western population, the prevalence of PCa in India was previously thought to be lessbut with the changing lifestyle and easy access to medical facilities, more cases of prostate cancer are diagnosed and it is being recognised that India is not leading far behind the rate from western countries (11). Estimated incidence, mortality and 5 year prevalence of Prostate Cancer per 100,000 population of India in 2012 is 19,095; 12,231 and 63,818 respectively (12). As per the Indian Council of Medical Research (ICMR), PCa is the second most

common cancer in Indian men with incidence rate of 9-10/100,000 population, which is quite higher than other parts of Africa and Asia but lower than Europe and USA (13).

ETIOLOGY

Relatively littleis known about the etiology of Prostate cancer though being such a common disease (14).

Established risk factors for PCa are:-

Older Age-Prostate Cancer is mainly the disease of the elderly men and most of the cases occurs in men aged 65 years and above (12).

Ethnicity-African-American (13).

Family history/genetics- Genetic factors are estimated to account for 42% of the risk of PCa. A Swedish study reported that family history is particularly significant in men whose one or more first-degree relatives were diagnosed with PCa at a relatively young age. The risk increases with decreasing age at PCa diagnosis of a first-degree relative (14).

PROSTATE CANCER AND DIABETES

The relation between PCa and T2DM risk is complex **[15]**. There is bidirectional association between androgens and diabetes in men in which low testosterone leads to diabetes and hyperglycemia leads to hypogonadism **[16].**T2DM is characterized by both hyperinsulinemia and hyperglycemia and has been thought to promote carcinigenesis in many epidemiological studies. Patients of diabetes experience a greater risk of developing site-specific cancers like colorectal, bladder, liver, endometrial, pancreatic and postmenopausal breast cancer compared with non-diabetic individuals. On the contrary, a history of T2DM has been related to a decreased risk of PCa (7, 17).

Some recently published studies investigated the possible association between T2DM and PCa in Asian countries but the finding from these studies were not confirmatory (18, 19). The time risk between PCa and T2DM is uncertain as few studies reported increased risk in the early-onset diabetes, highest risk being observed in 1-3 years of diagnosis.A reduced risk is observed in long-standing diabetesafter 5-10 years of diagnosis (15, 20).The possible explanation for the reduced risk in long-term diabetes may be reduced levels of Insulin, Insulin-like growth factor-1 (IGF-1) and testosterone over time after the diagnosis of diabetes. Also, reduced risk of PCa in diabetic men could also be due to involvement of medications for diabetes (21).

Large number of solid tumor cells adhere to Warburg effect but PCa has a significantly different phenotype. Recently there has been increasing interest in the role of metabolic factors such as, glucose metabolism, in the aetiology and pathogenesis of PCa. This is because life expectancy is increasing globally, but also because of global increase in the prevalence of diabetes, predicted to increase by 69% in developed countries over the next 20 years. AsPCa cells do not have the increased glucose uptake, therefore, the Warburg effect does not hold consistent in the pathogenesis of PCa. It is only in the late stage that PCa will have a large glucose uptake and begin showing the Warburg effect due to several mutation events**.** The association of diabetes with increased PCa mortality was driven by Obesity. In contrast, the protective effect of long-lasting diabetes may be explained by associated beta-cell exhaustion with insulin depletion (1, 22). A study done on mice model reported an increased level of insulin and IGF-1 and insulin receptor and also increase in AKT activation and rate of cell proliferation in neoplastic tissues in mice on a high carbohydrate diet compared to low carbohydrate diet (23). Another study reported higher risk of PCa, including high-grade cancer (Gleason score >7) in patients with poor glycemic control of Diabetes (24).

PROSTATE SPECIFIC ANTIGEN:

Prostate Specific Antigen (PSA), also called as Kallikrein-related peptidase 3,is a serine protease that is part of the kallikrein superfamily produced predominantly by the prostate and primarily by secretory luminal epithelial cells therein.S erum PSA is a most commonly used clinical biomarker for PCa (25).T2DM has also been associated with decreased level of PSA thus,lower rate of PCa diabetic patients may be due to decreasedserum PSA levels which leads to fewer biopsies and less detection of the disease in these men (26).Obesity also decreases serum PSA level due to hemodilutionand its co-existence with diabetes further impairsPCa detection (27). PSA is regulated by androgens in the prostate and the cellular effects of androgens are mediated by the Androgen Receptor (AR) (25).

ANDROGENAND ANDROGEN RECEPTOR SIGNALLING

Androgens are vital for development and functioning of normal prostate as well as for prostate cancer growth and progression (1). Androgens are considered the primary growth factors for thedifferentiation and development of prostate epithelial cells. AR dimerizes upon binding with Androgens and enters into the nucleus, where it specifically binds to the Androgen Response Elements (AREs), thus initiating the transcription of AR target genes. Androgen signaling is one of the vital drivers for prostate cell growth and development, thus making Androgen Deprivation

Therapy (ADT) as current standard treatment for PCa yielding 5 years survival rate. However, other than androgens, growth factors like insulin, IGFs family also play an important role in the Prostate cell growth and carcinogenesis by activating receptor's Tyrosine Kinase activity (17, 28-29).

INSULIN AND IGF-1 SIGNALLING IN PROSTATE CANCER

Diabetes might decrease the risk of PCa, as men with T2DM have lower androgen levels , which, have been directly associated with PCa risk. On the other hand, T2DM is related with changes in insulin levels and demand, which tend to be greater in pre- and early diabetic states. These lead to lowered insulin-like growth factor-I binding protein (IGF-1BP) levels which further leads to higher IGF-I, all factors possibly related with higher risk of malignancy in prostate gland (15,30). However, the circulating level of insulin declines as the diabetes progresses which also explains the reduced risk in long-duration diabetes (31). Elevated levels of serum insulin, homeostasis model assessment-insulin resistance (HOMA-IR) or C-peptide are indicators of insulin resistance in those with diabetes and have been reported to be risk factors for development of PCa. IGF-1 is also a vital growth factor in PCa and shares a part of the downstream signalling pathways of insulin. Approximately 42 meta-analysis reported increased IGF-1 level in blood with increased risk of PCa (32). Baseline insulin levels have also been shown to be the most significant predictor of PCa at time of PCa diagnosis which strongly suggests that insulin is a key factor in the PCa progression associated with metabolic dysfunction and also regulates the expression of novel gene transcrips in tumor tissues. Expression of Insulin Receptor (INSR), IGF-1R and hybrid INSR/IGF-1R is upregulated which further promotes insulin-driven cancer survival pathways in PCa (33)

Lutz SZ et. al, 2017reported overexpression of androgen receptor in tumor tissue with strengthened cell proliferationand higher tumor stage of men with diabetes. Possible underlying mechanisms for this AR overexpression could include insulin or IGF-1 signalling as they are known to activate AR (28).

Association between serum Testosterone levels and grading of Prostate Cancer has come under researchsince the last decade. Although high levels of Serum Testosterone is associated with higher risk of PCa but these levels showed negative association with grading of tumor. Also very little is known about the affect of serum IGF-1 levels on bioavailability of testosterone (34). Other Previous findings also reported reduced serum testosterone levels in men with diabetes (28).

IGF-1 RECEPTOR SIGNALLING

IGF-1 and to lesser extent IGF-2 promotes cell proliferation of normal as well as cancerous cells by stimulating cell cycle progression thorough its mitotic and antiapoptotic effects.Specific cell-membrane receptor IGF-1 receptor (IGF-1R) mediatesthe actions of IGF-1 on cell proliferation and apoptosis. Binding of IGF 1 to IGF1R activates the receptor tyrokinase activity, which initiates a cascade of reactions among a number of molecules involved in the signal transduction pathway. Two different main signal transduction pathways have been identified. One pathway activates Ras protein, Raf protein and mitogen-activated protein kinase (MAPK) while the other pathway activates phosphatidylinositol-3-kinase (PIK3), AKT (or protein kinase B). mTOR (mammalian target of rapamycin) and S6 kinase (S6K) (Fig 1). IGF-1 also promotes non-ligand activation of Androgen Receptor in a low androgen environment (35), therefore playing a vital role in the androgen-independent progression of prostate cancer (17) which explains mechanism for AR overexpression by activating AR signalling pathways in patients those are given ADT (28). However, the mechanisms behind AR-mediated transcription of PCa cells by IGF1 and other growth factors remain unclear (37). Several IGF-1R inhibitory reagents have been developed for potential cancer therapy that target IGF-1R ligands, inhibits of IGF-1 tyrokinase activity or down-regulates IGF-1R expression. Multiple pre-clinical and several clinical studies reported limited effect of monotherapy with an IGF-IR antagonist as compared to combined therapy of an IGF-IR antagonist with ADT (38). Elevated levels of IGF-1R are associated with invasion, aggressiveness cancer, and poorer prognosis (39).

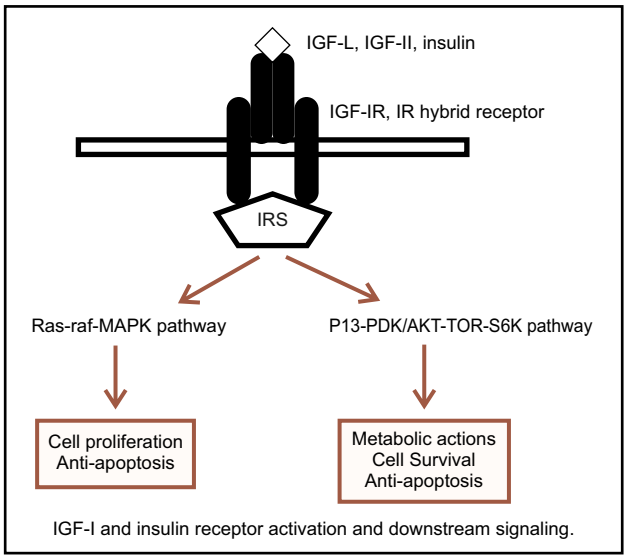

Fig 1: Lima GAB et.al, 2009 (13)

INSULIN RECEPTOR SIGNALLING

An association of high serum insulin levels and insulin resistance with an increased incidenceof PCais reported by some recent studies but not all.The knowledge of mechanism behind insulin signalling mediated regulation of AR function is lacking (35, 38)

Insulin has strong mitogenic and growth-stimulatory effect on the prostate and other tissues and alteration in its level can contribute to the development of tumor. The high level of circulating insulin reduces thehepatic production of IGF binding proteins-1 (IGFBP-1) and possibly IGFBP-2, which then increases the level of circulating free, bioactive IGF-1 (39) and also increases the production of advance glycation end products, which promotes carcinogenesis (13)

Insulin signalling starts at the level of IRwhen ligand binds to the receptor. IR belongs to a family of receptor tyrosine kinases which also includesthe receptor for IGF-1R. IR has two isoforms, IR-A and IR-B.Ligand binding to the IR activate numerous downstream pathways including phosphatidylinositol 3-kinase (PI3K)/Akt and Ras/MAPK pathways with many well-characterised downstream effects including increased glucose metabolism, inhibition of apoptosis and stimulation of cell proliferation (via mTOR pathway). While the role of IGF-1 in development and progression of cancer has been studied for over 20 years, the effect of the IR directly on prostate tumour tissue has only recently been reported. Study results show that increased INSR expression correlates with increasing Gleason grade and CRPC providing further evidence that insulin and insulin receptor signalling may have a critical role in progression of advanced prostate cancer (40).

CONCLUSION

Data from previous studies done on association of diabetes with PCa shows conflicting results. Some studies reported a positive association where as some reported negative association between diabetes and PCa. Further studies in both animal and human model is needed to explain this complicated relationship between diabetes and prostate cancer.

REFERENCES

1. Grossmann M, Wittert G. Androgens, diabetes and prostate cancer. Endocrine-Related Cancer. 2012; 19: F47-F62.
2. Choi JB, moon HW, Park YH, et al. The impact of diabetes on the risk of prostate cancer development according to body mass index: A 10-year nationwide cohort study. J cancer. 2016; 7(14): 2061-2066.
3. Long XJ, Lin S, Sun YN, et al. Diabetes mellitus and prostate cancer risk in asian countries: a meta-analysis. Asian Pacific J Cancer Prev. 2012; 13: 4097-4100.
4. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
5. Roith DL, Scheinman EL, Worms KB. The role of Insulin and Insulin-like growth factors in the decreased risk of cancer in diabetes. RMMJ. 2011; 2(2): E0043.
6. Mc Growder DA, Jackson LA , Crawford TV. Prostate cancer and metabolic syndrome: is there a link? . Asian Pac J Cancer Prev. 2012; 13: 1-13.
7. Noto H, Goto A, Tsujimoto T, et al. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoSONE. 2012; 7(3): e33411.
8. Kasper JS, Liu Y, Giovannucci E. Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. Int J Cancer. 2009;124(6):13981403.
9. Heni M, Hennenlotter J, Scharpf M, et al. Insulin receptor isoforms a and b as well as insulin receptor substrates-1 and -2 are differentially expressed in prostate cancer. PLoS ONE. 2012; 7(12): e50953.
10. Frayling TM, Colhoun H, Florez JC. A genetic link between type 2 diabetes and prostate cancer. Diabetologia. 2008; 51:1757-1760.
11. Jain S, Saxena S, kumar A. Epidemiology of prostate cancer in India. Meta Gene. 2014; 2: 596-605.
12. Sharma G, Sharma S, Sehgal P. Emerging trends in epidemiology of breast, prostate and gall bladder cancer. International Journal of Pharma Sciences and Research. 2014;5(7): 329-337.
13. Kachhawa P, Kachhawa K, Agaewal D, et al. A study of prostate cancer and its association with dyslipidemia, elevate dinsulin levels in blood, and relative insulin resistance prevalent in south east asia. Journal of Integrative Nephrology and andrology. 2018;5(1): 24-31.
14. Lange EM, Johnson AM, Wang Y, et al. Genome-wide association scan for variants associated with early-onset prostate cancer. PLoS ONE 2014; 9(4):e93436.
15. Tavani A, Gallus S, Bertuzzi M, et al. Diabetes mellitus and the risk of prostate cancer in italy. European Urology. 2005; 47:313–317.

16. Navarro G, Allard C, Xu W, et al. The role of androgens in metabolism, obesity, and diabetes in males and females. Obesity. 2015; 23: 713-719.
17. Lima GAB, Correa LL, Gabrich R, Miranda LCD, Gadelha MR. IGF-1, insulin and Prostate Cancer. Arq Bras Endocrinol Metab. 2009;53: 969-975
18. Hsieh MC, Lee TC, Cheng SM, et al. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the taiwanese. Exp Diabetes Res. 2012; 2012:413782.
19. Lee MY, Lin KD, Hsiao PJ, et al. The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metabolism. 2012;61: 242-249.
20. Tseng CH. Diabetes and risk of prostate cancer. Diabetes Care. 2011; 34:616–621
21. Meyer TE, Boerwinkle E, Morrison AC, et al. Diabetes genes and prostate cancer in the Atherosclerosis Riskin Communities study. Cancer Epidemiol Biomarkers Prev. 2010; 19(2): 558.
22. Eidelman E, Twum-Ampofo J, Ansari J et al. The Metabolic Phenotype of Prostate Cancer. Front. Oncol. 2017; 7:131.
23. Venkateswaran V, Haddad AQ, Fleshner NE et al. Association of Diet-Induced Hyperinsulinemia WithAccelerated Growth of Prostate Cancer (LNCaP) Xenografts. J Natl Cancer Inst. 2007; 99: 1793 -1800
24. Park J, Cho SY, Lee YJ, et al. Poor Glycemic Control of Diabetes Mellitus Is Associated with Higher Risk of Prostate Cancer Detectionin a Biopsy Population. PLoS ONE. 2014;9(9):e104789.
25. Lai J, Kedda MA, Hinze K, et al. PSA/KLK3 AREI promoter polymorphism alters androgen receptor binding and is associated with prostate cancer susceptibility. Carcinogenesis. 2007; 28(5):1032-1039.
26. Cohen DH, Roith DL. Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. Endocrine-Related Cancer. 2012: 19: F27-F45.
27. WU C, Moreira DM, Gerber L, et al. Diabetes and prostate cancer risk in the reduce trial. Prostate Cancer and Prostatic Disease. 2011; 14: 326-331
28. Lutz SZ, Hennenlotter J, Scharpf MO, et al. Androgen receptor overexpression in prostatecancer in type 2 diabetes. Molecular Metabolism. 2018; 8: 158-166.
29. Wang F, Koul HK. Androgen receptor (AR) cistrome in prostatedifferentiation and cancer progression. Am J Clin Exp Urol. 2017;5(3):18-24.
30. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma Insulin-Like Growth Factor–I and Prostate Cancer Risk: A Prospective Study. Science. 1998; 279(5350): 563-566
31. Bansal D, Bhansali A, Undela K, et al. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. Prostate Cancer and Prostatic Disease. 2013; 16:151-158.
32. Yanase T, Kawanami T, Tanaka M, et al. Impact of metabolic disorders on prostate cancer growth: Androgen and Insulin resistance perspectives. Reprod Med Biol. 2017; 16(3): 252-257.
33. Gunter JH, Lubik AA, McKenzie I, et al. The Interactions between Insulin and Androgens inProgression to Castrate-Resistant Prostate Cancer.Advances in Urology. 2012;2012:11.
34. Kim J, Kim JW, Kim JK, et al. Association between serum levels of insulin-like growth factor01, bioavailable testosterone, and pathologic Gleason score. Cancer Medicine. 2018;7: 4170-4180.
35. Fan WQ, Yanase T, Morinaga H, et al. Insulin-like growth factor 1/insulin signaling activates androgen signaling through direct interactions of foxo1with androgen receptor. The Journal of Biological Chemistry. 2007; 282(10): 7329-7338.
36. Wu J, Yu E. Insulin-like growth factor receptor-1 (IGF-IR) as a target for prostate cancer therapy. Cancer Metastasis Rev. 2014;33:607-617.
37. Zingales V, Distefano A, Raffaele M, et al. Metformin: A Bridge between Diabetes and Prostate Cancer. Front. Oncol. 2017; 7:243.
38. Fall K, Garmo H, Gudbjornsdottir S, et al. Diabetes Mellitus and Prostate Cancer Risk; A Nationwide Case–Control Study within PCBaSe Sweden.Cancer Epidemiol Biomarkers Prev. 2013;22:1102-1109.
39. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and Cancer: A Consensus Report. CA Cancer J Clin. 2010; 60: 207-221.
40. Gunter JH, Sarkar PL, Lubik AA, et al. New players for Advanced Prostate Cancer and the Rationalisation of Insulin-Sensitising Medicstion. Int J Cell Biol. 2013;2013:13.

How to cite this article : Khan A., Chandra A., Mahdi A.A., Sankhwar S.N. Prostate Cancer And Diabetes Link: Role Of Insulin And Insulin Like Growth Factors. Era J. Med. Res. 2019; 6(2): 147-151.