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Research Article

Diabetes Mellitus and Carcinoma of Prostate Gland: Review and Update

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Abstract

It has been pointed out that the global incidence of carcinoma of prostate gland is higher than the incidence of many other types of carcinomas that afflict human beings. Carcinoma of prostate gland is regarded as the second commonest cancer which afflicts men after carcinoma of the long and carcinoma of the prostate gland does constitute approximately 7% to 15% of newly diagnosed malignancies that afflict men. It has been noted that factors including age of the patient, race of the patient, family history of the patient as well as inherited changes in some genes are among the risk factors for the development of carcinoma of prostate gland. Furthermore, advanced stage of the prostate cancer, stage, high level of serum prostate specific antigen (PSA) at clinical initial manifestation, high Gleason score of the prostate cancer, lympho-vascular invasion of carcinoma of prostate gland, perineural invasion of the carcinoma of prostate gland, high proliferation index and positive resection margins of the carcinoma of prostate gland constitute unfavourable features for prostate cancer-specific sequelae. It is known in every country in the world that Diabetes Mellitus represents a clinical entity that afflicts millions of individuals all over the world the developed as well as developing countries. Results that had been reported from some epidemiological research, had documented diabetes mellitus is correlated with increased risk for the development of certain types of cancer. Malignant tumours of the breast, colon, rectum, endometrium, liver, pancreas and urinary bladder had been documented to be among these malignant tumours. On the contrary, a number of publications from various parts of the world had iterated that men who had been diagnosed as having diabetes mellitus do have a reduced risk for the development of carcinoma of prostate gland. Nevertheless, there is also some reported documentation in support of the association of diabetes mellitus with increased risk for the development of aggressive carcinoma of prostate gland. There had been conflicting reports regarding the association of diabetes mellitus and carcinoma of prostate gland. Raised insulin to promote proliferation of tumour, increased gene expression of androgen receptor and its substrates in the pathway, higher insulin receptor A/B ratio leading to production of mitogenic variants and decreased amount of oestrogen receptor ligands which inhibit androgen signalling, had been conjectured to be the underlying factors. Even though some data had been published to support the positive relation between the presence of diabetes mellitus and increased death from carcinoma of the prostate gland, some data do not support this postulate. Considering the fact that there is no global consensus opinion regarding a definite association between diabetes mellitus and increased risk or decreased risk for the development of prostate cancer, it is important for all clinicians in every part of the world read in detail all the amalgamation of articles that had been reported on the link between diabetes mellitus with a reduced risk or high risk for the development of prostate cancer in order to quickly establish a large scale global prospective study related to the association between diabetes mellitus and prostate cancer. It is also important for a large multi-centre global trial to investigate suggestions that treatment of diabetes mellitus with Metformin does reduce the risk for the development of prostate cancer as well as reducing the prognosis of treated prostate cancer in comparison with treatment of diabetes mellitus with other types of anti-diabetic medicaments.

Keywords: diabetes mellitus; carcinoma of prostate gland; incidence; prognosis; metformin

Introduction

It has been iterated that the prevalence of diabetes mellitus (DM) through out the world has been undergoing a rapid reported increase because population ageing, urbanization, as well as an because of life style changes. [1] It has been pointed out thar the number of individuals who are afflicted by diabetes mellitus (DM) globally had more than doubled over three decades preceding 2013. [1-3]

It had been iterated that diabetes mellitus (DM) had been noted to be associated with an increased-risk for the development of many carcinomas that afflict human beings some of which had been documented to include: (a) The pancreas [1,4], (b) biliary tract [1,36], (c) kidney [1,22], (d) endometrium [1,30], colon [1,51], and the thyroid gland [1,25]. Nevertheless, a meta-analysis had been published which had included 45 published studies by Bansal et al. [1,2] in 2012, which had concluded from a review of reported data on diabetes mellitus and prostate cancer in human beings that individual patients who had been afflicted by diabetes mellitus (DM) have a statistically significant decrease of fourteen (14%) with regard to the risk for the development of carcinoma of prostate gland. It has been documented that different grades and different stages of prostate cancer may entail utilization of different management options and the prognosis ensuing treatment of prostate would tend to be related to the different grades and stages of human prostate cancer. [2] It had been pointed out that previous studies on the association between diabetes mellitus (DM) and prostate cancer in human beings had reported controversial findings about the effect of diabetes mellitus (DM) upon prostate cancer (PCa) of different grades or stages. Considering the conflicting reports on the association and effect on carcinoma of human prostate gland by diabetes mellitus, the ensuing article has revisited the association and effect of diabetes mellitus (DM) on prostate cancer (PCa). The article has been divided into two parts: (A) Overview of Diabetes Mellitus which has discussed miscellaneous general aspects of diabetes mellitus and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, and Studies Related to Diabetes Mellitus and Prostate Cancer.

Aim

To review and update the literature related to the association between diabetes mellitus and carcinoma of human prostate gland.

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Diabetes Mellitus and Prostate Cancer; Diabetes Mellitus and Carcinoma of Prostate gland; Diabetes Mellitus and Prostatic Carcinoma; Prostatic Carcinoma and Diabetes Mellitus. Forty-one (41) references were identified which were used in writing the article which has been divided into two parts: (A) Overview of Diabetes Mellitus which has discussed miscellaneous general aspects of diabetes mellitus and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, and Studies Related to Diabetes Mellitus and Prostate Cancer.

Results

[A] Overview

Definition / general statement [5]

- It has been explained that diabetes mellitus (DM) is a chronic disorder of carbohydrate, fat and protein metabolism due to defective or deficient insulin secretory response [6]

Epidemiology [5]

- It has been documented that diabetes mellitus afflicts 3% of world population, 26 million within the United States of America but only 75% of cases of diabetes mellitus are clinically diagnosed [5]
- It has been stated that diabetes mellitus was the 7th leading cause of death in 2007 and that diabetes mellitus (DM) was the underlying cause on 71,382 death certificates in the United States of America in 2007. [7]
- It has been documented that the lifetime risk for the development of diabetes mellitus is: for type 1 diabetes mellitus 0.5%, and for type 2 diabetes mellitus 5%. [5]
- It has been pointed out that many variations of diabetes exist and all variations of diabetes mellitus (DM) manifest with hyperglycaemia. [5]

Aetiology [5]

- It has been iterated that diabetes mellitus does develop pursuant to the destruction of islets due to drugs including: steroids, thiazides, pentamidine; hemochromatosis (which is referred to as bronze diabetes due to hemosiderin deposition within the pancreas; and hereditary ceruloplasmin deficiency [8]; infections including: congenital rubella, CMV, coxsackievirus; [9] enteroviruses; [10], pancreatitis, surgery, tumours, endocrinopathies (including: pituitary, adrenal, pregnancy) or idiopathic

Type 1 Diabetes Mellitus [5]

- It has been explained that Type 1 Diabetes Mellitus is a chronic disease of carbohydrate, fat and protein metabolism due to reduction in beta cell mass causing severe, absolute lack of insulin.
- It has been iterated that Type 1 Diabetes Mellitus constitutes 10% of all cases of diabetes mellitus.
- It has been explained if patients who are afflicted by Type 1 Diabetes Mellitus are not treated with insulin, the patients would develop diabetic ketoacidosis (DKA), coma and death

Aetiology of Type 1 Diabetes Mellitus. [5]

- It has been iterated that Type 1 Diabetes Mellitus has been presumed to have an autoimmune cause for islet cell destruction; however, the precise aetiology has not been clarified [5,13]
- It has been iterated that even though Type 1 Diabetes Mellitus does afflict individuals all over the world, Type 1 Diabetes Mellitus usually has tended to afflict individuals of Northern European descent. [5]
- It has been documented that there is a 70% concordance of Type 1 Diabetes Mellitus in identical twins, as well as that type 1 Diabetes Mellitus is HLA-D linked
- It has been explained that genetic predisposition may affect immune responsiveness to a beta cell autoantigen or method of presentation to T cells. [5]

Viruses and IDDM in Type 1 Diabetes Mellitus: [5]

- It has been iterated that viruses might damage beta cells, thus exposing antigens which trigger an autoimmune response in cases of type 1 diabetes mellitus. [5]

- It has been explained that type 1 Diabetes Mellitus may develop following molecular mimicry in which immune response develops against shared amino acid sequences): GAD and Coxsackie B4 virus share a six amino acid sequence. [5]
- It had also been iterated that Retrovirus might serve as a superantigen for the development of type 1 diabetes mellitus. [5]

Autoimmune aspects of type 1 diabetes mellitus:

Some summations made related to the autoimmune aspects of type 1 diabetes mellitus include the ensuing: [5]

- Islet cell autoantibodies have tended to be present in 70% upon pathology examination of specimens of pancreas in cases of type 1 diabetes mellitus; also, there tends to be presence of CD8+ T cell infiltrate within islets upon immunohistochemistry staining studies of the pancreas in cases of type 1 diabetes mellitus. [5]
- It has been documented that the antigens that are found in cases of type 1 diabetes mellitus include: glutamic acid decarboxylase (GAD), islet autoantigen 2, insulin associated antibody, and gangliosides. [5]
- It has been explained that GAD antibodies precede clinical manifesting symptoms, and that GAD antibodies tend to be present in majority of newly diagnosed patients and 80% of first-degree relatives of patients who are afflicted by type 1 diabetes mellitus. [5]
- It had also been iterated that GAD antibody also causes stiff man syndrome, whose patients quite often confirm having a history of IDDM. [5]
- It has been documented that many patients who have IDDM also have antithyroid peroxidase, anti-parietal cell and anti-adrenocortical antibodies. [5]
- It has been pointed out that some patients who have NIDDM also have autoantibodies but no other features of IDDM. [5]
- It has been iterated that type 1 diabetes mellitus usually tends to be a chronic disease lasting over a number of years. [5]
- It has been iterated that type 1 diabetes mellitus does manifest as clinical disease when 90% of islet cells are destroyed. [5]

Clinical features of type 1 diabetes mellitus. [5]

- It has been iterated that the usual onset of type 1 diabetes mellitus is at an age that is less than (<) 20 years, and at onset of the disease the patients do have normal weight, unlike most individuals who are afflicted by non-insulin dependent diabetes mellitus (NIDDM). [5]
- It has been pointed out that the manifestation of type 1 diabetes mellitus is typified by PPP (which includes polyuria, polydipsia, polyphagia) and diabetic ketoacidosis (DKA). [5]
- It has been documented that polyphagia which is combined with weight **loss** is specific for IDDM; type 2 diabetes mellitus patients rarely have either. [5]
- It has been explained that the severe fasting hypoglycaemia that occurs in type 1 diabetes mellitus is due to cessation of glycogen storage in fat and muscle. [5]
- It has been explained that Glycosaemia causes glycosuria with depletion of water and electrolytes. [5]
- It has been iterated that in cases of type 1 diabetes mellitus, there tends to be also: low / absent plasma insulin, high plasma glucagon, unstable glucose tolerance (very sensitive to changes in insulin, diet, exercise, infection, stress), presence of free fatty acids (due to breakdown of adipose stores), which produces ketone bodies (acetoacetic acid and beta hydroxybutyric acid). [5]
- It has been pointed out that a patient who is afflicted by type 1 Diabetes Mellitus, might develop hyperosmotic nonketotic coma - dehydration due to hyperglycaemic diuresis with failure to drink enough fluids to compensate, often in an elderly person with diabetes and stroke / infection. [5]
- It has been documented that there is a scenario which is referred to as “Dead in bed syndrome”: which refers to sudden death in young people who are afflicted by type 1 diabetes, and the cause of this syndrome is not known [5] [14]

Type 2 diabetes mellitus [Non-Insulin Dependent Diabetes Mellitus (NIDDM)] [5]

- It has been pointed out that type 2 diabetes mellitus is also referred to as adult onset, non-insulin dependent diabetes mellitus / NIDDM, type 2. [5]
- It has been iterated that type 2 diabetes mellitus does constitute 80% to- 90% of cases of diabetes mellitus. [5,15]
- It has been documented that type 2 diabetes mellitus usually manifests in patients who are more than (>)30 years old, and who are obese (80% of cases, abdominal obesity more important than subcutaneous obesity), normal or increased blood insulin, rare diabetic ketoacidosis, no anti-islet antibodies. [5]

Pathophysiology of type 2 diabetes mellitus

Early Phase of type 2 diabetes mellitus: [5]

- It has been iterated that during the early phase of type 2 diabetes mellitus, there tends to be normal insulin secretion and plasma levels of insulin but there tends to be loss of pulsatile, oscillating pattern of secretion of insulin. [5]

- It has also been documented that during the early phase of type 2 diabetes mellitus, there is also, loss of rapid first phase of insulin secretion triggered by glucose. [5]
- It has been pointed out that during the early phase of type 2 diabetes mellitus NO insulinitis is present. [5]

Later Phase of type 2 diabetes mellitus: [5]

The ensuing summations had been made related to the later phase of type 2 diabetes mellitus: [5]

- During the later phase of type 2 diabetes mellitus there tends to be mild / moderate insulin deficiency, which may be due to beta cell damage. [5]
- It had been explained that during the later phase of diabetes mellitus, Beta cells might be "exhausted" as a result of chronic hyperglycaemia and persistent beta cell. [5] stimulation

Amylin:

- It has been iterated that 37 amino acid-peptide is normally produced by beta cells, packaged and co-secreted with insulin. [5]
- It had also been explained that in type 2 diabetes mellitus (in NIDDM) patients, Amylin tends to accumulate outside beta cells and resembles amyloid. [5]

Clinical features of type 2 diabetes mellitus [5]

- It has been pointed out that in type 2 diabetes mellitus, there is a 90%+ concordance in twins, which is apparently due to multiple genetic polymorphisms (no HLA association). [5]
- It has been iterated that type 2 diabetes mellitus is due to insulin resistance which tends to be associated with obesity and pregnancy; or to derangement in beta cell secretion of insulin. [5]
- It has been documented that type 2 diabetes mellitus tends to be associated with amyloid deposits within islets (amyloid associated with basement membrane heparan sulfate proteoglycan) [5,16] and pituitary gland. [5,17]

Maturity onset diabetes mellitus of the young [5]

- It has been documented that maturity onset diabetes mellitus of the young constitutes 1% to- 2% of all cases of diabetes mellitus. [5.18]
- It has also been iterated that maturity onset diabetes mellitus of the young is also referred to as monogenic diabetes. [5,9]
- It has been iterated that maturity onset diabetes mellitus of the young is a type 2 diabetes-like condition which occurs in more than two (2+) generations, with autosomal dominant inheritance [5,20]
- It has been stated that maturity onset diabetes mellitus of the young is an autosomal dominant entity but not a single entity and that mutations had been in 9 genes identified to date. [5]
    - It has been iterated that the common genes that are affected in maturity onset diabetes mellitus of the young are hepatic nuclear factor 1 or 4 alpha, glucokinase. [5]
    - It has been documented that the onset of maturity onset diabetes mellitus of the young is before age 25, and this tends to be associated with normal weight, and mild hypoglycaemia. [5]
    - It has been pointed out that in cases of maturity onset diabetes mellitus of the young, no GAD antibodies and found, and there tends to be no insulin resistance, and no beta cell loss but impaired beta cell function. [5]

Clinical complications of diabetes mellitus

General Complications of Diabetes Mellitus

Some of the general complications of diabetes mellitus had been summated to include the ensuing: [5]

- The main complications of diabetes mellitus include: [5]
    - ❖ microangiopathy,
    - ❖ retinopathy,
    - ❖ nephropathy,
    - ❖ neuropathy - all due to hyperglycaemia
- Kidneys that are transplanted into diabetic patients develop nephropathy within 3 years to 5 years but kidneys from diabetic patients transplanted into normal patients do have remission of nephropathy. [5]
- It has been noted that strict control of diabetes mellitus does delay the progression of microvascular complications of diabetes mellitus. [5]
- It has been iterated that the complications of diabetes mellitus tend to be due to nonenzymatic glycosylation and disturbances in polyol pathways. [5]

Nonenzymatic glycosylation

In diabetes mellitus, non-enzymatic glycosylation had been summarized as follows: [5]

- Glucose + protein => Schiff base (protein - NH = CH (CHOH)4-CH2OH) => Amadori product [5]

- (protein - NH-CH2-C = 0-(CHOH)3-CH2OH) => protein - protein cross linking via N-C-N bonding [5]
- Early reactions are reversible and related to HbA1c level [5]
- Advanced glycosylation end products (AGE) are not reversible [5]
- AGE traps LDL in blood vessels, enhances cholesterol deposition, accelerating atherosclerosis [5]
- AGE inhibition antagonizes diabetic complications in experimental models [5]

Vascular complications

Summations had been made related to the vascular complications of diabetes mellitus as follows: [5]

- The relative risk for the development of vascular complications in diabetes mellitus is 100:1 [5]
- Accelerated atherosclerosis in aorta and large / medium sized vessels does develop. [5]
- Myocardial infarction is the commonest cause of death, in which there is no gender preference [5]
- Gangrene of lower extremities does afflict patients who have diabetes mellitus. [5]
- Microscopic description of the vascular lesions: [5]
    - ❖ Hyaline arteriolosclerosis tends to develop associated with hypertension, and this tends to be more common / severe in diabetes but not specific
    - ❖ Amorphous hyaline thickening within arteriolar walls [5]
    - ❖ The vascular complication lesions are related to the severity of disease and hypertension [5]
    - ❖ Microangiopathy develops which tends to entail diffuse basement membrane thickening with protein leakage in capillaries of skin, skeletal muscle, retina, renal glomeruli, renal medulla, renal tubules, Bowman capsule, peripheral nerves, placenta [5]

Diabetic renal disease

Diabetes renal disease and diabetic nephropathy also does occur in relation to some cases of diabetes mellitus.

Ocular complications of diabetes mellitus [5]

- It has been stated that ocular complications of diabetes mellitus is the 4th cause of blindness in United States of America. [5]
- It has been iterated that ocular complications of diabetes mellitus are associated with retinopathy, cataracts, and glaucoma. [5]
- It has been explained that Polyol pathways in diabetes mellitus are: important in lens and other tissues (nerves, kidney, blood vessels) that don't require insulin for glucose transport [5]
    - ❖ High intracellular glucose plus aldose reductase produces sorbitol and later fructose, causing water influx and osmotic cell injury
    - ❖ In lens, causes swelling and opacity
    - ❖ Inhibition of sorbitol may reduce formation of cataracts and neuropathy

Neuropathy [5]

It has been iterated that in diabetes mellitus, Peripheral neuropathy does develop and this tends to be symmetric neuropathy of lower extremity most common, and sensory neuropathy is more common than motor neuropathy. [5]

Diagnosis [5]

- It has been stated that diabetes mellitus generally tends to be diagnosed with high fasting glucose or impaired glucose tolerance (without diabetes, oral glucose loads cause only slight rise in blood glucose due to brisk insulin response; with diabetes, blood glucose rises markedly for a sustained period) [5]

Treatment

The treatment of diabetes mellitus has been summarized as follows: [5]

- Type 1 diabetes mellitus: It has been stated that immunosuppressive therapy is effective in children who have new onset disease. [5]
- Type 2 diabetes mellitus: It has been stated that type 2 diabetes mellitus can be treated by: diet, exercise and education [5,15]
    - ❖ It has been iterated that lifestyle intervention and metformin does delay the onset of diabetes mellitus [5,21]

Microscopic (histologic) description

- **Type 1 diabetes mellitus** s: It has been iterated that in cases of type 1 diabetes mellitus, microscopy pathology examination of specimens of the pancreas does tend to demonstrate inconsistent reduction in the number and size of islets, as well as uneven insulinitis (T lymphocytes) [5]
- **Type 1 diabetes mellitus**: It has been iterated that in cases of type 1 diabetes mellitus, early insulinitis with marked islet atrophy and fibrosis and severe beta cell depletion tend to be seen [5,22]
- **Type 2 diabetes mellitus**: It has been stated that in type 2 diabetes mellitus, microscopy examination of the pancreas does demonstrate subtle reduction in islet cell mass, amyloid

replacement of islets due to amylin fibrils (also seen in aging nondiabetics); associated with marked fatty replacement [5]

- **Type 2 diabetes mellitus**: It has been stated that in type 2 diabetes mellitus microscopy pathology examination of the pancreas does demonstrate amyloid within the islets of Langerhans is the uniform pathologic feature. [5]

- **Gestational diabetes mellitus**: It has been iterated that in gestational diabetes mellitus, pathology and immunohistochemistry staining of the pancreas does demonstrate lower total insulin+ area due to smaller islets [5] [23]

- **Infants of diabetic mothers**: It has been iterated that pathology examination of pancreas of infants of diabetic mothers does demonstrate islet cell hypertrophy / hyperplasia [5]

[B] Miscellaneous Narrations and Discussions Related to Some Case Reports, Case Studies and Some Studies on Diabetes Mellitus and Carcinoma of Prostate Gland.

Feng et al. [24] prospectively examined the association between diabetes mellitus and risk of prostate cancer defined by clinical and molecular features. Feng et al. [24] reported that a total of 49,392 men from the Health Professionals Follow-up Study (HPFS) were followed from 1986 to 2014.Feng et al. [24] collected data on self-reported diabetes at baseline and updated biennially. The clinical features of prostate cancer included localised, advanced, lethal, low-grade, intermediate-grade, and high-grade. Molecular features included TMPRSS2: ERG and PTEN subtypes. Cox proportional hazards regression models were used to evaluate the association between diabetes and incidence of subtype-specific prostate cancer. Feng et al. [24] summarized the results as follows:

- During 28 years of follow-up, they had documented 6733 incident prostate cancer cases.

    - Relative to men who were free from diabetes, men who had diabetes had lower risks of total (HR: 0.82, 95% CI: 0.75–0.90), localised (HR: 0.82, 95% CI: 0.74–0.92), low-and intermediate-grade prostate cancer (HR: 0.77, 95% CI: 0.66–0.90; HR: 0.77, 95% CI: 0.65–0.91, respectively).

    - For molecular subtypes, the HRs for ERG-negative and ERG-positive cases were 0.63 (0.42–0.95) and 0.72 (0.46–1.12); and for PTEN-intact and PTEN-loss cases were 0.69 (0.48–0.98) and 0.52 (0.19–1.41), respectively.

Feng et al. [24] concluded that besides providing advanced evidence for the inverse association between diabetes mellitus and prostate cancer, their study was the first to report associations between diabetes and ERG/PTEN defined prostate cancers.

Lee et al. [25] stated the following:

- There are conflicting results as to the association between pre-existing diabetes mellitus and the risk of mortality in patients who have prostate cancer.

- They had undertaken a study to estimate the influence of pre-existing diabetes mellitus upon prostate cancer-specific mortality and all-cause mortality.

Lee et al. [25] searched PubMed and Embase to identify studies which had investigated the association between pre-existing diabetes mellitus and risk of death among men with prostate cancer. Lee et al. [25] calculated pooled risk estimates and 95 % confidence intervals using fixed-effects models or random-effects models. Lee et al. [25] conducted heterogeneity tests between studies. Lee et al. [25] analysed publication bias by using the *Egger's test, Begg's test*, and the trim and fill method. Lee et al. [25] summarised their results as follows:

- Out of the 733 articles they had identified, 17 cohort studies that had 274,677 male patients were included in this meta-analysis.

- Pre-existing diabetes mellitus was associated with a 29 % increase in prostate cancer-specific mortality [relative risk (RR) 1.29, 95 % CI 1.22–1.38, $I^2 = 66.68$ %], and with a 37 % increase in all-cause mortality (RR 1.37, 95 % CI 1.29–1.45, $p < 0.01$, $I^2 = 90.26$ %).

- Additionally, in a subgroup analysis that was a type specific analysis which had focused upon type 2 diabetes mellitus and was conducted only with three cohort studies, pre-existing type 2 diabetes was associated with all-cause mortality (RR 2.01, 95 % CI 1.37–2.96, $I^2 = 95.55$ %) and no significant association with prostate cancer-specific mortality was detected (RR 1.17, 95 % CI 0.96–1.42, $I^2 = 75.59$ %).

- There was significant heterogeneity between studies and no publication bias was found.

Lee et al. [25] made the following conclusions:

- This meta-analysis suggested diabetes mellitus may result in a worse prognosis for men who have prostate cancer.

- Considering heterogeneity between studies, additional studies should be undertaken to confirm these findings, and to allow generalization regarding the influence that each type of diabetes has on prostate cancer mortality.

Lin et al. [26] stated the following:

- Prostate cancer (PCa) and type 2 diabetes mellitus (T2DM) are prevalent conditions which often occur concomitantly.

- Nevertheless, many aspects of the impact of T2DM, particularly the duration of T2DM and antidiabetic medications, on PCa risk are poorly understood.

Lin et al. [26] assessed the association of duration of T2DM and antidiabetic medication with PCa risk, and they designed a matched case-control study, including 31,415 men with PCa and 154,812 PCa-free men in Prostate Cancer data Base Sweden (PCBaSe) 4.1. Lin et al. [26] summarised the results as follows:

- Overall, a decreased risk of PCa was observed for men who had T2DM (odds ratio (OR): 0.81, 95% confidence interval (CI): 0.78–0.84), as compared to men who did not have T2DM.

- The decreased risk of PCa was consistently demonstrated across the duration of T2DM.

- With regard to use of antidiabetic drugs, this inverse association with duration was also found for all medications types, as compared to men without T2DM, including insulin, metformin and sulphonylurea (SU) (for example: 3- < 5 year insulin OR:0.69, 95%CI:0.60–0.80; 3- < 5 yr metformin OR: 0.82, 95%CI: 0.74–0.91; 3- < 5 yr SU OR: 0.72, 95%CI: 0.62–0.83).

- When stratifying by PCa risk categories, this decreased risk was most evident for diagnosis of low and intermediate-risk PCa (low-risk OR: 0.65, 95%CI: 0.66–0.70, intermediate-risk OR: 0.80, 95%CI: 0.75–0.85).

Lin et al. [26] made the ensuing conclusions:

- The study had shown an inverse association between pre-existing T2DM and PCa across different durations of T2DM and all types of T2DM medication received.
- This inverse association was most evident for low- and intermediate-risk PCa, which had indicated that whilst T2DM and its medication may protect some men from developing PCa, the relationship warrants further study.

Jian Gang et al. [27] stated that in order to provide further insight into the association between type 2 diabetes mellitus (T2DM) and the pathophysiology of prostate cancer, they had undertaken an updated, detailed meta-analysis of 56 published case-control and cohort studies. Jian Gang et al. [27] reported that they had used MEDLINE and EMBASE to identify the literature published in April 2012 related to both diabetes mellitus and prostate cancer. Jian Gang et al. [27] undertook a sensitivity analysis, and they investigated potential confounding effects using a stratified meta-analysis. They also carried out a cumulative meta-analysis to evaluate the cumulative effect estimate over time. Jian Gang et al. [27] summarized the results as follows:

- A total of 24 case-control and 32 cohort studies with information on a total of ~8,000,000 subjects and ~140,000 individuals with prostatic cancer had shown published estimates of the association between diabetes and prostate cancer malignancy.
- The pooled effect estimate had demonstrated a relative risk (RR) of 0.88 (95% CI, 0.82-0.93). Interestingly, there was an increased trend for Asians (RR = 1.72, n = 7) but not Americans (RR = 0.82, n = 28) and Europeans (RR = 0.86, n = 21) regarding the association between diabetes mellitus and prostate cancer.
- The sensitivity analysis, excluding any one study, had not significantly changed the pooled RR.
- The range for the pooled RR when one study was omitted was 0.84-0.89.
- The findings of their meta-analysis provided strong evidence of an inverse association between diabetes and prostate cancer.

Jian Gang et al. [27] concluded that:

- Further research should focus upon limitations in current literature and re-assess the relationship between diabetes and prostate cancer by analysing the two different diabetes mellitus types separately.

Bansal et al. [28] stated the following:

- Emerging evidence had suggested that diabetes mellitus may increase the risk of cancers.
- However, available evidence on prostate cancer had been conflicting.
- They therefore examined the association between Type 2 diabetes and risk of prostate cancer by conducting a detailed meta-analysis of all studies published regarding this subject.

Bansal et al. [28] searched PubMed database and bibliographies of retrieved articles for epidemiological studies which had been published between 1970 and 2011, investigating the relationship between Type 2 diabetes and prostate cancer. Pooled risk ratio (RR) was calculated using random-effects model. Subgroup, sensitivity analysis and cumulative meta-analysis were also undertaken. Bansal et al. [28] summarised the results as follows:

- Forty-five studies which included 29 cohort and 16 case-control studies that involved 8.1 million participants and 132 331 prostate cancer cases had detected a significant inverse association between Type 2 diabetes and risk of prostate cancer (RR 0.86, 95% confidence interval (CI) 0.80-0.92).
- For cohort studies alone, the RR was 0.87 (95% CI 0.80-0.94), and for case-control studies alone, the RR was 0.85 (95% CI 0.74-0.96).
- Sensitivity analysis which was undertaken by excluding one outlier further strengthened their negative association (RR 0.83, 95% CI 0.78-0.87).
- They did not observe any evidence of publication bias.

Bansal et al. [28] concluded that:

- The meta-analysis had provided strongest evidence which supported the iteration that Type 2 diabetes is significantly inversely associated with risk of developing prostate cancer.

Kasper et al. [29] stated the following:

- Studies investigating the association between diabetes mellitus and prostate cancer had reported inconsistent findings.
- They examined this association by conducting a detailed meta-analysis of the studies published on the subject.

Kasper et al. [29] searched MEDLINE and EMBASE databases and bibliographies of retrieved articles. Kasper et al. [29] included studies which had investigated the relationship between diabetes mellitus and prostate cancer in the meta-analysis. Potential sources of heterogeneity between studies were explored and publication bias was evaluated by Kasper et al. [29]. Pooled relative risk (RR) was calculated by Kasper et al. [29] utilising the random-effects model. Numerous relevant subgroup analyses were also undertaken by Kasper et al. [29]. Kasper et al. [29] summarised the results as follows:

- **They had** included 19 studies, which were published between 1971 and 2005, in the meta-analysis and they found an inverse association between diabetes mellitus and prostate cancer [RR, 0.84, 95% confidence interval (CI), 0.76-0.93, P for heterogeneity <or= 0.01].
- For cohort studies alone, the RR was 0.81 (95% CI, 0.71-0.92, P for heterogeneity <or= 0.01) and for case-control studies alone, the RR was 0.89 (95% CI, 0.72-1.11, P for heterogeneity = 0.02).
- The significant heterogeneity was mitigated in some of the subgroup analyses.
- For studies which were undertaken before prostate-specific antigen screening was introduced as a common procedure, the RR was 0.94 (95% CI, 0.85-1.03, P for heterogeneity = 0.15), and for studies conducted after this time, the RR was 0.73 (95% CI, 0.64-0.83, P for heterogeneity = 0.10).
- For studies that adjusted for three or more potential confounders, the RR was 0.74 (95% CI, 0.65-0.85, P for heterogeneity = 0.06) and for studies that adjusted for less than three potential confounders, the RR was 0.93 (95% CI, 0.86-1.02, P for heterogeneity = 0.18).

Kasper et al. [29] concluded that:

The results of their study had suggested an inverse relationship between diabetes mellitus and prostate cancer.

Zhang et al. [30] stated the following:

- The association between diabetes mellitus and the risk of prostate cancer had been investigated widely.
- Nevertheless, the study results had remained inconsistent and contradictory.

- Utilising a meta-analytic approach, they had undertaken a study to explore the relationship incorporating more recent studies and to provide more powerful evidence without the limitations of any individual study.
- Relevant studies were identified by searching PUBMED and the Cochrane Central Register of Controlled Trials through May 18, 2012.
- They had assessed the strength of the relationship between diabetes mellitus and risk of prostate cancer utilising relative risk (RR).
- They used either a fixed effects or random effects model to calculate the pooled RRs.
- They conducted stratification analyses and sensitivity analyses, and publication bias was assessed by Egger's test and Begg's test.
- They had included twelve case-control studies involving 9,767 cases and 19,790 controls, and 25 cohort studies involving 118,825 cases.
- The person-years of follow-up of the patients had ranged from 29,963 to 6,264,890 among included cohort studies.
- Diabetes mellitus was not significantly associated with incidence of prostate cancer in their analysis of case-control studies only (RR = 0.846, 95 % CI [0.710, 1.009]) or that of cohort studies only (RR = 0.925, 95 % CI [0.811, 1.054]).
- Nevertheless, through subgroup analyses, statistically significant associations between diabetes mellitus and prostate cancer were found when considering population-based studies only (RR = 0.719, 95 % CI [0.637, 0.812]), cohort studies conducted in the United States (RR = 0.789, 95 % CI [0.727, 0.857]), and studies with follow-up of more than 5 years.
- Compared to the risk of prostate cancer among people without diabetes mellitus, diabetic patients using insulin treatment experienced reduced incidence of prostate cancer in both case-control and cohort studies.
- The results had suggested that diabetes mellitus is associated with decreased incidence of prostate cancer, specifically in the population of the United States.
- In addition, the time since onset of diabetes was positively associated with decreasing incidence of prostate cancer.
- Their conclusions should be considered carefully, nevertheless, and confirmed with further studies.

Thakkar et al. [31] stated the following:

- Accumulating evidence had suggested that patients who have type 2 diabetes mellitus (T2DM) and hyperinsulinemia are at increased risk for the development of malignancies.
- It remains to be fully ascertained whether utilisation of metformin, an insulin sensitizer, and/or sulfonylureas, insulin secretagogues, affect cancer incidence in subjects with T2DM.

Thakkar et al. [31] undertook a meta-analysis utilising PubMed, of randomized control trials (RCTs), cohorts, and case-control studies which were published through July 2012 that assesses the effects of metformin and/or sulfonylurea sulfonylureas on cancer risk at any site, in subjects who had T2DM. Fixed and random effects meta-analysis models were used by Thakkar et al. [31], and the effect size was summarized as relative risk (RR) for RCTs/cohorts and as odds ratio (OR) for the case-control studies.

Thakkar et al. [31] summarised the results as follows:

- Analysis of 24 metformin studies in subjects who had T2DM had demonstrated that metformin use is associated with reduced risk for the development of cancer, in both cohort (RR=0.70 [95% CI=0.67-0.73]) and case-control studies (OR=0.90 [95% CI=0.84-0.98]), but this finding was not supported by RCTs (RR=1.01[95% CI=0.81-1.26]).
- Data from 18 sulfonylurea studies in subjects with T2DM had shown that sulfonylurea use is associated with an increase in all-cancer risk, in cohort studies (RR=1.55 [95% CI=1.48 -1.63]), though data from RCTs (RR=1.17 [95% CI=0.95-1.45]) and case-control studies (OR=1.02 [95% CI=0.93-1.13]) failed to demonstrate a statistically significant effect.

Thakkar et al. [31] made the ensuing conclusions:

- Their analysis using pooled primary data had demonstrated that metformin use reduces, while sulfonylurea use may be associated with an increased cancer risk in subjects who have T2DM.
- These findings need to be confirmed through the undertaking of a large-scale RCTs before they are translated into clinical practice.

Xu et al. [1] stated the following:

- Previous studies had reported that diabetes mellitus might reduce the overall prostate cancer risk.
- They examined this association by undertaking a detailed meta-analysis of the studies published in peer-reviewed literature on the association between diabetes mellitus and prostate cancer risk of different stage or grade.

Xu et al. [1] undertook a comprehensive search for articles of MEDLINE and EMBASE databases and bibliographies of retrieved articles published up to October 23, 2012. Their methodological quality assessment of the trials was based upon the Newcastle-Ottawa Scale. Meta-analysis which was performed utilising STATA 12.0. Xu et al. [1] summarised the results as follows:

- They had included 9 studies in the meta-analysis in which 5 studies had examined the relation of different stage only, 2 studies for grade only, and 2 studies for both grade and stage), and found an inverse association between diabetes mellitus and prostate cancer of different stage or grade.
- The relative risk (RRs) was moderately stronger for low grade (RR 0.74, 95% confidence interval (CI), 0.64-0.86) and localized disease (RR 0.72, 95% CI 0.67-0.76) compared with high grade (RR 0.78, 95% CI 0.67-0.90) and advanced disease (RR 0.85, 95% CI 0.75-0.97).
- **Xu et al. [1] concluded that the results of their** study had indicated an inverse relationship between diabetes mellitus and prostate cancer of different stage or grade.
- They had noted and discusses possible biases underlying this association which they had discussed.

Long et al. [32] stated the ensuing:

- Diabetes mellitus (DM) is widely regarded to be associated with risk of cancer, but studies investigating the association between DM and prostate cancer in Asian countries had reported inconsistent findings.
- They had examined this association by conducting a detailed meta-analysis of studies published on the subject.

Long et al. [32] identified cohort or case-control studies by searching PUBMED, Embase and Wanfang databases through May 30, 2012. Pooled relative risk (RR) with its corresponding 95% confidence interval (95% CI) were calculated by Long et al. [32] using the random-effects model. Subgroup analyses were performed by Long et al. [32] by the study type.

Long et al. [32] summarised the results as follows:

- Finally, they had identified 7 studies which included four cohort studies and three case-control studies, with a total of 1,751,274 subjects from Asians.
- DM was found to be associated with an increased risk of prostate cancer in Asians (unadjusted RR= 2.82, 95% CI 1.73-4.58, P < 0.001; adjusted RR= 1.31, 95% CI 1.12-1.54, P = 0.001).
- Subgroup analyses by study design further confirmed an obvious association.

Long et al. [32] concluded that the findings from their meta-analysis had strongly supported the iteration that diabetes mellitus is associated with an increased risk of prostate cancer in Asians.

Hua et al. [33] stated the following:

- Biochemical recurrence (BCR), or an elevation in prostate-specific antigen in men after treatment for localized prostate cancer, is an early indication of clinical progression, distant metastases, and mortality.
- Correlations had also recently been established between diabetes mellitus and the incidence and mortality of prostate cancer.
- Nevertheless, it remains unknown whether diabetes may predict BCR.

Hua et al. [33[undertook a meta-analysis of published articles to investigate the prognostic value of diabetes for BCR in prostate cancer. Eight studies and 11,923 patients were included by Hua et al. [33] in their meta-analysis. The relative risk (RR) and its 95 % confidence interval (CI) were calculated by Hua et al. [33]. Hua et al. [] iterated that they had found no apparent association between diabetes and BCR (adjusted RR 1.04; 95 % CI 0.87-1.22). Hua et al. [33] concluded that the evidence of their meta-analysis had indicated that diabetes is not a predictor of risk of BCR in patients with prostate cancer.

Joentausta et al. [34] stated that metformin had been linked to improved survival among diabetic prostate cancer (PCa) patients, while hyperinsulinemia and insulin usage had been related to worse prognosis. Joentausta et al. [34] evaluated the association of metformin and other antidiabetic drugs with PCa death and androgen deprivation therapy (ADT). Joentausta et al. [34] reported that their study cohort included 14 424 men who had undergone radical prostatectomy in Finland during 1995-2013. The cases were identified, and their clinical data were collected from patient files and national registries utilising personal identification numbers. Joentausta et al. [34] collected information on the use of each antidiabetic medicament during 1995-2014 from prescription registry of the Social Insurance Institution of Finland. Joentausta et al. [34] analysed the risks of PCa death and initiation of ADT by antidiabetic medicament utilisation with the Cox regression method. Each antidiabetic drug group was analysed separately to model simultaneous usage. Joentausta et al. [34] analysed the pre- and post-diagnostic uses separately. Joentausta et al. [34] summarised the results and limitations of their study as follows:

- Pre-diagnostic utilisation of antidiabetic medicaments in general had no association with the risk of PCa death.
- Pre-diagnostic use of metformin was related to a reduced risk of ADT initiation (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.59-0.96), while high-dose insulin users had an increased risk.
- Overall, antidiabetic drug utilisation after PCa diagnosis was associated with an elevated risk of PCa death.
- Only post-diagnostic metformin utilization was found to be associated with reduced risks of PCa death (HR 0.47, 95% CI 0.30-0.76) and ADT commencement compared with nonusers.
- The study limitations included: missing information on glycemic control, smoking, living or exercise habits, prostate-specific antigen, and Gleason score.

Joentausta et al. [34] made the ensuing conclusions and patient summary:

- Among surgically treated prostate cancer (PCa) patients, utilization of metformin was found to be associated with improved disease-specific survival, while insulin and insulin secretagogues were associated with poor survival.
- Metformin might be a favourable diabetes treatment option among men who have PCa.
- In their Finnish nationwide study, they had ascertained that the risks of prostate cancer death and cancer progression were lowered among metformin users, but not among other antidiabetic drug users.

Haring et al. [35] stated the following:

- Diabetic men do have lowered overall prostate cancer (PCa) risk, while their risk of high-grade disease might be raised.
- The antidiabetic medicament metformin might reduce the risk.
- They had undertaken a study which evaluated PCa incidence among users of metformin and other antidiabetic drugs in the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC).
- The study population which included 78,615 men, was linked to the national prescription database.
- They had estimated the Hazard ratios (HRs) and 95% confidence intervals (CIs) for PCa were utilising Cox regression, with medication use as a time-dependent variable.
- They estimated the effect of diabetes by comparing antidiabetic drug users to non-users, while drug-specific effects were evaluated within antidiabetic drug users.
- They had performed the analyses in both study arms of FinRSPC.

Haring et al. [35] summarised the results as follows:

- Compared to non-users, men utilising antidiabetic drugs had reduced overall PCa risk (HR 0.85, 95% CI 0.79-0.92), and this association was not affected by PCa screening.
- Nevertheless, the risk of metastatic PCa had increased (HR 1.44, 95% CI 1.09-1.91).
- Among antidiabetic drug users, metformin had reduced overall PCa risk (HR 0.81, 95% CI 0.69-0.95) in a dose-dependent manner.
- When stratified by FinRSPC study arm, the risk reduction was observed only in the screening arm.
- Sulphonylureas increased the risk of metastatic PCa (HR 2.04, 95% CI 1.11-3.77).
- Use of thiazoledenediones or insulin was not associated with PCa risk.

Haring et al. [35] made the ensuing conclusions:

- Among antidiabetic medication users, metformin lowered the overall PCa risk, while the risk of metastatic disease was raised in sulphonylurea users.
- As sulphonylureas mimic insulin secretion, the results had indicated that hyperinsulinemia might be a risk factor for PCa.

Preston et al. [36] stated that Metformin might decrease prostate cancer (PCa) risk by reducing hyperinsulinemia-associated carcinogenesis or through direct effects on cancer cells. Preston et al. [36] evaluated the association between metformin use and PCa diagnosis.

Preston et al. [36] used the Danish Cancer Registry and the Aarhus University Prescription Database to conduct a nested case-control study among men residing in northern Denmark from 1989 to 2011. Preston et al. [36] identified 12 226 cases of PCa and utilised risk-set sampling to select 10 population controls per case (n=122,260) from among men alive on the index date and born in the same year. Preston et al. [36] conducted a sensitivity analysis using subjects who had prostate-specific antigen (PSA) testing prior to 1 year before the index date. Preston et al. [36] assessed Metformin exposure using prescriptions redeemed before the index date. Preston et al. [36] calculated the odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression. Preston et al. [36] determined the association between metformin use and PCa diagnosis, controlling for diabetes severity and other potential confounders. Preston et al. [36] summarized the results as follows:

- Metformin users were at decreased risk of PCa diagnosis in comparison with never-users (adjusted OR [aOR]: 0.84; 95% CI, 0.74-0.96).
- Diabetics on no medication (aOR: 0.98; 95% CI, 0.89-1.09) or on other oral hypoglycaemics (aOR: 0.98; 95% CI, 0.86-1.10) did not have a reduced risk of PCa, whilst users of insulin did have a reduced risk (aOR: 0.77; 95% CI, 0.64-0.93).
- In the PSA-tested group, metformin use was found to be associated with decreased risk of PCa in comparison with non-use (aOR: 0.66; 95% CI, 0.51-0.86).
- Diabetics on no medication (aOR: 1.03; 95% CI, 0.86-1.24), diabetics on other oral hypoglycaemics (aOR: 0.92; 95% CI, 0.70-1.20), and insulin users (aOR: 0.83; 95% CI, 0.56-1.24) did not have a statistically significant reduced risk of cancer.

Preston et al. [36] made the ensuing conclusions and patient summary:

- Metformin use was associated with decreased risk of PCa diagnosis, whilst, diabetics using other oral hypoglycaemics did not have any decreased risk.
- They had studied the relationship between metformin (a diabetic medication) and prostate cancer in Denmark.
- They found that metformin reduced the risk of prostate cancer diagnosis, whereas other oral antidiabetic medications did not.

Saarela et al. [37] made the ensuing iterations:

- Diabetes mellitus and cancer are common diseases both of which have enormous impact upon health burden throughout the world.
- The increased risk of several types of cancer among people with type 2 diabetes mellitus had been indicated repeatedly.
- They had undertaken a study which was aimed at exploring and describing the association between type 2 diabetes mellitus and cancer incidence.
- A cohort of 428,326 people who had type 2 diabetes mellitus was identified from the Finnish National Diabetes Register and followed up through a register linkage with the Finnish Cancer Registry for cancer incidence during 1988-2014.
- A total of 74,063 cases of cancer had occurred in this cohort in 4.48 million person-years.
- This accounted for 16% more than the expected cancer incidence in the Finnish general population; the standardized incidence ratio (SIR) was 1.16 (95% confidence interval [CI] 1.15-1.16).
- There was a statistically significant excess of cancers of lip (SIR = 1.40, CI = 1.28-1.53), liver (SIR = 2.44, CI = 2.35-2.53), pancreas (SIR = 1.75, CI = 1.70-1.79), stomach (SIR = 1.22, CI = 1.18-1.26), colon (SIR = 1.22, CI = 1.19-1.25), gallbladder and bile ducts (SIR = 1.29, CI = 1.21-1.36), non-melanoma skin (SIR = 1.18, CI = 1.15-1.22), kidney (SIR = 1.42, CI = 1.37-1.47), bladder (SIR = 1.17, CI = 1.13-1.21), and thyroid (SIR = 1.22, CI = 1.12-1.31).
- There was a small statistically significant decrease in the incidence of prostate cancer (SIR = 0.95, CI = 0.93-0.96).
- Their study had demonstrated an association between type 2 diabetes mellitus and the incidence of cancer at numerous sites within the Finnish population.

Baradaran et al. [38] stated the following:

- Diabetes mellitus (DM) had been associated with decreased risk of prostate cancer (PC) in many publications.
- Hormonal environment of diabetic patients is understood to be an important contributing factor in this regard.

Baradaran et al. [38] determined utilising data from a multi-centre case-control study in Iran, base line testosterone, sex hormone binding globulin (SHBG), oestradiol, and albumin levels as well as thorough demographic and medical characteristics of 194 newly diagnosed prostate cancer patients. There were 317 ethnicity-matched men with no cancer which served as controls as well. Baradaran et al. [38] analysed data for hormones of interest in DM patients regarding their cancer status. Baradaran et al. [38] summarized the results as follows:

- Out of f 511 enrolled patients, twenty-one cases and 63 controls had been diagnosed as DM.
- Patients who had DM were significantly less likely to have PC (OR: 0.44, P = 0.003).
- Time since DM diagnosis was also found to be inversely correlated with the risk of cancer (P trend < 0.0001).
- Control patients had significantly higher testosterone, oestradiol, and testosterone/SHBG ratio (P < 0.05).
- As time since DM diagnosis increased by quartiles, testosterone significantly increased (P trend < 0.05).
- The risk of PC had also significantly declined (P trend < 0.0001) following an initial remarkable increase early after DM diagnosis.
- After including the hormones in the logistic regression model, there was a weak, yet significant found inverse association of testosterone/SHBG and DM duration with the risk of PC.

Baradaran et al. [38] made the ensuing conclusions:

- Based upon their results DM duration was found to be inversely correlated with the risk of prostate cancer.

- Their results did not support the postulate that sex hormones, including testosterone, play a major role in the protective effect of DM against PC.

Kasper et al. [39] stated the following:

- Previous studies had indicated men who have diabetes mellitus may be at reduced risk for prostate cancer as compared to men without diabetes mellitus.
- In order to investigate potential biological mechanisms, they had compared hormonal profiles of diabetic men and non-diabetic controls.

Kasper et al. [39] reported that they had determined in the Health Professionals Follow-Up Study, plasma levels of C-peptide, testosterone, sex-hormone binding globulin, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 in 171 diabetic men and 3,001 non-diabetic controls. Kasper et al. [39] had conducted multiple linear regression analysis and they had calculated least square means for hormones of interest. Kasper et al. [39] summarized the results as follows:

- They had examined plasma levels of many hormones either < or =1, 1.1-6, 6.1-14.9, or > or =15 years after diagnosis with diabetes mellitus.
- As time since diabetes mellitus diagnosis had increased, plasma levels of C-peptide and IGFBP-3 had significantly decreased (p for trend: C-peptide =.05, IGFBP-3 =.03).
- While testosterone and SHBG levels both significantly had increased with increasing time since the diagnosis of diabetes mellitus (p for trend: testosterone =.02, SHBG =.002), the ratio of testosterone to SHBG decreased, which had suggested a reduction in bioavailable testosterone.
- Plasma IGF-1 levels were lower in diabetic patients than non-diabetics, but no significant time trend was noted.

Kasper et al. [39] concluded that their study of hormonal profiles of diabetic men versus non-diabetic men had identified changes in diabetic men which may be consistent with reduced prostate cancer risk

Frayling et al. [40] stated the following:

- Epidemiological studies had indicated that men who have type 2 diabetes are less likely than non-diabetic men to develop prostate cancer.
- The cause of this association was unknown.
- Recent genetic studies had highlighted a potential genetic link between the two diseases.
- Two studies had identified a version (allele) of a variant in the HNF1B, which is also known as TCF2 gene which predisposes to type 2 diabetes mellitus, and one of them had shown that the same allele does protect men from developing prostate cancer.
- Other, separate, studies had identified different variants in the JAZF1 gene, one associated with type 2 diabetes, another associated with prostate cancer.
- These findings would be unlikely to completely explain the epidemiological association between the two diseases; nevertheless, they do provide new insight into a possible direct causal link, rather than one that is confounded or biased in some way.

Melike Özçelik et al. [41] stated the ensuing:

- Diabetes mellitus is both a risk factor that is associated with increased incidence and a prognostic determinant for many types of cancer.
- They had undertaken a study which was aimed to evaluate the impact of diabetes mellitus upon carcinoma of prostate gland outcomes.

Melike Özçelik et al. [41] included patients who were diagnosed as having prostate cancer either at non metastatic stage at diagnosis and who subsequently developed metastasis or at metastatic stage at the time of initial manifesting diagnosis. The peculiarities of the prostate cancer including the age of the patient, date of diagnosis of the cancer, The Gleason score (GS) of the tumour, stage of the tumour, the serum prostate specific antigen (PSA) level of the patient, the time-to-distant metastasis development for non-metastatic disease at the time of initial diagnosis of the cancer and the time-to-castration resistance for metastatic disease, as well as presence of diabetes mellitus, last date of control were reviewed retrospectively by Melike Özçelik et al. [41]. Melike Özçelik et al. [41] summarised the results as follows:

- A total of 149 patients had been included in the study.
- The median overall survival of patients who had diabetes mellitus was 32 months whereas it was 66 months for those who did not have diabetes mellitus (HR=2; 95% CI:1.33–3; p=0.001).
- For non-metastatic disease at the time of initial diagnosis, the median time-to-distant metastasis development was 48 months for those who had diabetes mellitus, and 63 months for those who did not have diabetes mellitus (p=0.13).
- The median time-to-castration resistance was 12 months versus. 27 months for patients who had diabetes mellitus and those without diabetes mellitus (HR=3.66; 95% CI:2.46–5.45; p=0.000).

Melike Özçelik et al. [41] concluded that:

Presence of diabetes mellitus is a robust and reliable prognostic marker for predicting poor survival outcomes including time-to-distant metastasis, time-to-castration resistance and overall survival in prostate cancer.

Conclusions

- Conflicting results had been published regarding the association between diabetes mellitus and prostate cancer development.
- A number of studies had suggested an inverse relationship between diabetes mellitus and prostate cancer.
- Other studies had indicated treatment of patients who had been treated with Metformin do tend to be associated with a lower risk for the development of prostate cancer as well as better prognosis following treatment of prostate cancer
- On the contrary, few studies had reported aggressive biological behaviour associated with prostate cancers that are found in some men who have diabetes mellitus
- There is a urgent need for the establishment of a multi-centre global study to further assess the association between diabetes mellitus and the incidence of prostate cancer as well the outcome of prostate cancer in patients who have diabetes mellitus and those who do not have diabetes mellitus
- There is also a global need to confirm whether or not treatment of diabetes mellitus in patients who have prostate cancer with utilization of Metformin is associated with statistically significant improved prognosis in comparison with patients with diabetic patients with prostate cancer who have been treated with a different anti-diabetic medicament and not Metformin.

Conflict of Interest – Nil

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