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Metabolism and Target Organ Damage

Editorial

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Association between type 2 diabetes mellitus and prostate cancer

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RESEARCH PROGRESS ON THE ASSOCIATION BETWEEN TYPE 2 DIABETES AND PROSTATE CANCER

The prostate is a unique male organ with internal and external secretory functions. Prostate cancer (PC) is one of the most common malignancies in the United States and the second leading cause of worldwide cancer-related death[1]. In recent years, the role of metabolic factors such as glucose metabolism disorders and abnormal hormone regulation in the etiology and pathogenesis of PC has attracted more and more attention[1]. Recognized risk factors for PC include age, race, and family genetic history[2]. However, the relationship between the PC and diabetes mellitus (DM) is seldom studied.

DM is a common metabolic disease, which is a group of diseases characterized by hyperglycemia caused by abnormal insulin production and secretion or abnormal insulin action. It is mainly divided into type 1 and type 2. Among them, type 2 diabetes mellitus (T2DM) is the most common type of diabetes, also known as adult-onset diabetes, due to its more common occurrence in adults. This disease is caused by various causes, which lead to insufficient insulin secretion in the body or hinder the body's effective utilization of insulin,

resulting in a continuous increase in blood glucose levels[3].

Several prospective studies and meta-analyses have shown that T2DM can significantly increase the risk of colorectal, breast, liver, pancreatic, and bladder cancers[2,4]. T2DM increases cancer risk mainly through metabolic characteristics such as hyperinsulinemia, hyperglycemia, and inflammation[5]. However, it is worth noting that T2DM can reduce the risk of PC[2,4,6]. Studies have shown that T2DM is inversely associated with the risk of PC; that is, male patients with T2DM can reduce the risk of PC[7]. The biological and pathophysiological mechanisms are still not fully understood. The current studies on T2DM and PC are summarized in Table 1. Here, we, for T2DM with PC, summarized the research advances in developing the relationship.

BLOOD GLUCOSE

The results of existing studies on the association between PC and blood glucose levels and glycemic control are controversial. Murtola *et al*. believed that the fasting blood glucose level of untreated diabetic patients was a risk factor for PC, and the risk of PC increased with the increase of fasting blood glucose level in diabetic patients[13]. They did not support the view that T2DM had a protective effect on PC and believed that antidiabetic drugs reduced this risk. This indirectly supports the anticancer effect of antidiabetic drugs[13]. Ma *et al*. showed that patients with good blood glucose control in locally advanced PC had better prognoses[14].

However, the other part of the study showed the opposite result, indicating an inverse association between diabetes and prostate risk. Onitilo *et al*. suggested that high blood glucose has a protective effect on PC, and patients with normal blood glucose control have a significantly increased risk of PC compared with breast cancer and colon cancer, and speculated that low testosterone levels caused by high blood glucose may play a role in reducing the risk of PC[15]. A systematic review of 15 prospective studies showed an inverse correlation between hyperglycemia and the risk of PC (RR 0.88, 95%CI 0.78-0.98), and the risk of PC decreased linearly with the increase of fasting blood glucose level[16].

PC is accompanied by metabolic disorders, including the release of inflammatory factors and insulin resistance, which may also lead to glucose metabolism disorders. Therefore, further research is needed to confirm whether this causal relationship is established[16].

Glycosylated hemoglobin (HbA1c) level is the main indicator of blood glucose level in patients with type 2 diabetes mellitus (T2DM) and is widely used to monitor blood glucose control. Recently, Ma *et al*. reported that higher mean Hba1c after radical prostatectomy was associated with poor overall survival (OS), PC-specific mortality (PCSM), and anti-castration-resistant PC tumor-free survival (CRPC-FS) in patients with locally advanced PC[14]. The related study by UK Biobank also showed that glycosylated hemoglobin (HbA1c) was negatively correlated with PC risk[17]. Therefore, whether the blood glucose level accurately correlates with the occurrence and development of PC and the specific regulatory mechanism needs to be further studied.

INSULIN AND INSULIN-LIKE GROWTH FACTORS

Insulin is secreted by pancreatic beta cells, and its role is to promote tissue cells to accelerate the uptake, utilization, and storage of glucose, thereby reducing blood glucose. Studies have shown that the protective effect of hyperglycemia in reducing the risk of prostate cancer is more obvious in patients with T2DM with a long duration, which can be attributed to the changes in serum insulin concentration during the progression and deterioration of T2DM[16]. In the early stage of T2DM, decreased insulin sensitivity leads to

Table 1. Related clinical and epidemiological studies of T2DM and PC

Author	Year	Type of article	Method	Conclusion
Lavalette *et al.*[8]	2022	Case-control study	Logistic regression models adjusting for age, family history of PC, and race were used to assess the associations between T2DM, metabolic syndrome, and PC risk based on PC cases and age-matched control cases	The duration of T2DM is negatively correlated with the risk of PC. With the extension of T2DM treatment time, the risk of PC decreases. The role of metabolic factors, such as metabolic syndrome and its components, in the risk of PC is unclear and requires further investigation
Lin *et al.*[9]	2020	Case-control study	Based on the Swedish PC database, the association of T2DM duration and antidiabetic drugs with the risk of PCa was evaluated	The risk of PC was consistently reduced over the course of T2DM. The duration of glucose-lowering medication use, compared with men without T2DM, was also inversely associated
Fall *et al.*[10]	2013	Randomized controlled trial/case-control study	Based on the Swedish PC database and age-matched men from the general population, the risk of PC in men with T2DM was estimated	The risk of PC is decreased in men with T2DM, especially in those with low risk of PC
Turner *et al.*[11]	2011	Clinical trial/case-control study	The relationship between PC stage and T2DM duration was studied	T2DM is associated with a reduced risk of PC, and the degree of the negative association does not change with the duration of T2DM, and the negative association is greater in highly differentiated and poorly differentiated PC
Smith *et al.*[12]	2008	Randomized controlled trial	For the data of locally advanced PC after chemoradiotherapy, regression and proportional hazards models were used to evaluate the association between T2DM and PC mortality	Body weight, but not T2DM, is associated with higher mortality in men with locally advanced PC who receive chemoradiotherapy. Indicates that the association between obesity and high mortality in PC is mediated by mechanisms other than metabolic alterations unique to T2DM

increased blood insulin levels, which can directly stimulate the proliferation and metastasis of tumor cells and activate and enhance the expression of insulin-like growth factor-1 receptor (IGF-1R) on the surface of PC cells. Activation of phosphatidylinositol 3-kinase (PI3K)/Akt and Ras/Raf/mitogen-activated protein kinase(MAPK) signaling pathways promotes cell mitosis and angiogenesis, inhibits cell apoptosis, and enhances cell proliferation and infiltration capacity, which leads to a higher risk of PC[16,18]. With the progression of T2DM, the insulin and IGF-1 levels decrease due to the damage of islet β cells, reversing these processes and inhibiting PC cell proliferation and migration[16,19].

In addition, studies have shown that the application of diabetes drugs may also affect the change of insulin levels. Drugs that increase circulating insulin levels, such as exogenous insulin and insulin analogs, as well as drugs that promote insulin secretion tend to increase PC-related risks[15]. Levels, such as metformin and thiazolidinedione, reduce PC risk[15].

IGF-1R is a type 2 receptor tyrosine kinase in normal tissue, and many have been expressed in cancer cells, including PC. The IGF-1 in the blood circulation is mainly regulated by the growth hormone produced in the liver; the normal prostate stromal cells can also autocrine or paracrine in the locally produced IGF-I and IGF binding protein[20]. IGF-1 binds to IGF-1R, insulin receptor (IR) and IR/IGF-1R mixture to activate PI3K-AKT-TOR and RAF-MAPK pathways, thereby promoting the survival and proliferation of PC cells. The expression of the IGF-1 receptor is positively correlated with the risk of fatal PC[20].

Prospective studies have shown that the IGF -I concentration risk cycle was positively associated with PC, and the OR of IGF-I was 1.29 (95% CI: 1.16 1.43)[21]. IGF-1R mainly mediates IGF-1 to produce biological activity. After binding to its receptor, it activates the rapamycin (mTOR) signaling pathway's mammalian target, thereby promoting PC cell growth[22]. Heni *et al.* found that IR was over-expressed in PC, and the ratio of IR isoform A/B was increased in PC. Isomer A also had a high affinity for insulin-like growth factor

(IGF)-II and could promote the proliferation of PC cells[23]. Similarly, a recent study based on data from the UK Biobank also showed that men with higher levels of IGF-I in the blood circulation had a higher risk of PC and a higher risk of death due to PC, indicating that IGF-I is associated with the risk of more severe forms of PC and may increase the risk of PC progression[24]. Based on the above research progress, in order to graphically summarize the relationship between T2DM and PC [Figure 1].

ANDROGEN

Studies have shown that lower testosterone concentrations in male patients with T2DM are associated with a reduced risk of PC[4]. A recent study based on data from the UK Biobank also showed that men with higher free testosterone levels had a higher risk of PC. In comparison, those with higher levels of sex hormone-binding globulin (SHBG) had a lower risk of PC; total testosterone concentration was not associated with PC incidence or mortality[24]. The mechanisms of androgen deficiency in T2DM include reduced SHBG levels, suppression of gonadotropin release or testosterone production by Leyden cells, increased levels of inflammatory cytokines that inhibit steroid synthesis, and increased aromatase activity that results in the conversion of testosterone to estradiol[25]. At the same time, another solid evidence of decreased testosterone levels in diabetic patients has also been observed in in vitro cell experiments and animal models of PC. Studies have shown that increased glucose concentration leads to down-regulation of androgen receptor (AR) mRNA and protein levels through activation of activated B cells (NFkB) by nuclear factor kappa light chain enhancer[26].

More importantly, PC is an androgen-dependent malignant tumor, and androgen, represented by testosterone, plays an important role in the occurrence of PC. Yassin *et al.* reviewed prostate cancer, testosterone level, and testosterone replacement therapy and showed that a high level of androgen is an independent risk factor for the occurrence and development of PC, and there is a significant positive correlation between androgen level and the occurrence and development of PC[27]. Therefore, patients with T2DM may be due to reduced androgen levels in the body, inhibiting PC occurrence and development. However, some studies have shown that testosterone deficiency may also lead to the occurrence of PC, and testosterone replacement therapy can achieve good results in patients with testosterone deficiency[28]. We speculate that this is due to the complex relationship between metabolic disorders and circulating androgens in men[1], which needs to be clarified by further studies.

OBESITY

Obesity is one of the important components of metabolic syndrome (MS), usually defined as BMI > 30 kg/m^2. Studies related to the relationship between obesity and PC have shown inconsistent results. To some extent, this inconsistency may be due to the different effects of obesity on different levels of PC, or T2DM confounding the association between obesity and PC risk[29]. In addition, the combination of a lower prostate-specific antigen (PSA) level, a larger prostate volume, and inaccurate digital rectal examinations in obese men make it more difficult to detect PC[30].

Recently, Choi *et al.* used nationally representative Korean population data to confirm that men with higher BMI are more likely to suffer from PC without the influence of confounding variables[31]. However, it is worth noting that in a large prospective cohort study, there was no correlation between obesity and PC[32]. Similarly, Gong *et al.* showed that obesity was not associated with a lower risk of PC in patients with T2DM, but obesity alone increased the risk of high-grade prostate cancer, while reducing the risk of low-grade prostate cancer[29]. In addition, Wright *et al.* found that obesity was negatively correlated with PC[33]. At the same time, Suarez Arbelaez *et al.* found that when BMI > 35 kg/m^2(OR 0.89) and BMI > 40 kg/m^2(OR 0.76), BMI became inversely associated with prostate cancer risk[34].

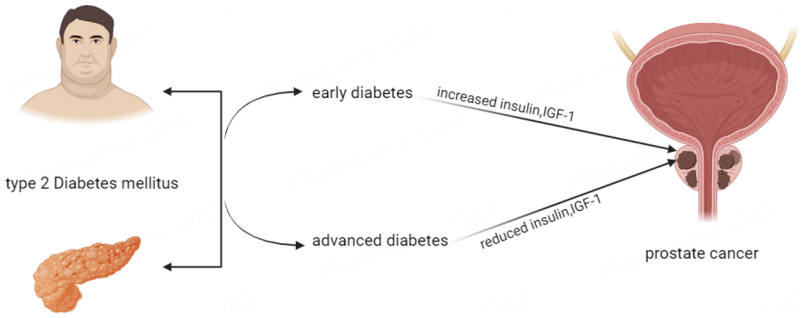

Figure 1. Changes in insulin and insulin-like growth factors during the development of PC in patients with early and advanced type 2 diabetes.

Race also plays a role in modifying the relationship between T2DM, obesity, and PC progression[30,35]. Barrington *et al.* studied the association between obesity and the risk of PC in African American (black American) and non-Hispanic white men and found that the association of obesity with increased prostate cancer risk was stronger in African Americans than in non-Hispanic white men[35]. Khan *et al.* studied the North Carolina PC treatment cohort and found that obesity was associated with PC progression only in whites and not in blacks[30]. Zhu *et al.*, who studied multi-ethnic populations, confirmed that obesity would increase the risk of invasive PC and found that obesity and diabetes were independently associated with intermediate and high-risk PC[36]. Studies have shown that patients with obesity and T2DM are more likely to have highly aggressive PC[37], and this relationship of increased aggressiveness is related to the reduction of adiponectin release from adipose tissue and the increase of leptin[37]. In vitro experiments have also confirmed that adiponectin inhibits the growth and proliferation of prostate cells, and antagonizes the proliferation of leptin and IGF-I in PC[38], while leptin can promote the progression of PC by promoting the proliferation, invasion and migration of PC cell lines PC3 and DU145, and inhibiting the apoptosis of tumor cells[39].

In conclusion, male patients with T2DM have a reduced risk of PC, and the mechanism may be related to HbA1c level, insulin level, IGF-1R expression, and circulating androgen concentration. Patients with PC should pay attention to monitoring and maintain a good HbA1c level. Active control of BMI in T2DM patients can reduce the risk of PC to a certain extent. At the same time, in clinical practice, we can utilize the concentrations of IGF-1R and circulating androgens in T2DM patients as screening parameters for identifying individuals at a high risk of developing PC. This approach can be employed to predict the high-risk group among T2DM patients for PC and facilitate early intervention in those at elevated risk.

In addition, recent studies have shown that metabolomics can be used as a relevant biomarker to identify the diagnosis, staging, and prognosis of PC and other cancers[40]. It has the potential to replace the current traditional methods of diagnosing cancer[41]. However, since there are few relevant studies, further large-sample prospective studies are needed to verify it in the future.

More importantly, studies have shown that people with T2DM and obesity warrant increased attention in research studies, because obesity combined with cardiovascular disease may cause poor prognosis[42]. Recent findings suggest that advances in our understanding of the pathophysiology, genetics, and epigenetics of obesity are expected to provide tailored management options. Therefore, careful risk assessment is necessary before intervention[40]. In conclusion, further investigation is warranted to determine the accuracy of the development of PC in individuals with T2DM and to elucidate specific regulatory mechanisms.

DECLARATIONS

Author's contribution

Designed the study: Zhanghuang C
Collected and analyzed the data: Zhanghuang C, Wang Z
Drafted the initial manuscript: Zhanghuang C, Wang Z
Revised the article critically: Zhanghuang C, Yan B
Reviewed and edited the article: Zhanghuang C, Yan B, Yao G

Availability of data and materials

Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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