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REVIEW ARTICLE

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Impact of metabolic disorders on prostate cancer growth: Androgen and insulin resistance perspectives

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Abstract

Background: A high prevalence of cancers in metabolic disorders, like metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM), recently has been noted, including prostate cancer (PC), which is androgen-sensitive. However, the pathological relationship among testosterone and insulin and insulin-like growth factor (IGF)-1 signaling in relation to MetS and T2DM with PC remains unclear.

Methods: Papers were reviewed, including those by the authors.

Results: In MetS or the initial stage of T2DM accompanying insulin resistance, insulin and IGF-1 signaling could be essential for PC growth. In the advanced stage of T2DM, the decrease in insulin secretion might work against PC growth. A decrease in testosterone concentration with T2DM also might suppress PC proliferation. Androgen deprivation therapy in patients with PC might increase the risk of MetS and/or T2DM and consequently cardiovascular events. Certain drugs for T2DM treatment, such as metformin and glucagon-like peptide-1 analog, potentially might be useful for the treatment of PC.

Conclusion: The improvement of insulin resistance appears to be essential for the prevention of PC growth. Further studies are needed to clarify the complicated pathophysiology of metabolic disorders in PC growth.

KEYWORDS

androgen, diabetes mellitus, insulin resistance, metabolic syndrome, prostate cancer

1 | INTRODUCTION

Several epidemiological studies have shown consistently that metabolic disorders that are characterized by hyperinsulinemia and insulin resistance, such as obesity and type 2 diabetes mellitus (T2DM), are associated with a significantly increased risk of cancer and cancer-specific mortality.[1] The links that underlie this association are not entirely clear and appear to involve a number of complex mechanisms. Although insulin is a major mediator of important metabolic functions, it is widely accepted that it might exert mitogenic functions through the activation of different signaling pathways. Hyperglycemia and increased free fatty acids in T2DM also are thought to cause oxidative stress, thus leading to DNA damage.[1,2] As a meta-analysis has suggested, the relationship between prostate cancer (PC) and T2DM or metabolic syndrome (MetS) is still under discussion.[3-7] However, a recent study has suggested that pre-existing T2DM also is associated with a higher level of mortality in patients with PC, similarly to other cancers.[8,9] In this review, the pathological relationship between obesity and/or T2DM with PC is examined, especially from the aspect of the impact of insulin resistance on PC growth.

2 | EPIDEMIOLOGICAL RELATIONSHIP BETWEEN PROSTATE CANCER AND METABOLIC SYNDROME

In an observational epidemiological meta-analysis that targeted >68 000 men, an increase in the body mass index (BMI) showed a weak correlation with the risk of developing PC (the relative risk was 1.05-fold a 5 kg/m^2 BMI increase). This relationship was much stronger in advanced PC.[10] Additionally, in a large-scale observational study on the relationship between MetS, based on the diagnostic criteria of the National Cholesterol Education Program, and PC, the increased risk of PC was 1.56-fold when more than three components of MetS were met.[11] However, no such relationship was observed in another report.[12] In a prospective study from Sweden, which tracked 2322 patients for 34 years, MetS was shown to be a significant risk factor for the development of PC, after excluding death from the other etiologies.[13] Hyperinsulinemia that is secondary to insulin resistance, as observed in MetS and early-stage T2DM, has been suggested as a possible risk factor in the development and exacerbation of PC.[8] Alternatively, the relationship between T2DM and PC has been shown in a report from the Health Professionals Follow-Up Study from 1986 to 2004 in the USA that T2DM is associated with a reduced risk of PC by 16%.[4] However, another study reported that such a risk reduction was observed after 5 years from the onset of T2DM.[14] The relative risk of PC also was reported to be decreased in studies of patients with T2DM who had been affected with T2DM for ≥6-15 years.[15] In patients with long-term and advanced T2DM, pancreatic β-cell exhaustion is assumed to take place and cause the decreased secretion of insulin. As insulin is known to be a growth factor for cancer in general, the reduction of the PC risk may be observed in long-term and advanced T2DM. In addition, serum testosterone (T) concentration has been shown, as described later, to decrease in T2DM. It is thus conceivable that a reduction in serum T in T2DM also could result in a decrease in the risk of developing PC, which is generally accepted to be an androgen-sensitive cancer. However, as described later, it is still controversial at present whether the relatively low concentration of T acts as suppressive or promotive with regard to PC progression.

Androgen-deprivation therapy (ADT), usually by a combination of androgen blockade and luteinizing hormone-releasing hormone agonist is the standard of care for patients with PC. The ADT has been reported to increase patients' visceral fat, thus leading to the risk of MetS and T2DM in observational studies.[16,17] The increased risk of developing MetS and T2DM leads to an increase in cardiovascular death, and indeed, in Europe and the USA, 30% of the patients with PC died of cardiovascular disease.[18] Although the prognosis of PC is relatively good, a concern with ADT therapy regarding its cardiovascular risk in Europe and the USA has been raised, but it almost remains unclear in Japan. In a prospective Japanese study[19] that targeted 58 men with PC who were treated with ADT for 6 months, the whole cohort did not show a significant change in arterial stiffness, as monitored with the Cardio-Ankle Vascular Index (CAVI), but 55.2% of the patients did show an increase in arterial stiffness. In addition, the low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio was higher in the group with, than without, an increased CAVI after 6 months of ADT, suggesting some impact of ADT on the lipid profile and successive development of arterial stiffness after ADT. However, more evidence concerning the impact of ADT on cardiovascular diseases in Japan is required.

3 | DOES INSULIN RESISTANCE PROMOTE THE PROLIFERATION OF PROSTATE CANCER?

Increased levels of serum insulin, C-peptide, or homeostasis model assessment-insulin resistance (HOMA-R) are indicators of insulin resistance in those with T2DM and have been shown to be risk factors for developing PC.[9] Insulin-like growth factor (IGF)-1 is regarded as an important growth factor in PC and shares a part of the downstream signaling pathways of insulin.[20] Even with 42 meta-analysis reports, an elevated IGF-1 concentration in the blood obviously increases the risk of PC (odds ratio: 1.21).[21] Insulin or IGF-1 binding to its IGF receptor (IGF-1R) activates a number of intracellular signaling pathways, especially the phosphoinositide 3-kinase (PI3K)/Akt pathway.[22] Specifically, increases in IGF-1 and/or IGF-1R expression[23-25] and the loss of the tumor suppressor gene, phosphatase and tensin homolog deleted from chromosome 10, elicit increased activity of the PI3K/Akt pathway and greatly contribute to PC progression. Recent studies also have revealed that high serum insulin levels, mostly observed in obese individuals, are associated with an increased incidence of PC.[26-28] The authors previously demonstrated that the transcription factor, Forkhead box protein O1, is a novel corepressor of androgen receptor (AR) transactivation and is functionally inactivated by the IGF-1 and insulin–PI3K–Akt signaling via Akt-mediated phosphorylation.[29] This is thought to be one mechanism by which AR is activated by IGF-1 and insulin signaling (Figure 1).[29] Even more interestingly, dihydrotestosterone (DHT)–AR stimulation resulted in the up-regulation of IGF-1 receptor expression in the PC cell line, lymph node carcinoma of the prostate (LNCaP) cells, and an amplification of the proliferative signal was found to occur (Figure 1).[29]

Concerning the involvement of adipocytokines and free fatty acids that also are related to the pathology of obesity and insulin resistance, leptin is reported to promote the PC cell proliferation in vitro and suppress apoptosis,[30] but the relationship between the serum leptin concentration and PC growth remains unclear.[31,32] Interestingly, a high concentration of serum adiponectin has been reported to decrease the risk of PC, independently of the BMI and serum C-peptide level.[32] As a mechanism, a direct inhibitory effect of adiponectin on the proliferation of tumor blood vessels[33] and tumor cells[34] has been suggested. The elevation of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-6 (IL-6), and IL-8 in association with MetS has been suggested to increase the PC risk via nuclear factor-kappa signaling.[31,35] However, saturated fatty acids that increase in the insulin-resistant state have been reported to promote PC growth by enhancing IGF-1 signaling, endoplasmic reticulum (ER) stress, and by impairing the innate immunity.[36] Epidemiologically, it has been

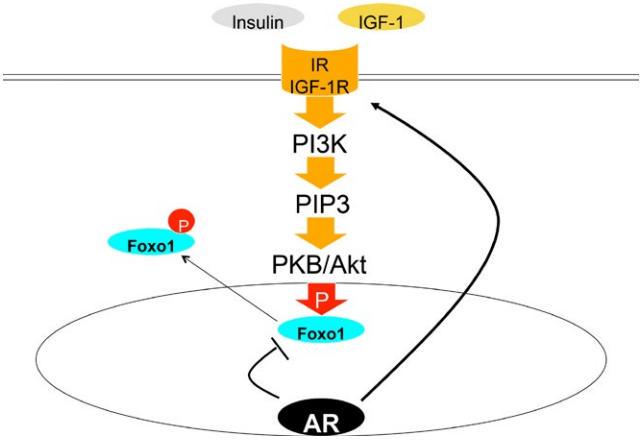

FIGURE 1 Insulin and insulin-like growth factor (IGF)-1 promote prostate cancer growth via androgen receptor (AR) transactivation. Forkhead box protein O1 (Foxo1) interacts with the C-terminal region of the AR in the presence of a ligand (androgens, such as dihydrotestosterone [DHT]) and interferes with the ligand-induced subnuclear compartmentalization of the AR, including the liganded receptor–target gene promoter interaction, thereby shutting down the AR transactivation. The modification of Foxo1 by the phosphoinositide 3-kinase (PI3K)-Akt system, which is activated by IGF-1 and/or insulin, weakens the Foxo1–AR interaction and ameliorates the inhibitory effects of Foxo1 on the AR.[28] IGF-1R, IGF receptor; IR, insulin receptor; PIP3, phosphatidylinositol-3,4,5-triphosphate; PKB, protein kinase B; P, phosphorylation

reported that the ingestion of polyunsaturated fatty acids of the ω3 series decreases the risk of PC, while the intake of the ω6-type polyunsaturated fatty acids increases the same risk.[37]

4 | RELATIONSHIP BETWEEN ANDROGENS AND PROSTATE CANCER

The relationship between T and PC is well known to be androgen-sensitive. The administration of DHT promotes the proliferation of PC cells and increases the amount of in vitro prostate-specific antigen. The AR antagonists (anti-androgens) antagonize the growth-promoting effect of DHT or T on PC. Clinically, it also has been confirmed that the survival rate of patients with PC improves as the T concentration decreases due to ADT. Consequently, it is clear that the serum T concentration is closely involved in the proliferation and progression of PC. While the promoting effect of androgens on tumor growth in patients with PC has been well established, it is not clear whether androgens can affect the onset of PC. According to 18 prospective studies (including a total of 3846 PC patients and 6438 control persons), there was no significant association between the serum concentrations of T, free T, estradiol, and dehydroepiandrosterone sulfate and the risk of PC.[38] Several meta-analyses have shown that PC does not increase as a result of exogenous T administration.[39-41] It is highly likely that endogenous T will promptly promote tumor growth in patients who already have latent or overt PC and that exogenous T administration in such patients should be strictly avoided. However, studies on the relationship between PC and the serum T concentration recently have reported that patients with low T values in the blood have more advanced PC, with poor differentiation,[42,43] suggesting that some cases of PC might be rather sensitive to T, even in the low concentration range. However, with such PC progression, an adaptation of AR signaling might function under low or absent androgen levels.[44]

5 | RELATIONSHIP BETWEEN ANDROGENS AND METABOLIC SYNDROME OR TYPE 2 DIABETES MELLITUS

Many meta-analyses have revealed that 30%-50% of middle-aged and elderly men with T2DM show decreased serum T levels. In a prospective study, men with a relatively high serum T level were reported to show a 42% risk reduction of future T2DM.[45] A similar relationship has been observed between MetS and the serum T level.[46,47] When the intrinsic serum T value of young healthy adults was lowered by the administration of gonadotropin-releasing hormone (GnRH) analog, an increase in the body fat percentage and a decrease in the resting energy consumption were observed,[48] strongly suggesting that the decrease in T concentration causes fat accumulation in men. As a fundamental study on the relationship between T and visceral fat obesity, the authors showed that male AR knockout mice exhibited late-onset visceral fat obesity that was related to decreased energy expenditure.[49] In addition, as mentioned earlier, during the course of ADT by GnRH agonists in patients with PC, an increase in body fat leads to MetS and the rapid aggravation of T2DM.[16,17] Lowered T bioactivity has been reported to increase lipoprotein lipase activity and triglyceride (TG) catabolism in the blood, causing TG uptake into the adipose tissue.[50] The exogenous administration of T decreases the amount of body fat and improves insulin resistance.[50] In addition, the endogenous DHT action system also suppresses the vascular endothelium and arteriosclerosis. Together with others, the authors have shown that a reduction of endogenous T accelerates the onset and progression of T2DM and arteriosclerosis.[51,52] Therefore, ADT surely is an important therapy for patients with PC, but it is also unclear whether a low level of T due to ADT can be linked to PC progression and/or castration-resistant PC in the long term by inducing MetS and hyperinsulinemia.

Metabolic syndrome or T2DM is thought to cause low T levels. Specifically, fat accumulation in the body is considered to suppress gonadotropin secretion, mediated by inflammatory cytokines from adipose tissue or by leptin resistance in the hypothalamus. With this hypothesis, a vicious cycle of low T and fat accumulation has been proposed.[50]

6 | DRUGS FOR TYPE 2 DIABETES MELLITUS AND PROSTATE CANCER

The oral hypoglycemic agent, metformin, is known for its anti-cancer effect. Metformin has been studied previously in vitro as a possible agent that could have a protective effect against PC or to delay disease

progression.[53-56] Clinical and epidemiological studies have been inconclusive because no impact of metformin use on PC risk[56,57] and a possible beneficial impact on disease progression and survival[58,59] have been reported, respectively.

Incretin therapy, which includes the delivery of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide (GLP)-1 receptor (GLP-1R) agonists, has become a popular treatment for T2DM. Recently, much attention has focused on incretin because of its reported tissue-protective effects beyond merely lowering glucose levels.[60] The authors revealed the anti-PC effect of Exendin (Ex)-4, a GLP-1, both in vivo and in vitro.[61] Particularly, it was observed that GLP-1R expression in human PC tissue and PC cell lines and Ex-4 attenuated PC growth both in vitro and in vivo via the inhibition of extracellular signal-regulated kinase–mitogen-activated protein kinase activation, leading to the inhibition of cell proliferation (Figure 2).[61] The authors' further study revealed that both Ex-4 and metformin significantly decreased PC cell proliferation, as shown by the decrease of Ki67 expression.[62] In this study, metformin, but not Ex-4, induced apoptosis in the LNCaP cells through the activation of 5′ adenosine monophosphate (AMP)-activated protein kinase (Figure 2). The combined treatment of Ex-4 and metformin attenuated PC growth more than by the separate treatments.[62]

7 | CONCLUSION

The relationships between T and PC, between insulin and IGF-1 with PC, and between T and MetS or T2DM are mutually and complicatedly

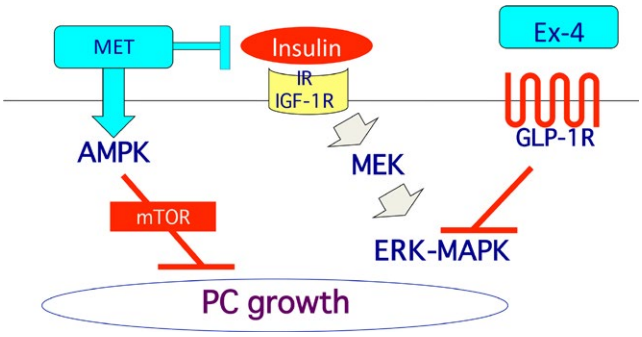

FIGURE 2 Effect of glucagon-like peptide (GLP)-1 analog and metformin on a prostate cancer (PC) cell line, lymph node carcinoma of the prostate (LNCaP), cells. The GLP-1 analog, Exendin (Ex)-4, attenuates PC growth through the inhibition of extracellular signal-regulated kinase–mitogen-activated protein kinase (ERK–MAPK) activation. Metformin attenuates cancer growth indirectly through the reduction in the serum insulin and insulin-like growth factor (IGF)-1 concentration that are caused by an improvement in insulin sensitivity and directly through cell cycle arrest and the inhibition of the mammalian target of rapamycin (mTOR) following 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation. Metformin, but not Ex-4, activated AMPK and induced apoptosis in the LNCaP cells. Exendin-4 and metformin attenuated the PC growth by inhibiting proliferation and metformin inhibited proliferation by inducing apoptosis. The combined treatment of Ex-4 and metformin attenuated the PC growth more than by the separate treatments.[60,61] GLP-1R, GLP receptor; IGF-1R, IGF receptor; IR, insulin receptor; MEK, mitogen-activated protein kinase kinase; MET, metformin

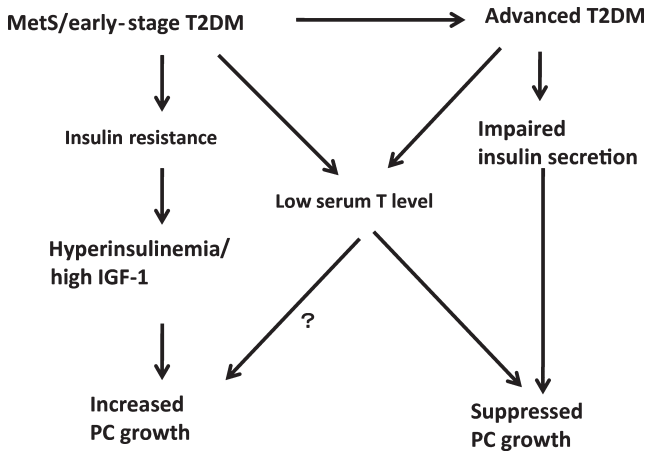

FIGURE 3 Relationship between metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) with prostate cancer (PC) (hypothesis). IGF, insulin-like growth factor; T, testosterone

associated. Based on the premise that PC is an androgen-sensitive cancer, the following hypothesis can be considered from the viewpoint of PC growth (Figure 3). In MetS or the initial stage of T2DM accompanying insulin resistance, hyperinsulinemia possibly works in a manner of promoting PC. Insulin and IGF-1 signaling might be essential for this mechanism. However, in the advanced stage of T2DM accompanying pancreatic β-cell failure, the decrease of insulin secretion might work against PC growth. It is also assumed that a decrease in the serum T concentration accompanying T2DM suppresses PC proliferation. Similarly, ADT in patients with PC suppresses PC growth, but it also might cause MetS and/or T2DM. The reduction of T is also a risk for arteriosclerosis, which could lead to an increase in cardiovascular events, combined with vascular disorders that are related to T2DM itself. Further studies are needed to clarify the complicated pathophysiology of T, PC, and MetS and T2DM. Finally, certain drugs for T2DM treatment, like metformin and GLP-1 analog, might be useful and practical for the suppression of PC growth.

DISCLOSURES

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committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. All the institutional and national guidelines for the care and use of laboratory animals were followed.

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