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Short Communication

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Diabetes and prostate cancer, an ambiguous relationship between two pathologies of high worldwide prevalence

Summary

Patients with diabetes mellitus (DM) have a lower risk of developing Prostate Cancer (PCa). This apparent "protection" is mainly due to a deficit in the insulin signal and a state of hypogonadism associated with insulin resistance (IR), which would bring about a decrease in available testosterone levels. On the other hand, the concomitance of DM in patients with PCa leads to higher morbidity and mortality, even in tumor stages with a good prognosis, in the context of a lower response rate to cancer treatments and a higher frequency of tumor recurrence. Glycemic control directly affects these prognostic factors, since an adequate clinical-nutritional approach is mandatory in this dual relationship pathology.

Keywords: cancer, prostate, diabetes mellitus, insulin resistance

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Materials and methods

A bibliographic search was carried out in the Pubmed database under the slogan "Prostate cancer AND diabetes" finding a total of 2634 articles from which those that had been published in the last 5 years were selected, emphasizing Reviews and Meta-analysis, finally obtaining the sum of 228 articles from which information was extracted to carry out the following review.

Epidemiology

PCa and DM are two pathologies with high incidence and prevalence worldwide, constituting a true Public Health problem.[1,2]

PCa is the second type of cancer in order of frequency in men and the sixth when analyzing the cause of death from cancer in the world. It is common in men older than 65 years and rare in men younger than 40 years of age. Risk factors include: age, family history, and ethnicity.[2]

For its part, DM is a chronic progressive disease, currently considered a pandemic and with not very encouraging data that shows an exponential growth.[3,4]

Research studies show that DM is inversely related to the risk of Prostate Cancer and this relationship is statistically significant.[1]

In a study using the Swedish Prostate Cancer database and the National Diabetes Registry, Fall et al. reported a reduced risk of PCa in all risk categories (OR = 0.80, 95% CI = 0.76–0.86) for men with DM2 compared with men without DM2, especially low-risk PCa (OR = 0.71, 95% CI = 0.64-0.80). The results also demonstrate a persistent decrease in the risk of PCa for all antidiabetic drugs regardless of the duration of treatment. Given the prevalence of DM2 throughout the world, it is important to bear in mind that both the disease per se and its treatment may protect some men from PCa, although not necessarily from developing high-risk disease.[2]

On the other hand, it is noteworthy that DM does not have a negative impact on the survival of patients with PCa. Furthermore, neither PCa nor its treatment affect glycemic control (Table 1).[5,6]

Table 1 Relative risk of tumors in men with diabetes mellitus

Type of tumor	Relative risk (RR)	IC 95%
Prostate	0.81	0.76-0.93
Lymphomas	0.98	0.79-1.22
Bladder	1.24	1.08-1.42
Colo-rectal	1.29	1.15-1.44
Biliary	1.31	1.17-1.47
Pancreas	1.73	1.59-1.88
Liver	2.1	1.59-2.78

Modified from Duarte et al.[6]

Pathophysiology and relationship between Prostate Cancer and Diabetes Mellitus

It is estimated that the risk of PCa in subjects with DM is 16 to 26% lower than in non-diabetic men.[7] This protective effect of DM is due to metabolic and hormonal pathophysiological changes, mainly associated with insulin signal deficit and hypogonadism.[8] On the other hand, testosterone levels decrease with age in men and the incidence of PCa increases. In fact, the relationship between lower testosterone levels in patients with DM2 could be explained by the fact that this is a disease that mainly affects the elderly and that physiological testosterone levels decrease with increasing age.[9]

In DM2, an IR component is described, that leads to hyperinsulinemia as an attempt to overcome it and control blood glucose levels. The lack of adequate glycemic control leads to decreased insulin and testosterone levels and thus to a lesser trophic effect at the prostate level, because of this hypogonadism (Figure 1).[8]

Insulin is associated with the growth of both normal and malignant prostate cells, but the decrease in the insulin signal can have an inhibitory effect on the development of cancer cells,[10] for which hyperinsulinemia and IR with alteration of the IGF pathway -1, and the decrease in testosterone concentration would be the intervening mediators in this decrease in risk and not insulin per se.[9]

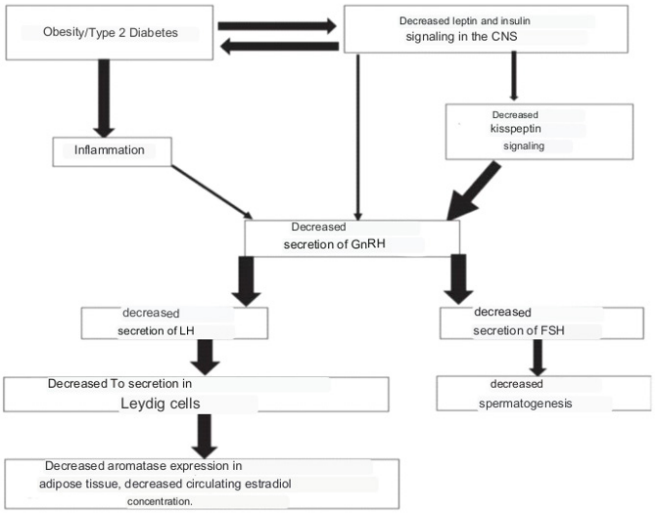

Figure 1 Hypogonadism in men with Diabetes.

Elevated testosterone levels increase the risk of PCa, testosterone is converted to a more potent androgen dihydrotestosterone, and both testosterone and dihydrotestosterone increase the proliferation of both normal and malignant prostate cells.[11] Testosterone increases the development of Prostate Cancer 2.34 times due to effects on DNA that increase the transcription and possibly the proliferation of malignant cells. Studies carried out in animals and in humans suggest that patients with DM have low testosterone levels with a decreased risk of the appearance of PCa.[4,11]

In addition to what has been described, the prolonged decrease in the insulin signal would lead to a decrease in leptin levels, a hormone produced by adipose tissue that regulates the use of body energy and is potentially associated with a greater risk of PCa.[10] Men with large prostate tumors have higher plasma leptin concentrations compared to those with small tumors. Several works have reported that in DM1 and 2 the circulating levels of leptin decrease dramatically. In any case, the exact role of leptin in this pathology remains unclear.[9]

Another reason why insulin signal deficiency would lead to a lower occurrence of PCa is that it limits the bioavailability of insulin-like growth factor (IGF1) which, when bound to its receptor, stimulates the proliferation of malignant prostate cells.[10]

The inverse association between DM and PCa has also been related to the presence of factors that independently influence both pathologies, such as changes in lifestyle, changes in the eating plan with replacement of foods that contain nutrients that reduce the proinflammatory and oncogenic state. In addition, it is very frequent that subjects with DM are treated with other drugs such as statins that could have an additional role in the potential development of PCa, although further studies are required to confirm this hypothesis.[1,12,13]

Some studies have found a relationship between the expression of some genes and this relationship between PCa and DM, such as HNF1B and JAZF1, but their role is still unclear.[9]

Microvascular complications could also cause microvascular dysfunction and tissue ischemia in prostate cells with limitation of their growth.[9]

Although in adults the inverse relationship between DM and PCa is independent of the BMI (Body Mass Index), in pre-adults obesity is related to low testosterone levels, which would have a protective

effect in relation to the evolution and metastasis of prostate cancer and this could influence later life.[1] Reduced energy intake from fat, limited intake of saturated fatty acids and consumption of omega-3 fatty acids, which are commonly recommended for patients with DM, could also have a preventive role against PCa initiation and recurrence. Recommending large amounts of vegetable and fruit intake, and the use of whole grains and taking some antioxidant supplements are also common approaches in the management of DM that could have an important role in PCa prevention. However, all relevant studies are limited.[9]

In general, the relationship between DM and PCa aggressiveness is not consistent. It could be that DM has less of a protective effect against the aggressive or advanced stages of this disease. A possible explanation for this phenomenon is that DM could have a protective role in the initiation phase, but not in the progression phase of PCa.[9]

There is also a lower PCa detection rate among individuals with DM2, which could be due to the association between DM2 and increased body fat mass with reduced androgen levels, which could lead to lower PSA levels in serum because the testosterone level controls the production of PSA.[6,14,15]

This inverse association between DM and PCa is apparently not related to the age of the DM patient or the time elapsed since its diagnosis.[2]

Glycemic control at the time of diagnosis of Prostate Cancer and after Radical Prostatectomy (RP)

No significant difference was found in terms of post-RP results when comparing patients with or without DM; but after RP a significant difference was found between patients with poor glycemic control represented by an elevated A1c (equal to or greater than 6.5%) with worse clinical evolution, positive resection margins, metastasis and lymph node invasion when compared with those patients with good glycemic control and low A1c (less than 6.5%).[1,16]

Patients with elevated A1c have a higher risk of recurrence after RP, evidenced by a PSA level greater than 0.2 ng/ml measured on 2 consecutive occasions within 4 weeks of performing the RP.[1,16]

Adequate glycemic control is a significant factor influencing oncological outcomes after RP.[1]

It is not a minor fact that patients with glycemia equal to or greater than 100 mg/dl have a 50% increased risk of PCa recurrence, and hyperglycemia has had a significant direct correlation with PCa mortality.[1,16]

There are several hypotheses that suggest the underlying mechanisms by which poor glycemic control influences the evolution and prognosis of PCa; malignant cells use more glucose than normal cells, the presence of hyperglycemia can lead to hyperinsulinemia with activation of the IGF 1 pathway, generating a more aggressive form of PCa. On the other hand, hyperglycemia leads to the appearance of glucotoxicity and lipid peroxidation that are genotoxic, damaging DNA and favoring the development of malignant cells. Poor glycemic control could alter the use of ascorbic acid by cells leading to a state of immunosuppression. The chronic inflammatory state that patients with DM present causes the release of cytokines that promote the progression of PCa. Another factor to take into account is the relationship between A1c and testosterone levels; Several studies have shown that low preoperative testosterone levels are related to a worse postoperative prognosis with greater recurrence of PCa.[1,2,16]

Metformin treatment for prolonged periods did not prove to improve the prognosis or survival of patients with PCa after RP.[1,17–19]

Some studies have suggested a possible synergism between metformin treatment and radiotherapy, since both affect the AMP Kinase and mTOR pathway, which decreases cell growth and cancer progression. In addition, preclinical research suggests that metformin inhibits the growth of malignant cells in advanced PCa, improving the survival of patients. These controversial results on the effect of metformin on PCa require more randomized and prospective studies that include variables such as the concomitant use of other drugs and other comorbidities.[1,5,17–19]

From all of the above, it can be deduced that adequate glycemic control is essential before, during and after PCa treatment, as said control influences its evolution and prognosis. This often involves the use of insulin, especially in the period of active cancer treatment.[1,20]

Thus, the suspicion and timely diagnosis of cancer is also very important in a patient with DM with a history of good glycemic control who presents hyperglycemic values without detecting other factors that may cause it, since adequate glycemic control within 30 days modifies the percentage of therapeutic success significantly.[1,20,21]

Conclusion

There is an inverse association between DM and CaP. This relationship implies a deficit in the insulin signal, decreased testosterone (hypogonadism), IGF 1 bioavailability and Leptin levels.

The relationship between PCa and DM does not observe an association with the age of the patient with DM or with the time of evolution of the DM.

The results after RP in terms of evolution and prognosis were not different in subjects with or without DM, however poor glycemic control (A1c > 6.5%) is associated with lower overall mortality, a lower rate of postoperative complications, and a lower rate of of recurrence.

Adequate glycemic control is key before, during and after PCa treatment, since it influences its evolution and prognosis.

Given the suspicion of PCa in a patient with DM, it is mandatory to ensure good early glycemic control in order to obtain benefits in any of the oncological treatment modalities.

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Conflicts of interest

Authors declare that there is no conflict of interest exists.

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