

RESEARCH ARTICLE

Diabetes Mellitus and HbA1c Levels Associated with High Grade Prostate Cancer

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Abstract

Purpose: The aim of this study to analyze the association between history of diabetes mellitus (DM) with risk of prostate cancer (PCa) and cancer grade among men undergoing radical prostatectomy for PCa. **Materials and Methods:** 50 patients with DM and 50 patients without DM who underwent radical prostatectomy (RP) were included in the study. Age at biopsy, height, weight, digital rectal examination (DRE), pre-biopsy PSA levels, prostate volume, histopathologic diagnosis after surgery and gleason scores were collected data from all patients. Histologic material obtained at biopsy was given a Gleason score; tumours with a Gleason score ≥ 7 were considered high grade and < 7 were considered low grade. **Results:** The mean age at the time of biopsy was 63.7 in patients with DM and 61.6 in patients without DM. Diabetic men had significantly lower PSA levels ($p=0.01$). Mean PSA level 7.04 ± 2.85 in patients with DM and 8.7 ± 2.86 in patients without DM, respectively. Also, diabetic men had higher RP tumor grade than men without DM ($p=0.04$). We found that HbA1c levels were higher in patients who have high grade prostate cancer ($p<0.05$). **Conclusions:** Diabetic men undergoing RP have lower PSA levels and have significantly higher grade PCa. We must be careful for screening PCa in patients with DM. Although the patients had lower PSA levels, they might have high grade disease.

Keywords: Diabetes mellitus - prostate cancer - HbA1c - gleason score - PSA

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Introduction

Diabetes and cancer are 2 common severe chronic diseases that lead to many deaths. Today, there are more than 250 million people with diabetes worldwide; and this number is expected to reach 380 million in 20 years (Vigneri et al., 2009). Several studies have suggested that diabetes significantly increases the risk for different cancers. One of these cancers; prostate cancer (PCa) and diabetes mellitus (DM) are very common conditions in the contemporary ageing population. An inverse association of diabetes with prostatic cancer has been noted in several studies, which may be due to reduced testosterone levels in diabetes, altered insulin and leptin concentrations, statins and metformin use, and changes in diet and lifestyle in controlling diabetes (Kasper and Giovannucci, 2006; Avci et al., 2013; Fall et al., 2013; Demir et al., 2014). Several studies have reported decreased PCa risk among those with DM, and others found either no protective effect or even an elevated risk (Bonovas et al., 2004; Gong et al., 2006; Leitzmann et al., 2008; Hong et al., 2011; Moreira et al., 2011; Wu et al., 2011; Long et al., 2012; McGrowder et al., 2012; Balasubramaniam et al., 2013; Xu et al., 2013). For example, Kasper and Giovannucci (Kasper and Giovannucci, 2006) performed a meta-analysis of 19 studies on this subject published between 1971 and

2005. They reported that the pooled relative risk for prostate cancer among diabetics was 0.84 (95%CI 0.76-0.93), indicating that patients with DM have nearly a 20% lower risk of developing prostate cancer. In addition, the mechanism through which DM and prostate cancer are related has not been fully elucidated. Men with DM are known to generally have lower prostate-specific antigen (PSA) level but larger prostate size than others not having DM (Hammarsten and Hogstedt, 2001; Berger et al., 2005; Werny et al., 2006; Fowke et al., 2007; Turgutalp et al., 2013). Also, it can be suggested that the reported protective effect of DM may be due to the differences in PCa screening among diabetic and non-diabetic patients.

Also, it is still unclear whether this correlation is consistent for all tumor grades. Recently, some authors (Leitzmann et al., 2008; Wu et al., 2011) classified the correlation between DM and PCa according to tumor grade and have reported that DM mainly decreases the risk of low-grade tumors and, to a lesser degree, the risk of high-grade tumors. Consequently, it is plausible to assume that DM changes the proportions of PCa grades favoring high-grade tumors. Recent analyses of patients undergoing radical prostatectomy (RP) have shown that DM is associated with a higher PCa grade (Jayachandran et al., 2010). However, a previous analysis of the CaPSURE database found no association between DM and PCa

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aggressiveness (Chan et al., 2005).

In present study, we want to analyze the association between history of DM with prostate cancer grade among men undergoing radical prostatectomy for PCA. We compared PSA levels, Gleason score levels, stage and prostate volume between the patients with and without DM who underwent radical prostatectomy (RP).

Materials and Methods

After obtaining Institutional Review Board approval, we retrospectively determined our 5 years datas and collected data from 100 consecutive patients who underwent RP at our hospital. 50 patients with DM and 50 patients without DM were included in the study. The patients' ages, family histories and other comorbidities from DM were similar between two groups. We choosed similar patients for controlling to reduce bias in selection. For patients with a history of DM, hypoglycaemic medication use, fasting glucose and hemoglobine A1c (HbA1c) measurements were retrospectively obtained from the medical records. Type of diabetes (Type 1 or Type 2) was not recorded but age at diagnosis was; most of men were older than 50 years at the onset of diabetes so were likely to have Type 2 diabetes. Also, diabetes duration was not recorded from medical records, because of that we could not evaluate the effect of diabetes duration on prostat cancer. This is the limitation of our study.

Age at biopsy, height, weight, digital rectal examination (DRE), pre-biopsy PSA levels, prostate volume, histopathologic diagnosis after surgery and gleason scores were collected data from all patients. Body mass index (BMI) was calculated as weight (Kg) divided by height squared (meters). Patients underwent transrectal ultrasound- guided systematic extended biopsies (12-14 cores) for the evaluation when the PSA level was >2.5 ng/mL or digital rectal examination (DRE) was abnormal. Prostate volume was determined by transrectal ultrasound in routine. After the diagnosis of prostate adenocarcinoma, all patients underwent RP. The pathologic gleason score (GS) was assigned according to the 2005 International Society of Urological Pathology consensus (Epstein et al., 2005). As known and also in a previous study, GS was pooled into 3 grades: low- (GS≤6), intermediate- (GS=7), and high-grade (GS≥8) prostate cancer (Van Praet et al., 2013). In an other study, Histologic material obtained at biopsy was given a Gleason score; tumours with a Gleason score ≥7 were considered high grade and <7 were considered low grade (Oliver et al., 2004). Because of statistical analysis, we included the GS=7 in high grade GS like this previous study.

All patients provided written informed consent before biopsy and RP.

Statistical analysis

The baseline characteristics of the controls and the subjects with MetS were compared using a two sample t-test or Mann-Whitney U-test for the continuous variables and a chi-square test or Fisher's exact test for the categorical variables. All statistical tests were two-tailed, and statistical significance was defined as p<0.05. All

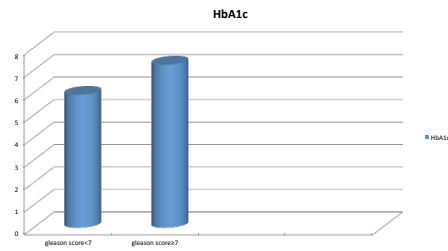


Figure 1. An HbA1c Level in Patients Who Have RP Gleason Score <7 and ≥7. Patients with high grade prostate cancer have higher HbA1c levels, statistically (p<0.001)

Table 1. Values of Diabetic and Nondiabetic Patients Who Underwent RP

	Men with DM	Men without DM	p value
No. of patients	50	50	
Age (mean±sd)	63.74±5.94	61.58±6.14	0.075
BMI (mean±sd)	28.93±2.89	27.35±2.93	0.011*
HbA1c levels (mean±sd)	7.29±0.81	5.36±0.32	<0.001*
preop PSA (mean±sd)	7.04±2.85	8.70±2.86	0.001*
PV (mean±sd)	47.06±16.78	51.16±18.2	0.316
RP gleason score≥7 (n%)	22 (44%)	9 (18%)	0.004*
RP gleason score<7 (n%)	28 (56%)	41 (82%)	

*Significant difference between values, DM: diabetes mellitus, RP: radical prostatectomy, BMI: body mass index, PSA: prostate specific antigen, PV: prostate volume

analysis were conducted using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

The mean age at the time of biopsy was 63.74 in patients with DM and 61.58 in patients without DM. There were no statistical difference between groups. Body mass indexes (BMI) were higher in men with DM than men without DM (p=0.11). Mean values of BMI was shown in Table 1. Diabetic men had significantly lower PSA levels (p=0.01). Mean PSA level 7.04±2.85 in patients with DM and 8.7±2.86 in patients without DM, respectively. There was no statistical difference for clinical stage between groups. Most patients in both groups had T1cN0M0 clinical stage. However, diabetic men had higher RP tumor grade than men without DM (p=0.04). 22 men had gleason score≥7 (44%) in diabetic group and 9 men had gleason score≥7 (18%) in nondiabetic group. We found that HbA1c levels were higher in patients who have high grade prostate cancer (p<0.05). We also evaluated the association between HbA1c levels and gleason scores with multipl logistic regression. Mean HbA1c levels were 5.91±0.46 in patients who had lower gleason scores and 7.25±0.74 in patients who had higher gleason scores, respectively. Higher HbA1c levels were significantly associated with the higher gleason score levels (p<0.05).

We found no correlation between DM and prostate volume in patients who underwent RP (p=0.316). Mean prostate volume was 47.0 ±16.78 in patients with DM and 51.16±18.2 in patients without DM. All values of patients with and without DM were shown in Table 1.

Discussion

Numerous studies have shown that DM may be

associated with a decreased risk of prostate cancer (Bonovas et al., 2004; Kasper and Giovannucci, 2006; Avci et al., 2013); however, less is known about its relationship between DM and prostate cancer grade. As for PCa grade, previous studies reported that patients with diabetes had a significantly higher percentage of developing high grade tumors among patients undergoing biopsy (Moreira et al., 2011), radical prostatectomy (Abdollah et al., 2011) or radiation therapy (Kang et al., 2012), which suggested DM to be a significant risk factor associated with the occurrence of high grade PCa.

In a published study from CaPSURE, a multicenter cohort of men all with prostate cancer, did not find any association between DM and grade at the time of diagnosis (Chan et al., 2005). Also, a recent study of the SEER population found no association between DM and disease aggressiveness, which included pathological Gleason score and local vs regional disease (Pierce et al., 2008).

Conversely, in an other study, DM was significantly associated with greater risk of high-grade disease (Daniel and Moreira, 2011). Like this study, in our series we found significant correlation between DM and high grade PCa in RP specimens. 22 of 50 diabetic men who underwent RP, had high grade disease. 22 men's gleason scores were ≥ 7 . The rate of low-grade PCa was apparently lower in patients with DM. Differently from this study, we also evaluated the patients' HbA1c levels and compared to PCa grade. The patients who have high grade PCa, also have higher HbA1c levels. Like our results, in a study of 247 men with DM and PCa, increasing HbA1c levels were significantly associated with a greater risk of pathological Gleason score $\geq 4+3$. In contrast, they did not find any statistically significant association between HbA1c tertiles and extracapsular extension, positive surgical margins, seminal vesicle invasion, or nodal metastasis (Howard et al., 2010). We can not fully explain why increasing HbA1c tertiles were associated with higher pathological Gleason score. Given that DM produces an environment unfavorable to the development of PCa, one possible explanation is that prostate tumors that do arise in diabetic men are of a more aggressive phenotype - recapitulating a theme of natural selection. It may be the case that the selected tumors may grow even more aggressive due to higher serum glucose levels reflective of poor glycemic control.

In a previous study, a retrospective analysis of 1,262 men treated with RP within the Shared Equal-Access Regional Cancer Hospital database demonstrated that DM was associated with a greater pathologic GS and seminal vesicle invasion (Jayachandran et al., 2010). An other study, demonstrated that DM was associated with greater biopsy GS (Hiroshi Fukushima et al., 2012). Deficiency of this study may be that a discordance of approximately 30% between the GS from biopsies and that from the RP specimens (true results) has been reported to date. Because of these deficiency, we used the pathologic specimens from RP materials for true results.

In a prospective cohort study of Caucasian men, ages 40-79, serum PSA levels increased at a rate of 3.6% per year. Older men had more rapid increases in serum PSA levels compared to younger men, and men without diabetes

had more rapid increases serum PSA levels compared to men with diabetes (Lauren et al., 2011) although data are not unequivocal (Woo et al., 2013). In an other study, Muller et al. (2009) found men with elevated and highly elevated hemoglobin A1C levels had 15% and 29% lower serum PSA levels, respectively. Men who were on insulin treatment and oral diabetic medications also had lower serum PSA concentrations (Muller et al., 2009). Using the National Health and Nutrition Examination Surveys, Werny and colleagues found 22% lower average serum PSA levels among men with type 2 diabetes (Werny et al., 2006). In present study, we also found that the diabetic men have lower PSA levels than nondiabetic men. This could explain, at least in part, the protective effect of DM seen on a population level by many investigators, because men with DM are less likely to undergo prostate biopsy and thus are less likely to be diagnosed with PCa (Waters et al., 2009).

Additionally, a gene predisposing to diabetes (TCF7L2) was found to be associated with advanced/high-grade (but not localised/low-grade) prostate cancer, suggesting that associations of diabetes with more aggressive prostate cancer may differ from more indolent forms. Further studies are needed for explanation this associations.

The present study is limited by the retrospective nature of our cohort. Our population represents patients at high risk for prostate cancer (elevated PSA and/or abnormal DRE) and thus may not be generalizable to all men at risk of prostate cancer. Moreover, we did not assess information on physical activity or diet, which are associated with DM, risk of prostate cancer, and potentially cancer grade at diagnosis (Antonelli et al., 2009). Finally, given DM is associated with other diseases and patients with DM usually receive specific therapeutic interventions (e.g., insulin therapy) and these data were also unavailable for all patients, we were not able to control for these potential confounders. Thus, whether our observations reflect the underlying disease (i.e., DM) or the treatment of the disease require further study.

In conclusion, diabetic men who underwent RP, have lower PSA levels and have significantly higher grade PCa. We must be careful for screening PCa in patients with DM. Although the patients had lower PSA levels, they would have high grade disease. Larger and multicenter studies are need to confirm our suggestion.

References

- Abdollah F, Briganti A, Suardi N, et al (2011). Does diabetes mellitus increase the risk of high-grade prostate cancer in patients undergoing radical prostatectomy? *Prostate Cancer Prostatic Dis*, **14**, 74-8.
- Antonelli JA, Jones LW, Banez LL, et al (2009). Exercise and prostate cancer risk in a cohort of veterans undergoing prostate needle biopsy. *J Urol*, **182**, 2226-31.
- Avci CB, Harman E, Dodurga Y, et al (2013). Therapeutic potential of an anti-diabetic drug, metformin: alteration of miRNA expression in prostate cancer cells. *Asian Pac J Cancer Prev*, **14**, 765-8.
- Balasubramaniam G, Talole S, Mahantshetty U, Saoba S, Shrivastava S (2013). Prostate cancer: a hospital-based

- survival study from Mumbai, India. *Asian Pac J Cancer Prev*, **14**, 2595-8.
- Berger AP, Deibl M, Halpern EJ, et al (2005). Vascular damage induced by type 2 diabetes mellitus as a risk factor for benign prostatic hyperplasia. *Diabetologia*, **48**, 784-9.
- Bonovas S, Filioussi K, Tsantes A (2004). Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* **47**, 1071-8.
- Chan JM, Latini DM, Cowan J, Duchane J, Carroll PR (2005). History of diabetes, clinical features of prostate cancer, and prostate cancer recurrence-data from CaPSURE (United States). *Cancer Causes Control*, **16**, 789-97.
- Demir U, Koehler A, Schneider R, et al (2014). Metformin anti-tumor effect via disruption of the MID1 translational regulator complex and AR downregulation in prostate cancer cells. *BMC Cancer*. **31**, 14-52.
- Epstein JI, Allsbrook WC Jr, Amin MB, et al (2005). The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol*, **29**, 1228-42.
- Fall K, Garmo H, Gudbjornsdottir S, et al (2013). Diabetes mellitus and prostate cancer risk; a nationwide case-control study within PCBaSe Sweden. *Cancer Epidemiol Biomarkers Prev*, **22**, 1102-9.
- Fowke JH, Motley SS, Cookson MS, et al (2007). The association between body size, prostate volume and prostate-specific antigen. *Prostate Cancer Prostatic Dis*, **10**, 137-42.
- Fukushima H, Masuda H, Kawakami S, et al (2012). Effect of diabetes mellitus on high-grade prostate cancer detection among Japanese obese patients with prostate-specific antigen less than 10ng/mL. *Urology*, **79**, 1329-35.
- Gong Z, Neuhaus ML, Goodman PJ, et al (2006). Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev*, **15**, 1977-83.
- Hammarsten J, Hogstedt B (2001). Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. *Eur Urol*, **39**, 151-8.
- Hong SK, Oh JJ, Byun SS, et al (2011). Impact of diabetes mellitus on the detection of prostate cancer via contemporary multi (12)-core prostate biopsy. *Prostate*, **72**, 51-7.
- Jayachandran J, Aronson WJ, Terris MK, et al (2010). Diabetes and outcomes after radical prostatectomy: are results affected by obesity and race? Results from the shared equal-access regional cancer hospital database. *Cancer Epidemiol Biomarkers Prev*, **19**, 9-17.
- Kang J, Chen MH, Zhang Y, et al (2012). Type of diabetes mellitus and the odds of Gleason score 8-10 prostate cancer. *Int J Radiat Oncol Biol Phys*, **82**, 463-7.
- Kasper JS, Giovannucci E (2006). A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **15**, 2056-62.
- Kim H, Presti JC Jr, Aronson WJ, et al (2010). Glycemic control and prostate cancer progression: results from the search database. *Prostate*, **70**, 1540-6.
- Leitzmann MF, Ahn J, Albanes D, et al (2008). Diabetes mellitus and prostate cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Causes Control*, **19**, 1267-76.
- Long XJ, Lin S, Sun YN, Zheng ZF (2012). Diabetes mellitus and prostate cancer risk in Asian countries: a meta-analysis. *Asian Pac J Cancer Prev*, **13**, 4097-100.
- Lu K, Song XL, Han SL, Wang CH, Zhong N, Qi LF (2014). Potential study perspectives on mechanisms and correlations between adiposity and malignancy. *Asian Pac J Cancer Prev*, **15**, 1057-60.
- McGrowder DA, Jackson LA, Crawford TV (2012). Prostate cancer and metabolic syndrome: is there a link? *Asian Pac J Cancer Prev*, **13**, 1-13.
- Moreira DM, Anderson T, Gerber L, et al (2011). The association of diabetes mellitus and high-grade prostate cancer in a multiethnic biopsy series. *Cancer Causes Control*, **22**, 977-83.
- Muller H, Raum E, Rothenbacher D, Stegmaier C, Brenner H (2009). Association of diabetes and body mass index with levels of prostate-specific antigen: implications for correction of prostate-specific antigen cutoff values? *Cancer Epidemiol Biomarkers Prev*, **18**, 1350-6.
- Oliver SE, Gunnell D, Donovan J, et al (2004). Screen-detected prostate cancer and the insulin-like growth factor axis: results of a population-based case-control study. *Int J Cancer*, **108**, 887-92.
- Pierce BL, Plymate S, Ostrander EA, Stanford JL (2008). Diabetes mellitus and prostate cancer risk. *Prostate*, **68**, 1126-32.
- Turgutalp K, Ozhan O, Helvacı I, et al (2013). Serum levels of cancer biomarkers in diabetic and non-diabetic proteinuric patients: a preliminary study. *Clin Chem Lab Med*, **51**, 889-95.
- Van Praet C, Libbrecht L, D'Hondt F, et al (2013). Agreement of gleason score on prostate biopsy and radical prostatectomy specimen: is there improvement with increased number of biopsy cylinders and the 2005 revised gleason scoring? *Clin Genitourin Cancer*, [Epub ahead of print].
- Vigneri P, Frasca F, Sciacca L, et al (2009). Diabetes and cancer. *Endocr Relat Cancer*, **16**, 1103-23.
- Wallner LP, Morgenstern H, McGree ME, et al (2011). The effects of type 2 diabetes and hypertension on changes in serum prostate specific antigen levels: results from the Olmsted county study. *Urology*, **77**, 137-41.
- Waters KM, Henderson BE, Stram DO, et al (2009). Association of diabetes with prostate cancer risk in the multiethnic cohort. *Am J Epidemiol*, **169**, 937-45.
- Werny DM, Saraiya M, Gregg EW (2006). Prostate-specific antigen values in diabetic and nondiabetic US men, 2001-2002. *Am J Epidemiol*, **164**, 978-83.
- Woo HY, Park H, Kwon MJ, Chang Y, Ryu S (2012). Association of prostate specific antigen concentration with lifestyle characteristics in Korean men. *Asian Pac J Cancer Prev*, **13**, 5695-9.
- Wu C, Moreira DM, Gerber L, et al (2011). Diabetes and prostate cancer risk in the REDUCE trial. *Prostate Cancer Prostatic Dis*, **14**, 326-31.
- Xu H, Mao SH, Ding GX, Ding Q, Jiang HW (2013). Diabetes mellitus reduces prostate cancer risk - no function of age at diagnosis or duration of disease. *Asian Pac J Cancer Prev*, **14**, 441-7.