INFLUENCE OF DIABETES MELITUS, BMI, AND HBA1C IN HIGH GRADE PROSTATE CANCER

[1]Exsa Hadibrata, [1]HR Danarto.

[1]Division of Urology/Department of Surgery, Faculty of Medicine/Gajah Mada University, Sardjito General Hospital, Yogyakarta.

ABSTRACT

Objective: This study aims to determine the effect of diabetes mellitus (DM) and body mass index (BMI) on the risk of prostate cancer and high grade prostate cancer. **Materials & method:** This study is a retrospective observational study with cross-sectional design, using secondary data to determine the relationship of diabetes mellitus, body mass index and HbA1c levels with the degree of differentiation histopathologic prostate cancer. Data were analyzed using Chi-Square test, T-test and Man Whitney test with a confidence level of $p<0.05$ and $=0.05$. **Results:** There are 78 samples diagnosed with prostate cancer. A total of 12 (15.4%) samples are diabetes mellitus, 18 (22.9%) samples classified as body mass index more than 23.4 (5.1%) samples have elevated levels of HbA1c levels >6.5. On histopathologic examination, it was found as many as 45 (57.7%) samples with high grade prostate cancer, as much as 9 (11.5%) samples with moderate grade prostate cancer, and as many as 24 (30.8%) samples with low grade prostate cancer. In bivariate analysis diabetes mellitus, BMI>23, and HbA1c level relationship with high grade prostate cancer is not statistically significant with $p>0.05$. **Conclusion:** There were no statistically significant relationship between diabetes, BMI and increased levels of HbA1c with high grade prostate cancer.

Keywords: Diabetes, body mass index, HbA1c, prostate cancer.

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk menentukan pengaruh diabetes mellitus (DM) dan body mass index (BMI) pada risiko kanker prostat dan kanker prostat tingkat lanjut. **Bahan & cara:** Penelitian ini adalah penelitian observasional restrospektif dengan desain cross-sectional, menggunakan data sekunder untuk menentukan hubungan diabetes mellitus, body mass index dan level HbA1c dengan derajat perbedaan histopatologi kanker prostat. Data dianalisa menggunakan uji Chi-Square, uji T and uji Man Whitney dengan level signifikan $p<0.05$ dan $=0.05$. **Hasil:** Terdapat 78 sampel didiagnosa dengan kanker prostat. Sebanyak 12 sampel (15.4%) adalah diabetes mellitus, 18 sampel (22.9%) diklasifikasikan BMI lebih dari 23.4 sampel (5.1%) dengan kenaikan level HbA1c >6.5. Pada pemeriksaan histopatologi, didapatkan sebanyak 45 sampel (57.7%) dengan kanker prostat tingkat lanjut, sebanyak 9 sampel (11.5%) dengan kanker prostat tingkat sedang, dan sebanyak 24 sampel (30.8%) dengan kanker prostat tingkat rendah. Pada analisa bivariate diabetes mellitus, BMI>23, dan level HbA1c hubungannya dengan kanker prostat tingkat lanjut secara statistik tidak signifikan dengan $p>0.05$. **Simpulan:** Tidak didapatkan hubungan yang signifikan secara statistik antara diabetes, BMI dan kenaikan level HbA1c dengan kanker prostat tingkat lanjut.

Kata kunci: Diabetes, body mass index, HbA1c, kanker prostat.

Correspondence: Exsa Hadibrata; c/o: Division of Urology/Department of Surgery, Faculty of Medicine/Gadjah Mada University, Sardjito General Hospital, Yogyakarta. Jl. Kesehatan No. 1, Yogyakarta. Phone: +62 274 587333; Fax: +62 274 543980. Email: exsa.hadibrata@gmail.com.

INTRODUCTION

Prostate cancer is the most type of non-skin malignancy in Western countries or the fourth most frequent malignancy in men worldwide after skin, lung, and large intestine cancers.[1] Around the world, more than 670.000 men per year were diagnosed with prostate cancer.[1,2] It was estimated that 1 out of 6 men in United States (US) was affected by this disease during their lifetime, while in many

countries in Asia and other developing countries this case was not many, even though the incidence of each country was different, but remained elevated. The lowest incidence was in Asia (Shanghai) equal to 1.9 per 100.000 population, the highest was in North America and Scandinavia, especially African-American equal to 272 per 100.000 population.[1] Data from the Indonesian Society of Urologic Oncology (ISUO) 2011 during the period of 2006-2010 there were 971 patients with prostate cancer. The mean of age was 68.3 years old, the highest was in the age of 70-79 years old age by 37.6%.

Some studies related cancer incidence with diabetes mellitus (DM) and obesity. One of cancer shaving increased risk due to diabetes mellitus was prostate cancer.[3] In another study, it was reported the opposite, decreased risk of prostate cancer in patients with diabetes mellitus. The decreased risk was because in diabetes mellitus there was a decrease in testosterone levels, changes in the levels of insulin and leptin, use of metformin, and changes in diet and lifestyle to control diabetes.[4-6]

Although there was a decreased risk of prostate cancer in patients with diabetes mellitus and obesity, but there was a significant correlation with the incidence of high-grade prostate cancer.[7] In the high-grade prostate cancer, patient prognostic also got worse. Prognostic patient was determined by TNM Stage, prostate specific antigen (PSA) level and Gleason score.[8]

Until now there is still debate about the effects of diabetes mellitus and obesity on prostate cancer. Although in general, DM increases the risk of some malignant disease, some research suggests that men with DM have decreased risk of prostate cancer.[6,9] The risk reduction is due to a decrease in serum levels of some essential growth factors including insulin, insulin-like growth factor (IGF-1) and testosterone.[10]

Other research shows, that there is a relationship between DM and degree of prostate cancer. Diabetes significantly causeshigh grade prostate cancer, seen from the biopsy results.[11] DM and increased levels HbA1c significantly correlate with high grade prostate cancer.[7] Experts cannot explain the exact cause of DM and increased levels of HbA1c on the increased level of Gleason score. However, there is a hypothesis stating that DM leads to a favorable environment for cancer growth. More over, in patients with DM, phenotype of prostate cancer is more aggressive types.[7] The high levels of glucose and poor control of blood sugar will cause

a decrease in testosterone levels. Low testosterone serum is a risk factor for high grade prostate cancer with a Gleason score of 8-10.[12]

Obesity and lack of activity are factors causing insulin resistance, hyperinsulinemia and metabolic syndrome. In patients with type 2 DM, prolonged insulin resistance, prolonged hyper-glycemia cause damaged pancreatic β cells.[13] Meanwhile, in the early stages of obesity and type 2 DM, they will be marked with compensatory hyperinsulinemia, increased insulin like growth factor-1, and the consequence is the emergence of a suitable environment for the growth of cancer.[13] In the obesity, insulin secretory capacity is bigger than the non-obesity with DM. This mechanism may explain the correlation between DM and high grade prostate cancer.

OBJECTIVE

Previous studies have not asserted the effects of DM and body mass index (BMI) on prostate cancer risk and the differentiation degree of prostate cancer. The objective of this study was to determine the relationship of DM, BMI, HbA1c levels and high grade prostate cancer.

MATERIAL & METHODS

This study was an observational study with retrospective cross-sectional design, using secondary data to determine the relationship between DM, BMI, HbA1c levels and histopathological differentiation degree of prostate cancer.

The experiment was conducted in May - June 2015 in the Anatomy Pathology Unit and Medical Records Unit of Dr. Sardjito Central General Hospital. The target population was all cases of prostate adenocarcinoma Dr. Sardjito Central General Hospital in 2013-2015.

The data were collected from patients with diagnosis of prostate cancer for two years, then each sample was seen retrospectively whether they had diabetes history as evidenced by the examination of blood sugar levels and HbA1c, as well as the measurement of weight and height to calculate BMI.

DM was assessed by the examination of GD2PP and GDP. Reference value for diagnostic DM was GDP ≥ 126 mg/dl, GDS ≥ 200 mg/dl on another day or results of Oral Glucose Tolerance Test (OGTT) ≥ 200 mg/dl. HbA1c levels were assessed using HbA1c normal levels by 4 to 6.5. The BMI was

calculated by WHO method, with the formula of weight in kilograms divided by the square of height in meters (kg/m^2). Then it was performed BMI classification according to Asia Pacific criteria, namely BMI above 23 and under 23. The differentiation degree of prostate carcinoma was assessed by Gleason score method. Gleason score grouping consisted of low grade ≤ 6, moderate grade 7 and high grade (8-10). From the data, then it was analyzed statistically and performed appropriate correlation test between the variables of DM, HbA1c levels, and BMI on the differentiation degree of prostate carcinoma. The statistical test used was T-test or Mann-Whitney test for numerical variables. Chi-square test or Fisher's exact test were performed for categorical variable.

RESULTS

In this study, there were 78 samples of patients with prostate cancer. Patients were categorized into two groups: diabetic and non-diabetic patients. Each group then divided by age, TAUS prostate volume, total PSA levels, GDS levels, BMI, differentiation degree of prostate cancer, and HbA1c levels.

In the 30-49 years old age group, it was obtained 2 (2.5%) patients, there were no patients with diabetes in this age group. In the 50-69 years old age group there were 36 (46.1%) patients with prostate cancer. In this group, there were 4 (5.1%) of

patients with diabetes. In the group age of ≥ 70 years old there were 40 (51.2%) patients with prostate cancer. In this group there were 8 (10.2%) of patients with diabetes.

Based on the distribution according to TAUS prostate volume, the mean of prostate volume in the group with diabetes was 51.83 ± 18.8 grams, while the mean of prostate volume in the non-diabetic group was 45.1 (10; 336) gram. Based on the distribution according to total PSA levels, the mean of total PSA level in the group with diabetes was 102.5 (7.5; 153) ng/dl, whereas the mean of total PSA level in non-diabetic group was 79.3 (0.1; 154) ng/dl.

BMI in patients with prostate cancer was divided based on the criteria of Asia Pacific. In this study, it was obtained 5 (6.3%) patients with obesity, and among of them there was 1 (1.2%) patient with diabetes. Patients with overweight category were 13 (16.6%) patients, and among of them there were 5 (6.4%) patients with diabetes. Patients with normal weight category were 58 (74.3%) patients, and among of them there were 5 (6.4%) patients with diabetes. Patients with less weight category were (2.4%) patients, and among of them there was 1 (1.2%) patient with diabetes.

In this study, patients with high grade prostate cancer category were as many as 45 (57.6%) patients. Patients with moderate grade prostate cancer category were as many as 9 (11.4%) patients. Patients with low grade prostate cancer category

Table 1. Patient characteristic with prostate cancer.

Variable	DM	Non DM
Age		
30-49 years	0	2 (2.5%)
50-69 years	4 (5.1%)	32 (41%)
>70 years	8 (10.2%)	32 (41%)
TAUS	51.83 ± 18.8 ml	45.1 (10; 336) ml
PSA Total	102.5 (7.5; 153) ng/dl	79.3 (0.1; 154) ng/dl
Blood Glucose	221 ± 38.5 mg/dl	113.5 ± 21.5 mg/dl
BMI		
Obese	1 (1.2%)	4 (5.1%)
Overweight	5 (6.4%)	8 (10.2%
Normoweight	5 (6.4%)	53 (67.9%)
Underweight	1 (1.2%)	1 (1.2%)
HbA1c level		
> 6.5	4 (5.1%)	0 (0%)
≤ 6.5	8 (10.2%)	66 (84.6%)

Table 2. Association DM, BMI, HbA1c level with grading Pca.

Variable		Grade P		
		High Grade Pca	Moderate Grade Pca	Low Grade Pca
DM	With DM	8 (10.2%)	2 (2.5%)	2 (2.5%)
	Without DM	37 (47.4%)	7 (8.9%)	22 (28.2%)
BMI	>23	8 (10.2%)	4 (5.1%)	6 (7.6%)
	<23	37 (47.4%)	5 (6.4%)	18 (23%)
HbA1c Level	>6.5	3 (3.8%)	0 (0%)	1 (1.2%)
	<6.5	42 (53.8%)	9 (11.5%)	23 (29.4%)
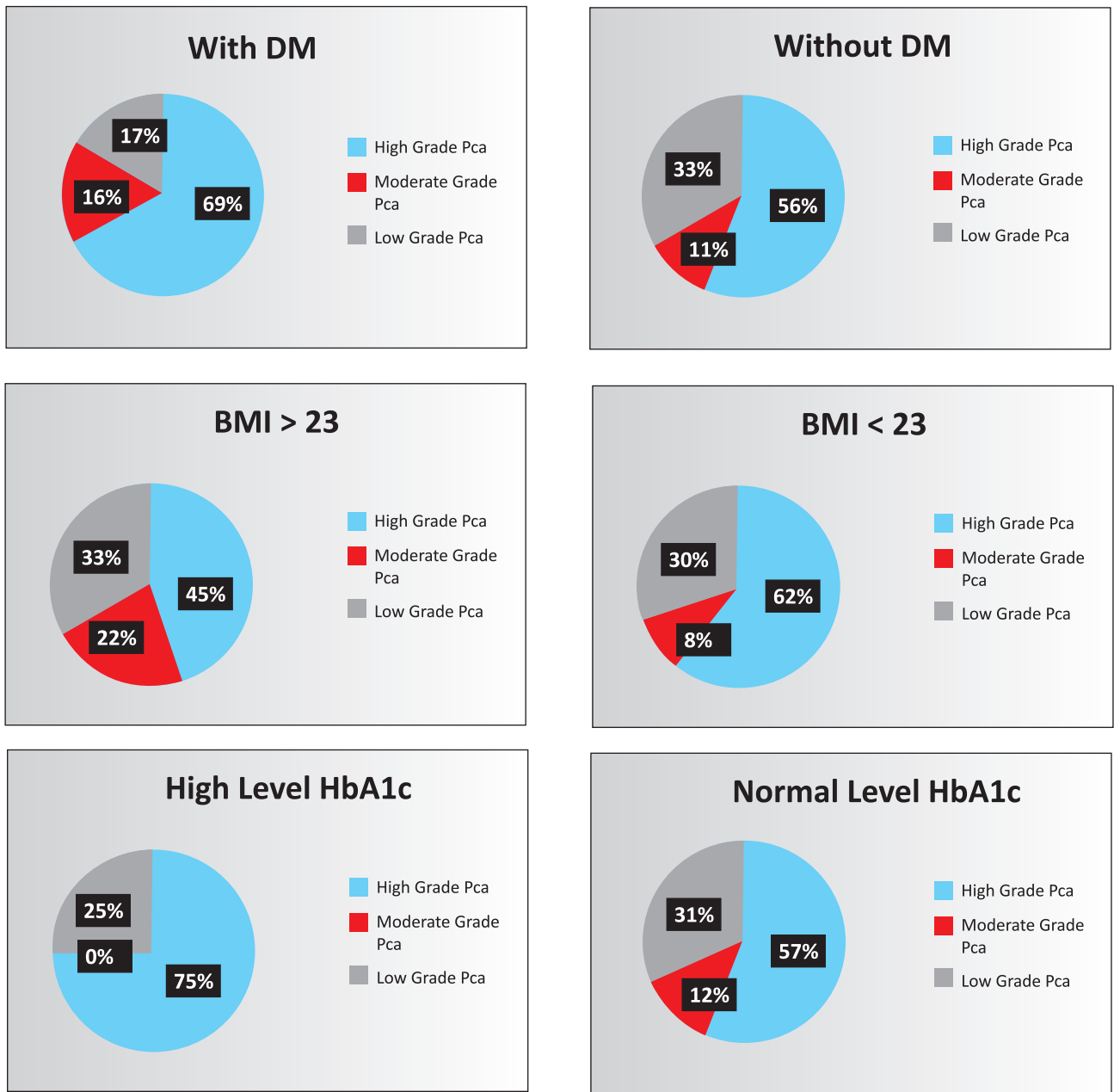
Graphic 1. Prostate cancer distribution.

Table 3. Correlation between DM, BMI, HbA1c level with grading Pca.

Variable		Grading Pca		p
		High grade	Non High grade	
Diabetes mellitus	Yes	8	4	0.494
	No	37	29	
BMI	> 23	8	10	0.195
	< 23	37	23	
HbA1c level	> 6.5	3	1	0.472
	≤ 6.5	42	32	

were as many as 24 (30.7%) patients.

In this study, it was also performed the distribution of prostate cancer patients based on HbA1c levels. Patients with HbA1c levels > 6.5 were 4 (5.1%) and all of them were patients with diabetes. Patients with HbA1c levels ≤ 6.5 were as many as 74 (94.9%) patients and among of whom there were 8 (10.2%) patients with diabetes. In the statistical analysis, it was not found significant relationship between the variables of diabetes mellitus, BMI >23, increased levels of HbA1c and high grade prostate cancer statistically with p > 0.05.

DISCUSSION

The percentage of patients with diabetes mellitus were 12 (15.4%) samples, patients with BMI >23 were 18 (22.9%) samples, and patients with increased levels of HbA1c were 4 (5.1%) samples. From the results, it can be seen that the percentage of patients with diabetes is less than non-diabetes patients, as well as patients with obesity and non-obesity. Based on epidemiological data currently available, diabetes lowers the risk of prostate cancer compared to non-diabetes with relative risk of 0.91 and 0.87.[6,9]

The results obtained are slightly different from previous research reporting the number of patients with diabetes in patients with prostate cancer having radical prostatectomy for 8 years as many as 147 (7.1%) samples and obesity patients as many as 27 (18.4%) samples.[14] Differences in percentage of patients with diabetes and obesity may be due to differences in sample size.

The data obtained in this study is consistent with ISUO data (2011), i.e., the mean of age of patients with prostate cancer is 68.3 years, with most in the 70-79 years old age interval. In Indonesia, the standard value of PSA for prostate cancer is more than 4 ng/ml.[8]

In the bivariate analysis, it was found no statistically significant relationship between the variables of diabetes, BMI >23, HbA1c level and high grade prostate cancer with p value >0.05. It is still being debated nowadays dealing with the effects of variables of diabetes, BMI and HbA1c levels on the incidence of high-grade prostate cancer. There are studies showing the significant relationship, but some studies indicate otherwise.

There are several reasons why there is no significant relationship between diabetes and high grade prostate cancer, as well as decreased risk of prostate cancer, one of reason is patient's life style changes. Once diagnosed with diabetes, patients will change the pattern of their life, diet, taking anti diabetic medication regularly, reducing the consumption of saturated fats that increase the risk of prostate cancer.[15] Metformin is the most common drug given to patients with diabetes mellitus. This drug may also reduces the risk of prostate cancer.[16]

Some hypotheses leading to decreased risk of prostate cancer in patients with diabetes are decreased levels in testosterone hormone and cancer growth factor in patients with diabetes, changes in behavior and life style of patients with DM, with screening and early detection of total PSA and prostate size, and diabetes drugs consumed have a protective effect against prostate cancer and prostate vascular damage.[17]

Although it is not statistically significant, this study indicates an increase in the percentage of high-grade prostate cancer incidence in people with diabetes, BMI >23 and increased levels of HbA1c. There are several theories and hypotheses that explain those, among others. DM leads to a favorable environment for cancer growth. Moreover in

patients with DM, phenotype of prostate cancer is more aggressive type.[7] Low testosterone serum is a risk factor for high-grade prostate cancer with Gleason scores of 8-10.[12] In the early stages of obesity and type 2 DM, it would be characterized by insulin resistance, hyperinsulinemia compensatory, increased insulin like growth factor-1, and the consequence is the emergence of a appropriate environment for the growth of cancer.[13] In obese patients, it is found increased angiogenesis, cell migration and inflammation, causing prostate cancer phenotype becomes more aggressive.[18] Low blood glucose control shown by an increase in HbA1c levels can lead to increased production of glycation end products capable of initiating lipid peroxidation, which in turn it leads to the production of genotoxic aldehydes increasing the aggressiveness of prostate cancer.[19,20]

The limitations of this study include all those inherent in a retrospective analysis. The number of patients was considered too small for accurate analysis of predictive factors. It is not performed measurement on the level of testosterone, insulin, or insulin-like growth factor, anti-diabetic drug therapy, activity factors and diet pattern that affect the nature and aggressiveness of prostate cancer. In further study, it is expected research involving these risk factors, and minimizing potential confounding variables.

CONCLUSION

From this study, the conclusion that can be drawn is that it is not found statistically significant relationship between diabetes, BMI >23 and increased levels of HbA1c and the occurrence of high-grade prostate cancer.

REFERENCES

1. Klein EA, Platz EA, Thompson IM. Epidemiology, etiology, and prevention of prostate cancer. In: Wein AJ, Kovoussi LR, Novick AC, Partin AW, Peters CA, 10th Ed. Campbell-Walsh Urology. Philadelphia: Saunders; 2012. p. 2854-73.
2. Mottet N, Schalken JA, Heidenreich A, Bastian PJ, Irani J, Salomon L, et al. Highlights on prostate cancer from urological and oncological congresses in 2007. Eur Urol. 2008; Suppl 7: 460-73.
3. Long XJ. Diabetes mellitus and prostate cancer risk in Asian countries: A meta-analysis. Asian Pacific J Cancer Prev. 2012; 13: 4097-100.
4. Demir U, Koehler A, Schneider R. Metformin anti-tumor effect via disruption of the MID1 translational regulator complex and AR down regulation in prostate cancer cells. BMC Cancer. 2014; 31: 14-52.
5. Fall K, Garmo H, Gudbjornsdottir S. Diabetes mellitus and prostate cancer risk; A nationwide case-control study within PCBaSe Sweden. Cancer Epidemiol Biomarkers Prev. 2013; 22: 1102-9.
6. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006; 15: 2056-62.
7. Ozbek E. Diabetes mellitus and HbA1c levels associated with high grade prostate cancer. Asian Pacific J Cancer Prev. 2014; 15(6): 2555-8.
8. Ikatan Ahli Urologi Indonesia. Panduan Penatalaksanaan Kanker Prostat; 2011.
9. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: A Meta-Analysis. Diabetologia. 2004; 47(6): 1071–8. [PubMed: 15164171].
10. Kasper JS, Liu Y, Pollak MN, Rifai N, Giovannucci E. Hormonal profile of diabetic men and the potential link to prostate cancer. Cancer Causes Control. 2008; 19(7): 703-10. [PubMed: 18340542].
11. Moreira DM, Anderson T, Gerber L. The association of diabetes mellitus and high-grade prostate cancer in a multiethnic biopsy series. Cancer Causes Control. 2011; 22: 977-83.
12. Xylinas E, Ploussard G, Durand X. Low pretreatment total testosterone (3ng/mL) predicts extra prostatic disease in prostatectomy specimens from patients with preoperative localized prostate cancer. BJU Int. 2011; 107: 1400-3.
13. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology. 2007; 132: 2208-25.
14. Abdollah F. Does diabetes mellitus increase the risk of high-grade prostate cancer in patients undergoing radical prostatectomy. Prostate Cancer and Prostatic Diseases. 2011; 14: 74-78.
15. Hua Xu. Diabetes mellitus reduces prostate cancer risk − no function of age at diagnosis or duration of disease. Asian Pacific J Cancer Prev. 2013; 14(1): 441-7.
16. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: Results from a population-based case-control study. Cancer Causes Control. 2009; 20: 1617-22.
17. Brandon Pierce. Why are diabetics at reduced risk for prostate cancer? A review of the epidemiologic evidence. Urologic Oncology: Seminars and Original Investigations. 2012; 30: 735-43.
18. Di Francesco Simona, Tenaglia RL. Obesity, diabetes and aggressive prostate cancer. Cent Eur J Urol. 2013; 66: 423-7.
19. Hammarsten J, Hogstedt B. Hyperinsulinaemia: A prospective risk factor for lethal clinical prostate

cancer. Eur J Cancer. 2005; 41: 2887-95.

20. Hong Sung Kyu. Significance of preoperative HbA1c level in patients with diabetes mellitus and clinically

localized prostate cancer. The Prostate. 2009; 69: 820-82.