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Association between Type 2 Diabetes Mellitus and Prostate Cancer Aggressiveness

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Abstract **Original Research Article**

Background*:** Type 2 diabetes mellitus (T2DM) and prostate cancer (Pca) are two different disease entities that occur frequently in the elderly populations. Researchers have identified some mechanisms that could link T2DM to the development, progression and prognosis of Pca. Although controversies surround this concept, T2DM has been reported to confer protection to the development of low grade Pca and to a lesser extent high grade Pca. ***Materials and Methods*:** One hundred and thirty-six (136) men with Pca were evaluated in this study. Information from their case-notes were retrospectively retrieved during their clinic visits including bio-data, history, physical examination findings, laboratory and radiological investigation results and reports of prostate biopsy. Patients were grouped as diabetic and non-diabetic based on the history and laboratory records. Age and prostate specific antigen (PSA) levels were also categorized. Collated data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20.0 software. ***Results: One hundred and thirty six (136) men with a mean age of 69.10±8.40 years ranging from 48 to 91 years and diagnosed with Pca were evaluated. Diabetic men were older and had higher mean serum PSA and Gleason score (GS) than non-diabetic men (Table3i – iii). ***Conclusion*:** Diabetic men in this study had higher values of variables portraying more aggressive Pca than non-diabetic men. Therefore, in evaluating this group of patients presenting with symptoms suspicious of Pca, concerns of probably dealing with highly aggressive tumours should be held strong.

Keywords: Diabetes mellitus, prostate cancer, Aggressiveness.

INTRODUCTION

Association between T2DM and Pca has been a subject of much concern globally for effective evaluation and identification of patients at risk of highly aggressive Pca. Several reports have made rounds about an inverse association between T2DM and incident Pca [1-4]. It is however doubtful whether these reports are consistent for all grades of the tumours. Some studies had thrown more lights in the subject matter and came up with conclusions that whereas T2DM mainly reduces the risk of low grade disease, it does that to a lesser extent for high grade tumours in both needle biopsy and radical prostatectomy (RP) specimens [5, 6]. Above reports were made across racial boundaries in North American men where incidence of Pca is said to be high and among Caucasians with intermediate risk. However, prior to this, analysis of the CAPSURE database found no association between T2DM and Pca aggressiveness [7]. Abdollah *et al*., [8] found that majority of their patients with T2DM had poorly differentiated Pca (GS $\geq$ 8) compared to non-diabetic patients in both biopsy and RP specimens (P = 0.001). They also found that there was a moderate risk reduction (28%) for high grade tumors compared to low grade tumours (47%).

Research works had been ongoing to possibly explain the link between T2DM and reduced risk of incident Pca. One of such reports is the fact that insulin as a growth factor for Pca is low in T2DM and may therefore slow its development [9]. On the other hand, factors that favour Pca aggressiveness in T2DM patients have also been well studied. Diabetic patients are known to have lower levels of serum testosterone which has recently been reported to be associated with Pca aggressiveness [10-12]. Lower levels of serum testosterone in T2DM is said to occur due to increased sex hormone binding globulin (SHBG) in long standing diabetics which lowers the bioavailability of serum testosterone [9, 13]. In this study our T2DM men had higher PSA and GS than non-diabetics portraying more aggressive disease.

MATERIALS AND METHODS

This was a retrospective study of prostate cancer patients who presented in the urology clinic of University of Uyo Teaching Hospital, Uyo for follow up treatments between September 2021 and March, 2022. Data from their case-notes were retrieved at the end of every clinic day and such folders coded to avoid duplication of information. Details of biodata, history of diabetes, physical examination, laboratory results for fasting blood sugar, renal function test, serum PSA and Prostate biopsy detailing the grades and Gleason score were documented. Also results of imaging studies mainly trans-rectal ultrasound scan and Abdomino-pelvic ultrasound scan were recorded. Exclusion criteria were patients with incomplete clinical, laboratory and imaging information, patients with histological diagnosis of prostate diseases other than Pca. Others were a diagnosis of bladder and ano-rectal cancers. This study centered on men with histological diagnosis of prostate cancer who had complete clinical, laboratory and imaging reports.

Patients' age were grouped in decades from 40-49 years in group one, 50-59 years in group two, 60-69 years in group three, 70-79 years in group four, 80-89 years in group five, 90 years and above in group six. Diabetic and non-diabetic men had groups 1 and 2 respectively. Serum PSA was categorized into groups 1-3 represented as <4.0ng/ml, 4.0-10.0ng/ml and >10.0ng/ml respectively. Data collated were entered into a spreadsheet and analysed using SPSS version 20.0 software. Frequency tables were constructed for categorical variables while means and standard deviation were calculated for continuous variables. Comparison of means of variables between diabetic and non-diabetic men was done using students' T-test and P-value <0.05 was assigned to be statistically significant.

RESULTS

One hundred and thirty six (136) prostate cancer patients who met the inclusion criteria were selected for this study. Mean age was 69.10±8.40 years ranging from 48 to 91 years. Mean Gleason score was 7.99±1.13 ranging from 5 to 10 while mean PSA was 52.89±36.47ng/ml ranging from 10 to 185.70ng/ml. Men in their 8th decade of life formed the majority (44.1%) Table 1(i). The prevalence of diabetes mellitus was 19.9% Table 1(ii). More men had PSA in excess of 10.0ng/ml (92.6%) Table 1(iii). Calculating mean difference of variables between diabetic and non-diabetic men; diabetic men were older, had higher values of both PSA and Gleason score (Table 3iii) and of course higher levels of tumour aggressiveness (Table 3iv).

Table 1: Frequency of Categorical variables:

(i)	**Age (Years)**	**Frequency (n)**	**Valid %**	**Cumulative %**
	40-49	1	0.7	0.7
	50-59	15	11.0	11.8
	60-69	48	35.3	47.1
	70-79	60	44.1	91.2
	80-89	11	8.1	99.3
	90 and above	1	0.7	100.0
	Total	**136**	**100.0**	
(ii)		**Frequency (n)**	**Valid %**	**Cumulative %**
	Diabetics	27	19.9	19.9
	Non-diabetics	109	80.1	100.0
	Total	**136**	**100.0**	
(iii)	**PSA (ng/ml)**	**Frequency (n)**	**Valid %**	**Cumulative %**
	< 4.0	2	1.5	1.5
	4-10.0	8	5.9	7.4
	>10.0	126	92.6	100.0
	Total	**136**	**100.0**	

Table 2: Mean and SD of variables

Variable	**Mean ±SD**	**Min.**	**Max**
Age (Years)	69.10±8.40	48	91
Gleason Score	7.99±1.13	5	10
PSA (ng/ml)	52.89±36.47	10	185.70

Table 3: Comparison of means of variables among diabetics and non-diabetics

(i) Age				
		N	**Mean± SD**	**T-test Statistics**
	DM	27	70.52 ± 8.93	
	Non-DM	109	68.74±8.26	t (134) = 983, P > 0.05
(ii) PSA (ng/ml)				
	DM	27	63.86±38.90	
	Non-DM	109	50.17 ±35.50	t (134) = 1.760, P > 0.05
(iii) Gleason Score				
	DM	27	8.19 ±1.07	
	Non-DM	109	7.94 ±1.14	t (134) = 1.022, P > 0.05
(iv) Aggressive* and non-aggressive* tumors in Diabetic and non-diabetic men				
		Non-Aggressive	**Aggressive**	**Total**
	Diabetic men (n)	4	23	27
	Percent (%)	**14.8***	**85.2***	100.0
	Non diabetic men (n)	25	84	109
	Percent (%)	**22.9***	**77.1***	100.0
	Total	29	107	136
	Total (%)	21.3	78.7	100.0

DISCUSSION

Men with T2DM had been known to have reduced risk of low grade Pca and to a lesser extent high grade tumours in both needle biopsy and RP specimens [5, 6]. However, some researchers found no association between T2DM and Pca aggressiveness even across racial groups [7]. This study further reported that obesity independent of T2DM is associated with aggressive Pca only in white Americans [14]. This is difficult to explain but may depend on the population studied as well as their method of diagnosis. However, obese men are likely to have lower levels of serum testosterone and higher levels of serum insulin creating an environment for aggressive Pca development [15]. A couple of studies including our work had documented more Pca aggressiveness in T2DM patients than in non-diabetics based on tumour grade and Gleason score spanning through pre-PSA and PSA era [6, 16]. This may well be due to low serum levels of testosterone in T2DM patients typically associated with aggressive Pca [10]. Again, T2DM patients are more likely to be obese with potentials for aggressive Pca [15, 17].

Our study was aimed at evaluating a possible association between T2DM and Pca aggressiveness. The mean age of all men in the study was 69.10±8.40 years. Similar mean age had been documented in studies of Pca patients in blacks [18-22]. Majority of them (44.1%) were in their 8th decade of the life [Table 1(i)]. A previous work in this centre on Pca patients had documented same information [18]. It is a well-known fact that Pca is more prevalent in the elderly population. T2DM men were older than non-diabetics (P>0.05) Table 3(i). Abdollah *et al*., [8] also documented same in a similar study. The prevalence of T2DM in this study was higher than in the general population in same geographical area (19.9% vs 7.0%) [21]. However, our work showed evidence of selection bias being hospital-based and the fact that both conditions are highly prevalent in elderly populations. Mean serum PSA was higher in T2DM [Table 3(ii)]. High serum PSA is one of the characteristics of invasive and aggressive Pca. In the European Randomized study of screening for prostate cancer conducted in 2008 in Nigeria, the study suggested that higher PSA values in African men were probably due to higher tumour stages in Africans than in American patients. Partin *et al*., also documented that poorly differentiated tumours are associated with higher serum PSA values [23]. Again, Pierorazio et al in their study of the relationship between pre-operative PSA and biopsy Gleason sum in men undergoing RP also inferred that higher levels of serum PSA (>50.0ng/ml) was associated with poorly differentiated histopathology (GS>7) [24]. Okolo *et al*., recorded a positive correlation between increasing PSA levels and higher Gleason score (r=0.4, P=0.001) [25].

Gleason score in this study was higher among diabetic men and with increasing percentage of tumour aggressiveness than in non-diabetic men (85.2% vs 77.1%) [Table 3 (iii & iv)]. Gleason score is one of the tools of Pca assessment that predicts both the pathologic stage and prognosis of the disease. The higher the Gleason Score the more aggressive the disease. With the above tumour characteristics in our population of men with diabetes, it follows that, intrinsically they harbor more aggressive tumours than non-diabetic men. Jayachandran *et al*., reported that T2DM men had a 1.73 fold higher risk of high grade GS (GS $\geq$ 7) than non-diabetics (P=0.002) [6]. Also T2DM was an independent predictor of high-grade Pca in patients referred to undergo RP in another study [26]. Further studies by Abdollah *et al*., [8] also documented higher grade tumours in T2DM than in non-diabetics and an apparent protection afforded primarily to low grade tumours [5].

So many research works had been done to collaborate the presence of diabetes and development of

aggressive Pca. More of such works identified insulin, insulin like growth factor-1 (IGF-1) and the presence of male hormone (testosterone) as likely molecules involved. T2DM is characterized by insulin resistance with hyperinsulinaemia, increased serum IGF-1 and low testosterone. Insulin and IGF-1 are known growth factors for Pca that promote cell proliferation, migration and reduces apoptosis favouring prostate carcinogenesis [27]. Diabetes has been associated with lower testosterone level [28] and contrary to previous knowledge, lower serum testosterone has recently been shown to be associated with aggressive Pca [28-31]. It has been documented that insulin profile in T2DM changes according to the duration of the disease being high in early and low in the later stages of the illness due to pancreatic B-cell exhaustion [6, 13]. Even at low serum insulin level, Jayachandran *et al*., still found a positive association between T2DM and Pca aggressiveness and hypothesized the concept of "Selection pressure" where only highly aggressive tumour can survive in this environment of poor growth potential [6]. From facts available, it therefore follows that T2DM independent of the duration are linked to Pca aggressiveness. Early Pca diagnosis in T2DM patients could be challenging being that most of them are likely to be obese than non-diabetics posing difficulty on digital rectal examination (DRE) and prostate biopsy [13, 32, 33] These could contribute to delayed diagnosis till advanced stage of the disease. From this body of knowledge, evaluating T2DM suspicious of Pca should be thorough bearing in mind the possibility of dealing with an aggressive tumour. Also, regular PSA should be advised in this population of men.

Limitations of this study stem from its retrospective nature; there was lack of information on the duration and severity of diabetes and medication intake. Although still controversial, metformin intake was said to reduce the risk of Pca in a meta-analysis [34] whereas Wu *et al*., in the same year reported no association [35]. Secondly, there was no information on patient's body mass index (BMI). Obesity was reported to correlate positively with Pca aggressiveness independent of diabetic status [14]. Thirdly, we used reports from prostate biopsy specimens which has been said to under-estimate high grade Pca in up to 38% of cases [36]. These could make our result less accurate without a final pathological grade from RP specimens. However, not all of them would have had indications for RP. Further prospective study with RP specimens is highly envisaged. The strength of this study is that of replicating same information in our locality that had been popularized by other researchers.

CONCLUSION

Our diabetic men have higher biochemical and histological markers for highly aggressive Pca than their non-diabetic counterparts. However, this information should be verified in a prospective study using pathological grade information before being applied in clinical practice.

Authors Contribution:

EAU: Substantial contributions to conception and design, Acquisition of data, Drafting the article, revising it critically for important intellectual content, data analysis and Final approval of the version to be published.

OEA: Substantial contributions to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

AEU: Substantial contributions to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

REFERENCES

1. Bonovas, S., Filioussi, K., & Tsantes, A. (2004). Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia*, *47*, 1071-1078.
2. Jemal, A., Siegel, R., Xu, J., & Ward, E. (2010). Cancer statistics, 2010. *CA: a cancer journal for clinicians*, *60*(5), 277-300.
3. Tsilidis, K. K., Allen, N. E., Appleby, P. N., Rohrmann, S., Nöthlings, U., Arriola, L., ... & Key, T. J. (2015). Diabetes mellitus and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *International journal of cancer*, *136*(2), 372-381.
4. Bansal, D., Bhansali, A., Kapil, G., Undela, K., & Tiwari, P. (2013). Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. *Prostate cancer and prostatic diseases*, *16*(2), 151-158.
5. Leitzmann, M. F., Ahn, J., Albanes, D., Hsing, A. W., Schatzkin, A., Chang, S. C., ... & Prostate, Lung, Colorectal, and Ovarian (PLCO) Trial Project Team. (2008). Diabetes mellitus and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Causes & Control*, *19*, 1267-1276.
6. Jayachandran, J., Aronson, W. J., Terris, M. K., Presti Jr, J. C., Amling, C. L., Kane, C. J., & Freedland, S. J. (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 epidemiology, biomarkers & prevention*, *19*(1), 9-17.
7. Chan, J. M., Latini, D. M., Cowan, J., Duchane, J., & Carroll, P. R. (2005). History of diabetes, clinical features of prostate cancer, and prostate cancer recurrence-data from CaPSURE TM (United States). *Cancer Causes & Control*, *16*, 789-797.
8. Abdollah, F., Briganti, A., Suardi, N., Gallina, A., Capitanio, U., Salonia, A., ... & Montorsi, F. (2011). Does diabetes mellitus increase the risk of high-grade prostate cancer in patients undergoing radical prostatectomy?. *Prostate Cancer and Prostatic Diseases*, *14*(1), 74-78.
9. Kasper, J. S., Liu, Y., Pollak, M. N., Rifai, N., & Giovannucci, E. (2008). Hormonal profile of diabetic men and the potential link to prostate cancer. *Cancer Causes & Control*, *19*, 703-710. Doi: 10./007/s10552-008-9133-x.

10. Spark, R. F. (2007). Testosterone, diabetes mellitus, and the metabolic syndrome. *Current urology reports*, *8*(6), 467-471.
11. Hoffman, M. A., DeWOLF, W. C., & Morgentaler, A. (2000). Is low serum free testosterone a marker for high grade prostate cancer?. *The Journal of urology*, *163*(3), 824-827.
12. Cao, Y., & Ma, J. (2011). Body mass index, prostate cancer–specific mortality, and biochemical recurrence: a systematic review and meta-analysis. *Cancer prevention research*, *4*(4), 486-501.
13. Pierce, B. L. (2012, September). Why are diabetics at reduced risk for prostate cancer? A review of the epidemiologic evidence. In *Urologic Oncology: Seminars and Original Investigations*, 30(5), 735-743.
14. Khan, S., Cai, J., Nielsen, M. E., Troester, M. A., Mohler, J. L., Fontham, E. T., ... & Bensen, J. T. (2016). The association of diabetes and obesity with prostate cancer aggressiveness among Black Americans and White Americans in a population-based study. *Cancer Causes & Control*, *27*, 1475-1485.
15. Hsing, A. W., Gao, Y. T., Chua Jr, S., Deng, J., & Stanczyk, F. Z. (2003). Insulin resistance and prostate cancer risk. *Journal of the National Cancer Institute*, *95*(1), 67-71.
16. Mitin, T., Chen, M. H., Zhang, Y., Moran, B. J., Dosoretz, D. E., Katin, M. J., ... & D'Amico, A. V. (2011). Diabetes mellitus, race and the odds of high grade prostate cancer in men treated with radiation therapy. *The Journal of urology*, *186*(6), 2233-2238.
17. Mokdad, A. H., Ford, E. S., Bowman, B. A., Dietz, W. H., Vinicor, F., Bales, V. S., & Marks, J. S. (2003). Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *Jama*, *289*(1), 76-79.
18. Udoh, E. A., Akaiso, O. E., & Ukpong, A. E. (2020). Correlation between prostate volume and Gleason score in patients diagnosed with prostate cancer. A 2-year hospital based study. *International journal of contemporary medical research*, *7*(5), E1-E4.
19. Udoh, E. A., David, D. E., & Eyo, A. E. (2020). Relationship between serum prostate specific antigen (PSA) and Gleason score in patients diagnosed with prostate cancer. A hospital based study. *EAS J. Med Surg*, *2*(2), 47-52.
20. Udoh, E. A., Charles, N. C., & Essiet, I. U. (2020). Is There any Relationship between Age of Patients and Prostate Cancer Aggressiveness?. *International Journal of Contemporary medical research 7*(5), E5-E10.
21. Enang, O. E., Otu, A. A., Essien, O. E., Okpara, H., Fasanmade, O. A., Ohwovoriole, A. E., & Searle, J. (2014). Prevalence of dysglycemia in Calabar: a cross-sectional observational study among residents of Calabar, Nigeria. *BMJ Open Diabetes Research and Care*, *2*(1), e000032.
22. The European Randomized Study of screening for prostate cancer (ERSPC). January 12, 2008: available at: http://www.erspc.org.
23. Partin, A. W., Carter, H. B., Chan, D. W., Epstein, J. I., Oesterling, J. E., Rock, R. C., ... & Walsh, P. C. (1990). Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. *The Journal of urology*, *143*(4), 747-752.
24. Pierorazio, P., Desai, M., McCann, T., Benson, M., & McKiernan, J. (2009). The relationship between preoperative prostate-specific antigen and biopsy Gleason sum in men undergoing radical retropubic prostatectomy: a novel assessment of traditional predictors of outcome. *BJU international*, *103*(1), 38-42.
25. Okolo, C. A., Akinosun, O. M., Shittu, O. B., Olapade-Olaopa, E. O., Okeke, L. I., Akang, E. E. U., & Ogunbiyi, J. O. (2008). Correlation of serum PSA and Gleason Score in Nigerian men with prostate cancer. *African Journal of Urology*, *14*(1), 15-22.
26. Federation, I. D. (2008). Third edition of diabetes atlas. Available from http://www.eatlas.idf.org (accessed 29 March, 2010).
27. Giovannucci, E. (1995). Insulin and color cancer. *Cancer causes Control*, *6*(2), 164-179.
28. Spark, R. F. (2007). Testosterone, diabetes mellitus, and the metabolic syndrome. *Current urology reports*, *8*(6), 467-471.
29. Cao, Y., & Ma, J. (2011). Body mass index, prostate cancer–specific mortality, and biochemical recurrence: a systematic review and meta-analysis. *Cancer prevention research*, *4*(4), 486-501.
30. Khera, M., Crawford, D., Morales, A., Salonia, A., & Morgentaler, A. (2014). A new era of testosterone and prostate cancer: from physiology to clinical implications. *European urology*, *65*(1), 115-123.
31. Hoffman, M. A., DeWOLF, W. C., & Morgentaler, A. (2000). Is low serum free testosterone a marker for high grade prostate cancer?. *The Journal of urology*, *163*(3), 824-827.
32. Kasper, J. S., & Giovannucci, E. (2006). A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiology Biomarkers & Prevention*, *15*(11), 2056-2062.
33. Freedland, S. J., & Platz, E. A. (2007). Obesity and prostate cancer: making sense out of apparently conflicting data. *Epidemiologic reviews*, *29*(1), 88-97.
34. Deng, D., Yang, Y., Tang, X., Skrip, L., Qiu, J., Wang, Y., & Zhang, F. (2015). Association between metformin therapy and incidence, recurrence and mortality of prostate cancer: evidence from a meta-analysis. *Diabetes/metabolism research and reviews*, *31*(6), 595-602.
35. Wu, G. F., Zhang, X. L., Luo, Z. G., Yan, J. J., Pan, S. H., Ying, X. R., ... & Zhang, G. F. (2015). Metformin therapy and prostate cancer risk: a meta-analysis of observational studies. *International journal of clinical and experimental medicine*, *8*(8), 13089-13098.
36. Moussa, A. S., Li, J., Soriano, M., Klein, E. A., Dong, F., & Jones, J. S. (2009). Prostate biopsy clinical and pathological variables that predict significant grading changes in patients with intermediate and high grade prostate cancer. *BJU international*, *103*(1), 43-48.