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Research Article

HYPERTENSION AND THE RISK OF PROSTATE CANCER AMONG TYPE 2 DIABETES MELLITUS SUBJECTS IN NORTHERN NIGERIA

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A B S T R A C T

Background: Recent studies have found a significantly reduced risk of prostate cancer among diabetic subjects however, similar relationships with hypertension or other cardio metabolic factors have not been documented conclusively especially among Nigerians.
Objective: The aim of the study is to establish the relationship between hypertension and the risk of prostate cancer and other related factors among diabetics and non diabetic subjects.
Methods: The study was a cross sectional conducted among male diabetic patients in a tertiary hospital in northern Nigeria. The subjects comprises 122 subjects mean age 53.5(11.6) years, range 34 to 73 years and 76 matched control subjects.
Simple convenient sampling technique was used. The study protocols was approved by the hospital ethics committee.
The data obtained included personal, blood pressure and anthropometric measurements while lipids, glucose and serum total prostate specific antigen (PSA) were determined using ELISA technique.
Serum PSA levels of >5.0 ng/ml is considered as risk of prostate cancer. Blood pressure reading of >140/90 mmHg is considered hypertension.
The data was analysed using SPSS 23 version.
Results: Among the 122 diabetic subjects screened, 62 were hypertensive (SBP=137±22.9) and 60 normal (SBP=116±12.6) and the mean ages were 55.9(7.9) years and 51.1(14.4) years $p<0.05$.
The mean serum PSA was lower in hypertensive group 2.02(1.71) than in Diabetic only group 4.00(2.56) ng/ml $p<0.05$ while duration of disease was high among the hypertensive group $p>0.05$.
The correlation analysis shows that PSA has a significant negative relationship between SBP, DBP and FBG in experimental group while in control group similar pattern was found with rising SBP.$p<0.05$
Multiple regression analysis indicates that SBP and FBG predicts PSA negatively in the study subjects $F(3, 116)=5.318$, Anova $p=0.02$. Also SBP and FBG predicts PSA negatively and positively among the control group respectively $(2, 117)=3.762$, Anova p-0.026.
Conclusions: Systolic hypertension is associated with reduced total serum PSA levels among both the diabetic and non diabetic subjects. This will tend to have masking effect when screening for prostate cancer among diabetic hypertensive.

INTRODUCTION

Prostatic specific antigen (PSA) is a glycoprotein produced by the epithelial cells of the prostate gland, found only in men and located under the bladder surrounding the urethra. Its regulation is under the control of androgens and progestins. It is a serine protease with chymotrypsin-like enzymatic activity and has a molecular weight of about 30kDa. It is secreted into seminal plasma at a high concentration whereas lower concentrations normally found in the circulation are the result of leakage from the prostate gland. PSA at lower concentrations has recently been also detected in many tissues, especially female breast [Livija *et al*, 2001].

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Serum PSA is age dependent, i.e. it tends to increase with age because the prostate enlarges with years and contains more PSA-producing tissue [Oesterling *et al*, 1993]. Alterations in the endocrine system, heredity, diet, micro-organisms, environmental factors, etc, have been linked to prostate disorders. Due to the fact that early detection of prostate disorder is central for effective management of the patient, the identification of risk factors and groups more at risk would certainly reduce the state of morbidity and mortality from the disorders [Lawrence *et al*, 2006].

PSA is the most useful biomarker for the detection and monitoring of prostate cancer, although not very sensitive. Elevated serum PSA concentrations are known to be connected with the three most common prostatic diseases, i.e prostate cancer, benign prostatic hyperplasia and prostatis [Livija *et al*, 2001]

Some studies [Anoop *et al*, 2002] [Duvnjuk *et al*, 2009] suggest that insulin resistance with secondary hyperinsulinemia, as the foundation of hypertension and other CV risk factors, is associated with prostatic enlargement. Insulin resistance occurs when there is a decrease in the responsiveness of peripheral tissues (skeletal muscle, fat, and liver) to the effect of insulin, with a concomitant hyperinsulinemia responsible for insulin like growth factor 1 (IGF-1) production in the liver.

In addition to insulin, IGF-1, which is significantly elevated in patients with insulin resistance, is known to stimulate growth of both androgen-sensitive and androgen-independent human prostate cancer cell lines in vitro, and elevated IGF-1 serum levels are associated with an increased prostate cancer risk in humans [Cosimo *et al*, 2012]

Hyperinsulinemia is in turn associated with an increased sympathetic nervous system activity and may contribute to increased smooth muscle tone of the prostate. Hyperglycaemia may play a role by increasing cytosolic-free calcium in smooth muscle cells and neural tissue, leading to sympathetic nervous system activation [Cosimo *et al*, 2012].

Although conflicting results exist, several studies [Anoop *et al*, 2002] [Duvnjuk *et al*, 2009] [Cosimo *et al*, 2012] have found that hypertension, insulin resistance and or DNA polymorphisms in the insulin gene itself are associated with an increased prostate cancer risk. A recent meta-analysis [Liang *et al*, 2016] have shown that hypertension may be associated with increased risk of prostate cancer.

However, the relative risk of prostate cancer was found to decrease significantly with increasing time from Type 2 Diabetes Mellitus diagnosis, suggesting the importance of insulin because of the fact that insulin levels decline with longer-standing Type 2 Diabetes Mellitus as a result of beta cell burnt out [Cosimo *et al*, 2012][David *et al*, 2006][Sarma *et al*, 2009]. Although significantly reduced risk of prostate cancer among diabetic subjects has been established however, similar relationships with hypertension or other cardio metabolic factors have not been documented conclusively especially among Nigerians.

MATERIALS AND METHODS

The study involves consecutive 122 males type 2 diabetic subjects attending endocrine clinic of Jigawa state specialist hospital, Dutse in northern Nigeria. The diagnosis of type 2 diabetes is according to American Diabetes Association (ADA) classification. The ages were recorded, anthropometry indices done and blood pressure were measured and recorded. The prostate specific antigen, fasting blood glucose (FBG) and lipid profile levels were measured, using a fasting venous blood, in all the diabetic subjects and 80 apparently healthy male subjects without prostate disease or history of prostatic disorder, history of diabetes mellitus and or hypertension were recruited as controls.

The relationships between serum PSA levels and variables including body mass index, waist circumference ,hip circumference, waist to hip ratio, blood pressure, duration of diabetes, fasting blood glucose and lipid profile were investigated.

Serum PSA levels was assayed using Enzyme Linked immunosorbent Assay (Monobind incorporation).

Fasting blood glucose was assayed using enzymatic method [Ngo *et al*, 2003]. Lipid profile parameters: Enzymatic methods were used to assay Total Cholesterol (TC) [Trinder, 1999], Triglyceride (TG) (Allain *et al*, 1974) High density lipoprotein(HDL) [McGowan *et al*, 1983]. Low-density Lipoprotein was calculated using the formula LDL-cholesterol = Total cholesterol − (HDL cholesterol−TG/2.2) [Gerald *et al*, 1992].

Approval for the study was obtained from the ethics and review committee of the Jigawa State Specialist Hospital Dutse, Jigawa state and informed consent was obtained from all participants using a pre-designed questionnaire.

Statistical analysis

The data were analysed statistically using SPSS package version 20.0 and presented as mean ± standard deviation and correlation coefficient (r-value) using Pearson's correlation with $p<0.05$ level as significant.

RESULTS

Among the 122 diabetic subjects screened, 62 were hypertensive (SBP=137±22.9) and 60 normal (SBP=116±12.6) and the mean ages were 55.9(7.9) years and 51.1(14.4) years $p<0.05$.

Table 1 showed a significant difference in age among the three groups n=198, p=0.000. p=0.002, However, there was no difference between the diabetic only and diabetic hypertensive groups p=0.362. There was a significant difference in duration of diabetes between the diabetic 5.2(4.4) years and diabetic + hypertensive 5.85(3.1) years groups, p=0.000.

However, there was no significant difference in FBG, TC, HDL, TG and BMI between subjects with diabetes only and the diabetic hypertensive group $p>0.05$

There was a significant difference in PSA across the three groups n=198, p=0.000. The mean serum PSA was lower in hypertensive group 2.02(1.71) than in Diabetic only group 4.00(2.56)ng/ml $p<0.05$ but higher than in control group 1.51(0.81) ng/ml.

Tables 2&3 showed the correlation analysis that PSA has a significant negative relationship between SBP, DBP and FBG in experimental group while in control group similar pattern was found with rising SBP.$p<0.05$

meta-analysis [Liang *et al*, 2016] on the relationship between

Table 1 Showing a Descriptive Statistics of the three groups

Group	Age	Weight	Height	BMI	WC	HC	WHR	SBP	DBP	FBG	TC	HDL	TG	LDL	PSA	Duration of DM
DM only (n=60)	51.10± 14.42	69.70±1 5.92	1.70±0.06	24.19±5.50	89.95±10.15	94.75±7.55	0.94±0.07	116.50±12.68	71.50±8.75	7.89±4.04	3.39±0.77	1.51±1.43	0.94±0.5	1.80±0.75	4.00±4.56	5.20±4.40
DM + HTN (n=62)	55.95± 7.90	69.30±2 0.85	1.71±0.06	23.85±7.86	87.00±19.88	90.95±17.42	0.95±0.08	137.00±22.96	77.50±13.33	7.82±4.73	3.30±0.93	1.69±1.45	0.92±0.79	1.59±0.71	2.02±1.71	5.85±3.08
Control (n=76)	40.45± 10.78	60.77±1 3.86	5.39±16.41	22.33±4.49	83.18±10.27	90.20±10.57	0.94±0.15	118.25±14.83	76.00±9.28	4.22±1.32	3.51±0.70	1.67±0.54	1.02±0.66	1.43±0.64	1.51±0.81	
f-value	44.79	8.78	3.064	2.72	5.66	3.012	0.302	30.9	5.86	38.95	1.53	0.53	0.54	5.91	21.05	13.58
p-value	0.000	0.000	0.49	0.068	0.004	0.051	0.74	0.000	0.000	0.000	0.22	0.59	0.58	0.003	0.000	0.000

BMI=body mass index, WC=waist circumference, HC=hip circumference, WHR=waist hip ratio, SBP=systolic blood pressure, DBP=diastplic blood pressure, FBG=fasting blood glucose, TC=total cholesterol, HDL=high density cholesterol, TG=triglyceride, LDL=low density cholesterol, PSA=prostatic specific antigen.

Table 2 Showing Correlation between PSA values and analytes among experimental group.

Experimental Correlation (n=122)		
	r- value	p-value
Age	-.125	.174
Weight	-.129	.162
WC	-.150	.101
SBP	-.264	.004
DBP	-.244	0.007
FBG	-.185	.043
LDL	-.121	.187

Multiple regression analysis among the experimental group indicated that SBP and FBG predicts PSA negatively in the study subjects F(3, 116)=5.318, Anova p=0.02.

Table 3 Showing Correlation between PSA values and analytes among control group.

Control Correlation (n=76)		
	r- value	p-value
Age	-.001	0.996
Weight	-0.022	0.811
WC	0.067	0.469
SBP	-2.0	0.028
DBP	-0.036	0.695
FBG	0.208	0.023
LDL	-0.117	0.202

Multiple Regression analysis for control group showed SBP and FBG predicts PSA negatively and positively among the control group respectively (2, 117)=3.762, Anova p-0.026.

Multiple regression analysis showed that SBP and FBG predicts PSA negatively in the study subjects F(3, 116)=5.318, Anova p=0.02. While SBP and FBG predicts PSA negatively and positively among the control group respectively (2, 117)=3.762, Anova p-0.026.

DISCUSSION

Diabetes and its complications are major causes of early death in most countries [Cai *et al*, 2015] [Friedwald *et al*, 1972]. Prostate cancer is a leading cancer diagnosed and cause of cancer-related deaths among Nigerian men. However, the true prevalence and the impact of hypertension on prostate cancer in Nigerian community is not known [IDF, 2013] because androgens have been implicated in tumourigenesis [Stephen *et al*, 2013]. Identification of diabetic subjects with hypertension, therefore, has therapeutic and management implications to prevent morbidity and mortality [Michiaki *et al*, 2008].

In our study serum PSA levels was found to be lower, figure 1, in diabetic-hypertensive group than in diabetic only and higher than in control group. This means there is an inverse relationship between hypertension and PSA values among diabetic-hypertensive subjects. This is in contrast to a recent cohorts, where it showed that hypertension was significantly associated with an increased risk of prostate cancer. Considering the fact that diabetes mellitus is associated with decreased risk of prostate cancer [Cai *et al*, 2015], hypertension among these category of patients provide a synergistic or additive effect which will further reduce or mask the chance of identifying the risk of prostate cancer among this group of patients. This may further buttress the fact that both hypertension and diabetes shared the same pathophysiology of insulin resistance which will lead to initial hyperinsulinaemia before eventual decline in insulin and PSA production.

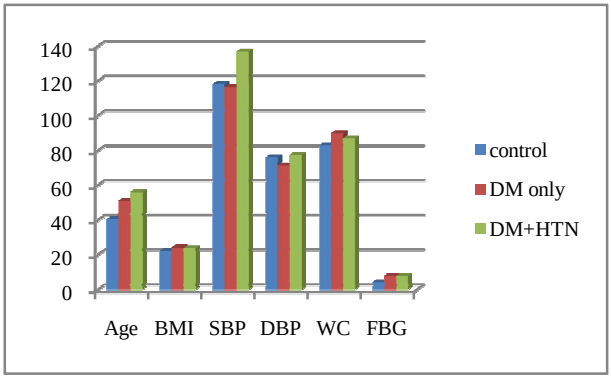

Figure 1 Showing the distribution of the variables among the three groups.

Although the duration of diabetes is a difficult to quantify parameter, as approximately 50% of type 2 diabetic patients may be undiagnosed in the population and known duration might be related to the degree of medical surveillance [Thompson *et al*, 2004] our study observed a negative correlation between PSA and the duration of Type 2 diabetes mellitus in the diabetic hypertensive subjects. The first date of diagnosis was used to quantify the duration of Type 2 diabetes in the subjects.

These results are consistent with the hypothesis that long term diabetes is associated with lower risk of prostate cancer.[David *et al*, 2006]

The PSA levels among the control group, figure 2, is much lower than the diabetic groups. This may be attributed to the fact that the control group is much younger with low mean age compared to the diabetic groups. It is known that age is in direct relationship with the size of the prostate gland and also the levels of PSA produced.[Oesterling *et al*, 1993]

Although low level of PSA may not exclude presence of prostate cancer as it was reported that some apparently healthy men with PSA levels below 4.0ng/ml may have prostate cancer and that many men with higher levels do not

have prostate cancer. [Ejiofor *et al*, 2015] Likewise it was reported that men with a higher BMI also have larger plasma volumes, which could decrease serum concentrations of soluble tumor markers.[Thompson *et al*, 2004][Mariko *et al*, 2012][Heiko *et al*, 2009]

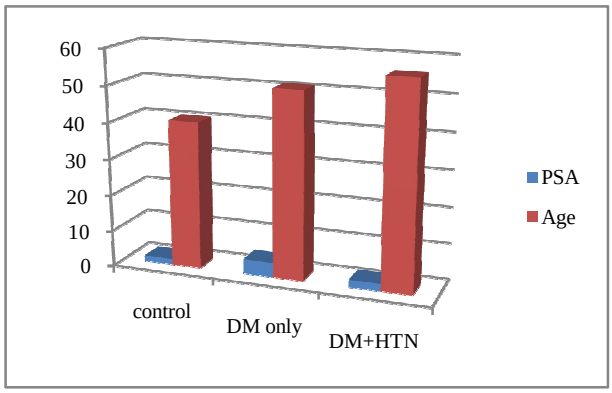

Figure 2 Showing the distribution of the PSA values and mean ages among the three groups

This study found a negative correlationship between total serum PSA and SBP, DBP and FBG amongst the diabetic groups while the control group exhibits a similar relationship with SBP only. The SBP and FBG in this study was also found to predict low PSA values. This result was not in concordance with previous study that showed a positive association between PSA levels and hypertension among normal population [Liang *et al*, 2016]. This may be explained by the same reason diabetes behaves with PSA as both the two shared similar pathophysiology of insulin resistance. [Anoop *et al*, 2012][Cosimo *et al*, 2012].

It is concluded, in this study, that presence of hypertension in diabetic subjects, especially those with long duration of disease, will further reduces the levels of PSA and hence reducing or masking the risk of prostate cancer. It also revealed that systolic hypertension and fasting blood glucose independently predicts lower chance of prostate cancer identification, in respective of age or duration of disease, among this population.

This study is limited by the small sample size used and the inability to conduct a further screening exercise using scanning procedure to assess the sizes of the prostate glands so as to further complement the recorded levels of PSA for proper interpretation. The findings in this study cannot be generalized until subjects with hypertension only, perhaps not on any medication, are followed up to establish a more reflective relationship between hypertension and PSA levels. The outcome of our study implied that caution is needed when screening for the risk of prostate cancer, using PSA levels, among these category of patients in the studied population. The low levels of PSA recorded in these subjects may mask the presence of prostate cancer as such this warrants to establish a new critical PSA value for diagnosis and use of scanning, physical assessment and probably biopsy for diagnosis of prostate cancer in this group of patients.

It is recommended that future studies involving a large cohort to follow the hypertensive subjects only, with and without medication, on one hand and diabetic-hypertensive on the other be carried. This may assist in better understanding of the relationship between hypertension and the risk of prostate cancer in both groups.

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