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Association Between Prostatic Volume, Metabolic Syndrome and Left Ventricular Mass: A Cross Sectional Study

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Abstract: Ageing in men is associated with increased prevalence of cardiovascular risk factors and benign prostatic hyperplasia (BPH) with both entities possibly representing downstream manifestations of a common pathogenesis. There is paucity of data on the association of BPH and left ventricular hypertrophy (LVH). This study evaluated relationship between prostate volume, common cardiovascular risk factors and LVH. It was a cross sectional, prospective, hospital-based study. Thirty patients with benign prostatic enlargement (BPE) and 30 age- matched male controls without BPE were studied. All the subjects had clinical, biochemical, prostate ultrasound and echocardiographic evaluation done. SPSS IBM 20 was used to analyze data. Mean age was 65.60 ± 8.11 years (range: 54-82years). Subjects with BPE compared to those without did not significantly differ in age (66.50± 7.75 vs. 64.70±8.49; p=0.39). Significantly higher percentage of subjects with BPE had abnormally low HDL-cholesterol and high blood pressure compared with subjects without BPE. Eight (26.7%) of subjects with BPE in contrast to none of the subjects without BPE had metabolic syndrome (Chi2 = 9.231; p=0.002). Left ventricular mass index were significantly higher in subjects with BPE than in those without. None of the subjects without BPE as compared with 7 (23.3%) of subjects with BPE had echocardiographic determined LVH. Echocardiographic indices that significantly correlated with prostatic volume were: LVPWd (r=0.326, p= 0.011), IVSTd (r= 0.267, p=0.039), LVMI(r=0.308, p= 0.017), LAD (r= 0.494, p<0.0001) and AOD (r= 0.352, p= 0.006). The conclusion was that BPE is associated with increased left ventricular mass index and metabolic syndrome, mostly driven by elevated blood pressure and low serum HDL-cholesterol.

Keywords: Benign Prostatic Hypertrophy, Prostatic Volume, Left Ventricular Hypertrophy, Metabolic Syndrome, Left Ventricular Mass Index

1. Introduction

Associated with ageing in men are increased prevalence of cardiovascular risk factors and benign prostatic hyperplasia (BPH) [1, 2]. Many details of the pathogenesis of BPH remain obscure, although some reports suggest an association with cardiovascular disease [1]. Benign prostatic hyperplasia (BPH) is the most common benign disease in older men. Autopsy studies have revealed histologic evidence of BPH in 42% of men aged 51–60 years, rising to 85% among men older than 80 years [2]. Severe BPH leads to deterioration in the quality of life of afflicted men, and its treatment has serious economic implications [3].

In the future with a changing demographic profile and an

increasingly ageing population in almost all societies, it is inevitable that this disorder will become even more prevalent and a major challenge for all health care systems [4].

For over a century, there have been two known etiologic factors for the pathogenesis of BPH: ageing and testicular androgens [5]. In addition, family history, race/ethnicity, hypertension, non-insulin dependent diabetes, obesity, body height, cigarette smoking, low HDL-C, and high insulin levels have been reported to be prevalent in patients with BPH [6-8]. This emerging interest in the relationship between components of Metabolic Syndrome and prostatic volume suggests the need for their investigation as new targets for prevention, diagnosis and treatment of benign prostatic enlargement [9].

The association of BPH and heart disease, independent of other variables, had also been described [10, 11], suggesting that both entities represent downstream manifestations of a common pathogenesis. Epidemiological study showed that elevated free PSA levels, heart disease, and the use of b-blocker medications increase the risk of BPH [10]. Increasing age also increase prevalence of cardiovascular risk factors and benign prostatic hyperplasia (BPH). The link between BPH and LVH, independent of systemic hypertension and other components of metabolic syndrome may be due to autonomic nervous dysfunction with sympathetic bias (impaired parasympathetic system). It has been suggested that this promotes prostatic hyperplasia and lower urinary tract symptoms [12] as well as myocardial apoptosis leading to cardiac remodeling including left ventricular hypertrophy [13].

In the present study we set out to evaluate the relationship between prostate volume, common cardiovascular risk factors and LVH. There is paucity of data, if any, on the association of prostate volume and LVH despite that BPH and cardiovascular diseases are common in elderly men.

2. Subjects and Methods

This is prospective, cross-sectional study of patients that presented to the Urology, Medical and General Outpatient Clinics of a tertiary health institution in Nigeria. The study period was between June, 2015 and May, 2016.

A total of 60 patients consisting of 30patients with benign prostatic enlargement (BPE) and 30 age- matched male controls that were considered not to have BPE were studied.

Inclusion criteria:

a) Patients who were willing to participate in the study.
b) Patients with serum PSA of ≤ 10ng/ml
c) Patients who did not have any of the exclusion criteria

Exclusion Criteria

Patients with:

a) serum PSA level >10ng/ml [14];
b) previous prostatic surgery;
c) BPH already on treatment with alpha-1 antagonist medication;
d) heart failure, renal failure, previous myocardial infarction;
e) chronic obstructive disease, sickle cell disease, HIV/AIDS, or any other diseases known to significantly affect cardiovascular status and;
f) diabetes mellitus on antidiabetic or any patients currently on 5 -reductase inhibitors or lipid-lowering medication.

2.1. Ethical Issue

Written informed consent was obtained from each subject and control before enrollment in the study. The study was approved by the Institutional Review Board of the hospital and was performed in accordance with the principles of the Declaration of Helsinki.

Procedures

2.2. Anthropometric Data

Height and weight were measured while subjects were wearing light clothing without shoes. Waist circumference was measured midway between the costal margin and the iliac crest at the end of a normal expiration. Blood pressure was measured with a mercury sphygmomanometer on the right arm with subjects in the sitting position after a minute rest. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

2.3. Transurethral Ultrasound and Definition of BPE

Transabdominal scanning method was used to measure largest anteroposterior height (*H*), transverse width (*W*) and cephalocaudal diameter (*L*) wherein ellipsoid formula [15] was used to calculate prostate volume as follows:

$$0.524\ (H \times W \times L \times л/6)$$

Prostate volume >30 mL; and (ii) PSA level of <10 ng/mL were used to define BPE. Patients with prostate volume <=30ml and PSA level of <10 ng/mL were considered not to have BPE [15].

2.4. Echocardiography

All subjects and controls had transthoracic two-dimensional (2D) and 2D derived M-mode echocardiography performed according to standard procedure [16], while in the left lateral decubitus position using the SonoScape 1000 Ultrasound Imaging System with 4-2MHz transducer. Left ventricular end-diastolic measurements were taken during at least three cardiac cycles according to American Society of Echocardiography convention [17]. These included the left ventricular internal diameter (LVIDd), left ventricular posterior wall thickness in diastole (LVPWd) and interventricular septal thickness in diastole (IVSTd). Left Ventricular (LV) mass was estimated from the Devereux's formula [18] $=0.80\{1.04(\text{LVIDd} + \text{LVPWd} + \text{IVSTd})^3 - (\text{LVIDd})^3\} + 0.6\text{g}$ and normalized to $\text{height}^{2.7}$ ($\text{ht}^{2.7}$).

Upper normal limits for LV mass index were >48 g/ $m^{2.7}$ to define LVH [19]. Relative wall thickness (RWT) was defined as (2 × PWT)/ LVIDd [19]. A partition value of 0.42

for relative wall thickness was used[19]. Left atrial anteroposterior linear dimension (LAD) obtained from the parasternal long –axis view was taken from the trailing edge of the posterior aortic wall to the leading edge of the posterior left atrial wall at the end-ventricular systole when the LA chamber was at its greatest dimension [19].

2.5. Electrocardiogram

A resting 12 leads ECG was done in both subjects and controls to determine cardiac rhythm, presence or otherwise of atrioventricular nodal and intraventricular conduction blocks. The duration of the QT interval was also determined.

2.6. Blood Sample Collection

Blood samples were obtained in the morning after fast of 8 hours. Plasma glucose was measured by the hexokinase method using an autoanalyzer (Randox Glucose kit and spectrophotometer). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were also measured using an autoanalyzer (Randox Lipid kit).

Definition of metabolic syndrome was done using the 2006 IDF consensus worldwide definition of the Metabolic Syndrome [20]. According to these criteria, subjects with metabolic syndrome are those with central obesity (waist circumference ≥ 94cm) and any combination of two or more of the following risk determinants: fasting plasma glucose ≥ 5.6 mmol/L or on antidiabetic treatment, blood pressure ≥ 130 / 85 mmHg or on antihypertensive treatment, plasma triglycerides ≥ 1.7 mmol/L and plasma HDL cholesterol < 1.03 mmol/L.

2.7. Data Collection

All data collected were entered into a proforma and subsequently transferred to SPSS version 20 for analysis.

2.8. Statistical Analysis

Means (Standard deviations) were used to describe the distributions of continuous variables. Percentages were used to describe categorical variables. Comparisons of categorical data were performed with the use of Pearson's chi-square test. For continuous data, a Student t-test was used to compare means. We conducted bivariate correlation to determine the relationship between prostate volume with components of metabolic syndrome and echocardiographic indices. P- value < 0.05 was considered statistically significant. All statistical analyses were performed with computer program IBM SPSS 20 (IBM Corporation, 2011).

3. Results

3.1. Bio-demographic Parameters

The study population consisted of 60 adult male subjects with mean age of 65.60 ± 8.11 years (range: 54-82years) divided into two groups. Group I comprised 30 subjects (sample) with benign prostatic enlargement and group II had 30 subjects (control) who did not have benign prostatic enlargement. As seen in Table 1, the two groups did not significantly differ in age (66.50± 7.75 vs. 64.70±8.49; p=0.39). Similarly, there were no statistically significant differences in body weight, height and body mass index. Seventeen (56.7%) of subjects in group I and 16(53.3%) of subjects in group II were overweight/obese with BMI> 25kg/m2. No significant difference in the frequency of cigarette smoking between the two groups.

All the subjects were in sinus rhythm on ECG. Subjects in group I (those with BPE) had significant longer PR interval (181.50 ± 34.09ms vs. 3.27±19.16ms; p=0.01) and corrected QT (422.50 ± 23.99ms vs. 399.03± 31.80ms; p=0.002) on ECG than group II (those without BPE).

Table 1. *Biographic and Electrocardiographic Parameters.*

Variables (n=30)	BPE (n=30)	Controls	p- value
Age(years)	66.50 ±7.75	64.70± 8.49	0.39
Weight(Kg)	68.18 ±11.81	68.93± 7.75	0.77
Height(m)	1.67 ± 0.07	1.67 ± 0.05	0.93
Body Mass Index(kg/m^2)	24.47 ± 4.20	24.66± 2.58	0.83
Pulse rate(min^{-1})	75.50 ±13.40	80.47± 9.03	0.18
BMI > 25.0 kg/m^2 n(%)17(56.7)	16(53.3)	0.79	
History of cigarette smoking n(%)	7(23.3%)	4(13.3%)	0.253
PSA(ng/ml)	5.80 ± 3.79	3.38 ± 1.93	0.003
Prostatic volume(ml)	114.02±50.05	22.86±4.14	<0.0001
ECG PR Interval(ms)	181.50 ± 34.09	163.27± 19.16	0.01
ECG QRS duration(ms)	96.83 ± 18.90	97.73± 13.53	0.83
ECG QTc(ms)	422.50 ± 23.99	399.03± 31.80	0.002
ECG-T Wave inversion	6(20.0)	2(6.7)	0.13

BMI=Body mass index; PSA=Prostatic specific antibody

3.2. Metabolic Syndrome and Its Components (Table 2)

The mean systolic and diastolic blood pressures were significantly higher in group I subjects compared to group II subjects. Otherwise, there were no significant differences in the two groups in the other components of metabolic syndrome studied. However, significantly higher percentage of subjects with BPE had abnormally low HDL-cholesterol and high blood pressure compared with subjects without BPE. Eight (26.7%) of subjects with BPE in contrast to none of the subjects without BPE had metabolic syndrome (Chi2 =

9.231; p=0.002).

Table 2. *Components of Metabolic Syndrome.*

Variables (n=30)	BPE (n=30)	Controls	p-value
Waist circumference(cm)	86.97± 18.29	86.13 ± 11.71	0.83
Systolic Blood Pressure(mmHg)	138.47 ± 15.12	129.73 ± 11.18	0.01
Diastolic Blood Pressure(mmHg)	85.63 ± 10.54	77.70 ± 6.08	0.001
Fasting plasma glucose(mmol/L)	4.89 ± 1.11	4.63± 0.84	0.31
Total Cholesterol(mmol/L)	4.00± 1.09	3.99± 0.65	0.94
HDL-Cholesterol(mmol/L)	0.98± 0.46	1.13 ± 0.15	0.12
LDL-Cholesterol(mmol/L)	2.55± 0.87	2.44 ± 0.65	0.58
Triglycerides(mmol/L)	1.07 ± 0.55	0.90± 0.16	0.11
Waist ≥ 94 cm n(%)	11(36.7)	5(16.7)	0.14
HDL < 1.03 mmol/l n(%)	20(66.7)	8(26.7)	0.002
Triglycerides ≥ 1.70 mmol/l n(%)	2(6.7)	0(0)	0.15
Blood glucose ≥ 5.6 mmol/l n(%)	6(20.0)	4(13.3)	0.49
Blood pressure ≥ 130/85 mm Hg n(%)	22(73.3)	6(20.0)	<0.0001
Metabolic syndrome n(%)	8(26.7)	0(0)	0.002

HDL: High density lipoprotein; LDL: Low density lipoprotein

As shown in Table 3, HDL-cholesterol inversely correlated with prostatic volume while systolic and diastolic blood pressure positively correlated with prostatic volume. No significant correlation between the remaining components of metabolic syndrome and prostatic volume.

Table 3. *Correlation coefficients of Prostatic Volume with Components of Metabolic Syndrome and Echocardiographic Indices.*

Variables	Rho	P- value
Waist circumference(cm)	0.077	0.557
Systolic Blood Pressure(mmHg)	0.446	<0.0001
Diastolic Blood Pressure(mmHg)	0.467	<0.0001
HDL-Cholesterol(mmol/L)	- 0.318	0.013
Fasting plasma glucose(mmol/L)	0.070	0.594
Triglycerides(mmol/L)	0.078	0.555
PSA(ng/ml)	0.459	<0.0001
ECG PR Interval(ms)	0.295	0.022
ECG QTc(ms)	0.446	<0.0001
IVSTd(mm)	0.267	0.039
LVPWd(mm)	0.326	0.011
LVIDd(mm)	0.068	0.604
LVIDs(mm)	0.031	0.817
LVMI(g/m^2)	0.308	0.017
LAD(mm)	0.494	<0.0001
AOD(mm)	0.352	0.006

HDL: High density lipoprotein; PSA=Prostatic specific antibody; LVIDd:Left ventricular internal diameter in diastole; LVIDs: Left ventricular internal diameter in systole; LVPWd: Left ventricular posterior wall thickness in diastole; IVSTd: Interventricular septal thickness in diastole; LVMI: Left Ventricular mass index; LAD: Left atrial dimension; AOD: Aortic root dimension; LVH: Left ventricular hypertrophy

3.3. Echocardiographic Indices

Subjects with BPE had significantly higher left ventricular wall thickness than subjects without BPE. As shown in Table 4, mean interventricular septal wall thickness and left ventricular posterior wall thickness were significantly higher in subjects with BPE than in those without. Relative wall thickness and left ventricular mass index were also significantly higher in subjects with BPE compared to those without. Mean left ventricular internal dimensions in diastole and systole did not significantly differ between the two groups. None of the subjects without BPE as compared with 7 (23.3%) of subjects with BPE had echocardiographically determined left ventricular hypertrophy. Only 1(12.5%) of the 8 patients with metabolic syndrome had LVH and 11.5% of those without metabolic syndrome had LVH (Chi2= 0.006, p=0.94).

Table 4. *Echocardiographic Indices.*

Variables(n=30)	BPE (n=30)	Controls	p –value
IVSTd(mm)	11.45± 1.33	10.19± 0.87	<0.0001
LVPWd(mm)	11.65± 1.30	10.30 ± 0.71	<0.0001
LVIDd(mm)	42.37 ± 6.56	41.91± 5.43	0.77
LVIDs(mm)	29.56 ± 7.01	29.27± 6.08	0.88
RWT	0.56 ±0.09	0.50± 0.06	0.008
LVMI(g/m^2)	98.89± 26.60	80.09 ± 13.52	0.001
LAD(mm)	34.50± 6.30	32.57 ± 3.92	0.16
AOD(mm)	33.75± 3.66	31.21 ± 2.28	0.002
Echo- LVH	7(23.3)	0(0)	0.005

LVIDd:Left ventricular internal diameter in diastole; LVIDs: Left ventricular internal diameter in systole; LVPWd: Left ventricular posterior wall thickness in diastole; IVSTd: Interventricular septal thickness in diastole; LVMI: Left Ventricular mass index; LAD: Left atrial dimension; AOD: Aortic root dimension; LVH: Left ventricular hypertrophy

Other echocardiographic indices that significantly correlated with prostatic volume were: LVPWd (r=0.326, p= 0.011), IVSTd (r= 0.267, p=0.039), LVMI(r=0.308, p= 0.017), LAD (r= 0.494, p<0.0001) and AOD (r= 0.352, p= 0.006). There was no significant correlation between left ventricular internal dimensions in diastole (LVIDd) and systole (LVIDs) [Table 3].

4. Discussion

In this study, it was demonstrated that subjects with BPE as evidenced by large prostatic volume were more likely to have metabolic syndrome and LVH compared to those without BPE.

The increased prevalence of metabolic syndrome in subjects with BPE in our study is probably driven by abnormally low HDL-cholesterol and elevated blood

pressure. In a systematic review and meta-analysis of eight studies involving 5403 patients, Gacci et al [21] suggested that the occurrence of metabolic syndrome in elderly men with a larger prostate could represent a major contributing factor in BPE progression. In ameta-regression analysis of the meta-analysis, the authors further suggested that obese, dyslipidemic (low serum HDL concentration in particular) and aged patients were more at risk of having metabolic syndrome as a determinant of their increased prostate size. However, the major metabolic syndrome-related determinant of BPE was HDL-cholesterol. In contrast, hyperglycaemia and increased triglyceride levels were not significantly associated with prostate enlargement. The contribution of hypertension in that meta-analysis was not specifically addressed by meta-regression, due to insufficient data. In our study, there was a modest correlation of serum HDL-cholesterol and prostatic volume in an inverse relationship while systolic and diastolic blood pressure positively correlated to prostatic volume.

It is not clear the mechanism by which dyslipidemia promote prostate growth. Vignozzi et al [22] recently showed that lipids (oxidized low-density lipoprotein, LDL) increase in vitro the secretion of growth (VEGF, b-FGF) and pro-inflammatory factors (interleukin 6 [IL-6], IL-8, and IL-7) by human stromal BPH cells in culture.

In addition, Vignozzi et al [23] proposed a three-hit hypothesis on the development of BPH, which may also be helpful in understating the mutual relationship between BPH and metabolic syndrome. According to this hypothesis, an overt or subclinical inflammation (first hit) could be auto-sustained or overlapped by metabolic alternations (second hit) and changes in sex-hormone levels (third hit). The combined effects of these may result in overexpression of toll-like receptors, transformation of prostatic cells into antigen-presenting cells, and up-regulation of growth factors (andromedins), leading to prostate enlargement.

This study also showed that prostatic volume is associated with increased left ventricular walls thickness (IVSTd and LVPWd) but not left ventricular internal dimensions (LVIDd and LVIDs). Prostatic volume is also associated with left ventricular mass index, left atrial dimension and aortic root dimension. Subjects with BPE had increased prevalence of LVH compared with those without BPE. There is paucity of literature on the association of BPE and LVH. It is not unlikely that both entities represent downstream manifestations of a common pathogenesis with metabolic derangement as seen in metabolic syndrome theoretically the inciter. In this study, subjects with BPE had significant higher systolic and diastolic blood pressure with blood pressure being significant correlate of prostatic volume. It is known that hypertension induces left ventricular hypertrophy through increase in cardiac afterload that result in increased left ventricular wall stress but this may not explain its effect on prostatic growth. Independent of systemic hypertension and other components of metabolic syndrome, autonomic nervous dysfunction with sympathetic bias (impaired parasympathetic system) have also been suggested to promote prostatic hyperplasia and lower urinary tract symptoms [12] as well as myocardial apoptosis leading to cardiac remodeling including left ventricular hypertrophy [13].

This study is not without its limitations. Being a cross-sectional, hospital-based study with limited sample size; caution must be taken in applying the findings to the general population. Due to its observational nature, the associations observed between prostate volume and metabolic syndrome as well as LVH may not be causal, on account of some unknown confounding or reverse causality. Nonetheless, this study has provided information on the subject matter relevant to clinical practice, especially in the study area.

5. Conclusion

Benign prostatic enlargement is associated with increased left ventricular walls thickness and metabolic syndrome, mostly driven by elevated blood pressure and low serum HDL-cholesterol. The mechanism(s) for the association is not yet clearly known but may be due to the presence of pro-inflammatory cytokines and autonomic nervous dysfunction with sympathetic bias.

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