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Evaluation of N-acetyl-β-D-glucosaminidase, creatinine and estimated glomerular filtration rate in patients with benign prostatic hyperplasia/ prostate cancer in NAUTH, Nnewi, Nigeria

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Abstract

Benign prostatic hyperplasia (BPH), also called prostate enlargement, is a noncancerous increase in size of the prostate gland while prostate cancer (PCa) is malignant tumor of the prostate, the gland that produces some of the components of semen. Urine N-acetyl–β-D-glucosaminidase (uNAG), urine creatinine (uCr), serum creatinine (sCr), estimated glomerular filtration rate (eGFR) and ratio of uNAG to uCr (uNAG/uCr) in BPH/PCa were assessed with height, weight and BMI. This cross-sectional study recruited 120 men using convenient sampling technique which comprised 40 BPH, 40 PCa and 40 apparently healthy age matched control individuals attending urology clinic of NAUTH, Nnewi, Anambra State. Five (5) milliliters of blood/ urine samples were collected from the patients and the necessary data were obtained from clinical records of the patients. The weight (kg) and height (m) were measured using standard beam balance scale and a stadiometer respectively and the BMI calculated. uNAG (u/l) was estimated by enzyme immunoassay technique, creatinine was determined spectrophotometrically using Jaffe slot alkaline picrate method while eGFR was calculated using an online calculator for the Modification of Diet in Renal Disease (MDRD) formula for Adults. Data analysis was conducted using SPSS version 21.0. The results were presented as median. Kruskal Wallis was used to determine significant differences between the mean values. The results showed significantly higher median values of uNAG and uNAG/uCr in patients with BPH/PCa when compared with the control. Despite the significant increase in uNAG and uNAG/uCr in this study, serum creatinine, urine creatinine and eGFR remained normal. The increase in uNAG in patients with BPH/PCa is an indication of early renal impairment.

Keywords: Benign prostatic hyperplasia; Prostate cancer; Acute kidney infection; N-acetyl-β-D-glucosaminidase (NAG); Creatinine; eGFR

1. Introduction

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are among the risk factors of kidney disease. They are common urological disorders in western society and belong to the most frequent diseases in aging men [1, 2]. BPH is a

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nonmalignant enlargement of the prostate gland and refers to the stromal and glandular epithelial hyperplasia that occurs in the transition zone of the prostate while prostate cancer is malignant tumor of the prostate gland [3, 4]. The enlargement of the prostate can produce voiding symptoms, which can lead to pathological changes in the urinary bladder and the kidney [5, 6]. The symptoms are similar, ranging from mild to severe as in the case of prostate cancer. The symptoms include frequent urination, trouble starting to urinate, weak stream urine, urinary retention, loss of bladder control or inability to urinate, hematospermia, hematouria, erectile dysfunction [4]. Metastatic symptoms of prostate cancer include weight loss, loss of appetite, lower extremity pain, bone pain with or without pathologic fracture, edema, uremic symptoms. Complications can include urinary tract infections, bladder stones, and chronic kidney problems [4, 6]. Globally, the odds of developing PCa are 1 in 18 and the odds range from 1 in 52 for low socio-demographic index (SDI) countries to 1 in 9 in high SDI countries [7]. An estimated 14,334 deaths in the year 2020 were as a result of prostate cancer [8]. Prostate cancer represents the second most common cancer in men worldwide and accounting for 4% of cancer-associated death [4].

In Africa, prostate cancer is the most common cancer among men [9]. Nigeria had the highest number of deaths from prostate cancer (among men 0-84 years) with 8,382 (58.5%) deaths out of 14,334 [8]. Benign prostate hyperplasia (BPH) accounts for 78.3% of all prostate-related diagnoses and increases from 20% to 90% in men who are 40–80 years of age [10, 11]. Diagnosis is typically based on symptoms and examination after ruling out other possible causes. The screening method for benign prostatic hyperplasia and prostate cancer relies on a combination of prostate specific antigen (PSA) assay and a digital rectal examination (DRE) while biopsy is done to confirm if there is suspicion of cancer [6]. Acute kidney infection (AKI) has been defined conceptually as a rapid decline in glomerular filtration rate (GFR) that occurs over hours and days. It is a common clinical entity which main outcome is a rapid decline of renal function [12]. It propels to a clinical syndrome characterized by a rapid decrease in renal excretory function, with the accumulation of products of nitrogen metabolism such as creatinine and urea clinically unmeasured waste products [13, 14]. Even though early recognition of AKI is essential as it could improve patient outcomes, its early diagnosis remains a challenge.

Kidney injury starts by inducing biological and molecular changes that, over time, evolve into cellular damage [12]. Therefore, the discovery and validation of a reliable biomarker for AKI prediction and early diagnosis seems provident, as it would allow early diagnosis and inform on the progression of AKI, thereby improving treatment strategies [15]. This study is intended at detecting early kidney disease in patients with BPH and PCa thereby reducing renal disease complications in these patients. Hence this study aimed at evaluating urine N-acetyl-β-D-glucosaminidase (uNAG), serum and urine creatinine, estimated glomerular filtration rate (eGFR) and ratio of uNAG to uCr (uNAG/uCr) in patients with BPH and PCa.

2. Material and methods

A total of 120 subjects which comprised 40 BPH, 40 PCa and 40 apparently healthy age matched control individuals were recruited in this cross-sectional study using convenient sampling technique. Patients with known history of diabetes, renal diseases and patients on drugs were excluded from the study.

Necessary data of the patients were obtained from their clinical records. Five (5) milliliters of blood/urine samples were collected from patients with BPH and PCa attending urology clinic of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State, Nigeria and dispensed in plain containers and sterile universal container respectively. The blood samples were centrifuged at 4000rpm for 10 minutes after clotting to obtain the serum for the determination of serum creatinine (sCr) while the urine samples were for the determination of urine NAG (uNAG) and urine creatinine (uCr). Samples were stored at -20°C prior to analysis.

uNAG was determined by double-antibody sandwich enzyme immunoassay technique as described by [16]. The determination of sCr and uCr were by Jaffe Slot alkaline picrate method as described by [17]. The estimated glomerular filtration rate (eGFR) was calculated using an online calculator for the Modification of Diet in Renal Disease (MDRD) formula for Adults [18]. The formula is given as: GFR (ml / min /1.73m2) = 186 x [plasma creatinine (µmol / l)]-1.154 x [age]-0.203 x [1.210(if black)] x [0.742 (if female)]. Body mass index (BMI) was calculated as weight in kilogram divided by height squared in meters, BMI (Kg/m2) = Weight(kg)/Height(m2).

Ethical approval to carry out this study was sought and obtained from the Ethics Committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi. Informed consent was sought and obtained from all the participants before recruiting them in the study.

Data analysis was conducted using SPSS version 21.0 (IBMInc, Chicago, IL). Values were assessed for normality by checking for skewdness. The results were presented as median. Kruskal Wallis was used to determine significant differences between the mean values. Statistical significance was set at $p<0.05$. Relationship or strength of the association between parameters was assessed using Pearson's correlation.

3. Results

As shown in table 1, there were no significant differences in the median ages of patients with BPH (68.00) when compared with control subjects (70.00)(P = 0.138). Similarly, no significant difference was observed in the median ages of patients with PCa (75.00) when compared with control subjects (70.00)(P = 0.090). A significantly higher median age value was observed in PCa (75.00) when compared with BPH (68.00)(P = 0.005). Also, a significantly higher median age value was observed in PCa and BPH when compared with the control individuals (P = 0.013). There was no significant difference in the median value of weight in BPH (69.500) and PCa (76.000) when compared with the control subjects (73.500)(P = 0.093). A significantly higher median value of weight was observed in PCa (76.000) when compared with BPH (69.500)(P = 0.037). There was no significant difference in the median value of height in patients with BPH (1.750) and PCa (1.790) when compared with the control subjects (1.775)(P = 0.282). Also, there was no significant difference in BMI of patients with BPH (23.441) and PCa (24.100) when compared with the control individuals (23.790)(P = 0.316).

Table 1 Median values of age, weight, height and BMI in BPH, PCa and control group

Group	Age (years)	Weight (kg)	Height (m)	BMI (kg/m²)
BPH (A)	68.00	69.500	1.750	23.441
PCa (B)	75.00	76.000	1.790	24.100
Control (C)	70.00	73.500	1.775	23.790
Kruskal Wallis	8.653	4.748	2.528	2.307
P value	0.013*	0.093	0.282	0.316
A vs B	0.005*	0.037*	0.152	0.118
A vs C	0.138	0.153	0.232	0.603
B vs C	0.090	0.405	0.557	0.386

Keys: *p<0.05 = significant, p>0.05 = not significant, BMI= Body Mass Index, BPH = benign prostatic hyperplasia, PCa = prostate cancer

As presented in table 2, median level of uNAG was significantly higher in BPH (10.253) and PCa (9.714) when compared with the control group (9.093)(P = 0.032). A significantly higher median level of uNAG was observed in BPH (10.253) when compared with PCa (9.714)(P = 0.008). Similarly, median level of uNAG was significantly higher in BPH (10.253) when compared with the control group (9.093)(P = 0.015). There was no significant difference in the median sCr level in BPH (76.253) and PCa (81.648) when compared with the control subjects (83.188)(P = 0.279). No significant difference was observed in the median level of uCr in BPH (2.286) and PCa (2.193) when compared with the control subject (2.527)(P = 0.197). There was no significant difference between the median eGFR level in BPH (86.750) and PCa (86.550) when compared with the control subject (90.900)(P = 0.974). The ratio of uNAG to uCr (uNAG/uCr) was significantly higher in BPH (4.691) and PCa (3.912) when compared with the control subjects (3.692)(P = 0.005). The ratio of uNAG to uCr (uNAG/uCr) was also significantly higher in BPH (4.691) when compared with the control subjects (3.692)(P = 0.001).

Table 2 Comparison of median values of sCr, uCr, eGFR, uNAG and uNAG/uCr in BPH, PCa and control group

Group	sCr (µmol/l)	uCr (g/l)	eGFR (ml/min/1.73m²)	uNAG (u/l)	uNAG/uCr
BPH (A)	76.253	2.286	86.750	10.253	4.691
PCa (B)	81.648	2.193	86.550	9.714	3.912
Control (C)	83.188	2.527	90.900	9.093	3.692
Kruskal Wallis	2.554	3.249	0.053	6.905	10.716
p-value	0.279	0.197	0.974	0.032*	0.005*
A vs B	0.256	0.870	0.897	0.008*	0.062
A vs C	0.146	0.101	0.908	0.015*	0.001*
B vs C	0.515	0.121	0.825	0.543	0.132

Keys: *p<0.05 = significant, p>0.05 = not significant, sCr = serum creatinine, uCr = urine creatinine, eGFR = estimated glomerular filtration rate, uNAG = urine N-acetyl-β-d-glucosamindase, uNAG/uCr = urine N-acetyl-β-D-glucosamindase to urine creatinine ratio, BPH = benign prostatic hyperplasia, PCa = prostate cancer.

4. Discussion

Benign prostatic hyperplasia and its urinary tract infection complication is a major risk factor for the development of chronic kidney disease (CKD) [19, 20, 21]. CKD represents a global public health problem and is associated with substantial morbidity, reduced life expectancy and high healthcare resource utilization [22, 23]. Evidences suggest an increased risk of kidney disease in BPH as well as prostate cancer [24, 25]. Patients with benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are at high risk for acute kidney disease owing to the coexistence of obstructive uropathy, older age, and pre-existent chronic kidney disease (CKD) [20, 21]. This current study aimed at evaluating urine N-acetyl-β-D-glucosaminidase (uNAG), serum and urine creatinine, estimated glomerular filtration rate (eGFR) and ratio of uNAG to uCr (uNAG/uCr) in patients with BPH and PCa.

In this study, a significant difference in median age value was observed in PCa and BPH when compared with the apparently healthy control individuals. Although, age is a risk factor for the development of BPH and prostate cancer but other factors like family history also contributes to the development of BPH and PCa [1, 2, 26]. There was no significant difference in the weight, height and BMI of patients with BPH and PCa when compared with the control group. In contrast, studies have reported the association between obesity and many cancers including PCa [27, 28, 29].

This current study revealed a significantly higher median level of urine N-acetyl-β-D-glucosamindase (uNAG) in patients with benign prostate hyperplasia (BPH) and prostate cancer (PCa) when compared with the control group. The significantly higher median urine level of NAG is in agreement with the findings of [30] who reported an increase in uNAG in patients with type 2 diabetes. Several studies investigated the relation of urinary NAG excretion to the severity of kidney disease as assessed by albuminuria and the estimated glomerular filtration rate (eGFR) in patients with diabetes [31]. [32] reported that uNAG was increased in patients with idiopathic membranous nephropathy, compared with healthy controls. Previous studies have shown that elevated levels of N-acetyl-β-D-glucosaminidase in neonates born with meconium-stained amniotic fluid indicated the existence of tubular dysfunction, probably due to prenatal distress. [33] also stated that uNAG can predict progression of renal involvement in diabetic nephropathy. Specifically, elevations in urinary concentration of NAG have been demonstrated in mice exposed to gentamicin [34] and in rats exposed to cisplatin [35] or lithium [36]. In the lithium study, antioxidant treatment attenuated the nephrotoxicity [36]. Furthermore, increased levels of uNAG were also found in a study group of pediatric patients with AKI and has been considered to be a sensitive tubular biomarker for AKI [37, 38]. Because NAG cannot be filtered through the glomerulus, it might be more logical that the presence of urinary NAG is exclusively caused by its secretion from proximal tubular cells, and an increase in urinary NAG along with a decrease in eGFR implies glomerulo-tubular damage. This is in support with the finding of [39] who observed increased urinary NAG/urinary creatinine (uNAG/uCr) ratio in children with pyelonephritis.

Also, this current study observed a significant increase in uNAG/uCr in patients with BPH and PCa when compared with the control group. The increase in the ratio of urinary NAG to creatinine is in agreement with study of [40] and [41] who reported that uNAG increases progressively along with the diabetic nephropathy stages. This indicates that uNAG/uCr might be an early predictive biomarker for diabetic nephropathy.

Our study revealed no significant difference in the median levels of serum creatinine, urine creatinine and eGFR in patients with BPH and PCa when compared with the control group. Serum creatinine has been shown not to be a sensitive marker in early detection of renal injury. This is in accordance with the findings of [42] who reported that creatinine lacks high predictive value in the early detection of renal injury. Creatinine concentrations were increased in serum only when approximately 40–50% of renal parenchyma was reversibly or irreversibly damaged [42, 6]. Reduced eGFR and increased urinary protein and albumin excretion as well as higher degrees of tubulo-interstitial atrophy and fibrosis are associated with poorer chronic kidney disease (CKD) prognosis [6].

5. Conclusion

From the findings of this research, there was significant increase in the levels of urine NAG (uNAG) and urine NAG to urine creatinine ratio (uNAG/uCr) in patients with BPH and PCa. The levels of serum and urine creatinine as well as eGFR remained normal. The increase in uNAG indicates that uNAG is a sensitive marker for early renal injury than creatinine.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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