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Serum gonadotropins, cortisol, PSA, and micronutrient levels among men with prostate carcinoma

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Abstract

Background: Prostate cancer (PrCa) is a malignant tumour of the prostate that has many associated risk factors. There is continuous rise in the incidence among adult blacks which is a reflection of racial differences in testosterone concentrations.

Methods: The study involves 50 PrCa patients attending or referred to two tertiary health Institutions and 25 healthy men as controls. Weight and height of participants were measured, and body mass index (BMI) was calculated. Ten millilitres of venous blood sample was collected from each participant, allowed to clot, and then centrifuged at 5000 rpm for 5 min at room temperature (22–28 °C) to obtain the serum. Serum cortisol, testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), total prostate-specific antigen (TPSA), free prostate-specific antigen (FPSA), selenium, copper, magnesium, and zinc were determined. Prostate ultrasonography and biopsy were also done for histopathological studies.

Result: From this study, a significant increase ($p < 0.05$) in weight, BMI, serum FPSA, TPSA, and copper; a non-significant increase ($p > 0.05$) in serum cortisol, testosterone; a significant decrease ($p < 0.05$) in serum LH, selenium, zinc, and magnesium; and a non-significant decrease ($p > 0.05$) in serum FSH were observed among people living with PrCa when compared to the controls. However, no significant difference ($p > 0.05$) was observed in the height between the two groups. Ultrasonography and histology revealed evidence of prostatitis, hypertrophy, and carcinoma among the test group.

Conclusion: It can be concluded that PrCa is associated with increase serum cortisol, testosterone, and copper; and decreased serum LH, FSH, selenium, zinc, and magnesium concentrations and combination of biochemical, ultrasonographic, and histologic features are of diagnostic importance.

Keywords: Prostate, Testosterone, Cortisol, Gonadotropins, Trace elements

1 Background

Prostate cancer (PrCa) is the most commonly diagnosed cancer and a leading cause of cancer-related deaths among men in Nigeria [1]. The exact prevalence of PrCa

in Nigerian population is not known, but in the USA the incidence was reported to be higher among adult black American men than white American men [2]. High incidence of PrCa among adult blacks is a reflection of racial differences in testosterone concentrations which has been found to be higher in Blacks than Whites during young adulthood, and the difference reduces with age and completely disappears after the age of 60 years [3].

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Androgens notably testosterone, gonadotropins, oxidative stress, and reactive oxygen species (ROS) have been implicated in PrCa. In the prostate, testosterone is converted to a more potent intracellular androgen known as 5 α -dihydrotestosterone (DHT) by 5 α -reductase enzyme. The most bioavailable and active form of testosterone is the unbound or free testosterone form, while the remaining is primarily bound to sex hormone-binding globulin (SHBG), albumin, and corticosteroid-binding globulin with SHBG having the highest affinity for testosterone [4]. Reactive oxygen species boost PrCa development by activating transcription factor NF- κ B through destruction of the inhibitory unit I κ B α and increase in the inflammatory cytokines, interleukins, and chemokines [5]. They are critical to tumour cell survival through the transduction pathways and play a crucial role in cell proliferation, angiogenesis, and metastasis [6].

In early course of PrCa, the disease is rarely symptomatic, as it arises mainly in the peripheral portion of the prostate gland. Symptoms such as hesitancy, slowing of urinary stream, intermittent urine flow, haematuria, haemospermia, decreased ejaculatory volume, erectile dysfunction, and bony pain are present in situations of metastasis [7].

Diagnosing PrCa is a challenge usually confronted by urologist. Some of the employed diagnostic tools include digital prostate examination (DPE), serum prostate-specific antigen (PSA), ultrasonography (transrectal prostate scan), and prostate biopsy for histological studies. The availability of blood PSA screening test for the diagnosis of PrCa makes more people to have been diagnosed early enough before metastatic or advanced presentation rather than using DRE which makes patients to be diagnosed with more advanced disease. However, there are controversies on the use of PSA as screening and diagnostic tool and roles played by gonadotropins, cortisol, and antioxidants in the pathogenesis of PrCa. This study thus determined serum concentrations of these parameters in newly diagnosed PrCa patients.

2 Methods

2.1 Study design

The study is a case–control cross-sectional study involving 55 newly diagnosed PrCa patients attending or referred to two tertiary health Institutions and 25 healthy men as control subjects.

2.2 Inclusion and exclusion criteria

Included in the study were newly diagnosed PrCa patient as tests and healthy male subjects as controls. Excluded from the study were PrCa patients on medications, subjects with metabolic diseases such as diabetes mellitus, smokers, chronic alcoholics, participants with history of

hard drug and antioxidant use, and those who did not consented to partake in the study.

2.3 Clinical and physical examinations

Prostate cancer was inferred clinically by the cross-examination of urologist and confirmed by laboratory investigations and histopathological studies. Physical examination was done on all participants with interest in pallor, poor or diffused urine stream during micturition, and weight loss. Manual palpation of the prostate for enlargement and consistency and regional lymph nodes for lymphadenopathy were also done (after blood sample collection). Weight and height of participants were measured using a weighing scale and stadiometer, respectively, and body mass index (BMI) was calculated using $BMI = \text{Weight (kg)} / \text{Height (m)}^2$ (kg/m²). A questionnaire was administered to obtain data on demography, social habits, and urinary symptoms from participants.

2.4 Blood sample collection

Ten millilitres (10 mL) of venous blood sample was aseptically collected at 8 AM, after overnight fast, from the antecubital vein of each participant, transferred into a clean plain labelled tube, allowed to clot, and then centrifuged at 5000 rpm for 5 minutes at room temperature (22–28 °C). The clear serum was separated and kept at – 20 °C until assayed.

2.5 Biochemical parameters

Serum cortisol, testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were assayed by enzyme-linked immunoassay (ELISA) method using Accubind ELISA kits supplied by monobind Inc., USA, based on standard method [8–10]. Serum prostate-specific antigen (total and free) was determined by ELISA method using prostate-specific antigen ELISA kit supplied by Phoenix Pharmaceuticals Inc., USA. Serum copper, magnesium, and zinc were determined using atomic absorption spectrophotometry method, and serum selenium (Se) was determined using flameless graphite furnace atomic absorption spectrophotometry [11, 12].

2.6 Prostate gland ultrasonography, biopsy, and histology

Transabdominal prostate ultrasonography was done using SAMSUNG MEDISON SONOACE X6 with the patients positioned on the back, haven ensured a well-filled urinary bladder which constitutes an “acoustic window” for the ultrasound waves penetrating the abdominal cavity to the prostate gland. The transducer was applied transversely just above the pubic symphysis, slid in a fan-like movement to search for the largest section of the prostate gland.

Prostate biopsy was performed using a 18-gauge tru-cut needle which allows for obtaining bioptic specimens of 15 mm of length and 1 mm of diameter or thickness. The biopsy was aseptically performed in the treatment room with the tru-cut needles and the needle guide sterile and subjects given antimicrobial protection (oral ciprofloxacin 500 mg 2 times daily). The needle was placed in the automatic biopsy gun, which after loading (stretching the spring), unlocking and pressing the trigger allow for taking bioptic specimens. The prostate tissue was fixed in 10% formalin, dehydrated in 95% ethanol, and then cleared in xylene before embedded in paraffin. Micro-sections (4 µm) were prepared and stained with haematoxylin and eosin (H&E) dye and were examined under a light microscope by a histopathologist who was ignorant of the treatment groups.

2.7 Ethical issue

The ethics approval and consent to participate were obtained from the Research Ethical Committee of the teaching hospital, written informed consent was also obtained from all participants after the procedures, and potential benefits or risks had been explained to them at the beginning of the study. Participation was voluntary, and all information obtained was treated with utmost confidentiality.

3 Data analysis

The statistical analysis was done using statistical package for the social sciences (SPSS) software version 21. Descriptive statistics were used to describe and represent variables. Independent *t* test was used to compare differences in mean between the two groups. The level of statistical difference was set at *p* < 0.05.

4 Results

4.1 Biophysical parameters

Result of biophysical parameters showed a significant increase (*p* < 0.05) in weight and BMI, while there was no significant difference (*p* > 0.05) observed in the height among people living with PrCa when compared to the control group.

4.2 Makers of prostate cancer

Result of serum marker of PrCa revealed a statistically significant (*p* < 0.05) increase in serum FPSA, TPSA, and FPSA/TPSA ratio among people living with PrCa when compared to the control subjects.

4.3 Serum hormones

Result of serum hormones revealed a statistically significant (*p* < 0.05) decrease in serum LH; a non-statistically significant (*p* > 0.05) decrease in serum FSH; and a

non-statistically significant (*p* > 0.05) increase in serum cortisol and testosterone among people living with PrCa when compared to the control subjects.

4.4 Serum micronutrients

Result of serum trace elements revealed a statistically significant (*p* < 0.05) decrease in serum selenium, zinc, and magnesium concentrations and a statistically significant (*p* < 0.05) increase in serum copper concentration among people living with PrCa when compared to the control subjects.

4.5 Ultrasonography and histology

The ultrasonogram showed normal sized prostate with homogeneous echotexture and regular outline among the controls and enlarged prostate with heterogeneous echotexture and irregular outline among some members of the PrCa group. Also, result of histological studies showed features of adenocarcinoma among some members of PrCa group and features of atrophic changes in others.

5 Discussion

Obesity (BMI > 30 kg/m²) is associated with an increased risk of several cancers, but conflicting results have been reported by researchers on the association between BMI and risk of PrCa. While some reported a significant interaction between BMI and PrCa [13], others reported no association between height, BMI, and risk of PrCa [14]. Result obtained from this study showed a significant increase (*p* < 0.05) in weight and BMI among people living with PrCa when compared to the control group (Table 1). However, no significant difference (*p* > 0.05) was observed in the height between the two groups. These findings are in support of the work of some researchers [13, 14]. In the recent time, some associations have been found to exist among other indicators such as waist circumference (WC), waist–hip ratio (WHR), and abdominal obesity [15]. The predictive effect of BMI on the risk of PrCa is strongly determined by genetic susceptibility of individuals to having the disease. It is worthy of note that obesity

Table 1 Biophysical parameters of the prostate cancer patients and controls

Parameters	Test	Control	t value	p value
Weight (kg)	72.56 ± 1.38	65.14 ± 1.41	3.39	0.001
Height (m)	1.62 ± 0.01	1.61 ± 0.01	0.948	0.345
BMI (kg/m ²)	27.64 ± 0.46	25.24 ± 0.58	3.092	0.003

This table shows weight, height, and BMI among people living with PrCa and control groups. Values are Mean ± Standard error of mean, and statistically significant difference was set at *p* < 0.05

might have a detrimental effect on screening for PrCa by lowering serum PSA concentrations in obese men, who also tend to have larger prostates, making detection by transrectal ultrasound-guided biopsy more difficult [16].

Markers of predictive importance in PrCa include prostatic acid phosphatase (ACP), prostate-specific antigen (TPSA and FPSA), prostate-specific antigen density (PSAD), prostate-specific antigen velocity (PSAV), and prostate health index (PHI). Blood PSA concentration is usually explored to screen, detect, and monitor progression and treatment response. However, PSA is of low sensitivity and specificity in identifying PrCa, being known to increase in other prostate pathological conditions such as BPH and prostatitis. Using TPSA, PrCa is diagnosed with values >4 ng/mL, while values in the range of 4.0–10.0 ng/mL have been described as a diagnostic “Grey-Zone” which necessitate prostate biopsy. The result obtained from this study revealed a statistically significant increase ($p < 0.05$) in serum FPSA and TPSA among people living with PrCa when compared to the control subjects (Table 2). Similar finding had earlier been reported in a similar study [17]. High concentration of free inactive PSA is associated with increased likelihood of benign prostate hypertrophy (BPH) rather than PrCa [18, 19]. The observed high serum total PSA (free and complexed PSA) concentration and free PSA among people living with PrCa indicate some degree of hyperplastic changes in the epithelial cells of the prostate gland which result in increased secretions into the lumen and some degrees of dysplasia that is pathognomonic of PrCa. Free-to-total PSA ratio is employed to improve the specificity of total PSA for “Grey-Zone”, to determine the relative risk of PrCa and selection of men to benefit from prostate biopsy. Value of free-to-total PSA ratio obtained from this study revealed a non-significant increase ($p > 0.05$) among people living with PrCa when compared to the control subjects. This indicates existence of PrCa among the test group.

Result of serum hormone obtained from this study showed a non-significant increase ($p > 0.05$) in serum cortisol among people living with PrCa when compared with the control group (Table 3). This finding

Table 2 Serum marker of prostate cancer among prostate cancer patients and controls

Parameters	Test	Control	T value	p value
FPSA (ng/mL)	1.74 ± 0.10	0.55 ± 0.05	7.514	0.000
TPSA (ng/mL)	48.84 ± 3.57	2.03 ± 0.04	8.813	0.000
FPSA/TPSA	0.59 ± 0.54	0.27 ± 0.03	0.391	0.697

This table shows serum marker of prostate cancer among prostate cancer patients. Values are Mean ± Standard error of mean, and statistically significant difference was set at $p < 0.05$

Table 3 Serum hormone among prostate cancer patients and controls

Parameters	Test	Control	T value	p value
Cortisol (ng/mL)	0.89 ± 0.04	0.87 ± 0.08	0.192	0.849
LH (mIU/mL)	6.72 ± 0.53	13.33 ± 0.61	-7.472	0.000
FSH (mIU/mL)	10.26 ± 0.81	12.11 ± 0.60	-1.457	0.149
Testosterone (mIU/mL)	1.12 ± 0.07	1.05 ± 0.13	0.529	0.598

This table shows serum hormones among PrCa patients. Values are Mean ± Standard error of mean, and statistically significant difference was set at $p < 0.05$

is consistent with previous studies and indicates the contribution of cortisol to PrCa [20, 21]. The observed hypercortisolism could be due to activation of hypothalamic–pituitary–adrenal (HPA) axis which stimulates tumour or causes immunosuppression, thereby influencing the progression of PrCa [22, 23]. Cortisol in synergy with other hormones such as estradiol, leptin, and insulin acts to stimulate P₄₅₀ aromatase resulting in increased aromatase activity which leads to increased intracellular oestrogen, abdominal fat deposition, and PrCa [20, 24, 25].

There are conflicting reports on the role of endogenous testosterone in the pathogenesis of PrCa. Some studies reported elevated testosterone [26, 27], and some reported lower testosterone [28, 29], while some reported no association of testosterone with PrCa risk [30, 31]. However, serum testosterone can be measured as a therapeutic target to verify response to androgen deprivation therapy (ADT) and ensure that castration levels are achieved during ADT [32]. Result obtained from this study revealed a non-significant increase ($p > 0.05$) in serum testosterone among people living with PrCa when compared with the control subjects (Table 3). This corroborates the earlier reported increased testosterone concentrations in PrCa [26, 27]. This observation provides answer to the frequently asked questions of whether testosterone promotes PrCa pathogenesis in humans or not. Meanwhile, serum testosterone level was reported to decline with age, increasing body mass index, and presence of chronic illness [33–36].

The involvement of gonadotropin-releasing hormone (GnRH), FSH, and LH in PrCa has also been suggested. Studies in human revealed that benign and malignant prostate cell produces both FSH and its receptor with a likelihood of increased FSH receptor gene expression in PrCa cells [37]. The testes and prostate produce prostatic inhibin peptide (PIP) which is an important modulator of the FSH pathway that decreases production and secretion of FSH by both the anterior pituitary

and prostate glands [38]. Considering serum gonadotropin concentrations, result obtained from this study revealed a non-significant decrease ($p > 0.05$) in serum FSH and a significant decrease ($p < 0.05$) in serum LH among people living with PrCa when compared with the control subjects (Table 3). The observed decreased serum FSH and LH concentration corroborate that of other researchers [39]. This observation in serum gonadotropin concentrations among people living with PrCa indicates reduced GnRH secretion from the hypothalamus, up-regulation of PIP production by either or both the testes and prostate, and reduced GnRH receptors in the pituitary gland during malignancy resulting in decreased gonadotropin production and secretion from the anterior pituitary and prostate glands, respectively.

Oxidative stress has also been implicated in PrCa. Oxidative stress activates the extracellular signal-regulated kinase (ERK) subfamily, Akt, and the p38 subfamily leading to activation of various transcription factors involved in cell cycle to allow the tumour cells to rapidly progress through it [40]. Akt inhibits apoptosis by deactivating

caspase-9 and Bcl-2-associated death promoter, promotes tumour cell survival, and suppresses antioxidant activity [5, 41]. Result of serum antioxidant micronutrients revealed a significant decrease ($p < 0.05$) in serum selenium, zinc, magnesium, and a significant increase ($p < 0.05$) in serum copper among people living with PrCa when compared with normal subjects (Table 4). This finding corroborates the reported decrease in serum selenium, zinc, and magnesium and increase in serum copper among people living with PrCa [42, 43]. An inverse relationship was observed to exist between serum selenium, zinc, magnesium, and PrCa.

The use of ultrasonography in diagnosing PrCa is limited as 60–80% of PrCas are hypoechoic, 30–40% are isoechoic, and 1.5% are hyperechoic [44]. Benign conditions like benign prostatic hypertrophy, prostatitis, prostate atrophy, and prostate infarction may be hypoechoic on ultrasonography [45]. The ultrasonogram obtained from this study showed normal sized prostate (8–10 cm³ in volume) with homogeneous echotexture and regular outline in the control group, while an enlarged prostate (127–134 cm³ in volume) with heterogeneous echotexture and irregular outline was observed in the PrCa group (Fig. 1). This finding is suggestive of PrCa but not confirmatory due to limitations in the sensitivity and specificity of ultrasonography which range between 40 and 50% for detecting PrCa [45].

Abnormal serum markers, abnormal DRE, and abnormal ultrasonography require histological confirmation. Prostate biopsy is needed for the understanding of pathological changes found during the DRE (a mass, asymmetry, an induration), raised serum PSA concentration, and evident structural changes of the prostate gland in order to obtain a histopathological diagnosis and to assess the

Table 4 Serum trace elements among prostate cancer patients and controls

Parameters	Test	Control	T value	p value
Selenium µg/dL)	61.50 ± 3.44	95.62 ± 1.39	6.554	0.000
Zinc (µg/dL)	4.33 ± 0.33	13.99 ± 0.77	13.518	0.000
Magnesium (µg/dL)	68.65 ± 5.95	168.13 ± 7.23	9.860	0.000
Copper (µg/dL)	0.13 ± 0.00	0.07 ± 0.00	7.960	0.000

This table shows serum trace elements among PrCa patients. Values are Mean ± Standard error of mean, and statistically significant difference was set at $p < 0.05$

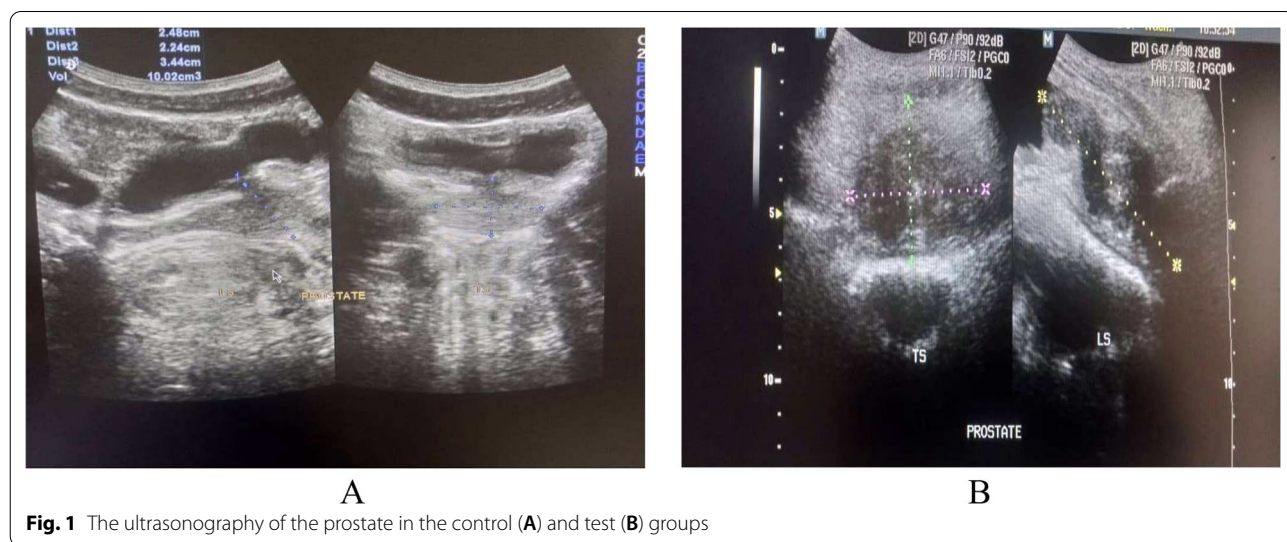


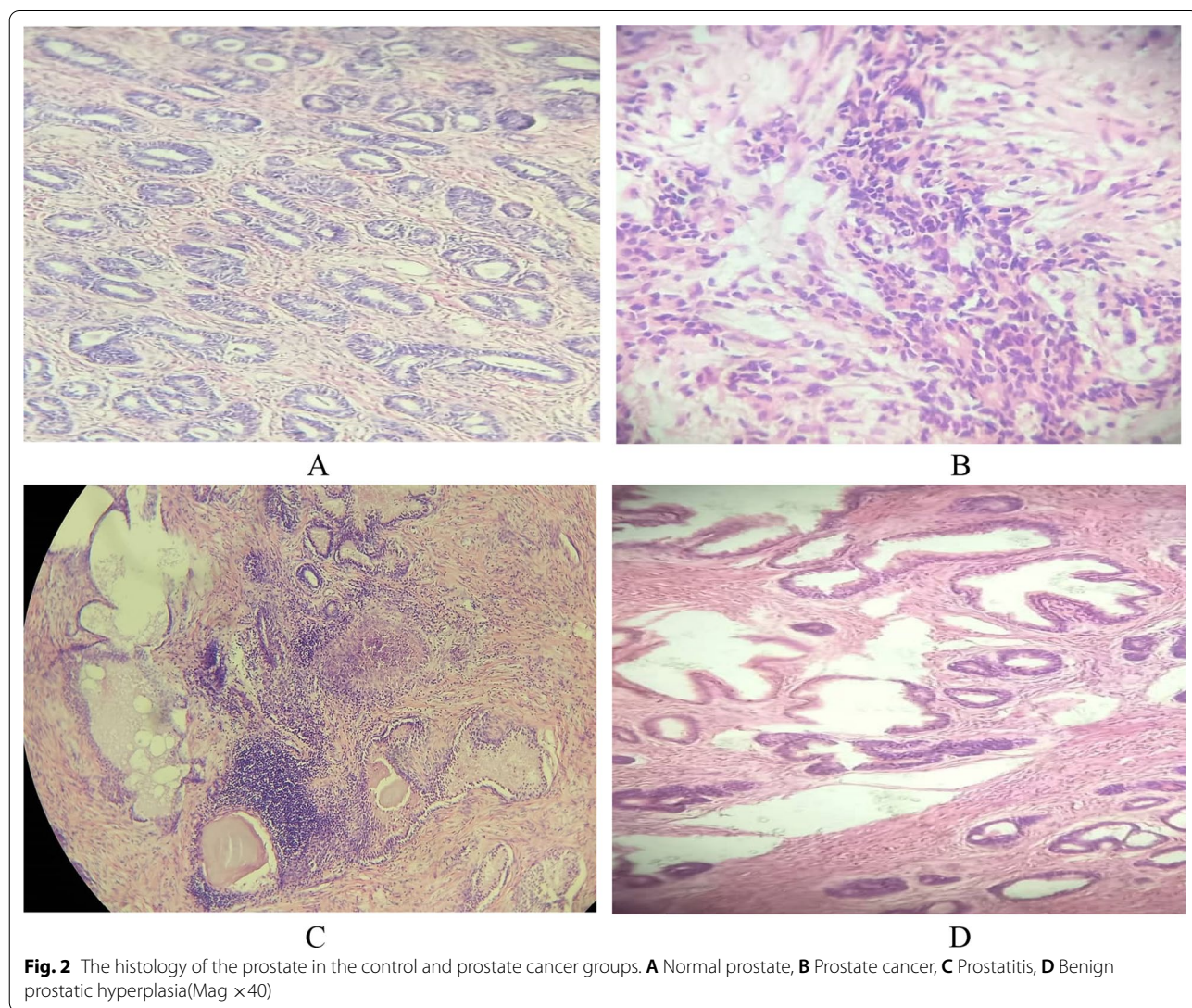
Fig. 1 The ultrasonography of the prostate in the control (A) and test (B) groups

degree of cytoarchitectonic impairments among other reasons. Result obtained from this study revealed features of adenocarcinoma which occurred in about 92% (46 out of 50) of the test, while the remaining 8% (4 out of 50) showed atrophic changes and features suggestive of prostatitis (inflammatory lymphocytic cells and cystic gland dilatation) and BPH (Fig. 2). Histological features seen in this study that are suggestive of prostate cancer include fragments of prostate tissue with effaced architecture due to malignant proliferation of prostatic ductal cells; small cells with hyperchromatic nuclear and scanty cytoplasm glands and fibromuscular stroma; variable single and fused glands with little intervening stroma; and cribriform pattern. Others showed prostatic glandular tissue with features of nodular hyperplasia with dense stroma reaction, absence focus of malignancy, several seminiferous tubules containing spermatozoa in various

stages of development, demonstrable thick walls and dilated vessels, and atrophic testes consistent with age. Some of these findings are not limited to PrCa but are also observed in inflammatory and age-related changes in the prostate, implying that prostate biopsies do not always singly confirm PrCa as there are possible undetected PrCas, indicating imprecise nature of both the PSA test and biopsies when used alone.

6 Conclusions

Using results obtained from this study, it can be concluded that PrCa is associated with increased serum cortisol, testosterone, and copper and decreased serum LH, FSH, selenium, zinc, and magnesium concentrations. Blood PSA (TPSA and FPSA) and hormonal (testosterone, cortisol, gonadotropins) concentrations in conjunction with DRE and histologic studies could



thus be explored to screen, confirm diagnosis, monitor treatment response, prognosticate PrCa, and capture most PrCa cases that would have otherwise been missed. Also, the observed pattern of serum gonadotropins indicates the therapeutic use of LHRH agonist and GnRH antagonist in malignant prostate conditions.

List of abbreviations

PrCa: Prostate cancer; DRE: Digital rectal examination; ROS: Reactive oxygen species; BMI: Body mass index; WC: Waist circumference; WHR: Waist-hip ratio; BPH: Benign prostate hypertrophy; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; GnRH: Gonadotrophin-releasing hormone; PSA: Prostate-specific antigen; TPSA: Total prostate-specific antigen; FPSA: Free prostate-specific antigen; PSAD: Prostate-specific antigen density; PSAV: Prostate-specific antigen velocity; PHI: Prostate health index; ELISA: Enzyme-linked immunosorbent assay; SPSS: Statistical package for the social sciences; ADT: Androgen deprivation therapy.

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Authors' contributions

OEW conceptualise the research and contributed to data collection and manuscript writing; OAA contributed to recruitment and physical examination of participants and contributed to manuscript revision; AOO contributed to recruitment of participants, data collection, and manuscript writing; and FAO contributed to recruitment of participants, data collection, and manuscript writing, while AAA contributed to data analysis, manuscript editing, and manuscript revision, and OO contributed to sample biopsy taking, slide preparation, and reporting. All authors have read and approved the manuscript.

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Availability of data and materials

The data collected, analysed, and used for this study are available from the corresponding author specifically on reasonable request.

Declarations

Ethics and consent to participate

The ethical approval was obtained from Research Ethical Committees of Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, with ethical approval number HREC/OOUTH/284/2019AP. Written informed consent was also obtained from all participants after the procedures, and potential benefits or risks had been explained to them at the beginning of the study. Participation was voluntary, and all information obtained was treated with utmost confidentiality.

Consent for publication

Not applicable.

Competing interests

The authors declared that there are no competing interests.

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