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# *Insulin like Growth Factor-1, Human Growth Hormone and Testosterone as Potential Biomarkers in Laboratory Diagnosis and Prognosis of African Blacks before and after Bilateral Orchidectomy: A Prospective longitudinal survey*

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## *Abstract*

***Introduction:*** *Mortality is high in African men, who are at high risk for castrate resistant Prostate Cancer (PCa). Bilateral ochidectomy (BO) is the most preferred treatment option due to late presentation and advanced disease. Prostate specific antigen (PSA) has limited value in laboratory diagnosis of PCa. Elevated Insulin like growth factor-1 (IGF-1), human growth hormone (hGH) and testosterone levels appear to increase PCa risk. The importance of IGF-I in the early detection of PCa has been suggested and is therefore investigated in this study.*

***Methods:*** *142 male participants aged 50-90 years were enrolled into this prospective cohort study in the Urological Clinic of a teaching hospital in Ibadan and environs. PCa (n=53) group was age matched with benign prostate hyperplasia (BPH, n=45) and Control (apparently healthy men, n=44) groups. PCa and BPH were diagnosed histologically while BO was performed among PCa group only (BOP, n=22). Serum obtained from fasting blood (5mL) was obtained for HGH, IGF-1, testosterone and PSA estimation by enzyme linked immunosorbent assay. All indices were assessed at baseline and 12 months after BO in BOP only. Data analysed using Student's t-test and multiple regression were considered significant at $p<0.05$.*

***Results:*** *The levels of PSA, hGH and IGF-1 were significantly higher in PCa than BPH and ControI groups ($p<0.05$). Only PSA level was significantly elevated when BPH group was compared with Control ($p<0.001$). Testosterone levels were however, similar in all groups at baseline. After BO, testosterone and IGF-1 levels reduced while the PSA and hGH levels increased. At baseline, mortality (28%) observed in PCa group only was associated with increased hGH and reduced testosterone levels ($p= 0.002$, 0.025 respectively). There were also significantly positive relationships among PSA, IGF-1 and hGH ($p=0.003$).*

***Conclusion:*** *IGF-1 may be considered as a better potential prognostic laboratory biomarker than hGH and testosterone in males with PCa.*

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## Introduction

Cancer is of great public health concern globally and affects all categories of people, WHO rated cancer a top cause of mortality worldwide, with seventy percent of deaths occurring in developing countries [1]. Prostate cancer (PCa) is the most regularly detected malignancy in men in Nigeria and worldwide, it is the second most typical cause of mortality among men with being older than 50 years and having African ancestry as significant risk factors [2-7]. The majority of men having PCa in Africa present with advanced disease; as a result, hormone ablation (ADT), which is typically accomplished by bilateral orchidectomy (75%), is still the only treatment for this stage of the disease. Only a small number of patients are treated with either LHRH agonist or anti-androgens (flutamide /casodex) [8,9].

The laboratory index of PCa diagnosis is PSA of > 4ng/mL, which is non-specific (American Cancer Society, 2019). Although, numerous risks have been linked with PSA-based screening and subsequent diagnostic assessments. Over diagnosis and excess of therapy are regular occurrences that are linked to treatment-related complications [10]. PSA is still predominantly used as a current indicator of possible presence of PCa. However, its use as a component of a strategy, integrating multiple diagnostic approaches for PCa screening has been suggested [11,12].

Insulin-like growth factor-1 has been reported to be elevated in early stages of prostate carcinoma (PCa) also in its progression and reported to have no relationship with benign prostate hyperplasia (BPH)) [13-16]. Insulin-like growth factors are polypeptides similar to insulin in structure and exhibits growth promoting and metabolic effects like insulin, but the most significant of the IGFs is the IGF-1, a stimulator of cell growth and proliferation and an effective apoptosis inhibitor [17-19]. Growth hormone stimulates the liver to produces IGF-1 into circulation, exerts all of its known physiologic effects by binding to its specific receptor (IGF-1R), and its effects are modulated by multiple IGFBPs [20,21].

Evaluation of IGF-1 plasma concentrations according to studies have been discovered might assist in identifying men at high risk of having prostate cancer [14,16]. Another study speculated that not only does IGF-1 promotes the start and growth of tumours but may as well aid invasion and metastasis. Investigators concluded that the risk of advanced stage prostate cancer could be predicted by measuring IGF-1 and IGF-1 binding protein 3 (IGFBP-3) levels, years before the actual diagnosis is done [14,22]. Yet another study observed that Laron syndrome patients do not develop cancer [23].

## Methods

### Study Design

This prospective case control study carried out on Nigerian males newly diagnosed of prostate cancer (PCa), benign prostate hyperplasia (BPH) and apparently healthy asymptomatic males (control). Ethical approval (UI/UCH EC Registration Number: NHREC/05/01/2008a) was obtained from the Health Research Ethics Committee of University of Ibadan (UI)/University College Hospital (UCH), Ibadan.

### Participants

A total of 142 participants aged 50-90 years consisting of 53 and 45 newly diagnosed males with PCa and BPH,

respectively age matched with 44 control males enrolled into the study. The participants diagnosed with PCa and BPH were clinically examined by Urologists at the Urology Clinic and categorized based on histologic diagnosis of prostate cancer and benign prostate hyperplasia respectively. The males in the control group were confirmed healthy by the Physicians in the Geriatic /Family Medicine Clinic of the University College Hospital, Ibadan. They were parous, asymptomatic no previous surgery and no urinary tract malignancy or infection. They attended the clinic for routine medical check, eye check and medically certified travel document. The PCa group were followed up for 12months after surgical treatment (Bilateral Orchidectomy). Out of the 53 PCa participants, 22 (BOP) went through bilateral orchidectomy.

### Sample Collection

After an overnight fast (10-12 hours) by the participants, five milliliters (5mls) of each participant's venous blood was collected aseptically via venipuncture and dispensed into plain non- anticoagulated bottles then allowed to clot for 1-2hours to obtain serum for the determination of serum testosterone, total blood PSA, growth hormone and insulin-like growth factor-1. The samples were centrifuged at 4000 rpm for five minutes, thereafter the resulting serum were collected and stored in small aliquots at -20$^0$C until analysis.

### Biochemical Indices

Serum testosterone, prostate specific antigen (PSA), growth hormone (hGH) and insulin-like growth factor-1 (IGF-1) were estimated by enzyme linked immunosorbent assay (ELISA). All indices were assessed at baseline and 12 months after BO in BOP only.

### Statistical Analyses

Data were analyzed using the Statistical Package for Social Science (SPSS) software 20.0 version. Analysis of variance (ANOVA) followed by Post Hoc tests were used for comparison of quantitative variables. Multiple regression model was used to assess the interrelationship between variables. Student's T-test was used to test significance of means between two observations. Data obtained were significant at $p<0.05$.

## Results

### Biochemical Parameters

Table 1 shows the intra-group comparison of biochemical parameters, in PCa participants, the PSA, hGH and IGF-1 levels were significantly higher ($p < 0.001$) than corresponding control values while in participants with BPH, only PSA levels were significantly higher ($p =0.001$) compared to control values. The mean level of PSA, hGH AND IGF-1 were higher in PCa than BPH and controls. However, the increase in PSA values between PCa and BPH was not statistically significant ($p=0.140$). The mean level of testosterone was comparable among the groups ($p > 0.05$).

**Table 1:** Comparison of Biochemical parameters among Participants.

| Variables | PCa (N=53) | BPH (N=45) | Controls (N=44) | P | P1 | P2 | P3 |
|---|---|---|---|---|---|---|---|
| PSA (ng/ml) | 37.88 (13.33 – 70.75) | 22.34 (2.68 – 23.24) | 10.37 (2.31 -20.29) | 0.000* | 0.14 | 0.000* | 0.001* |
| hGH (µIU/ml) | 4.75 (0.01 – 26.46) | 2.12 (0.01 – 13.26) | 1.34 (0.08 – 9.57) | 0.002* | 0.035* | 0.002* | 0.32 |
| Testosterone (ng/ml) | 7.2±2.5 | 7.9±2.5 | 7.1±2.4 | 0.387 | | 0.879 | 0.123 |
| IGF-1 (ng/ml) | 94.3±25.4 | 71.6±21.7 | 80.5±23.2 | 0.000* | | 0.004* | 0.071 |

P= Probabilty obtained from ANOVA, P1 = Probability value of PCa & BPH, P2 = Probability of PCa & Control,

P3 = Probability of BPH & Control, Testosterone & IGF-1 values are in means ± SD while PSA & hGH values are in median (IQR), PSA=prostate specific antigen, IGF-1=Insulin like growth factor-1, hGH=human growth hormone, BPH=benign prostatic hyperplasia group, PCa=prostate cancer group, control= apparently healthy group, N=number of participants, *Significant difference at p<0.05.

Table 2 presents the pattern of biochemical changes before (baseline) and after bilateral orchiectomy in participants that were diagnosed with prostate cancer. Comparing baseline and after surgical treatment, significantly different levels were observed in PSA, hGH, testosterone and IGF-1 (p<0.05). Significant reductions in testosterone (5.9±2.9ng/ml, 2.1±1.7ng/ml, p=0.001) and IGF-1 (89.5±18.0ng/ml, 73.5±8.0ng/ml, p=0.001) levels were observed while PSA (23.65(5.89 – 50.24) ng/ml, 41.45(22.47 – 69.68) ng/ml, p=0.035) and hGH (0.4(0.01 – 50.24) µIU/ml), 7.8(2.01 – 27.81) µIU/ml, p<0.001) had significant elevations after bilateral orchidectomy in the participants.

**Table 2:** Pattern of Biochemical changes in participants diagnosed with prostate cancer before and after Bilateral Orchiectomy

| Variables | Before BO (N=22) | After BO (N=22) | Difference | t | P-value |
|---|---|---|---|---|---|
| PSA (ng/ml) | 23.65(5.89 – 50.24) | 41.45(22.47 – 69.68) | - | -2.112 | 0.035* |
| Testosterone (ng/ml) | 5.9±2.9 | 2.1±1.7 | 3.8±4.0 | 4.082 | 0.001* |
| hGH (µIU/ml) | 0.4(0.01 – 50.24) | 7.8(2.01 – 27.81) | - | -3.621 | 0.000* |
| IGF-1 (ng/ml) | 89.5±18.0 | 73.5±8.0 | 16.0±17.9 | 3.787 | 0.001* |

Testosterone & IGF-1 values are in means ± SD while PSA & hGH values are in median (IQR), *Significant difference at p<0.05, hGH=human growth hormone, PSA=prostate specific antigen, IGF-1=Insulin like growth factor-1, BO=bilateral orchidectomy, n=number of participants.

### Comparison of Biochemical Parameters in Alive and Dead participants with Prostate Cancer

Out of the 53 participants diagnosed with prostate cancer, 15 were dead during the period of this study which accounted for 28.3% mortality rate among studied participants. Table 3 presents the comparison of baseline clinical indices in the participants with prostate cancer that are living and participants with prostate cancer that died. Significant reductions in mean testosterone were observed in the participants that died compared to the living participants (6.5±4.0ng/ml, 7.3±2.4ng/ml, p<0.05) and significantly elevated human growth hormone were also observed in the dead participants compared with the survivors (83.25(42.2 – 154.47) µIU/ml, 11.18(0.55 – 48.82) µIU/ml, p=0.002).

**Table 3:** Comparison of Baseline Physical and Biochemical parameters in Living and Dead participants with prostate cancer

| Variables | Alive (N=38) | Dead (N=15) | t | P |
|---|---|---|---|---|
| PSA (ng/ml) | 44.58(8.79 – 70.78) | 70.69(8.95 – 94.07) | 0.014 | 1 |
| Testosterone (ng/ml) | 7.3±2.4 | 6.5±4.0 | 5.433 | 0.025* |
| hGH (µIU/ml) | 11.18(0.55 – 48.82) | 83.25(42.2 – 154.47) | 10.638 | 0.002* |
| IGF_1 (ng/ml) | 95.6±27.4 | 69.9±35.1 | 6.597 | 0 |

Testosterone & IGF-1 values are in means ± SD while PSA & hGH values are in median (IQR), *Significant difference at p<0.05, hGH=human growth hormone, IGF-1=Insulin like growth factor-1, PSA=prostate specific antigen, n=number of participants

**Table 4:** Relationships between Variables in Participants

| PCa | | | BPH | | | Controls | | | BO | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Indices** | **β** | **p** | **Indices** | **β** | **p** | **Indices** | **β** | **p** | **Indices** | **β** | **p** |
| PSA/ hGH | 0.521 | 0.003* | - | - | - | - | - | - | PSA/IGF-1 | -0.818 | 0.005* |
| PSA/IGF-1 | 0.532 | 0.003* | | | | | | | IGF-1/PSA | -0.745 | 0.005* |

PSA=prostate specific antigen, IGF-1= Insulin like growth factor-1, hGH= Human growth hormone

A summary of the multiple regressions of variables was shown in table 4. In participants diagnosed with prostate cancer, PSA was observed to positively predicted IGF-1 (β=0.532, p=0.003), hGH (β=0.521, p=0.003) and vice versa while in participants that have undergone Bilateral Orchidectomy (BO), multiple regression model showed IGF-1 negatively predicted PSA (β=-0.818, p=0.005) and vice versa (β=-0.74, p=0.005).

## Discussion

The diagnosis of PCa in this study was achieved by clinical and laboratory investigations. The PSA was significantly increased in both PCa and BPH, the increase was more pronounced in the former when compared with the control. However, the cut off of PSA > 4 ng/ml was not appropriate as a lone tool for diagnosis of PCa or BPH as values in apparently healthy controls were also greater than 4ng/ml. Anunobi et al. (2011) reported that in male Nigerians, raised PSA values could be caused by PCa, BPH or BPH with prostatitis. Therefore, this study demonstrates increased PSA levels in men having PCa and BPH than controls, but no significant difference between PCa and BPH.

Significantly higher levels of IGF-1 and human growth hormone were observed in participants with prostate cancer when compared with BPH and control groups in this study similar to previous reports [19,24,25]. Unlike in PCa where IGF-1 was significantly elevated, the mean IGF-1 levels were reduced in BPH. This probably suggesting that assessment of both PSA and IGF-1 may be important in the diagnosis of PCa. In this study, the associated increase in growth hormone with the increase in IGF-1 might indicate the part growth hormone plays in controlling IGF-1 in PCa. Increased IGF-1 levels, produced due to growth hormone's action on the growth hormone receptor, have been reported to be associated with tumor growth, also earlier studies have suggested that malignant prostate cancer cells produce more IGF-1 and use it to upregulate their own growth [19,26]. IGF-1 has been reported to be elevated early in PCa and its progression, but have no relationship with BPH [25]. This implies that elevated levels of PSA, IGF-1 and human growth hormone were observed in PCa group compared to other groups. In vivo studies reported that in IGF-1-deficient hosts, PC-3 prostate cancer cell lines have significantly low rates of proliferation than the control hosts while IGF-1 administration exogenously amplified the prostate cancer DU145 cell line's capacity to be invasive, which was IGF-1R, the P13K pathway and ERK MAPK pathways dependent [27]. Normal and malignant growth, tissue homeostasis, and cellular metabolism, differentiation and proliferation have all been reported to be IGF system regulated [19].

Studies have reported that decreased testosterone levels in males with advanced PCa may indicate a more aggressive disease and a worse prognosis, another study stated that the presence of PCa alters testosterone levels, thus hinder the negative feedback in the hypothalamic- pituitary-gonadal axis's ability to secrete testosterone found that the greater the level of testosterone in serum before administering a gonadotropin-releasing hormone analogue to males with metastatic PCa, the better the prognosis [28-31]. Models of androgen receptor (AR) knockout mouse showed evidently that insufficiency of androgen reduces lipolysis and is the primary cause of obesity and testosterone deficiency has been reported a cardiovascular risk factor [32,33]. Comparing the participants diagnosed with PCa who died during the course of this study with the ones alive, the baseline values show that the human growth hormone was significantly elevated while baseline testosterone value was significantly reduced in those that died. Bartke, observed equally in mice and humans, that growth hormone (GH) levels that are elevated into the supranormal (pathological) range are related with higher risks of disease

and decreased life expectancy probably demonstrating accelerated aging [34]. Different forms of cancer seem to be impacted by the activation of GH/IGF-I axis. Prostate, endometrial, colorectal and breast neoplasms express both GH and GH receptor and other cancers express GH releasing hormone, by overexpressing GH, the proliferation and survival of different cancer cell lines are boosted [35]. In many animal models, the likely function of the GH-IGF axis in the emergence of cancer has also been demonstrated. Animals having reduced GH and IGF-1 production/action are carcinogenesis resistant while an earlier study also stated a significant relationship between elevated growth hormone and death from cancer [36,37]. The mean growth hormone level observed in participants diagnosed with PCa that died in this study was above the normal reference range, these and the significantly reduced testosterone in the dead participants may be accountable for the observed 28.3% mortality in these participants.

For decades, it has been well recognized that prostate cancer is an androgen dependent condition and the cornerstone of treatment for metastatic prostate cancer is Androgen Deprivation Therapy (ADT). Androgen deprivation can be accomplished by either surgical castration (bilateral orchiectomy) or chronic therapy with a gonadotropin-releasing hormone (GnRH) agonist to decrease androgen/ androgen receptor (AR) signaling activites [38]. According to reports, late presentation is the norm among Nigerian prostate cancer patients with nearly two-thirds of the patients having metastatic prostate cancer and over 90% presented with complications [39,40]. In this present study, the consequence of treatment with bilateral orchidectomy decreased serum concentration of testosterone significantly. These have a wide range of negative consequences which include decreased libido, hyperlipidemia, decrease of muscular mass, increased fat mass, central obesity, and an elevated risk of cardiovascular death [41]. Androgen deprivation therapy has been reported to alter lipid profiles, as ADT results in severe hypogonadism [12,42].

The mean level of PSA was observed to be elevated after bilateral orchidectomy compared to the baseline value. About 20 to 40% of patients having prostate cancer have been reported to experience biochemical recurrence of prostate cancer evident by a rise in prostate-specific antigen (PSA) [43]. However, recurrence with rising PSA level has been reported after 18-36 months of serum concentrations of castrate androgen levels which is called castrate-resistant prostate cancer (CRPC) while in this study a significant increase in mean PSA level was observed in 12 months of androgen deprivation [44]. The recurrence of PSA expression after androgen deprivation therapy's nadir has been reported to indicate the androgen receptor (AR) activity reactivation during the transition to castrate resistance [15]. Various mechanisms are accountable for the reactivation of AR, these include mutations or splicing in the AR ligand-binding domain which overthrow the response to AR antagonists, causing these agents to instead promote agonist activity [45]. The AR gene amplification has been stated to be frequently associated with an increase in AR stabilization and these has been observed to exist in 30% of tumor samples [46]. Another study observed that in spite of reduced circulating levels of androgen after ADT, intratumoral androgen production from inactive precursors, enhanced the expression of AR Leon et al. and Gunter et al. demonstrated that Prostate tumors that are treated with ADT upregulate the expression of enzymes that allow the tumors de novo synthesis of their own androgens causing a significant abundance of androgens in the prostate tumor microenvironment for AR-driven pathways reactivation through paracrine and autocrine mechanisms and thus promoting CRPC [15,32,45,47]

Also in this study, the growth hormone (GH) level was observed to be significantly elevated after bilateral orchidectomy while the IGF-1 mean level was significantly reduced. Although anabolic hormone levels (e.g. IGF-1) have been reported to decline around middle age into old age, increased GH levels could be caused by a change in hypothalamic/pituitary control or a decrease in feedback inhibition which can be an outcome of low IGF-I levels, decreased IGF-I availability to key receptors, or increased inhibitor levels (possibly the small binding protein) [48,49]. In states of malnutrition, growth hormone levels were reported normal or increased in the presence of low IGF-I levels; this is acquired GH resistance condition, characterized by an abnormal response to GH at the liver level and is likely an adaptive reaction to reduced energy intake [50]. Escalating over nutrition in the continuous existence of undernutrition characterize

many resource deprived settings such as Nigeria [51].

The actions of IGF-I are controlled by IGF binding proteins and with altered lipid profile favoring obesity, there is a significant dysregulation of IGF binding protein secretion, leading to changes in blood IGF-I concentration and IGF-I actions [52]. The increased lipid components observed after bilateral orchidectomy may be accountable for the reduced IGF-1 observed in these participants. An overall observation is that obese patients having decreased plasma IGF-1 levels are inclined to have a poorer cardiovascular disease prognosis than those with mid-normal to high-normal IGF-1 levels [53]. In experimental animals, cytokines associated with increased metabolic components, for instance C reactive protein, have been demonstrated to lower the level of IGF-I in circulation and this may have a role in the link between low blood level of IGF-I and the likelihood of poor cardiovascular outcomes [54].

## Conclusion

High prostate specific antigen (PSA) and high insulin like growth factor-1 (IGF-1) associated with high human growth hormone (hGH) were characteristic features found in PCa. The diagnostic utility of combined PSA and IGF-1 measurement may be important in the diagnosis of prostate cancer. Reduced testosterone in prostate cancer prior to treatment might be important in specific regional fat redistribution inducing obesity and may lead to increased disease risk and reduced life expectancy. After bilateral orchidectomy, a significant increase in PSA level was observed within 12 months after bilateral orchidectomy which could indicate the advent of castrate resistant prostate cancer. This study therefore suggests that IGF-1 may be considered as a better potential prognostic laboratory biomarker than hGH and testosterone in males with PCa.

## Recommendation

Assessment of IGF-1 may complement PSA in the diagnosis of prostate cancer.

## Conflict Of Interest

The authors declare that there is no conflict of interest.

## Declarations

Ethics approval and consent to participate: Ethical approval was obtained from The University of Ibadan / University College Hospital Joint Ethical Committee with Registration Number NHREC/05/01/2008a. All participants gave both verbal and written informed consent to participate in the study and the study was carried out in accordance with the Helsinki declaration.

**Clinical Trial:** Not Application

**Consent for publication:** All Authors gave consent for publication of the study

Availability of data and material: All relevant data involved in this study are available on reasonable request from the corresponding Author.

Competing Interest: All Authors declare that there are no competing interests. Funding: There was no funding for this study Authors' contribution: AHO conceived the study, conducted the major part of the research, literature search and manuscript writing. MAC supervised the research, participated in the literature search and manuscript writing, OEO is the surgeon whose patients make up bulk of the participants, supervised the research, data management and manuscript writing. JIA supervised the research, participated in literature review and manuscript writing. EOA supervised the overall research, analysis, literature review, participated in data management and manuscript writing. All authors reviewed the manuscript.

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