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PROSTATE CANCER ASSOCIATED CHANGES IN COAGULATION AND HAEMATOLOGICAL PROFILES IN WESTERN NIGERIA

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ABSTRACT

Background: Prostate cancer is the most frequently diagnosed cancer among males. Prostate cancer has been associated with coagulation and haematological abnormalities which have contributed to the disease progression, development of disseminated intravascular coagulopathy, metastasis and other complications. This study assessed the coagulation and haematological profile of prostate cancer patients in this region. **Materials and Methods:** Forty prostate cancer patients and thirty apparently healthy male controls within the age range of 50-90 years old were recruited for the study. Prothrombin time (PT), partial thromboplastin time with kaolin (PTTK), packed cell volume (PCV), total white cell count (TWBC), platelet count, differential count and erythrocyte sedimentation rate (ESR) were determined using plasmascan, hemoscan reagents, Sysmex KX2-IN autoanalyser, Leishman staining technique and Westergren method respectively. **Result**: The study reveals a statistically significant increase in the mean ± SD of the PT, PTTK and platelet, TWBC, ESR and Neutrophils in the prostate cancer patients while the mean ± SD of the PCV, Lymphocytes and basophils decrease significantly when compared with their controls ($p < 0.05$). However, the monocytes and eosinophil in the patient group are not significantly different from those of the control group ($p > 0.05$). **Conclusion**: The profiles estimated shows that the disease progression in prostate cancer is associated with presence of the cancer procoagulant as well as inflammatory markers of immunity produced in response to the condition.

KEYWORDS: Prostrate cancer, haematological profiles, Coagulation profiles, Disease progression.

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer, estimated as 15% of all male cancers[1] and the sixth leading cause of cancer death among American males and in males around the world as well.[2,3,4] The incidence of this disease is highest among Caucasians and African-American males, with reported incidences of 161/100,000 and 256/100,000 respectively.[5] In Nigeria, studies revealed that Kano, Zaria, Benin and Maiduguri states show prostate cancer incidence as 16.5%, 9.2%, 7.13% and 6.15% of all male cancers respectively.[6,7,8,9] Invasive prostatic carcinoma has been discovered to be up to 29 percent in men within the age of 30 to 40 years and 64 percent in men between 60 to 70 years.[10]

Most prostate cancers are slow growing; however, some grow relatively fast.[1] Prostate cancer may initially cause no symptoms, however in later stages it can cause difficulty urinating, blood in the urine, or pain in the pelvis, back or when urinating.[11]

Prostate cancer can be diagnosed by screening for prostate specific antigen (PSA) in patients with prostate cancer. Biopsy can then be done followed by medical imaging to determine if the cancer has spread to other parts of the body.[12] Other diagnostic method to gather additional information about prostate cancer includes digital rectal examination (DRE), cystoscopy, transrectal ultrasonograpy and prostate magnetic resonance imaging (MRI) which has better soft tissue resolution than ultrasound.[13]

The European Association of Urologists (EAU) as at 2013 recommended that PSA screening can be done on an individual basis and this could be accompanied by prostate biopsy for diagnosis.[14] Active surveillance is an option in low-risk prostate cancer and watchful waiting is an alternative to androgen-deprivation therapy in locally advanced prostate cancer not requiring immediate local treatment. EAU also recommended that radical prostatectomy is the only surgical option and radiation therapy can be external or delivered by way of prostate implants while the treatment follow-up is based on the PSA level.[14]

Prostate cancer has in history been associated with coagulation abnormalities.[15] The disorder of prostate cancer is associated with disseminated intravascular coagulation which ranges from acute bleeding diathesis to thrombosis and embolic events, which is commonly observed in patients with prostate cancer[16]. Disseminated intravascular coagulation can be chronic or acute in nature and is characterized by the increased production of fibrin, increased fibrinolysis and unchecked coagulation throughout the systemic circulation.[17,18]

The clotting process (coagulation), the process by which blood changes from a liquid to a gel potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion and aggregation of platelets along with deposition and maturation of fibrin.[19] The coagulation pathway is classified into intrinsic and extrinsic pathways, both of which converge on factor X activation. The classical theory of blood coagulation is particularly useful for understanding the in vivo coagulation tests, but fails to incorporate the central role of cell based surface in vivo coagulation process.[20]

Clotting profiles should be monitored closely in patients with prostate cancer. Cancer patients who are on anticoagulation therapy might have an increased risk of hemorrhage due to tumor, thrombocytopenia, or concurrent coagulation disorders.[21] Coagulation in prostate occurs as a result of the release of procoagulant substances, such as tissue factor, into the blood stream.[22] Haematological parameters are important diagnostic factors which represent the body's state in response to the present condition of an individual whether physiological or pathological. The platelet and lymphocyte counts are routinely assessed parameters in prostate cancer due to their vital association with disease prognosis; pretreatment high platelet to lymphocyte ratio (PLR) has been associated with increased risk for disease recurrence, cancer specific mortality and all-cause mortality.[23] This has been a significant clinicopathological features indicating an independent association of high pretreatment PLR with adverse outcomes.[23]

Periodic haematologic changes has been associated with pre-,in and post-treatment of prostate cancer especially with androgen deprivation therapy (DPT)[23], radiation therapy (RT)[24,25] etc. and its evaluation will enable the monitoring of disease progression and development of metastasis[26] and other associated complications.[25]

This study to the best of our knowledge is the first cross sectional study which assesses the haematologic and coagulation profiles in pretreated prostate cancer patients in this region. It is therefore designed to provide more information on the parameters for future assessment, monitoring of disease progression and treatment of these patients.

MATERIALS AND METHODS

Subjects selection

The subjects included in this study were 40 newly diagnosed and pretreated patients, aged 44 years and above, who were diagnosed by presenting symptoms such as presence of cancerous cell in prostate biopsy and prostate specific antigen (PSA) above normal range (i.e. >4ng/ml), at the surgical clinic of the LAUTECH Teaching Hospital, Ogbomoso. A total of 30 age-matched apparently healthy male individuals whose PSA are within the normal range (<4ng/ml) served as control subjects.

Blood samples collection and analysis

Six mililitres (6 mls) of peripheral blood was collected from each patient and control subjects that have given consent to participate in the study with 2 mls dispensed into the 0.25ml of trisodium citrate anticoagulant (anticoagulant, blood ratio, 1:9) for the coagulation studies; 2 mls were dispensed into EDTA contained vials for the complete blood count and the remaining 2mls dispensed in 0.5ml trisodium citrate contained vials (anticoagulant, blood ratio, 1:4) for erythrocyte sedimentation rate (ESR) analysis. The citrated blood for coagulation studies was separated by centrifugation at 1500rpm for 15 minutes to obtain platelet rich plasma which was stored frozen at – 20°C until analysed.

The Coagulation parameters determined in this study include: prothrombin time (PT) and partial thromboplastin time with Kaolin (PTTK) while the haematological parameters estimated include packed cell volume (PCV), total white cell count (TWBC), platelet count, differential count and erythrocyte sedimentation rate (ESR). PT and PTTK were determined using plasmacan and Hemoscan reagents (Diagnostic reagents Ltd.UK); PCV, TWBC and platelet count were estimated using Sysmex KX-21N instrument[27]; differential count was estimated using Leishman's staining technique while ESR was determined using Westergren method.[28]

Statistical Analysis

Student't'-test was employed for the data analysis with a bar chat using SPSS version 20. $p<0.05$ denotes a significant difference between groups.

RESULTS

The mean ± SD of the coagulation and haematological parameters of the Prostate Cancer patients and their corresponding control subjects are detailed in Table1. The mean±SD PT, PTTK and platelet count in prostate cancer patients and control subjects are 35.75 ± 8.17, 71.10 ± 24.12, 120.18±55.33 and 14.40 ± 1.38, 40.00 ± 2.65, 232.80±90.80 respectively. The outcome reveals a statistically significant increase in the mean±SD of the coagulation parameters and some haematological parameters such as TWBC, ESR and Neutrophils in the prostate cancer patients when compared with their controls while a significant decrease was observed in the mean±SD of the PCV indicating associated anaemia in the prostate cancer patients, lymphocytes and basophils ($p< 0.05$).

The normal range (for the age group studied) of parameters estimated are as follows; 11-16secs, PT; 36-50secs, PTTK; 1-1.25, INR (using Plasmascan and Hemoscan reagents);0.40-0.54L/L PCV;4.0-10.0 $X10^9$/L TWBC;150-450 $X10^3$/L platelet count; up to 10mm/hr ESR; 40-75%Neutrophils;21-40% Lymphocytes;2-10 Eosinophils;1-6% Monocytes; 0-1%Basophils.[28]

The comparison between the mean PT and PTTK in the patient and control subjects is illustrated in Figure 1. The results represented in Table 2 shows the mean ± standard deviation of prothrombin time ratio and international normalized ratio in prostate cancer patients.

Table 1: Mean ± SD of the coagulation and haematological parameters of Prostate Cancer patients and their control population.

Parameters	Patients	Controls	p-value
PT (seconds)	35.75 ± 8.17	14.40 ± 1.38	0.00
PTTK (seconds)	71.10 ± 24.12	40.00 ± 2.65	0.00
Platelet count (10^9/L)	120.18±55.33	232.80±90.80	0.00
ESR (mm/hr)	33.16±6.00	6.60±0.82	0.00
WBC (10^9/L)	10.64±3.72	7.60±1.96	0.01
PCV (L/L)	0.29±0.54	0.44±0.32	0.00
NEUTROPHIL (%)	55.90±8.59	48.40±6.50	0.01
LYMPHOCYTES(%)	41.05±8.46	49.20±6.82	0.01
MONOCYTES (%)	1.15±0.58	1.40±0.50	0.92
EOSINOPHIL (%)	1.60±1.41	1.20±1.41	0.10
BASOPHIL (%	0.05±0.51	1.40±0.51	0.01

PT- Prothrombin Time; PTTK- Partial Thromboplastin Time with Kaolin; INR-International Normalised Ratio.

Table 2: Prothrombin ratio and International normalized ratio of prostate cancer patients

Group	Prothrombin Ratio	International Normalized Ratio
Prostate cancer patients	2.54 ± 0.59	4.59 ± 1.73
Control	1.20±0.17	0.98±0.13

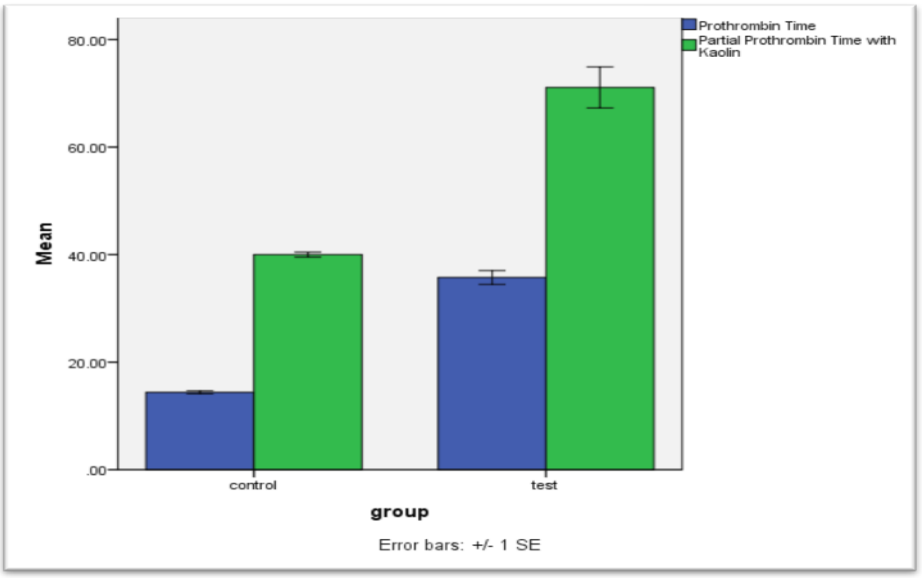

Figure 1: Comparison between the PT and PTTK of prostate cancer patients and their control counterparts.

DISCUSSION

Prostate cancer which has been ranked to be the most frequently diagnosed non-skin malignancy in men is associated with various hematological disorders such as thrombotic thrombocytopenia, primary fibrinolysis, sterile thrombotic endocarditis, and thrombosis.[29,16] Disseminated intravascular coagulopathy (DIC) is however the most common hematological ailment observed in prostate cancer patients (13–30%)[16,30], however, the core pathophysiology of the association between DIC and prostate cancer is incompletely tacit.[31]

Systemic inflammatory response has been known to affect survival in a number of malignancies.[32,33] White blood cells are key mediators in this inflammatory response[32] and this is inclusive of platelets, which are involved in mechanisms promoting tumor growth and metastasis.[34-36] Various blood count parameters, including neutrophil-to-lymphocyte ratio, platelet count, mean platelet volume and platelet-to-lymphocyte ratio, have been reported as potential markers for predicting the progression or recurrence of disease and/or overall survival in several forms of cancer.[37-40]

The survival figures after detection of haemoglobin < 10 g/dL and platelet count < 50×10^9/L should be viewed as an initial estimate[26] of the onset of metastasis in prostate cancer hence the need for immediate treatment. Metastasis has been observed to be a common event in prostate cancer especially if the patient was not diagnosed early thus declining bone marrow function continues to occur during the course of prostate cancer with skeletal metastases. It contributes significantly to morbidity and mortality and poses challenges to those involved in palliative care for these patients.[26]

In this study, the coagulation parameters assessed show that the mean ± standard deviation of PT, PTTK in prostate cancer subjects is significantly different from the control subjects ($p < 0.05$) with the patient having increased values of the parameters assessed than the control subjects (Table1 and Figure1) and this harmonizes with previous studies with case reports of patients with prostate cancer presenting with severe bleeding as a result of excessive fibrinolysis and DIC.[41, 42] The most frequent laboratory abnormalities observed in prostate cancer are prolonged prothrombin time and partial thromboplastin time with kaolin.[43] Disseminated intravascular coagulation as a manifestation in prostate cancer leads to frequent coagulation disorder in the patients and abnormalities of routine test of blood coagulation have been reported to occur in as many as 92% of patient with prostate cancer.[44]

Thrombocytopenia which is defined as decrease in platelets count could be mild ranging from 100,000 to150, 000/ul; moderate ranging from 50,000 to 100,000/ul and less than 50,000/ul when severe with scanty platelet appearance in the blood film.[45] Thrombocytopenia is also one of the abnormalities in haematological profile of patients with advanced malignancies, particularly those that metastasizes to the bone marrow, like prostate cancer and others.[46] These tumors interferes with normal haemopoesis and result in thrombocytopenia, anaemia, leucopenia, or even pancytopenia.[47] This study which also assessed the platelet count of these prostate cancer patients had their mean±SD platelet count as 120.18±55.33 which categorized their thrombocytopenic states to be between mild and moderate even as newly diagnosed patients. Previous studies have revealed thrombocytopenia in prostate cancer with symptom of epistaxis which is associated with DIC[48,49,50] while some other studies revealed epistaxis as a symptom but not associated with DIC.[50] In addition, systemic inflammation has been associated with the release of several pro-inflammatory mediators such as interleukin (IL)-1, IL-3 and IL-6 that are known to stimulate megakaryocyte proliferation leading to thrombocytosis. Consequently, platelet aggregation and degranulation along with the release of platelet-derived pro-angiogenic mediators have been suggested as the important determinant of tumour growth.[51]

Prothrombin time is converted to International normalized ratio, which is a standardized ratio to express the prothrombin time results that allows a better control of patients. The mean ± standard deviation of Prothrombin ratio and International normalized ratio of 2.54 ± 0.59 and 4.59 ± 1.73 (Table 2) in this study are indicators of disseminated intravascular coagulation, a major manifestation in prostate cancer, which leads to acquired coagulation disorder that may occur in a wide variety of clinical condition.

The TWBC, ESR, neutrophils and basophils in this present study show a significant difference ($p<0.05$) (Table 1) when compared with the controls with the patient group having increased values, this support the evidences from previous studies that the innate and adaptive immunity play vital role during the development and progression of prostate cancer.[52] Determination of haematological changes in prostate cancer is vital in order to observe disease progression, treatment and monitoring, this led to the conclusion by Pinkawa *et al* in 2015, when studying hematologic changes during prostate cancer radiotherapy, that early hematologic changes are predictive for late urinary and bowel toxicity during prostate cancer radiotherapy.[25] In addition, Langsenlehner *et al*. also contributed that platelet – lymphocyte ratio (PLR) may predict prognosis in patients with prostate cancer and may contribute to the future individual risk assessment in these patients.[53]

Furthermore, significant decrease was observed in the mean±SD of the PCV, lymphocytes and basophils ($p< 0.05$) (Table 1) this finding correlate with a previous finding which discovered that there is an association between anaemia and decreased survival in men with newly diagnosed metastatic prostate cancer.[54] In

addition Nakashima demonstrated that patients with lower Hb had more advanced disease on bone scan.[55]

However, the monocytes and eosinophil in the patient group are not significantly different from those of the control group ($p>0.05$) hence the need for future study on the markers of inflammation produced by these cells in the patient and control groups.

In conclusion, this study showed that the PT, PTTK, TWBC, ESR and Neutrophils, of the test subjects were significantly higher when compared with the control subject. This could be as result of the presence of the cancer procoagulant as well as inflammatory markers of immunity which are present in the development and progression of the disease. There is, therefore, the potential for primary activation of the fibrinolytic pathway and these are some of the major indicators of DIC in these newly diagnosed patients in this region. Therefore a differential diagnosis of DIC, metastasis and other associated complications are essential by estimating coagulation and haematological profile in management and treatment of prostate cancer.

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