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A literature review on Haemostatic disorder (VWF and Antithrombin) in prostate cancer patient

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ABSTRACT

Background: Prostate cancer is a significant cause of morbidity and mortality in male above forty years. Thromboembolic complication is the second cause of mortality among prostate cancer patients.

Aim: these study seek to review the available literature on thrombotic complication among prostate cancer patient with emphasis on Von Willebrand Factor (VWF) and antithrombin activity among prostate cancer patients as this will help to raise the awareness of thromboprophylaxis and risk assessment score use respectively, to improve quality of life and management outcome.

Method: A comprehensive literature search was performed using the internet search engineslinked to academic databases including Pubmed, Google Scholar, Ebsco, Hinari, Scopus, etc. Studies involving hemostatic disorders in Nigeria were thoroughly searched, and the references of such articles were also searched for any probable relevant informations.

Conclusion: Haemostatic disorder in prostate cancer is a serious condition that is associated with increase morbidity and mortality due to it hypercoagulable and prothroembolic state. There is paucity of information on this disorder in our environment with inconsistency in the available studies. More studies with further research on the level of other natural anticoagulant are required to verify the correlation between this disorder and thromboembolic complication among prostate cancer subjects.

Key words: VWF, antithrombin, prostatecancer

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INTRODUCTION

The human prostate is a compound tubular-alveolar gland [1]. The rudimentary prostate gland develops in the human embryo as an epithelial bud growing laterally from the urogenital system at the site of Mullerian tubercle under the influence of testosterone which is synthesized by the fetal testis and also involved is the Anti-Mullerian Hormone (AMH) [1]. McNeal divided the prostate gland into three major histologically distinct and anatomically separated zones [2]. These areas include the non-glandular fibromuscular stroma that surrounds the organ and two glandular regions termed peripheral and central zones respectively. These zones form the seat of the three major causes of morbidity; benign prostate hyperplasia, prostatitis and prostate cancer [3, 4]. As such it commands more attention than might be expected from such an organ.

Prostate cancer which is one of the morbidity arising from the peripheral zone of the prostate is characterized by abnormal and uncontrollable proliferation of the glandular tissue that comprises that zone of the prostate [5]. Prostate cancer is the second most common cause of cancer death in men in most developed countries and the fifth leading cause of cancer death among men worldwide [5,6]. It has been reported to be the leading cause of cancer death in 46 countries with highest mortality reported in Sub-Sahara Africa and the Caribbean [6]. Globally, the highest incidence was reported in France (Guadeloupe) with age-standardized rate reported as 189.1 per 100,000 individuals and the highest mortality rate was also reported in Barbados [5, 6]. High incidence rates are also seen in New Zealand (90.8, age standardized rate per 100,000), UK (80.7) and in America [7]. Although, mortality rates differ from the incidence, elevated mortality rates are seen in the Sub-Saharan Africa. Studies in Africa have shown variable incidences ranging from 3.2 per 100,000 in Zimbabwe, 5.2 in Uganda, 4.4 in Senegal [8-10]. Eminent scholars in Nigeria have reported varying but relatively high incidence rates among Nigerian men [11-13]. A high incidence of 37.4% was reported in Port Harcourt by Obiorah *et al.* [7].

A total of 1.3 million new cases of prostate cancer were recorded in 2018 with an estimate of about 174,650 new

cases and about 31,620 deaths from prostate cancer in 2019 as estimated by the America Cancer Society [14]. There is a direct correlation between prostate cancer and age. Prostate cancer is rare in males less than 40 years but its incidence increases exponentially with age [15-17].

Prostate cancer is a known prothrombin and hypercoagulable disease state in which there is significant alteration of the hemostatic system which is characterized by increased level of Von Willbrand Factor (VWF.Ag), increase P-Selectin, increase platelet adhesion and aggregation, increase thrombin generation and depletion of anticoagulant such as antithrombin, protein C. All these predispose to increase thrombosis formation [18]. Thromboembolism has been reported as the second most common cause of mortality in prostate cancer [19].

VWF is a sensitive marker of endothelia dysfunction, it has been reported that the level of VWF antigen and antithrombin III activity and their ratio are markers of hypercoagulability and prothrombotic state and have also been described in connection with thromboembolic complication. several studies have demonstrated elevated level of VWF antigen in patient with prostate cancer [20, 21]. Their level has been reported to correlate with tumor stage of disease; this increase in the level of VWF has been attributed to the endothelia proliferation and may be part of the acute phase reaction in response to vascular abnormalities [22, 23]. VWF has shown to be involved in the pathogenesis of binding tumour cells to platelet, the implication of this is that it predisposes the disease condition to a hypercoagulable state leading to thromboembolic complication [24–26].

Several observations have been reported on antithrombin activity in prostate cancer when compared with health controls [27]. Honeggaret al reported a decrease in plasma level of anti-thrombin in prostate cancer patients while Yuc Cao reported that a wide spread level of anti-thrombin is expressed in prostate cancer but it's gradually lost in tumour of high Gleason grade [28, 29]. Reduced plasma antithrombin activity is said to be associated with increased risk of thrombosis in patients with cancer of the prostate [30].

There is paucity of information on hypercoaguability in prostate cancer with emphase on VWF and antithrombin activity among prostate cancer subject and their contribution to thrombosis in our environment. Prostate cancer is a significant cause of morbidity and mortality in male above forty years. Thromboembolic complication is the second cause of mortality among prostate cancer patients [25, 26]. Hence these study seek to review the available literature on thrombotic complication among prostate cancer patient with emphasis on VWF and antithrombin activity among prostate cancer patients as this will help to raise the awareness of thromboprophylaxis and risk assessment score use respectively, to improve quality of life and management outcome.

Epidemiology and aetiology of prostate cancer

Prostate cancer is reputed to be the most common non-skin cancer among men in majority of High Development Index (HDI) populations [31]. The aetiology of prostate cancer is still largely unknown in spite of its high morbidity [32]. Some of the established risk factors includes: advancing age, race, and a family history of prostate cancer. Some putative risk factors have also been identified including androgens (hormones), diet, physical activity, sexual factors, inflammation, obesity, vasectomy, smoking and genetic susceptibility, have been implicated. Although, their roles in prostate cancer aetiology remain speculative and yet to be fully elucidated [33].

The reported age-adjusted prostate cancer incidence rates differ significantly worldwide [5]. Incidence rates among the African-Americans are reported to be the highest in the world (185.4 per 100,000 person-years), followed by Caucasian-Americans with incidence rate of 107.8 per 100,000 person-years. Incidence rates in countries with large populations of African descent like Brazil and the Caribbean are analogous to the rates among the Caucasians (ref). Central and other parts of South America in contrast, have a lower incidence rates (between 28-42 per 100,000 person-years) [6]. Variable rates are observed in Europe ranging from 15-36 per 100,000 person-years [7]. In Asia (the continent with the lowest prostate cancer incidence rate), a significant variation also existed in the reported prostate cancer incidence [6]. The more westernized countries like Israel, Japan and Philippines have incidence rates ranging from 22-47 per 100,000 person-years, showing a remarkably high incidence rates when compared with countries like Thailand, India and China with prostate cancer incidence rates ranging from 3-7 per 100,000 person-years [7].

Prostate cancer is the most common cancer among men in Africa and the third most common cancer with estimated 59,500 incident cases per annum [5, 6, 31]. Sub-Saharan Africa carries most of the burden with incident rate representing 20.3% of all cases of cancer in men. High incidence rates are reported in Uganda and Zimbabwe with incidences of 38.1 and 37.1 per 100,000 person-years respectively [8, 9]. In Nigeria, incidence rates are reported from hospital based studies. Oluwoleet al reported an incidence rate of 4.1% from all cancers and 10.1% of male malignancies in Zaria, northern Nigeria [34]. In Lagos, South-West Nigeria, 29.3% was reported [35]. In the Abuja the Federal capital territory, an incidence of 38.7% was reported from a retrospective screen-detected prostate cancer study [33]. In Port Harcourt South-Southern Nigeria, in a histopathological study of carcinoma of the prostate, an incidence rate of 37.4% was also reported [16].

Pathology of prostate cancer

Pathophysiology of prostate cancer:

The prostate gland is located in the male pelvis at the base of the penis. It is below the urinary bladder and immediately anterior to the rectum. The prostate is roughly 3 centimeters long, about the size of a walnut, and weighs approximately 20 grams. Its function is to produce about a third of the total seminal fluid [36]. The prostate surrounds the posterior part of the urethra, but this can be misleading. The posterior urethra, prostatic urethra, and proximal urethra all describe the same anatomy as there is no difference between the internal lining of the prostate and the urethra; they are the same entity [37].

The prostate is primarily made up of glandular tissue which produces fluid that constitutes about 30% to 35% of the semen. This prostatic portion of the semen nourishes the sperm and provides alkalinity which helps maintain a high pH. (The seminal vesicles produce the rest of the seminal fluid [38].

The prostate gland requires androgen (testosterone) to function optimally. This is why hormonal therapy (testosterone deprivation) is so effective. Castrate resistant tumors are thought to generate intracellular androgens [39].

Cancer begins with a mutation in normal prostate glandular cells, usually beginning with the peripheral basal cells [40].

Prostate cancer develops when the rates of cell division and cell death are no longer equal, leading to uncontrolled tumor growth. Following the initial transformation event, further mutations of a multitude of genes, including the genes for p53 and retinoblastoma, can lead to tumor progression and metastasis. Most prostate cancers (95%) are adenocarcinomas [41].

Approximately 4% of cases of prostate cancer have transitional cell morphology and are thought to arise from the urothelial lining of the prostatic urethra. The few cases that have neuroendocrine morphology are believed to arise from the neuroendocrine stem cells normally present in the prostate or from aberrant differentiation programs during cell transformation [41].

Squamous cell carcinomas constitute less than 1% of all prostate carcinomas. In many cases, prostate carcinomas with squamous differentiation arise after radiation or hormone treatment of prostate cancer cases, 70% arise in the peripheral zone, 15%-20% arises in the central zone, and 10%-15% arises in the transitional zone. Most prostate cancers are multifocal, with synchronous involvement of multiple zones of the prostate, which may be due to clonal and non-clonal tumors.

Presentation:

The clinical presentation of prostate cancer includes urinary retention, hesitancy, nocturia, haematuria and secondary presentation with loss of weight.

Prognosis:

The most important and established indicators of prognosis for prostate carcinoma include the Gleason grade, the extent of tumor volume, and the presence of capsular penetration or margin positivity at the time of prostatectomy. High-grade prostate cancer, particularly the percentage of Gleason grades 4 and 5 that are present, is associated with adverse pathologic findings and disease progression. Conversely, low-grade prostate tumors are infrequently dangerous.

In a review of 11,521 patients treated with radical prostatectomy at 4 academic centers from 1987 to 2005, Eggener et al reported an overall 15-year prostate cancer–specific mortality rate of 7%. High-grade cancer and seminal vesicle invasion were the prime determinants of prostate cancer–specific mortality [42].

Depending on the PSA value, pathologic stage, and histologic grade of the tumor, approximately 30% of patients with clinically localized prostate cancer are estimated to progress despite initial treatment with intent to cure.

The Cancer of the Prostate Risk Assessment (CAPRA) score for predicting prognosis is calculated on the basis of the following:

- PSA level
- Gleason score
- Percentage of biopsy cores positive for cancer
- Clinical tumor stage
- Age at diagnosis

In a research involving 10,627 men with clinically localized prostate cancer who had underwent primary radical prostatectomy, radiation therapy, androgen deprivation monotherapy, or watchful waiting/active surveillance, and had at least 6 months of follow-up after treatment, Cooperberg et al found that the CAPRA score was accurate for predicting metastases, cancer-specific mortality, and all-cause mortality [31].

In a retrospective study of patients who underwent radical retropubic prostatectomies, the researchers found an association between an opioid-sparing approach to anesthesia and reductions in prostate cancer progression and overall mortality. The researchers reviewed 1642 procedures performed with general anesthesia and 1642 prostatectomies performed with an opioid-sparing approach (general anesthesia supplemented with a neuraxial block), in patients diagnosed with prostate cancer between 1991 and 2005. Median follow-up in the study was 9 years [43, 44]. Their findings indicated that the risk of systemic progression of prostate cancer was almost 3 times greater and the mortality risk was 30% higher in the general anesthesia patients than in those anesthetized with an opioid-sparing approach [43, 44].

In a multivariate analysis, biochemical recurrence and disease-specific mortality were seen to be much higher in men who were smokers at the time of diagnosis versus those who had never smoked. A higher number of pack-years were associated with significantly increased risk for prostate cancer mortality but not for biochemical recurrence. Men who had

quit smoking 10 years prior to diagnosis or who had quit more recently but smoked for <20 pack-years had prostate cancer–mortality risks similar to those of men who had never smoked [45].

In a retrospective study at Johns Hopkins Medical Center in Baltimore, a greater connection between cigarette smoking and risk of prostate cancer recurrence was identified in men who had been treated with radical prostatectomy [46].

2.2.3 Grading of prostate cancer

2.2.3 Staging of prostate cancer

2.2.4 Diagnosis

Antithrombin

Antithrombin (AT) is a plasma protein that is produced in the liver and it inhibits thrombin and factors Xa, IXa, and XIa and inactivates several enzymes of the coagulation system, thereby inhibiting thrombosis. Antithrombim possesses a molecular mass of approximately 58kd and contains 432 amino acids [29]. It contains three disulfide bonds and a four possible glycosylation sites. α- Antithrombin is the dominant form of antithrombin found in blood plasma and has an oligosaccharide occupying each of its four glycosylation sites. A single glycosylation site consistently remains unoccupied in the minor form of antithrombin, β-antithrombin. Antithrombin has a half-life in blood plasma of around 3 days. The normal antithrombin concentration in human blood plasma is high at approximately 0.12 mg/ml, which is equivalent to a molar concentration of 2.3 μM. Antithrombin is a serpin (serine protease inhibitor) and is thus similar in structure to most other plasma protease inhibitors, such as alpha 1-antichymotrypsin, alpha 2- antiplasmin and Heparin cofactor II. Because antithrombin inhibits thrombin and factors Xa, IXa, and XIa, deficiency of antithrombin predisposes to venous thrombosis. The inhibitor also inactivates kallikrein and plasmin, also involved in blood coagulation. However, it inactivates certain other serine proteases that are not involved in coagulation such as trypsin and the C1s subunit of the enzyme C1 involved in the classical complement pathway. AT inactivates several enzymes of the coagulation system. AT is a serine protease inhibitor and possesses similar structure to other plasma protease inhibitors, such as alpha 1-antichymotrpsin, alpha 2-antiplasmin and Heparin cofactor II [47]. The importance of the role of antithrombin in regulating normal blood coagulation is shown by the correlation between deficiency of antithrombin and an increased risk of an individual developing thrombotic disease. Found that antithrombin reduces diffuse intravascular coagulation and other outcomes although they reported that antithrombin has not been found to confer any benefit in critically ill people with sepsis [47].

Von Willebrand factor:

Von Willebrand factor (VWF) plays a critical role in primary hemostasis by promoting platelet adhesion to the sub-endothelium at vascular injury site and platelet aggregation [47]. It participates indirectly in coagulation process by binding non-covalently to factor VIII, thereby protecting the coagulation factor from proteolytic degradation, efficiently localizing it at the site of vascular injury and also prolonging its half-life.

Von Willebrand Factor (VWF) is a large multimeric plasma protein that is synthesized by endothelial cells and megakaryocytes and are present in platelet. Considering the critical role VWF plays in hemostasis, it has been suggested that VWF might promote cancer.

Synthesis and secretion of VWF:

VWF is a large glycoprotein synthesized by both endothelial cells and megakaryocytes.It is encoded distally on the short arm of chromosome 12. The gene of 178 – 180kd with 52 exons encode the VWF monomer with a molecular weight of 250 kd–270 kd which consist of areas of internal homology determined as A, B, C and D domains providing binding sites to a variety of proteins (47). The gene producta 2,813 amino acids (AA molecule) are composed of a signal peptide of 22 residues, a large pro-peptide of 741 and a mature subunit of 2,050 residues (pre-pro-VWF). Pro-VWF dimerise through disulphide bonds near their carboxyl terminal (tail to tail) within the Endoplasmic Reticulum (ER), subsequently VWF dimers are transported to Golgi apparatus to form large multimers sizing up to 20,000kd via N-terminal disulphide bonding (head to head) [48].

VWF circulates in plasma as a series of heterogeneous multimers that mediate platelet tethering, translocation and adhesion to traumatised endothelium under high physiological arterial blood flow condition above a critical level of 500 s^{-1}-1000 s^{-1} shear rate [49]. It also protects coagulation factor VIII (FVIII) from rapid proteolytic inactivation [50]. Plasma VWF is majorly from the endothelium and is constitutionally secreted to a plasma concentration of 10 μg/ml, whereas the remainder is stored in the cytoplasmic granules (Weibel-Palade bodies) or in the α-granules of platelets and are secreted via a regulated pathway [51]. Schematic diagram of VWF processing is shown in (Figure 1).

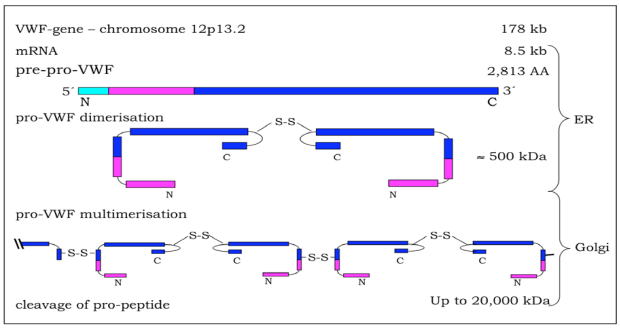

Fig. 1. Schematic diagram of VWF processing

Haemostatic change in prostate cancer

Prostate cancer paradoxically is associated with both hypercoagulable state and bleeding diathesis [52]. Hypercoagulability manifest in both venous and arterial thrombosis [53]. Hyprcoagulability shows the imbalance of the coagulation cascade following the procoagulant condition [54]. Prostate cancer is a prothrombic state and associated with increasing thrombin generation with depletion of natural anticoagulant. Tissue factor is the primary initiator of coagulation cascade in prostate cancer induces pro-inflammatory response via synthesis of the following cytokines 1L-1β, TNF-α, VEGF and the degree of tissue factor expression of TF in prostate cancer correlates with level of circulating antigen [55, 56]. Over-expression of TF plays a role in mediating tumour growth and metastasis [57].

There are markers supporting the concept of hypercoagulability and thrombin generation which significantly alter the haemostatic system, which is characterized by increase VWF, P-selectin, fibrinogen, FSP, FVIII and FPA with normal to reduced anti-thrombin level [58].

Anththrombin VWF and prostate cancer

There has been increasing evidence suggesting various changes in the level of antithrombin and VWF.Ag in prostate cancer patient. Cao et al reported a widespread AT expression on prostate cancer but it level is said to reduce as prostate cancer advances [59]. Similar study by Becken et al. reported a significant reduction in the level of AT [60]. Furthermore, Hong et al. reported similar finding [61]. However, Hamid Al-Mondhury reported normal level of ATIII this was similar to the finding by Walker ID [62].

Prostate cancer induce over expression of TF and pro-inflammatory responses these leads to endothelia activation, VWF antigen is one of the marker of endothelia activation, its level is said to be elevated even in clinically asymptomatic state indicating continuous endothelia activation Al-Mondhury reported elevated level of VWF in prostate cancer. Similarly Rohsig reported similar finding. Furthermore, Richard also reported elevated level of VWF.Ag in prostate cancer compare to benign prostate hyperplasia [63-65].

CONCLUSION

Haemostatic disorder in prostate cancer is a serious condition that is associated with increase morbidity and mortality due to it hypercoagulable and prothroembolic state. There is paucity of information on this disorder in our environment with inconsistency in the available studies. More studies with further research on the level of other natural anticoagulant are required to verify the correlation between this disorder and thromboembolic complication among prostate cancer subjects.

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