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A Case Report of Scrub Typhus: Secondary Acute Arrest of Hemopoiesis with Multiple Organ Dysfunction Syndromes

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Abstract

Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi* (*O. tsutsugamushi*) in which humans are accidental hosts. Acute arrest of hemopoiesis (AAH) always manifests in pancytopenia and with supportive treatment or inducement removal, the AAH patients would show significant improvement in blood routine for about a week. As a rapidly progressive and potentially life-threatening organ function disorder syndrome, multiple organ dysfunction syndrome (MODS) is often induced by many factors including infection, illness and injury. We received a rare case of scrub typhus rapidly presenting with AAH and MODS 2 weeks ago. The clinical data of a 32-year-old female with *O. tsutsugamushi*-induced AAH and MODS was summarized retrospectively and analyzed with a literature review. In this case, we selected tigecycline and moxifloxacin as treatment regimens for scrub typhus. When the potential infection was controlled, her pancytopenia and hepatic function rapidly improved in a few days.

Keywords

Scrub Typhus, *Orientia tsutsugamushi*, Acute Arrest of Hemopoiesis, Multiple Organ Dysfunction Syndrome

1. Introduction

Scrub typhus, also known as tsutsugamushi disease, is a natural focal disease caused by infection with *O. tsutsugamushi*, with rodents as the main source of infection and Chigger mite larvae as the vector. *Orientia tsutsugamushi* (from Japanese *tsutsuga* meaning "illness", and *mushi* meaning "insect") is a mite-borne bacterium belonging to the family Rickettsiaceae and is responsible for a disease

called scrub typhus in humans [1]. Patients mostly have a history of field work, and an incubation period of 5 - 20 days. They are characterized by complex and diverse clinical manifestations, and numerous complications, often leading to multiple organ damage, and a high rate of early misdiagnosis [2]. In some cases, the pathogens form eschar-like inflammatory lesions when they enter the body site. Various antibiotics, such as chloramphenicol, tetracycline, doxycycline, macrolides, quinolones, and rifampicin, have been used to treat scrub typhus [3]. The failure of two or more vital organ systems is termed multi-organ dysfunction syndrome (MODS) and resembles a very critical condition associated with high morbidity and mortality [4]. Scrub typhus is a serious disease that can result in multiple organ dysfunctions in some individuals, with a maximum mortality rate of 30% if left untreated [2]. Nevertheless, cases of aplastic crisis due to scrub typhus have been rarely reported. A case of acute arrest of hemopoiesis with multiple organ dysfunction syndrome secondary to scrub typhus was admitted to the Department of Hematology, the Second Affiliated Hospital of Chongqing Medical University, which was diagnosed promptly and successfully cured with tigecycline, was presented here for analysis and review of the literature.

2. Case Presentation

A 32-year-old female was admitted to our hospital with recurrent fever for 2 weeks and abnormal hemogram for 2 days. Two weeks before, she had fever of unknown origin at the highest temperature of 40.0˚C with fatigue, dizziness and muscle soreness. The first blood routine in the local hospital showed: hemoglobin, 141 g/L; white blood cell count, 3.74×10^9/L and platelet count, 72×10^9/L. Thirteen days after this examination, she rechecked the blood routine and other imaging examinations: hemoglobin, 45 g/L; white blood cell count, 2.50×10^9/L; platelet count, 18×10^9/L; chest computed tomography (CT) suggested a fibrous cord lesion in the middle lobe of the right lung, a small amount of effusion in bilateral pleura and pericardium; abdominal CT showed a significantly enlarged spleen. At this time, pancytopenia appeared on her body and she was treated with andrographolide, dexamethasone and blood component transfusion without any response. There were still many symptoms on her body: fever at a highest temperature of 40.3˚C, chills, cough, expectoration, tired out of breath, polypnea, dizziness, headache and leg muscle soreness. Therefore, she was brought to emergency department of our hospital and rapidly screened by professional doctors to send to the hematology department.

On physical examination, the temperature was 40.3˚C, the pulse rate was 125 beats/min, the respiratory rate was 35 breaths/min, and the blood pressure was 99/62mmHg. The patient presented an acutely ill face with mild yellow staining of the bilateral scleral icterus, pale palpebral conjunctiva, slightly swollen left submaxillary lymph nodes touched soft without pain, coarse breath sounds in both lungs with little moist rales, soft abdomen that pressed mild pain and spleen could be touched 2 cm below the ribs, mild pitting edema in both lower

limbs.

Laboratory testing and imaging examinations showed the following (Table 1): hemoglobin, 114 g/L; white blood cell count, 8.77 × 10^9/L; platelet count, 41 × 10^9/L; neutrophilic granulocyte percentage of 76%; absolute reticulocyte count, 0.049 × 10^9/L; procalcitonin level, 0.87 ng/ml; prothrombin activity (PTA), 85%; prothrombin time (PT), 14.3 s; activated partial thromboplastin time (APTT), 51.8 s; fibrinogen (FIB), 1.98 g/L; fibrinogen degradation products (FDPs), 11.18 ug/L; total protein (TP), 53 g/L; albumin (ALB), 27.9 g/L, alanine aminotransferase (ALT), 258 U/L; aspartate aminotransferase (AST), 298 U/L; alkaline phosphatase (ALP), 172 U/L; γ-glutamyltransferase (GGT), 122 U/L; prealbumin (PAB), 39 mg/L; β2-microglobulin, 5.71 mg/L; lactic dehydrogenase (LDH), 590 U/L; plasma D-dimer, 3202 ng/ml; immunoglobulin G (IgG), 10.5 g/L; immunoglobulin A (IgA), 2.97 g/L; immunoglobulin M (IgM), 3.59 g/L; light chain κ, 10.9 g/L; light chain λ, 5.94 g/L; complement C3, 0.64 g/L; complement C4, 0.24 g/L; anti-mitochondrial M2 antibody, 36.2 RU/ml; interleukin-2 receptor (IL-2R), 1126 U/ml; interleukin-1β (IL-1β), 8.24 pg/ml; ferritin, 1321 ng/ml. The examination of HIV, syphilis, hepatitis A, B, C, D and E testing showed negative results. Similarly, the results of blood culture, fungal G and GM test, Epstein-Barr virus DNA, human cytomegalovirus DNA, antinuclear antibody testing and vasculitis-associated antibodies didn't show obvious abnormalities. TORCH examination was positive for herpes simplex virus IgM. Bone marrow morphology test showed: hyperplasia of bone marrow was obviously active, mainly granular cell hyperplasia; hyperplasia of erythroid cell was severely reduced; atypical lymphocytes were seen, and plasma cells were more active. PNH examination in peripheral blood (CD55 and CD59) and flow cytometry in bone marrow: no abnormality was found in flow cytometry of lymphocytes and plasma cells.

Table 1. A part of laboratory examinations during hospitalization.

Title	Reference range	Day 1	Day 2	Day 5	Day 6	Day 7	Day 9
WBC (×10^9/L)	3.5 - 9.5	8.7	5.5	6.6		6.6	4.0
HB (g/L)	130 - 175	114	51	112		112	115
PLT (×10^9/L)	100 - 300	41	42	130		156	187
ALB (g/L)	40 - 55	27.9	24.8	24.5		31	34.7
ALT (U/L)	7 - 40	258	203	74		40	38
AST (U/L)	13 - 35	298	256	48		48	32
PT (s)	11 - 14.5	14	15.7	13.8	17.5	16.4	14.4
APTT (s)	31.5 - 43.5	51.8	74.5	55.7	67.2	61.2	48.9
FIB (g/L)	2 - 4	1.98	1.21	1.3	0.71	0.82	1.08
D-D (ng/ml)	0 - 550	3202	1665			1672	

On the first day of hospitalization, she had recurrent fever, chills and her state of illness rapidly progressed on the next day: the intensity of polypnea, dizziness and headache increased and new symptoms like nausea, emesis, abdominal pain, diarrhea and dyspnea, occurred. Therefore, we repeated the physical examination: the blood pressure was 87/54mmHg, the pulse rate was 125 beats/min, the respiratory rate was 35 breaths/min, and the body temperature was 40.0˚C. The upper and left lower harder abdomen pressed moderate pain without rebound pain. The circumstance of edema worsened and the limbs started to become cold. A signature eschar was observed in the sacrococcygeal region (**Figure 1**). The results of emergency examinations showed the following (**Table 1**): hemoglobin, 51 g/L; white blood cell count, 5.50×10^9/L; platelet count, 42×10^9/L; PT, 15.7 s; APTT, 74.5 s; FIB, 1.21 g/L; ALB, 24.8 g/L; ALT, 203 U/L; AST, 256 U/L; plasma D-dimer, 1665 ng/ml; CT of the chest and abdomen indicated bilateral lung scattered inflammation and bilateral chest cavity filled with little to medium amount of effusion, pulmonary edema, splenomegaly. On further questioning, more medical history details revealed that the patient lived in Fengqing County, Lincang City, Yunnan Province which is a major agricultural province and there were similar patients with recurrent fever like her in the surrounding area. They all had a history of farming or getting unknown insect bites before the initiation of the disease. Based on the clinical, laboratory and even medical history findings, we highly suspected that this patient had scrub typhus. Until then, she had secondary septic shock, pulmonary infection, liver damage, multiple organ dysfunction syndrome (MODS), coagulation dysfunction and aplastic crisis. Empirical intravenous administration of tigecycline and moxifloxacin was initiated immediately. Human immunoglobulin 20 g per day was given for 4 consecutive days to enhance immunity and resist potential virus infection. Human serum albumin (HSA) and plasma were infused for edema remission and coagulation factors complement. Glutathione was administered for liver protection. In addition, quantity fluid resuscitation, oxygen inhalation and other support treatments were added to the regimen. On day 5 of hospitalization, after 3 days of treatment with tigecycline and moxifloxacin, the clinical manifestations, liver function, coagulation function and aplastic crisis improved greatly (**Table 1**). At the same time, the result of the high throughput DNA test of blood pathogens was back: *O. tsutsugamushi* as sequence number 447 was discovered. Until day 9 of hospitalization, we reexamined some indicators: blood biochemical indexes basically recovered (**Table 1**); bone marrow smear and biopsy showed the hyperplasia of hematopoietic cells; CT of chest and abdomen suggested that the pulmonary infection and chest cavity fluid were obviously fade away, meanwhile, the size of spleen reduced. She spent 12 days during hospitalization, and she was discharged with basic recovery. After discharge, she was continued with a course of oral minocycline. During nearly 9 months of follow-up, she was left with sequelae of lung infection that she felt out of breath after moderate-intensity physical activity. Beyond that, she didn't feel any discomfort.

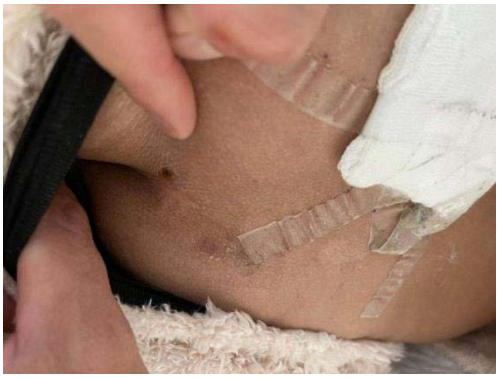

Figure 1. Eschar in the sacrococcygeal region.

3. Discussion

Scrub typhus is a zoonosis caused by the pathogen *O. tsutsugamushi* which is classified as a separate genus in the Rickettsiaceae family. It is described as an acute febrile illness and is confined to a definite geographic region. The "tsutsugamushi triangle" extends from northern Japan and far eastern Russia in the north, to northern Australia in the south, and to Pakistan and Afghanistan in the west [5]. Scrub typhus is a serious public health problem in the Asia-Pacific area. There is an estimated one million new scrub typhus infections each year, and over one billion people around the world are at risk. Without appropriate treatment, the case fatality rate of scrub typhus can reach 30% or even higher[6]. Based on previous studies, rickettsiae are located in endothelial cells in all the organs evaluated, namely heart, lung, brain, kidney, pancreas, appendix, and skin, and within cardiac muscle cells and in macrophages located in lymph node, liver and spleen [7] [8]. The manifestation of disease varies from mild to severe, some just have fever and some cases get fatal syndromes like MODS. According to previous studies, liver dysfunction accounted for 89%, lung involvement accounted for 65%, splenomegaly accounted for 47%, gastro-intestinal haemorrhage accounted for 25% and there were variant reports on the injury of other organ systems [9]. Typical symptoms include eschar, fever, gastrointestinal disturbance, malaise, cough, myalgia, and headache. Diagnosis is often missed in the early stage of the disease, as it presented as an acute febrile illness which is similar to other tropical febrile infections. However, the characteristic eschar-like rash, endemic area, and history of mite bites can assist doctors in rapid diagnosis. In most cases, the timely administration of antibiotics brought out a good outcome [2] [10].

Splenomegaly is a common hematological manifestation in typhus, seen in up to 47% of patients [9], furthermore, disseminated intravascular coagulopathy (DIC) [11] [12], hemophagocytic lymphohistiocytosis (HLH) [13] [14], thrombopenia [15], monoclonal gamma-globulinemia [16] and thrombosis [17], all of which have been reported in some cases. AAH, also known as aplastic crisis, is a sharp decline in hematopoietic function of bone marrow under the interaction of infection, drugs, immune disorders and other inducement, manifested as

erythropenia, hyperplasia of bone marrow and erythroid hematopoietic cells differentiation disorder. Scrub typhus can be secondary to various infectious diseases containing virus infection, which is the most common, especially the B19 virus infection. Specifically, hemoglobin of this case progressive declined in the short term and the bone marrow suggested hypoplasia of erythroid hematopoietic cells. During the hospitalization, after treatment of anti-infection and symptomatic treatment, her symptoms, signs, blood parameters and hypoplasia of erythroid hematopoietic cells recovered rapidly. After case analysis, we considered AAH in scrub typhus was secondary to infection and immune disorders.

As previous articles indicated, there are many literatures summarizing the manifestations of scrub typhus secondary multiple organs involvement. It usually presents as an acute febrile illness, with high fever, malaise, headache and cough. The most characteristic clinical feature of scrub typhus is the presence of an eschar at the site of the bite of the mite [9]. In this case, the transaminase level increased 5 times over than standard values which showed the liver dysfunction. Besides, the level of WBC and PLT decreased sharply and weak erythroid hematopoiesis in bone marrow reflected the further impairment of hematologic system. This specific case, scrub typhus involving AAH and MODS progressed promptly. With medical history details and typical eschar found, correctly diagnosis was given by our experienced doctors. Thanks to timely therapy, this patient rapidly recovered and the expected treatment outcome was achieved.

4. Conclusion

Scrub typhus involving AAH and MODS is not frequently seen in clinical. Apart from careful medical history questioning, witness of eschar is the critical evidence. As shown in our case, people with common febrile illnesses in the tsutsugamushi triangle must be carefully evaluated by the screening of eschar and after treatment of antibiotics, the symptoms and laboratory indicators improved promptly.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Some Oxidative Stress Biomarkers among Patients with Prostate Cancer in Sokoto, North Western Nigeria

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Abstract

Globally, prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related death in men. It is a significant contributor to the burden of diseases and affects over a million men. This study investigated the levels of malondialdehyde and plasma total antioxidant capacity among patients with prostate cancer in Sokoto. This case-control study was conducted among 28 confirmed prostate cancer patients attending the Urology clinics in Usmanu Danfodiyo University Teaching Hospital and Sokoto Specialist Hospital in North Western Nigeria. Twenty-eight age-matched healthy males were monitored as controls. Determination of Total Antioxidant Capacity (TAC) was determined using Ferric Reducing Antioxidant Power (FRAP) reagent while the Malondialdehyde in serum was determined as a conjugate with Thiobarbituric acid (TBA) acid. Data were collected using a semi-structured interviewer-administered questionnaire. Data were processed using SPSS version 20 and results were reported as Mean ± Standard deviation. The malondialdehyde level was significantly increased ($p < 0.0001$) among subjects with prostate cancer (0.215 ± 0.06) compared to controls (0.073 ± 0.04). The plasma total antioxidant capacity decreased significantly among the subjects (247.9 ± 63.3) compared to controls (743.3 ± 104.40) ($p < 0.0001$). The findings from this indicated a high Malondialdehyde (lipid peroxidation indicator) and low levels of Total Antioxidant Capacity among prostate cancer patients as evidence of redox imbalance. Subjects in monogamous relationships compared to polygamous, rural dwellers, farmers, individuals of Hausa ethnicity and subjects who reported no family history of the disease were more predisposed to prostate cancer. Further epidemiological

studies are needed to determine the predisposing factors and the potential role of these markers in the diagnosis, prognosis and management of prostate cancer patients in Sokoto in particular and Nigeria in general. We recommend that Malondialdehyde and Total Antioxidant Capacity be routinely monitored among patients with prostate cancer patients in the area.

Keywords

Some Oxidative Stress Biomarkers, Prostate Cancer, Sokoto, North Western Nigeria

1. Introduction

Globally, prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related death in men. It is a significant contributor to the global burden of disease and the second most frequent malignancy after lung cancer in men worldwide accounting for 1,276,106 new cases and causing 358,989 deaths which amount to 3.8% of all deaths caused by cancer in men [1]. Annual incidence of PCa stands at approximately more than 1.1 million [2]. It is a major public health problem in developing countries where the incidence continues to increase and the mortality is still high [3]. Prostate cancer (PCa) is an adenocarcinoma or glandular carcinoma. It starts when the semen secreting epithelial cells mutate and become cancerous resulting in deregulation of prostate growth [4]. Despite its high incidence, little is known about the causes of the disease. The incidence rate of prostate cancer varies across the regions and populations. In 2018, 1,276,106 new cases of prostate cancer were registered worldwide, representing 7.1% of all cancers in men [1]. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions. With an estimated 307,000 deaths in 2012, prostate cancer is the fifth leading cause of death from cancer in men (6.6% of the total men deaths). Prostate cancer incidence rates are highly variable worldwide. The age-standardized rate (ASR) was highest in Oceania (79.1 per 100,000 people) and North America (73.7), followed by Europe (62.1). Conversely, Africa and Asia have incidence rates that are lower than those of developed countries (26.6 and 11.5, respectively) [2]. The definitive risk factors for cancer of the prostrate are ageing, the presence of testes and dihydrotestosterone and estrogen testosterone imbalance [5]. Dietary fat, hormones, vasectomy, cadmium, vitamin A, vitamin D deficiency and sexual behaviour are probable and potential risk factors. It is characterized by clinical manifestations of locally advanced or metastatic disease such as weight loss, bone pain, lethargy, lower urinary tract symptoms of bladder outlet obstruction or irritable symptoms [5]. Although the causes of the high incidence of prostate cancer are poorly understood, epidemiological, experimental and clinical studies, suggest that oxidative stress (OS) plays a major role

in explaining prostate cancer development and progression [6] [7].

The redox equilibrium is important in preserving the correct functionality of cellular vital functions [8]. Oxidative stress is defined as the imbalance in the redox characteristics of some cellular environment which can be the result of either biochemical processes leading to the production of reactive species, exposure to damaging agents (environmental pollutants and radiations), or limited capabilities of endogenous antioxidant systems [9] [10]. Reactive oxygen and nitrogen species (ROS/RNS) produced under oxidative stress are known to damage all cellular biomolecules (lipids, sugars, proteins, and polynucleotides) [11] [12]. Thus, several defense systems have been involved within the cells to prevent uncontrolled ROS increase. These systems include non-enzymatic molecules (glutathione, vitamins A, C, and E, and several antioxidants present in foods) as well as enzymatic scavengers of ROS, with superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) being the best-known defense systems (8). Mitochondria are the predominant source of ROS in all cell types [13]. Superoxide ($O2^{\bullet -}$) is mainly generated at the level of the mitochondrial electron transport chain and can be converted to hydrogen peroxide (H_2O_2) by SOD or undergo spontaneous dismutation [8]. In the presence of transition metal ions, for example, iron and copper ions, H_2O_2 can generate via Fenton reaction the highly reactive hydroxyl radical (HO•). Reactive species may also be enzymatically produced by xanthine oxidase (XO), uncoupled nitric oxide synthases (NOS), and NADPH oxidase (NOX). ROS production is related not only to cell damage or death, but physiological and signalling roles for ROS have also been ascertained.

Production of malondialdehyde (MDA), a well-known end product of lipid peroxidation, is up-regulated in response to an increased number of free radicals. Studies have shown that increased levels of MDA contribute to the pathogenesis of several metabolic diseases including diabetes, and cancer [14]. Malondialdehyde (MDA) is an extensively utilized biomarker to predict the pattern of various diseases such as diabetes, hypertension, cancer, heart failure and atherosclerosis. MDA has been used as a potent biomarker in both in vivo as well as in-vitro studies [15]. In patients suffering from osteoarthritis, MDA can be detected in the sections of joint tissue. In both patients suffering from lung cancer as well as glaucoma, the concentration of MDA is high; thereby validating the reliability of MDA assay to find out oxidative stress in relation to pathology of various diseases [16] [17]. A Study in a tertiary hospital in Nigeria reported lipid peroxidation with a decrease in antioxidant activity [18] among breast cancer patients.

Among the various cellular and tissue systems, red blood cells (RBCs) are uniquely vulnerable to oxidative stress due to the lack of nucleus and mitochondria, inability to synthesize fresh protein along with degradation of detoxifying enzymes, etc. So, they are among the first cells to be affected by alterations in the redox status of the body and can be explored for the early detection of pathophysiological alterations of the body in early stages [19]. A number of studies

have shown that systemic inflammation plays an important role in the development and progression of various cancers [20].

In Nigeria, with a population of nearly 180 million people, complex diseases such as cancer are currently emerging as important health care priority for the future. The subsequent attendant increase in life expectancy is likely to lead to an increase in the incidence of all types of cancers, as a higher proportion of the population reaches the complex disease-bearing age [21]. In a descriptive 10 (2006-2015) years analysis of all diagnosed cancers in the department of histopathology, Usmanu Danfodiyo University Sokoto [22], the most frequent cancers in male was prostate 267(16.00%), having a higher incidence than bladder cancer which was the most common cancer in this hospital between (1999-2004) [23]. Despite the increasing incidence of prostate cancer in Nigeria and Sokoto, and the role of oxidative stress in the pathogenesis of malignant diseases, to our knowledge, we have not seen baseline data for the level of oxidative stress in a patient with prostate cancer in Sokoto to serve as a guide for health intervention measures and future researches. Although various studies have evaluated the role of oxidative stress among patients with prostate cancer, there is limited literature available in Nigeria. The aim of this study was to assess the level of some oxidative stress biomarkers (Malondialdehyde and Total antioxidant capacity) among patients with prostate cancer attending Sokoto Specialist Hospital and the Urology Clinic in Usmanu Danfodiyo University Teaching Hospital (UDUTH) in Sokoto, North Western Nigeria.

2. Materials and Method

2.1. Background of the Study Area

The study was carried out in collaboration with the Urology Centre of Usmanu Danfodiyo University Teaching Hospital Sokoto Nigeria, the only teaching hospital serving people of Sokoto, Kebbi, Zamfara States and some neighbouring Niger and Benin Republic and Sokoto State Specialist Hospital. Sokoto State is one of the 36 states in Nigeria, located to the extreme north western part of Nigeria between longitude 4Â˚8'E and 6Â˚54'E and latitudes 12Â˚N and 13Â˚58'N. It shares common border with Niger Republic to the North, Kebbi State to the Southwest and Zamfara state to the East. The total land area is about 32,000 sq.km. In terms of vegetation, the state falls within the savannah zone. Rainfall starts late and ends early with mean annual falls ranging between 500 mm to 1300 mm. The dry season starts from October, lasts up to April in some part and may extend to May or June in other parts. The wet season on the other hands begins in most parts of the state in May and last up to September or October.

Sokoto State had a population of 3,696,999 based on the 2006 general census with estimated population of 5,297,612 projected for 2018 [24]. The inhabitants of the area are predominately Muslims and of the Hausa and Fulani ethnic groups. Other minority groups include the Zabarmawa and Tuareg. All these groups speak Hausa as a common language. The Fulani speaks Fulfulde. Other ethnic groups resident in the area Igbo, Yoruba, Nupe, Ebira, Igala, etc. It has 23

local government areas (LGAs), Five (5) of which are urban and eighteen (18) rural LGAs. The classification of urban rural areas in the state is by the National Population Commission based on a location of 16km radius from the centre of the state. The population of the area, availability of modern facilities, utilities, access road networks, banks, secondary health facilities, the state leadership and schools are available in the region. The major industrial and social infrastructure and facilities are located in the urban areas in addition to modern business and commercial ventures.

The state is divided into four health zones with 586 functional health facilities (2 tertiary, 19 secondary and 565 primary health facilities. The main economic activities in the area are farming, business, and cattle rearing. Agriculture is the backbone of the economy and riverine food plains provide cash crops such as rice, onion, groundnut, while upland areas are planted with sorghum, millet, beans and cassava. There is a generally low literacy level in western education not only of the dependent population but also the adult population with more affected. Literacy rate for women is 9% as compared with 45% for men [25]. Most women in the area are financially dependent on their husbands and most decisions on how to run the family, health issues and even social events are made by the husband and his parents [25]. Other cultural practices include "Purdah" where married women are restricted from going out except with their husband's permission and when going out have to cover their bodies fully including the face.

2.2. Study Population

The study population for this cross-sectional study comprised of prostate cancer subjects attending the Urology clinics of Usmanu Danfodiyo University Sokoto and Specialist Hospital Sokoto with apparently healthy male monitored as controls.

2.3. Inclusion Criteria

Patients with confirmed cases of prostate cancer attending Urology clinics in UDUTH and SSH, who gave a written informed consent to participate in the study were consecutively recruited until the sample size was attained.

2.4. Exclusion Criteria

Patients with confirmed cases of prostate cancer attending the Urology clinics in UDUTH and SSH, who refuse to offer a written informed consent to participate in the study, and those with prostate cancer and other comorbidities were excluded from participating in the study.

2.5. Sample Size Determination

The minimum sample size was determined using this formula [26]:

$$n = \frac{Z^2 pq}{d^2}$$

where n = minimum sample size

z = two-sided percentage of point of the normal distribution corresponding to the required significant Level (=0.05) = 1.96

p = prevalence of prostate cancer in a previous study = 2.5% [27] = 0.025

q = complimentary probability of $p = 1 - p$

d = tolerable alpha error or level of precision = 5% = 0.05

$n = 1.96 \times 0.025 \times (1 - 0.025/0.052) = 3.8416 \times 0.025 \times 0.932/0.0025$

$n = 38$

2.6. Blood Sample Collection

Three millilitres (3 mls) of blood samples were collected by venepuncture into the plain tubes. The blood sample was allowed to clot and centrifuged at 3000 rpm for 5 minutes. The serum was harvested and sample will be stored at −20˚C until used for assay.

2.7. Laboratory Analysis

Determination of Total Antioxidant Capacity (TAC) was determined using Ferric Reducing Antioxidant Power (FRAP) reagent as previously described [28]. The principle is based on the fact that at low pH, reduction of 2,4,6-tripyridyl-s-triazine (TPTZ)-ferric complex to Ferrous form (which has an intense blue colour). The colour change can be monitored by measuring the change in absorbance at 593 nm by spectrophotometry. The reaction is non-specific, any half reaction that has a lower redox potential under reaction conditions than that of ferric-ferrous half reaction will drive the ferrous ion formation. The change in absorbance is therefore directly related to the combined or total reducing power of the electron donating antioxidants present in the reaction mixture. Malondialdehyde in serum was determined as a conjugate with Thiobarbituric acid (TBA) acid. Serum proteins were precipitated by Trichloroacetic acid (TCA) and then removed by centrifugation. The MDA TBA complex was measured by spectrophotometry at 534 nm [29].

2.8. Data Collection and Management

An interviewer-administered questionnaire was used as the data collection instrument. The interviews took place within the wards and clinic at the Urology centre of UDUTH and SSH. Data processing and statistical analysis was done using a Statistical Package for Social Sciences (SPSS) version 2.3. Results were expressed as mean ± Standard Deviation. Group comparisons was made using one-way analysis of variance (ANOVA), paired comparisons were carried out using the Student's t-test. A p-value of equal to or less than 0.05 ($p \leq 0.05$) was considered as significant.

2.9. Ethical Considerations

Ethical approval was obtained from the Ethics and Research Committee of UDUTH and SSH Sokoto. Written informed consent was obtained from all study participants before enrolment.

3. Results

This study assessed some oxidative stress biomarkers among patients with prostate cancer in Sokoto. The peak age of incidence of prostate cancer was 50 - 60 years (6th decade) as shown in Figure 1. The majority of the patients in this study were of the Hausa ethnic groups representing 78.6%) (Figure 2). The distribution of the subjects based on their occupation indicated that majority were farmers (85.7%) while 14.3% were civil servants as shown in Figure 3. With regards to residence, rural dwellers (85.7%) accounted for the majority of the prostate cancer subjects compared to urban dwellers (14.3%) (Figure 4). Subjects in monogamous relationship constituted a significant number (71.4%) compared to those who practice polygamy (28.6%) as shown in Figure 5. A large percentage of the prostate cancer subjects (96.4%) reported no family history of the disease compared to 3.6% that reported history of family history of the disease (Figure 6). A total of 96.4% of the subjects were on therapy (chemotherapy, radiotherapy or combined therapy) while 3.6% were treatment naïve.

Biochemical Parameters of Study Participants

The values of MDA of test subjects were significantly increased compared with controls ($p < 0.0001$) as depicted in Table 1. The mean values of TAC of test participants decreased significantly when observed in comparison with controls ($p < 0.0001$).

Table 1. Mean Comparison of Biochemical parameters test and control subjects.

Parameters	Control (n = 28)	Test (n = 28)	t-value	p-value
MDA (µm/ml)	0.073 ± 0.04	0.215 ± 0.06	9.64	0.0001 (s)
TAC (µm/L)	743.3 ± 104.40	247. 9 ± 63.3	−21.46	0.0001 (s)

Values are presented as Mean ± SD MDA = Malondialdehyde, TAC = Total antioxidant capacity, (s) = significant, (ns) = not significant.

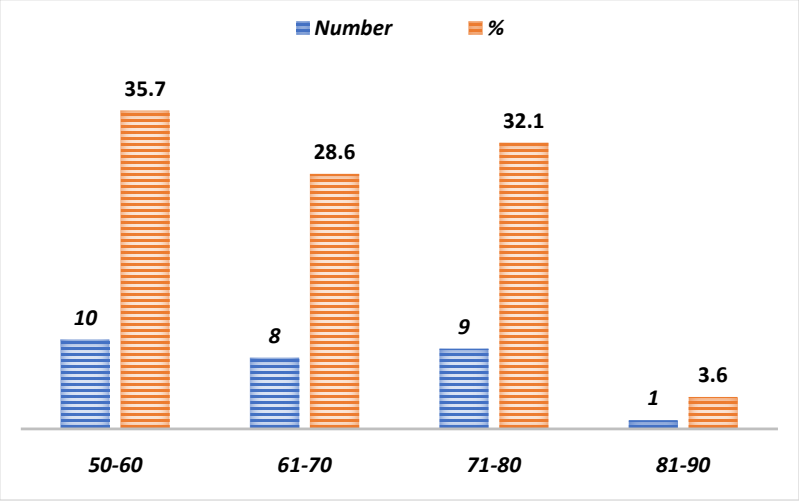

Figure 1. Age distribution of the prostate cancer subjects.

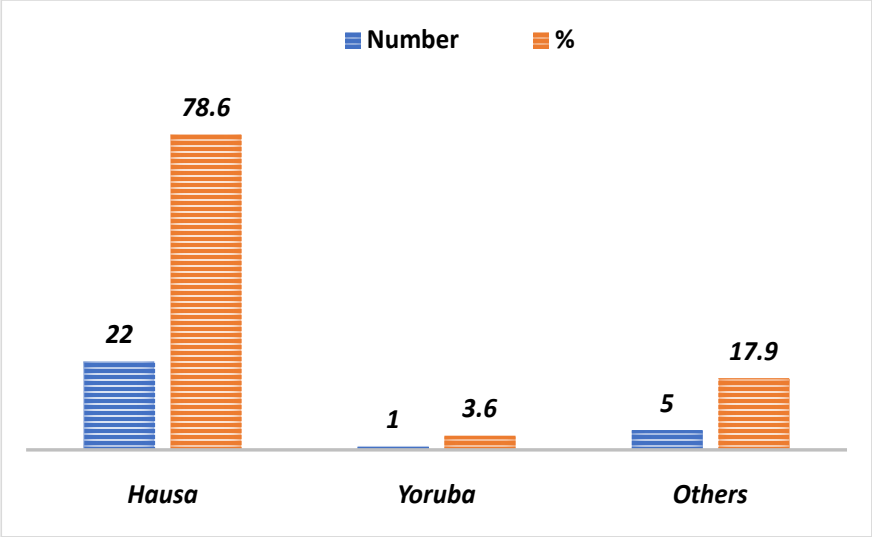

Figure 2. Distribution of prostate cancer subjects based on ethnicity.

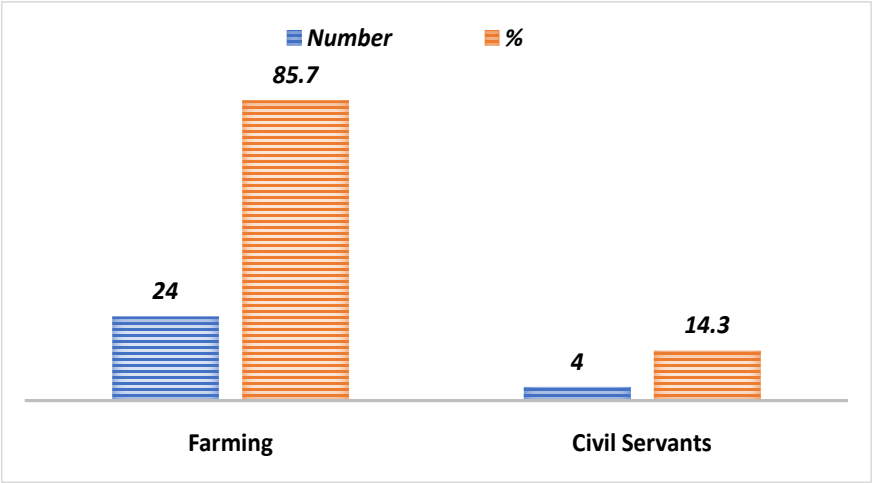

Figure 3. Distribution of prostate cancer subjects based on their occupational group.

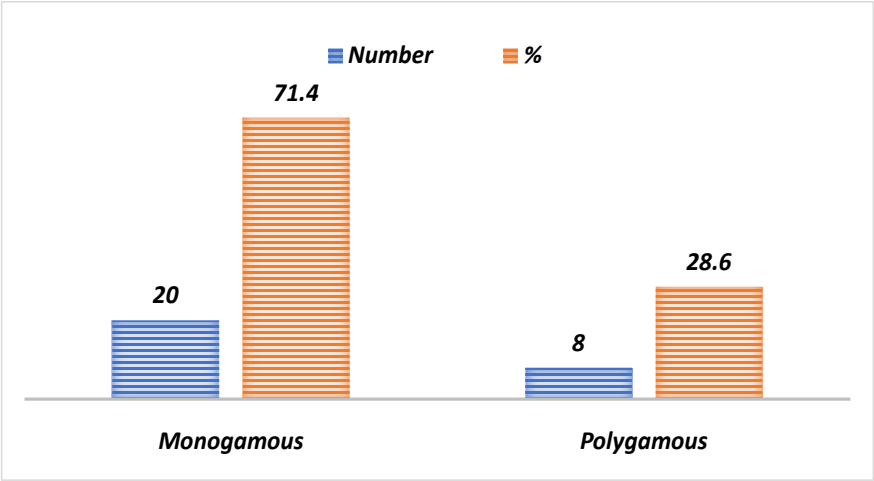

Figure 4. Distribution of the prostate cancer subjects based on their sexual orientation.

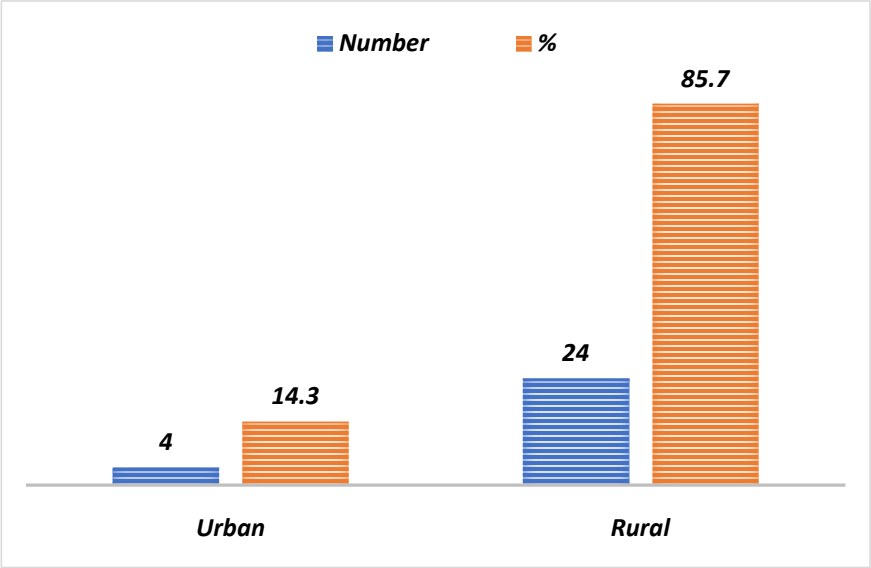

Figure 5. Distribution of prostate cancer subjects based on residence.

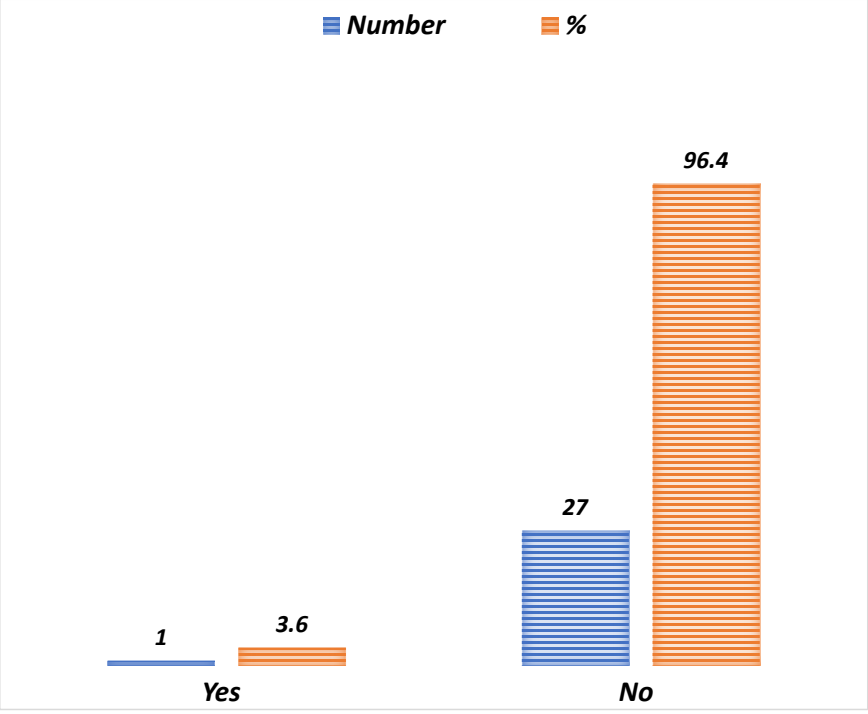

Figure 6. Distribution of the prostate cancer subjects based on family history of the disease.

4. Discussion

Prostate cancer is the second most common malignancy and the leading cause of death in men worldwide [2]. Excessive generation of oxygen-derived radicals with compromised antioxidant defense systems can cause oxidative stress. The pathogenesis of malignant processes has not been clarified yet, but substantial evidence suggests that free radicals, particularly oxygen radicals, play an impor-

tant role in the complex course of multistep carcinogenesis. Free radical generation is controlled by a large number of antioxidant systems that act as protection against free radicals. The disturbance of the pro-oxidant-antioxidant balance —resulting from increased free radical production—antioxidant enzyme inactivation or excessive antioxidant consumption is a causative factor in oxidative damage [30] [31] [32]. This study measured malondialdehyde and total antioxidant capacity of prostate cancer patients and compare with that of apparently healthy men.

In this study, the MDA value was significantly increased among the patients with prostate cancer when compared with the control groups. This is an indication of increased lipid peroxidation among the patients. The Oxidation of lipid or lipid peroxidation is one of the most commonly reported indices of oxidative stress which is recognized as a pathological factor contributing to chronic disease including cancer and aging [33] [34]. Our finding is consistent with a previous reported that oxidative stress may be involved in prostate cancer as evidenced by the higher MDA levels and lower GSH levels [35]. Our finding is consistent with previous studies that measured lipid peroxidation status in adenocarcinoma of breast and colorectal cancer [36] [37] [38] [39]. Similarly, correlation of OS and the risk of cancer in various tumours groups reported a significantly increased lipid peroxidation and DNA damage in lung, liver, head, and neck cancers and squamous cell carcinoma [40] [41] [42] [43]. These studies found higher reactive oxygen species production and enhanced lipid peroxidation in malignancies which support the oxidative stress hypothesis in carcinogenesis. In a study conducted in a tertiary hospital in Nigeria [44] to assess the levels of malondialdehyde and total oxidant capacity among prostate cancer patients undergoing androgen deprivation therapy. Results indicated that, the ADT-treated patient had higher malondialdehyde (MDA) than the controls. There was a significantly positive correlation between MDA and duration of treatment ($r = 0.280$, $p = 0.018$) in ADT-treated patients with CaP. The study demonstrated that patients with CaP have higher levels of MDA compared with men without CaP.

The study showed that oxidative stress is increased and antioxidant status decreased in patients with CaP irrespective of treatment status and that MDA levels increased with duration of treatment. This is consistent with our findings. Our finding is consistent with a previous report [45] who found high lipid peroxidation among patients with prostate cancer compared with lower levels in the control groups ($p < 0.001$). Antioxidant systems are capable of removing free radicals, thereby protecting from free radical attack from such destructive molecules as hydrogen peroxide (H_2O_2) the alkoxyl radicals ($RO^{\bullet}$), peroxyl radicals ($ROO^{\bullet}$) and superoxide dimutase ($O2^{\bullet -}$) radicals. The main groups of antioxidants make up the antioxidant defense system. These include primary, secondary and tertiary defense. Primary antioxidants prevent the formation of new free radical species. These include SOD, GPx, and metal-binding proteins (e.g. ferri-

tin or ceruloplasmin). Secondary antioxidants trap radicals thereby preventing chain reactions. These include vitamin E, vitamin C, beta-carotene, uric acid, bilirubin, and albumin. Tertiary antioxidants repair biomolecules damaged by free radicals. These include DNA repair enzymes. The concentrations of this antioxidant can be measured individually, but it is time-consuming and expensive. The total antioxidant system by FRAP assay measures the total antioxidant effect of these three defense systems in circulation. TAC measurements provide a tool for establishing links between antioxidant capacity and the risk of disease, as well as for the monitoring of antioxidant therapy [46].

The age distribution of the prostate cancer subjects indicated the incidence was highest in the 50 - 60 years' age group followed by the 71 - 80 years' age group. Our finding is consistent with a previous report which indicated that prostate cancer incidence increases with age [2]. Similarly, 1 in 350 men under the age of 50 years will be diagnosed with prostate cancer [47]. The incidence rate increases up to 1 in every 52 men for ages 50 to 59 years. The incidence rate is nearly 60% in men over the age of 65 years [48]. For African-American men, the incidence rates are higher when compared to the White men, with 158.3 new cases diagnosed per 100,000 men and their mortality is approximately twice as White men [49]. Reasons for this disparity have been hypothesized to be due to differences in social, environment al and genetic factors [47] [48] [49].

In this study, the mean plasma total antioxidant value was significantly lower in prostate cancer patients compared to that of healthy control. The findings of decreased antioxidant status are in agreement with the findings in Nigeria [47], Turkey [48] and the USA [49]. Similarly, a previous report [50] reported significantly decreased antioxidant enzymes (glutathione peroxidase and superoxide dismutase) and vitamins (vitamin C and vitamin E) in the patients with benign prostate hyperplasia and prostate cancer when compared with the control group ($p < 0.005$). In another study [18], an increased lipid peroxidation with decreased antioxidant status was observed among breast cancer patients of African Descent in Sokoto, Nigeria. Similarly, a previous report [51] proved that the antioxidant capacity of plasma in chronic obstructive pulmonary disease patients increased about 2 folds as compared with normal subjects measured using the ferric reducing ability of plasma assay. Our finding is in agreement with a previous report which indicated that there is alteration in the in the antioxidant defence system in prostate cancer patients compared to Benign Prostatic Hyperplasia (BPH) patients [50] [52]. Imbalance between the antioxidants and oxidative stress may play a role in the development of prostate cancer [53]. Our finding is however at variance with a previous report [54] who did not find any significant change in lipid peroxidation or antioxidant system parameters in the plasma of patients with BPH and prostate cancer.

The majority of the patients in this study were of the Hausa ethnic groups representing (78.6%) compared to other ethnic groups. People of Hausa/Fulani ethnicity constitute the predominant ethnic group in the study area. Previous

report in the USA indicate that African Americans are twice and three to four times as likely to develop or die from prostate cancer compared to individuals of European and Asian Americans respectively [55]. Also, prostate cancers diagnosed in African Americans tend to be of a more aggressive in nature and tend to be advanced or metastatic disease at diagnosis compared to those of European Americans [56]. Similar observations of high incidence and increased mortality have been seen among men of African descent in areas outside of USA in Jamaica and Ghana [57] [58]. The reason for this disparity in prostate cancer disposition and mortality among African men is unknown. However, environmental, genetic factors and socioeconomic factors are thought to play a role [59]. The age of attainment of puberty is also hypothesize to play a role in the increased susceptibility to prostate carcinogenesis. African American boys initiate genital development a 1 year earlier and go through longer periods of pubertal maturation compared with European American boys. Age of attainment of puberty is believed to be a potential factor in the increased susceptibility among African American men [60].

In this study, we observed that occupation seems to play a role in prostate cancer disposition. Majority of the prostrate can subjects were involved in farming (85.7%) as an occupation compared to 14.3% who were civil servants. Farming in the study area is associated with the use of fertilizers and pesticides. Exposure of these farmers to fertilizers and pesticides may be responsible for this occupational-related prostate cancer disposition. Our finding is consistent with a previous retrospective study which indicated that a range of occupations (farming, metal working, and the rubber industry) has been associated with prostate cancer [61]. Similarly, a previous report in Canada observed that persons in white collar, construction, transportation, and protective services occupations were more predisposed to prostate cancer and recommended the need for regular assessment of job-specific exposures, sedentary behaviour, psychological stress and shift work [62]. The International Agency for Research on Cancer (IARC) has reported that there is limited evidence of occupational risk factors for prostate cancer including jobs associated with exposure to arsenic, cadmium compounds, the insecticide malathion, radiation, and the rubber production industry [63]. Other occupation predisposition of prostate cancer including agriculture occupations, firefighting occupations, shift work, and whole-body vibrations has been reported [64] [65] [66] [67].

We observed a variation in the distribution of subjects with prostate cancer based on their residence. Rural dwellers (85.7%) accounted for the majority of the prostate cancer patients compared to those living in urban areas (14.3%). Our finding is consistent with a previous report which indicated that there are urban–rural variations in cancer incidence [68]. Our finding however at variance with several studies which suggest that cancer rates are higher in urban than rural areas [69] [70] [71] [72].

Subjects in monogamous relationship were 2.5 times more at risk of prostate

cancer compared to those who practice polygamy (71.4% compared to those 28.6%) respectively. The people in the study area are predominantly Muslims and Polygamy associated with marriage to a maximum of 4 wives is permissive. Our finding is at variance with previous reports which indicated that there may be an association between the number of sexual partners and prostate cancer [73] [74]. Similarly, a previous report that various dimension of sexual activity including the; age of first sexual debut, number of sexual partners, gender of the sexual partners, frequency of ejaculation and presence of sexually transmitted disease may play a role in the aetiology of prostate cancer [75] [76] [77].

A large percentage of the prostate cancer subjects (96.4%) reported no family history of the disease compared to 3.6% that reported history of family history of the disease. The question then arises whether prostate cancer does run in families and whether any genetic or hereditary factor in the predisposition to prostate cancer. A previous review provided an overview of the genetic basis underlying hereditary predisposition to prostate cancer and recommended that cost-efficient genetic testing of patients and families who may be at an increased risk (based on clinical features, family history, and ethnicity) of developing prostate cancer. There are epidemiological studies that reported that first-degree relatives of a prostate cancer patient have a two- to three-fold increased risk of developing the disease compared to the general population and the risk increases even further depending on the number of affected relatives [78]. Similarly, evidence of familial aggregation of fatal prostate cancer have been with the first-degree relatives of a patient who died of disease having a two-fold increased risk of death from prostate cancer compared to men without a family history of the disease [79].

5. Conclusion

The findings from this indicated a high Malondialdehyde (lipid peroxidation indicator) and low levels of Total Antioxidant Capacity among prostate cancer patients as evidence of redox imbalance. Subjects in monogamous relationships compared to those in polygamous relationships, rural dwellers, farmers, individuals of Hausa ethnicity and subjects who reported no family history of the disease were more predisposed to prostate cancer.

6. Recommendations

Further epidemiological studies are needed to determine the predisposing factors and the potential role of these markers in the diagnosis, prognosis and management of prostate cancer patients in Sokoto in particular and Nigeria in general. We recommend that Malondialdehyde and Total Antioxidant Capacity be routinely monitored among patients with prostate cancer patients in the area. There is need to improve the economic status of men in the study area. Enlightenment program is needed to change food custom in the region to encourage men to eat balanced diet and refrain from unhealthy food that may increase their

predisposition to prostate cancer. Access to quality healthcare should be enhanced to potentially reduce the poor prognosis associated with late diagnosis of the disease. Working habit should be improved along with the provision of protective and safety gadgets for men in the region who are occupationally predisposed to prostate cancer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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