Anthropometric Assessment of Nutritional Status of Children with Congenital Heart Disease in the Niger Delta Region of Nigeria

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ABSTRACT

Worldwide, congenital heart disease is a significant cause of morbidity and mortality in children being accountable for about one-third of all congenital defects. Malnutrition is known to be prevalent in this group of children owing to a multiplicity of factors. In this environment, because of the underlying burden of malnutrition, children with congenital heart disease may be more predisposed to malnutrition than in other climes. This study aimed to assess the nutritional status of children with congenital heart disease using anthropometric indices and to compare them with healthy age and sex-matched controls to elucidate possible factors influencing their nutritional status. Anthropometric indices of children with congenital heart disease and healthy age and sex-matched controls were taken. WHO and CDC charts were used to assess their nutritional status and subsequently, both groups were compared statistically. Two hundred and thirty children were recruited into the study, 115 each to the study and control groups, respectively. Underweight, stunting and wasting were present in 45.3%, 46.1% and 33% of the children with congenital heart disease compared to 5.2%, 7.8% and 3.5% respectively in the control group and these differences were statistically significant p<0.001. The presence of multiple lesions and ventricular septal defects were significant predictors of malnutrition in children with congenital heart disease. Malnutrition is significantly more common in children with congenital heart disease when compared to normal controls.

Keywords: Congenital, heart, disease, malnutrition, children

INTRODUCTION

Congenital heart diseases occur in about 1% of all live births worldwide[1] and account for about a quarter of all congenital defects.[2] Survival of children with congenital heart disease has been greatly improved with advances in surgical interventions.[3] Poor nutritional status and growth failure, however, can affect the suitability for and outcome of the surgery.[4,5]

The prevalence of malnutrition in children with congenital heart disease has been recorded to be as high as 64% in developed countries.[6] Two studies done in Southern Nigeria gave prevalence rates of 90% and 92% respectively.[7,8] The cause of malnutrition in these children has been attributed to multiple factors such as inadequate intake due to feeding difficulties and poor absorption of nutrients from congestive cardiac failure.[6,9] Other contributory factors to malnutrition in children with congenital heart disease include the increased caloric requirements that are needed to sustain the higher myocardial, respiratory, and neuro-humoral demands that they have as well as the presence of associated chromosomal anomalies/genetic syndromes like trisomy 21.[6,9] Repeated chest infections may also increase metabolic demands.[6,7,9] In developing countries such as Nigeria with a high underlying burden of malnutrition,[10] many of these children with CHD may already be nutritionally compromised in settings of food insecurity and poverty and thus severe malnutrition is fairly common occurring in up to 90% of all children with congenital heart disease.[7,8]

The widespread availability of corrective surgery and appropriate nutritional support for children with congenital heart disease in developed countries has attenuated the effect of malnutrition on disease outcome.[11] It has also been shown that early corrective surgery can significantly improve

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somatic growth deficits in these children.[11,12] The absence of well-established paediatric cardiac surgery programmes in settings such as ours makes it imperative that malnutrition is detected early in children with congenital heart disease so that appropriate interventions can be instituted while corrective surgery is planned.

Therefore, this study aimed to assess the nutritional status of children diagnosed with congenital heart disease using anthropometry and compare them to age and sex-matched controls of otherwise healthy children to elucidate possible factors influencing their nutritional status.

MATERIALS AND METHODS

Study Setting

The study was carried out at the Paediatric Cardiology units of the University of Uyo Teaching Hospital, Uyo, Akwa Ibom State and the Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State. Both hospitals are tertiary health facilities located in the Niger Delta region of Nigeria. The Paediatric Cardiology units of both hospitals receive referrals for children with suspected congenital heart disease from other units within the Paediatrics Department and other health facilities within their respective states.

Study Design

This was a comparative cross-sectional study carried out for two years (1st January 2017 to 31st December 2019) among one hundred and fifteen children with congenital heart disease and the equal number of age and sex-matched controls. Inclusion criteria into the study group were those with congenital heart diseases confirmed by echocardiography using the *Vivid iq ultrasound machine (GE brand)* recruited from the paediatric cardiology clinic while the controls were healthy children recruited from the children's outpatient clinic. Children with chronic illnesses such as Tuberculosis, Human Immunodeficiency Virus, Sickle cell disease and Cancers were excluded from the study. Children without a definitive echocardiographic diagnosis of congenital heart diseases and those whose cardiac defects had been repaired or surgically palliated were also excluded from the study

Study Procedure

An interviewer-administered semi-structured questionnaire was used to obtain demographic data such as age, sex, and contact details from the study participants. The socioeconomic class was determined using the methods described by Oyedeji *et al.*[13]

Each study participant had a thorough physical examination and anthropometry performed. The weights for children less than 2 years was measured using a bassinet weighing scale (Hana^{R}) which measures to the nearest 0.05kg and a maximum weight of 13kg. A calibrated bathroom weighing scale was used for children older than 2 years, using standard methods. The length was measured for children below two years with a Seca^{R} infantometer with a fixed headboard and a mobile footboard. Heights of children over two years was measured using a stadiometer which measures to the nearest 0.1cm.

The CDC charts for children were used in assessing and evaluating the anthropometric parameters in these children.[14] Nutritional status was determined using the WHO method of classification of malnutrition using the respective Z-score tables assessing weight-for-age, height-for-age and BMI-for-age.[15]

Definition of nutritional parameters

Underweight was classified into (a) Underweight if weight for age (WAZ) - 3 to <- 2SD, (b) Severely underweight if WAZ <- 3SD, (c) Normal weight if WAZ ≥-2 to +2SD (d) Overweight for age if WAZ > +2SD.

Stunting was classified into (a)Stunted if height for age Z-score (HAZ) - 3 to < - 2SD (b) Severe stunting if HAZ <- 3SD (c) Normal height for age if HAZ ≥2 to +2SD. (d) Tall for age if HAZ > +2SD.

Wasting was classified into (a) Wasting if body mass index for age Z score(BAZ) - 3 to < -2SD (b) Severe wasting

if BAZ < -3SD (c) Normal if BAZ ≥ - 2 to 2SD (d) Overweight if BAZ > +2SD

Ethical considerations

Written informed consent was obtained from the parents of the children before including them in the study. Ethical approval was obtained from the Research and Ethics Committees of both institutions before the commencement of the study.

Data Analysis

The data were analyzed using the STATA 14.0 Statistical Package (Texas 77845, USA). Frequency tables were constructed for categorical variables with a Chi-square test of proportions used to assess differences between the case and control groups. Logistic regression was carried out to identify significant predictors of malnutrition among the study population.

RESULTS

Sociodemographic characteristics of children in the case and control group

Two hundred and thirty children (230) were recruited for the study of which one hundred and fifteen (115) children were in both the study and control groups, respectively. As shown in Table 1, most of the children in the study were less than 60 months old (67.0%), and over half of them were males with a male: female ratio of 1.3:1. Chi-square test of proportions shows no significant difference in the age and sex distribution in both the study and control groups ($p > 0.05$). However, more children in the study group were reportedly from lower socioeconomic class parents than children in the control group.

Distribution of Congenital heart defects in the affected children

Table 2 presents the distribution of the structural heart defects among the children with Congenital heart diseases with ASD, VSD, and PDA affecting 38.3%, 36.5% and 20.0% of the children, respectively. Multiple structural heart defects were present in slightly less than a third of the children (29.6%) with acyanotic lesions accounting for 4 in every 5 structural defects (80.9%).

Nutritional status of Children with Congenital Heart Disease

Table 3 shows that there were significantly more cases who were underweight, stunted and wasted compared to the controls which were mostly (87%) children of normal weight ($p<0.001$)

Risk factors associated with malnutrition among children with CHD

Table 4 shows factors associated with an increased likelihood of malnutrition occurring among children with CHD in this study. The odds of malnutrition were noted to decrease with increasing age in the study group however, this observation was only statistically significant between the age group 60-119 months (OR-0.32: p-0.042) (Table 4). Children with multiple heart defects (OR-2.86; p-0.015) and those with VSD (OR-2.49; p-0.023) displayed an increased likelihood of being malnourished when compared to those with single heart defects and those without VSD respectively (Table 4). Table 5 shows that several defects (OR-2.54; p- 0.038) and presence of VSD (OR-2.35; p-0.044) are independent predictors of malnutrition among children with CHD in this study.

Table 1: Sociodemographic characteristics of children in the study and control groups

Characteristics	Total N = 230 (%)	Study Groups Case N = 115 (%)	Control N=115 (%)	Chi-square	P-value
Sex					
Male	129(56.1)	68(59.1)	61(53.0)	0.86	0.352
Female	101(43.9)	47(40.9)	54(47.0)		
Age group					
< 60 months	154(67.0)	80(69.6)	74(64.3)	0.73	0.693
60-119 months	42(18.3)	19(16.5)	23(20.0)		
>120 months	34(14.8)	16(13.9)	18(15.7)		
Social Class					
Lower Class	21(9.1)	20(17.4)	1(0.9)	22.18	<0.001*
Middle Class	89(38.7)	34(29.6)	55(47.8)		
Upper Class	120(52.2)	61(53.0)	59(51.3)		

Table 2: Distribution of Structural heart defects among children with Congenital Heart Disease

Characteristics	Frequency (N = 115)	Percent (%)
Congenital heart disease*		
Atrial Septal defect	44	38.3
Ven tricular septal defect	42	36.5
Patent ductus arteriosus	23	20.0
Pulmonary Stenosis	7	6.1
Transposition of Great Arteries	7	6.1
Tetralogy of Fallot	7	6.1
Atrioventricular Canal Defect	6	5.2
Atrioventricular septal defect	6	5.2
Dextrocardia	5	4.3
Cor Triatriatum Dexter	3	2.5
Pulmonary Atresia	2	1.6
Others[+]	16	14.0
Number of Structural Defects		
Single Structural Defect	81	70.4
Multiple Structural Defects	34	29.6
Type of Structural Defect		
Acyanotic	93	80.9
Cyanotic	22	19.1

*More than one structural defect co-exists

[+]Aortic Valve stenosis, Aortic Incompetence, Ebstein Anomaly, Mitral Atresia, Taussig Bing Syndrome, Single ventricle, Pulmonary Valve Stenosis, Mitral Incompetence, Truncus Arteriosus, Tricuspid Incompetence, Hypoplastic left ventricle

Table 3: Nutritional Status among Cases and Control groups

Characteristics	Study Groups Case N= 115 (%)	Control N=115 (%)	Chi-square	P-value
Weight-for-age (WAZ) [+]				
Severely underweight (WAZ < -3)	31(27.0)	1(0.9)	51.89	<0.001*
Underweight (WAZ - 3 to <- 2)	21(18.3)	5(4.3)		
Normal (WAZ >-2 to +2)	61(53.0)	100(87.0)		
Overweight for age (WAZ > +2)	2(1.7)	9(7.8)		
Height-for-age (HAZ) [++]				
Severe stunting (HAZ < -3)	31(27.0)	5(4.3)	42.77	<0.001*
Stunted (HAZ - 3 to < - 2)	22(19.1)	4(3.5)		
Normal (HAZ > - 2 to +2)	56(48.7)	96(83.5)		
Tall for age (HAZ >+2)	6(2.6)	10(8.7)		
Weight-for-height				
Severe Wasting (BAZ [+++] < - 3)	23(20.0)	3(2.6)	34.86	<0.001*
Wasting (BAZ - 3 to < - 2)	15(13.0)	1(0.9)		
Normal (BAZ > - 2 to +2)	68(59.1)	103(89.6)		
Obese (BAZ > +2)	9(7.8)	8(7.0)		

[+]WAZ-weight for age Z-score, [++]HAZ-height for age z-score, [+++]BAZ-Body mass index for age Z-score

Table 4: Risk factors associated with malnutrition among children with Congenital Heart Disease

Characteristics (Reference group)	B coefficient	UOR	95%CI Min	95%CI Max	P-value
Sex (Male)					
Female	0.33	1.39	0.66	2.94	0.384
Age Group (< 60 months)					
60-119 months	-1.16	0.32	0.10	0.96	0.042*
120-179 months	-1.04	0.35	0.10	1.22	0.099
>180 months	-0.82	0.44	0.04	5.05	0.510
Social Class (Lower Class)					
Middle class	-0.68	0.51	0.17	1.57	0.240
Upper class	-0.14	0.87	0.31	2.45	0.792
Type of defects (Acyanotic heart defect)					
Cyanotic heart defect	0.24	1.27	0.50	3.33	0.617
Number of defects (Single Defect)					
Multiple defects	1.14	3.12	1.35	7.18	0.008*
Patent Ductus Arteriosus (No)					
Yes	-0.09	0.92	0.36	2.30	0.851
Ventricular Septal defect (No)					
Yes	0.92	2.51	1.15	5.46	0.021*
Atrial Septal defect (No)					
Yes	0.16	1.18	0.55	2.51	0.670
Transposition of Great Arteries (No)					
Yes	0.51	1.67	0.36	7.81	0.517
Tetralogy of Fallot (No)					
Yes	0.19	1.21	0.23	6.26	0.822

*Statistically Significant; UOR Unadjusted Odds ratio.

Table 5: Independent Predictors of malnutrition among children with Congenital Heart Disease

Characteristics (Reference group)	B coefficient	aOR	95%CI		P-value
			Min	Max	
Age Group (< 60 months)					
60-119 months	-1.17	0.31	0.09	1.01	0.052
120-179 months	-0.86	0.43	0.12	1.57	0.200
>180 months	-1.17	0.31	0.02	4.18	0.377
Number of defects (Single Defect)					
Multiple defects	0.93	2.54	1.05	6.13	0.038*
Ventricular Septal defect (No)					
Yes	0.85	2.35	1.02	5.38	0.044*

*Statistically Significant; aOR-adjusted Odds ratio

DISCUSSION

Congenital heart disease (CHD) continues to be a significant source of morbidity and mortality in children in developing countries such as ours with extremely limited resources available for early diagnosis, care, and surgical management of these patients.[16] Furthermore, malnutrition is a scourge that is still present in our environment with the prevalence of malnutrition in children aged between 6-59 months being 14%.[17] Thus, besides the malnutrition that is prevalent in children in the general populace, CHD predisposes affected children even further to malnutrition as a result of factors such as decreased intake arising from feeding difficulties, repeated chest infections, anaemia, heart failure, cyanosis, pulmonary hypertension and delay in surgical correction of the lesions which is a major constraint in resource-poor environments such as ours.[18]

In this study, males showed a slight preponderance of affectation of CHD when compared to female subjects. There is a sustained variation in the ratio of males to females affected by CHD in studies done by different researchers.[7,18,19] Acyanotic congenital lesions were the most common lesions seen compared to cyanotic cardiac lesions. This pattern is corroborated by several authors who have documented the same and appears to be the pattern globally.[5,8,20,21,22]

Assessment of the nutritional status of subjects with CHD in this study revealed that 33.0%, 46.1% and 45.3% of them were wasted, underweight or stunted respectively with the difference in the rates of malnutrition between the study and the control groups being statistically significant. Batte *et al.* observed similar findings with the prevalence of wasting, underweight and stunting being 31.5%, 42.5% and 45.4% respectively.[18] Differing findings were observed in children in Lagos and Zaria where Okoromah *et al.* had a lower prevalence of stunting (28.8%) and underweight (20.5%) while Isezuo *et al.* had a much higher prevalence of wasting (60.7%), underweight (72.9%) and stunting (57.8%) in the northern part of Nigeria.[5,7] Regional differences in the rates of underlying malnutrition in children not affected by CHD have also been observed with higher rates noted in the northern parts of the country.[17] This variation may explain the further exacerbation that is seen in cardiac patients in these regions.

Younger age group, presence of multiple defects and ventricular septal defects were factors found to be associated with significant risk for the development of malnutrition in our study subjects. Furthermore, only the presence of multiple defects and ventricular septal defects were significant predictors of malnutrition in children with CHD in this study. The finding of age as a significant risk factor for the development of malnutrition in children with CHD has been corroborated by other researchers.[7,8] In particular, younger children

are more predisposed compared to older children with CHD. This may be a reflection of their dependence on caregivers for their nutrition and the increased growth requirements in that age group although dietary adequacy was not assessed in this study which was a study limitation.

The presence of multiple cardiac lesions and ventricular septal defects as significant predictors of malnutrition may be due to the increased metabolic demands placed by these lesions on the growth of the affected children. Indeed, it has been found that children with complex cardiac lesions require greater than 120% of their energy intake to have reasonable growth rates.[23] Also, children with VSD who also make up a significant proportion of children with congenital heart disease, are predisposed to developing heart failure and repeated chest infections depending on the size of the lesion. The resulting heart failure in itself is a significant predictor of malnutrition in children with CHD.[7,18,23,24] Also, the delay in the surgical repair which is a major constraint in our environment predisposes these children to later development of pulmonary hypertension which has also been found to be significantly associated with malnutrition in these patients.[6,8,24]

In conclusion, this study demonstrates that children with CHD are at increased risk of developing malnutrition than their normal counterparts. Also, those with multiple cardiac lesions and VSD are more susceptible to malnutrition. Therefore, it becomes imperative that a nutritional program is put in place to cater for these children. Also, the need for timely surgical repair of these lesions to prevent the development of complications that further predispose these children to malnutrition cannot be overemphasized.

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Association between Fibrinolysis and Sickle Cell Anaemia Vaso-Occlusive Crisis: A Cohort Study in a Tertiary Health Facility in Benin City

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ABSTRACT

Sickle cell anaemia (SCA) is associated with hypercoagulability. There is inconclusive evidence on the contribution of abnormal fibrinolytic activity to vaso-occlusive crisis (VOC) in SCA patients. The study aims to evaluate the association between SCA vaso-occlusive crisis and abnormal fibrinolysis using tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1) and to correlate their levels with some haematological parameters of the SCA patients. This is a cohort study. Thirty SCA subjects recruited from the adult haematology clinic of the University of Benin Teaching Hospital Benin City in steady-state were followed up to the onset of a vaso-occlusive crisis. Thirty HbAA subjects were recruited from the donor clinic as controls. The t-PA and PAI-1 levels were estimated using enzyme-linked immunosorbent assays at recruitment and then following onset of VOC. Haematological parameters were determined with haematology auto-analyzer. Data were analyzed using SPSS 21. Statistical significance was set at 0.05. The median t-PA levels did not differ significantly between SCA VOC and steady-state (1.36 vs. 0.12ng/ml; p = 0.796). Similarly, median PAI-1 did not differ significantly between SCA VOC and steady-state (11.93 vs. 11.30ng/ml; p = 0.197). There was a negative correlation between t-PA and haematocrit during VOC (r = 0.922, p = 0.001). There was a positive correlation between tPA and PAI-1 but no significant correlation between tPA and PAI-1 with white blood cell count and platelet count. There were no correlations between tPA, PAI-1, white blood cell counts and platelet counts (p>0.05). Vaso-occlusive crisis is not associated with abnormalities in fibrinolytic proteins in SCA patients. T-PA correlated negatively with haematocrit level in VOC state.

Keywords: Sickle Cell, Anaemia, Vaso-occlusive, Crisis, Fibrinolysis

INTRODUCTION

Vaso-occlusive crisis is a cause of significant morbidity in sickle cell disease patients. It accounts for a significant proportion of hospital admissions, correlates with disease severity and contributes significantly to impaired quality of life in SCA patients.[1,2] Hypercoagulability has been implicated in the pathogenesis of VOC in SCA.[3] Significant alterations of haemostatic activities have been reported to contribute to the hypercoagulability in patients with SCA. Depletion of natural anticoagulant proteins (proteins C, protein S, antithrombin), elevated activated coagulation markers (fibrinogen and factor VIII), altered fibrinolytic activity, presence of lupus anticoagulant among others have been reported in patients with SCA.[3,4]

Fibrinolysis is a component of haemostasis and constitutes the enzymatic cascade which ultimately leads to the degradation of fibrin formed during haemostasis.[5] Fibrinolysis is important in moderating blood clot formation following endothelial injury to prevent occlusion of the blood vessels during haemostasis. Altered fibrinolysis can result in significant blood vessel occlusion and damage to body tissues and organs. Tissue hypoxia resulting from the occluded blood vessel may thus provoke episode of VOC. An association between fibrinolysis and VOC may have therapeutic implications. It may provide potential targets for the treatment of vaso-occlusive crisis such as the use of fibrinolytic agents in the management of VOC.

Fibrinolysis is mediated by several plasma proteins including plasminogen, plasminogen activator and plasminogen activator inhibitors (PAI-1). Plasminogen is the proenzyme form of plasmin which is the main enzyme of the fibrinolytic system responsible for the degradation of fibrin into soluble degradation products.[5] Plasminogen is activated by plasminogen activator. The

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activator exists in two forms; tissue-plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) in urine.[5]

Tissue type plasminogen activator is a serine protease, a polypeptide containing 527 amino acid residues with a molecular mass of 72kDa, secreted mainly by the endothelial cells.[6] It cleaves a single peptide bond in plasminogen to generate plasmin which dissolves clots in the vasculature. Fibrinolysis provides an extremely efficient pathway for vascular thrombolysis and its high affinity for fibrin in conjunction with a fibrin dependent stimulation of t-PA activity ensures that activation of plasminogen by t-PA is localized to the fibrin thrombus and reduces systemic plasminogen activation.[7]

Plasminogen activator inhibitors (PAIs) are the primary physiologic inhibitors of plasminogen activators in blood. There are two families of PAI. The serpins (plasminogen activator inhibitor-1 (PAI-1), plasminogen activator inhibitor-2 (PAI-2), and alpha 2- antiplasmin) and non serpins (Thrombin activated fibrinolysis inhibitor (TAFI), alpha2-macroglobulin, C1 esterase inhibitor).[8,9] PAI-1 members of the serpin is widely associated with disease processes.[5] PAI-1 is a serine protease with single-chain glycoprotein of 379 amino acids and it is secreted into blood from the granule of platelets and megakaryocytes.[10] Plasma concentration ranges from 15- 80µg/L.[11]

Available studies on the association between SCA vaso-occlusive crisis and abnormal fibrinolysis have yielded conflicting outcome. Some studies have reported a significant association between abnormal fibrinolysis and SCA; however others did not find any association.[12-15] Fibrinolytic activities in SCA vaso-occlusive crisis has not been adequately investigated in Nigeria. This study aims to investigate the association of sickle cell anaemia VOC with altered fibrinolysis using t-PA and PAI-1 as markers of fibrinolysis, and to correlate plasma t-PA and PAI-1 levels of SCA patients in VOC with their haematological parameters. This outcome may reveal potential targets for therapeutic interventions in SCA patients in VOC.

MATERIALS AND METHODS

This is a cohort study conducted at the University of Benin Teaching Hospital (UBTH) Benin City between January and July, 2019. Thirty consenting adult SCA patients were recruited in steady-state and followed up to the onset of a vaso-occlusive crisis. SCA patients were recruited during a routine clinic visit at the Consultant Outpatient Department. When in crisis, they were requested to present to the emergency room for treatment and re-evaluation of their fibrinolytic state. VOC was defined as acute onset of excruciating bone pain in a sickle cell disease patient.[1] Steady-state is a state characterized by relatively stable disease state in which the patient is symptom-free and not on any active medical treatment lasting for at least 2 weeks.[16] Thirty apparently healthy subjects (HbAA) were recruited as controls from the blood donor clinic.

Inclusion criteria for the SCA patients include a haemoglobin phenotype of SS (Sickle cell anaemia) and at least 18 years of age. Excluded were patients on antiplatelet (aspirin), antifibrinolytic agents, hormonal contraceptives, pregnant women, patients on hydroxyurea, and non-consenting subjects.

The sample size was estimated with the formula for comparing two means using a study power of 90% and 95% confidence interval.[17] The mean difference and standard deviation of a t-PA in a study by Colombatti *et al.* were used to calculated sample size.[18] A sample size of 27 was reached. Based on an attrition rate of 10%, 30 subjects were finally recruited.

After adequate counseling, socio-demographic and medical history was documented on a proforma at recruitment. At recruitment and during VOC, 7mls of venous blood each was collected from the antecubital vein. Four and a half millilitre of the blood was dispensed in a plain sample bottle containing 0.5ml of 0.109M sodium citrate (3.2%). The citrated plasma was separated immediately after centrifugation at 3000g for 15minutes. The supernatant platelet-poor plasma was transferred to a

clean plastic tube and stored at (-80^{0}c) until completion of study for estimation of t-PA and PAI-1 levels using enzyme-linked immunosorbent assay kits (ELISA) by Bioassay Technology Laboratory Shangai China. The t-PA kit has a batch no: E3707Hu; Lot no: 201905009; manufacture date: 15/05/2019 and expiry date: 15/05/2020. The PAI-1 has a batch no: E1159; Lot no: 201905009; manufacture date: 15/05/2019, expiry date: 15/05/2020).

The remaining 2.5ml of blood was dispensed into an ethylenediamine tetra-acetic acid sample bottle for estimation of complete blood count using an automated blood count analyzer at the haematology laboratory.

The study was approved by the institutional ethical review board of UBTH, Benin City. Participants were adequately counseled and participation was voluntary. Data collected were de-anonymized to minimize risk to participants and they were treated as confidential.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 21. Normally distributed outcome variables (blood count parameters) were summarized as mean and standard deviation while skewed variables (t-PA, PAI-1) were summarized as median and interquartile range. The difference in mean of blood count between VOC and steady-state was compared using analysis of variance test (ANOVA) while the difference in median of t-PA and PAI-1 were compared using independent sample median test. Pearson's correlation test was used to correlate t-PA, PAI-1 and blood counts. Statistical significance was set at 0.05.

RESULTS

Socio-demographics

The ages of the SCA patients and Controls ranged from 20-51 years and 20-43 years respectively. There was no significant difference in their mean ages (26.5 vs. 27.0 years; p = 0.698 respectively). The SCA subjects include 15(50%) males and 15(50.0%) females, while the Controls comprised 18(60.0%) males and 12(40.0%) females.

Fibrinolytic Markers

The difference in median t-PA across the groups (SCA in VOC, SCA in steady state and controls) was not statistically significant (p = 0.052) (Table 1). The median (interquartile range) t-PA of SCA patient was 1.36 (0.21-8.44ng/ml) during vaso-occlusive crisis and 1.24 (0.67-3.77ng/ml) in the steady-state while in the controls, it was 7.22 (5.31-18.71ng/ml). The difference in median t-PA was not statistically significant (p = 0.052). The median (IQR) of PAI of the SCA subjects during VOC and steady-state was 11.93 (7.97-16.86ng/ml) vs. 11.30 (7.97-18.61) respectively while the controls had 6.31 (1.14-10.71ng/ml). The difference in median PAI-1 was statistically significant (p = 0.005). Median PAI-1 between SCA subjects in VOC and during steady states did not differ significantly (p = 0.197) (Table 1).

Haematological Parameters

The mean WBC count was significantly increased in the VOC state (16.4± 0.6 x10^{9}cells/L) compared to steady-state (8.8 ± 3.2 x10^{9}cells/L) and controls (6.6 ± 1.7 x10^{9}cells/L), p<0.001. The mean haemoglobin concentration of the SCA subjects was significantly lower during VOC compared to the steady-state and controls (7.8± 1.2g/dl vs. 8.6 ± 1.3g/dl vs. 13.5 ± 1.4g/dl; p < 0.001). Similarly, the mean haematocrit was lower during VOC than in steady-state and Controls (23.6 ± 3.5 vs. 25.8 ± 3.8% vs. 40.7 ± 4.2%; p<0.001). The mean platelet count was significantly higher in the SCA groups (VOC and steady state) compared to the controls (341.4 ± 177.9 × 10^9/L vs. 305,484.1± 15,761.0 × 10^9/L vs. 220.6 ± 67.1 x10^9/L respectively; p = 0.008 (Table 2). However platelet count did not differ significantly between VOC and steady-state, p = 0.271).

Relationship between haematological parameters and fibrinolytic markers

During VOC, t-PA had a moderate negative correlation with haemoglobin concentration and haematocrit. No significant correlation was found between

t-PA and other haematological parameters. Similarly, there was no significant correlation between PAI-1 and haematological parameters during VOC (Table 3). There was a strong positive correlation between t-PA and PAI-1 (r = 0.922, p = 0.001) during VOC.

In the steady-state, no significant correlation was found between t-PA, PAI-1 and haematological parameters (Table 4). There was a strong positive correlation between t-PA and PAI-1 (r = 0.922, p = 0.001) in steady-state (Table 4).

In the Controls, no significant correlation was found between t-PA, PAI-1 and haematological parameters. Moderately positive correlation was found between t-PA and PAI-1 (r = 0.562, p = 0.001) in the Controls (Table 5).

Table 1: Tissue Plasminogen Activator and Plasminogen Activator Inhibitor 1 levels in SCA VOC and Steady States

	SCA VOC Median (IQR)	SCA Steady state Median (IQR)	Controls Median (IQR)	P- value
tPA (ng/mL)	1.36(0.21 - 8.44)	0.67(0.12 -3.77)	7.22(5.31 -18.71)	0.052
PAI -1 (ng /mL)	11.93(7.97 -16.86)	11.30(7.97 -18.61)	6.31(1.14 -10.71)	0.005

Table 2A: Haematological Parameters in SCA VOC and Steady State

	SCA VOC Crisis n = 30 Mean ± SD	SCD Steady n = 30 Mean ± SD	Control n = 30 Mean±SD	P- value
WBC× 10^9/L	16.4 ± 0.6	8.8 ± 3.2	6.7 ± 1.7	<0.001
Hb (g/dL)	7.8 ± 1.2	8.6 ± 1.3	13.5 ± 1.4	<0.001
PCV (%)	23.6 ± 3.5	25.8 ± 3.8	40.7 ± 4.2	<0.001
Platelet× 10^9/L	341.4 ± 177.9	305.5±157.6	220.6 ± 67.1	0.008

Table 3: Correlation of tPA, PAI-1 and haematological parameters in SCA patients in VOC state

	tPA		PAI -1	
	r	P-value	r	P-value
WBC	0.152	0.424	0.086	0.651
Hb	-0.498	0.005	-0.270	0.149
PCV	-0.501	0.005	-0.269	0.150
Platelet	-0.248	0.186	-0.025	0.898
tPA	1.000		0.632	0.001
PAI -1	0.632	0.001	1.000	

WBC: white blood cell count, Hb: haemoglobin; HCT: haematocrit; t-PA: tissue Plasminogen activator; PAI-1: Plasminogen activator inhibitor 1.

Table 4: Correlation of t-PA, PAI-1 and Haematological Parameters in SCA Steady State

	t-PA		PAI -1	
	r	P-value	r	P-value
WBC	-0.320	0.091	-0.293	0.123
Hb	-0.290	0.127	-0.233	0.223
PCV	-0.288	0.130	-0.231	0.228
Platelet	-0.290	0.128	-0.331	0.080
tPA	1.000		0.922	0.001
PAI -1	0.922	0.001	1.000	

WBC: white blood cell count, Hb: haemoglobin; HCT: haematocrit; t-PA: tissue Plasminogen activator; PAI-1: Plasminogen activator inhibitor 1.

Table 5: Correlation of t-PA, PAI-1 and Haematological Parameters in Controls

	tPA		PAI -1	
	r	P -value	r	P -value
Age	0.063	0.746	-0.039	0.842
WBC	0.061	0.752	-0.046	0.811
Hb	-0.254	0.184	-0.119	0.538
PCV	-0.260	0.173	-0.121	0.531
Platelet	-0.095	0.626	-0.023	0.906
tPA	1.000		0.562	0.001
PAI -1	0.562	0.001	1.000	

WBC: white blood cell count, Hb: haemoglobin; HCT: haematocrit; t-PA: tissue Plasminogen activator; PAI-1: Plasminogen activator inhibitor 1.

DISCUSSION

Fibrinolysis is an important and integral part of the haemostatic system acting as a balance to blood coagulation by preventing thrombotic occlusion of blood vessels. Altered fibrinolysis has been reported in various disease conditions especially those associated with thromboembolism.[5] However, there are conflicting reports in the literature on the association of abnormal fibrinolysis with vaso-occlusive crisis in SCA patients.

Using plasma levels of t-PA and PAI-1 as markers of fibrinolysis, we found no significant difference in their levels between SCA vaso-occlusive crisis and steady states. The lack of a significant difference in the fibrinolytic proteins between steady state and VOC may suggest that abnormal fibrinolysis does not preclude vaso-occlusive crisis in SCA patients neither does VOC result in abnormal fibrinolysis in SCA patients. This finding is consistent with reports of Ekwere *et al.* who reported no significant difference in t-PA alongside other coagulation and fibrinolytic markers (D dimer, fibrinogen, plasminogen) between SCA steady-state and VOC.[12] Earlier experimental works by Gordon *et al* also showed that SCA patients in VOC do not have decreased fibrinolysis.[13] Francis also reported no difference in plasma t-PA antigen and activity in SCA patients in steady-state and VOC.[14] Some authors have reported conflicting findings.[15] Nisiri *et al.* reported normal t-PA levels in SCA patients but a significantly increased PAI-1 suggesting that there is an imbalance between procoagulation and fibrinolysis due to increased PAI-1 levels in the SCA subjects.[15] Famodu *et al.,* reported increased fibrinolysis in VOC.[19] The later reflects the capacity of the

haemostatic system to adjust to the physiologic demand arising from the crisis rather than being responsible for the crisis. The increased endothelial injury and activation of coagulation factors associated with VOC require commensurate fibrinolytic response to maintain haemostasis.[3]

The index study also demonstrated a positive correlation between t-PA and PAI-1 both in the SCA VOC crisis and steady-state. The correlation was stronger in the steady-state compared to during VOC. This reflects the balance between both fibrinolytic markers is maintained during VOC and steady-state; it also reflects the capacity of compensatory adjustment to maintain haemostasis in the SCA population.

The mean total white blood count of the SCA subjects during VOC was significantly increased compared to the steady-state. This is consistent with most reports in literature on white blood cell count during VOC events.[20, 21]Chronic leukocytosis in SCA subjects is intensified during VOC due to continuous activation of neutrophils and monocytes, and an increase in several proinflammatory mediators including TNF- , IL-6, and IL-1 .[22] Further study suggests that haem-linked iron is released during intravascular haemolysis in sickle cell anaemia patients, contributes to the inflammation and activation of monocytes through toll-like receptors signaling increment.[23] In some instances, the VOC is provoked by episodes of acute infections capable of stimulating leukocytosis.[24]

The mean haemoglobin and haematocrit concentrations of the SCA subjects in VOC were significantly lower compared to the steady-state values. Haemolysis of the red blood cells is accentuated during VOC. The sickled cells area damaged both intravascularly and extravascularly because of their rigidity during VOC and thus contributed to the reduced haematocrit and haemoglobin. Damaged red cells release haemoglobin scavenges nitric oxide, further increasing vasoconstriction and thus creating a vicious circle of sickling.[25] Organ sequestration and clearance of the rigid sickled cells by the reticuloendothelial system may also contribute to worsening anaemia during VOC.[25]

Platelet counts did not differ significantly between the steady-state and during VOC despite a high mean difference. Reports on platelet count differences between VOC and steady-state are variable.[13,26-29] Some have reported an increase in count during VOC and others otherwise. However, what is consistent is that there is increased activation of platelets during VOC.[27, 28] Platelet count is reported to decline transiently at the onset of VOC and increase during recovery.[26]Therefore, it is possible to document reduced or increased count during VOC depending on the phase of the event. Heterogeneity in the study population (different subjects in VOC and steady states) may contribute to variation in platelet counts reported in literature However the index study involved estimating parameters of the same subject at steady-state and during crisis and thus would be more likely to reflect the true relationship between platelet during VOC and steady states.

Tissue plasminogen activator was found to correlate negatively with haematocrit and haemoglobin levels in SCA subjects in VOC. There was no significant correlation with other haematological parameters. Similarly, no relationship was found between PAI-1 and haematological parameters. Increased coagulation activation in vaso-occlusive crisis provokes a compensatory increase in t-PA secretion for adequate fibrinolysis and red cells are consumed in the process resulting in a decline in haemoglobin and haematocrit levels. There is paucity of studies on the relationship between t-PA and haematological parameters.

The study has some strengths and limitations. This main strength of the study is that the SCA participants were recruited in steady-state and followed up to when they were in crisis for re-evaluation. This approach removes any confounder associated with the heterogeneity of the study

population between both states. The limitation of the study is that t-PA and PAI-1 antigens were evaluated. Assays involving the functional activity of the proteins may better reflect the fibrinolytic activity. However, studies involving antigen and functional activities of the fibrinolytic proteins showed a good correlation between the antigen levels and functional activity.[14] Another limitation is that t-PA and PAI-1 are regulators of fibrinolysis. Inclusion of a direct assay such as the euglobulin clot lysis test may better represent fibrinolysis. However, the levels of these markers correlate well with fibrinolysis.

In conclusion, there is no significant association between fibrinolysis and SCA vaso-occlusive crisis. Tissue plasminogen activator correlated negatively with haemoglobin and haematocrit levels. We recommend further studies to explore the association of SCA vaso-occlusive crisis and abnormal fibrinolysis.

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Pattern of Some Haemostatic Profile among Diabetes Mellitus Patients Attending Aminu Kano Teaching Hospital, Kano

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ABSTRACT

Diabetes mellitus is a heterogeneous disorder that affects cellular metabolism in many ways, and haemostatic profiles were reported to be adversely affected. This study was aimed to determine the pattern of some haemostatic profiles of subjects with Diabetes mellitus attending Aminu Kano Teaching Hospital, Kano. This cross-sectional study was carried out on eighty (80) participants comprising forty (40) diabetic patients along with forty (40) healthy controls. Five millilitres of venous blood was collected from each participant and placed in appropriate containers for prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count (PLC). The mean ± standard deviation of PLC and APTT of studied groups showed a statistically significant difference (p-value = 0.0373 and <0.0001 respectively) while PT of diabetic subjects and controls revealed no statistically significant difference (p-value=0.9128). We inferred that reduced APTT and increased PLC may contribute to a hypercoagulable state in subjects with Diabetes mellitus.

Keywords: Diabetes, Prothrombin Time, Activated Partial Thromboplastin Time, platelet count

INTRODUCTION

Diabetes Mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period of time. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding to the insulin produced, which gives rise to Type 1 and Type 2 Diabetes mellitus respectively.[1] Another type of Diabetes is Gestational Diabetes mellitus which occurs when pregnant women without a previous history of Diabetes develop a high blood glucose level. Diabetes mellitus is an endocrine disease with multiple aetiologies and results in significant morbidity and mortality from diverse complications.[2] Thrombo-haemorrhagic complications are well recognized among Diabetes populations.[3] The haematological disturbances in Diabetes are characterized by alterations in platelet count and activity, coagulopathy, fibrinolytic aberration, haemorrheologic factors and changes in endothelial metabolism.[4]

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Several articles have reported Diabetes mellitus related abnormalities in haemostasis.[5] Diabetes mellitus is associated with an increased risk of atherosclerosis, and coronary artery disease is a leading cause of death in patients with diabetes.[6] In Nigeria and the world at large, about 90% of Diabetic patients are non- insulin-dependent (type II) while about 10% are insulin-dependent (type I).[2] The global prevalence of Diabetes mellitus has been estimated at 347 million individuals and is rapidly increasing.[7] The mortality associated with Diabetes is due to thrombotic and cardiovascular complications in 80% and 75% of cases respectively, while other causes of death are from cerebrovascular events and peripheral vascular disease.[8] The vascular endothelium is the primary site of defence against thrombosis and it is functionally impaired in patients with Diabetes.[9]

Body of evidence suggests that certain haematological indices are altered in patients with Diabetes-glycation of haemoglobin and clotting factors such as prothrombin and fibrinogen, results from persistent hyperglycaemia.[10,11] The glycation results in the incomplete activation and function of both the intrinsic and extrinsic clotting cascades.[2,12] Prothrombin time (PT) and activated partial

thromboplastin time (APTT) are important haemostatic parameters which give an insight into the coagulation status of patients.[13]

Most studies done on Nigerians with Diabetes were from the West and Southeastern part with the scarcity of information on subjects in our study area in Northern Nigeria. We evaluated some haemostatic profiles of patients with Diabetes mellitus attending Aminu Kano Teaching Hospital.

MATERIALS AND METHODS

Study design/area

This was a cross-sectional study carried out at Aminu Kano Teaching Hospital (AKTH), for the period of seven months (June through December 2017). The Hospital is located within Kano metropolis. Kano state is a state located in the North-western Nigeria.[14] It lies between latitude $11^{0}30`N$ and longitude $8^{0}30`E$. Kano state was created on May 27, 1967, from the then Northern Region. Kano state borders Katsina to the north-west, Jigawa State to the north-east, Bauchi State to the south-east and Kaduna state to the south-west.[15]

Study Population

A total of 80 subjects were recruited in this study, 40 were diabetic patients attending AKTH and 40 healthy individuals.

Inclusion Criteria

Diabetic patients attending AKTH and healthy individuals who fasted for 8-12 hours and consented to participate were recruited into the study.

Exclusion Criteria

Subjects with the following conditions were excluded: pregnant women, oncology patients, patients with thrombotic tendencies and those on anticoagulant therapy, due to the effect of this conditions on haemostatic profiles.

Ethical Clearance

Ethical clearance to conduct the research was obtained from the ethics committee of Aminu Kano Teaching Hospital. Permission to carry out the study in the selected departments was also obtained from the respective Head of Departments. Informed Consent was obtained from all the participants before sample collection

Sample Collection and Analysis

All specimens for APTT, PT, platelet count, and fasting blood sugar (FBS) estimation were obtained by venipuncture in the morning after fasting for at least 12 hours. Sterile 5ml syringe was used to withdraw 5ml of blood specimen from each subject and was divided into three aliquots (Two milliliter (2ml) into fluoride oxalate vial for FBS, 2ml into vial containing 0.2ml of 3.2% tri-sodium citrate and mixed properly for **PT and APTT and** the remaining 1.0ml was placed into EDTA tube (pediatric EDTA) for platelet count**.** The FBS was estimated using glucose oxidase peroxidase method. Platelet-poor plasma was separated from citrated blood by centrifugation at 3000rpm for 15 minutes and stored at -80°C until required. APTT, PT and the platelet count were assayed manually.

Data Analysis

Data were analyzed using statistical package for social science (SPSS) software version 20. The mean and standard deviation were calculated and unpaired t-test was used for comparison of values of Diabetic patients and those of apparently healthy individuals. All statistical analyses were at 95% confidence interval i.e. $P \leq 0.05$ and considered statistically significant.

RESULTS

A total of eighty (80) participants were enrolled in this study. Forty (40) were diabetic patients while forty were (40) were healthy controls. Among the Diabetes subjects, eighteen 18(45%) were males while the remaining twenty-two 22(55%) were females. The mean age of subjects and controls were 39.1±12.3 years and 35.1±8.3 years, respectively.

In table 1, we present mean ± Standard Deviation (M±SD) of platelet count,

PT and APTT in Diabetic patients and controls. The mean FBS in Diabetic patients was 7.9±3.1mmol/L while in controls it was 4.3±0.7mmol/L. The mean PT in Diabetic patients was 14.2±2.0 seconds while in controls it was 14.2±2.2 seconds. The mean APTT in Diabetic patients was 21.6±4.0 seconds while in controls it was 27.9±4.2 seconds. The mean platelet count in Diabetic subjects was 289.6±19.2 x 10^9/L while in controls it was 280.2±20.9 x 10^9/L. There was statistically significant higher FBS among the Diabetic patients than in the controls (p-value = <0.0001). No statistically significant difference in PT was observed between Diabetic patients and controls (p-value = 0.9128). There was statistically significant lower APTT among the Diabetic patients than controls (p-value = <0.0001). There was also a statistically significant higher platelet count among the diabetic patients than in controls (p-value = 0.0373).

Table 2: Indicated the PLC, PT and APTT in male and female Diabetic patients. The mean platelet count among males and females was 295.4±18.8 X 10^9/L and 284.9±18.7 X 10^9/L respectively, and no statistically significant difference was observed (p-value = 0.0866). The mean PT among males and females was 14.6±2.2 seconds and 13.8±1.8 seconds, respectively, and no statistically significant difference was observed (p-value = 0.1945). Also the mean APTT among males and females was 20.9±3.7 seconds and 22.2±4.3 seconds, respectively, and no statistically significant difference was observed (p-value = 0.3199).

Table 1: Biochemical, Haematological and Haemostatic parameters in subjects and controls

Test/Assay	Study Population		
	Diabetic (N=40)	Controls (N=40)	P- value
FBS (mmol/L)	7.9 ± 3.1	4.3± 0.7	<0.0001
PT (sec)	14.2 ± 2.0	14.3 ± 2.3	0.9128
APTT (sec)	21.6 ± 4.0	27.9 ± 4.2	<0.0001
PLC (x10?/L)	289.7 ± 19.2	280.2 ± 20.9	0.0373

KEY: PLC = Platelet count, PT= Prothrombin time, APTT=Activated partial thromboplastin time, N = Number of subjects, Sec = Seconds

Table 2: Haemostatic Parameters by gender in Diabetic patients

Parameters	Males (N=18)	Females (N=22)	p-value
PLC (x10^9/L)	295.4±18.8	284.9±18.7	0.0866
PT (seconds)	14.7±2.2	13.8±1.8	0.1945
APTT *(seconds)*	20.9±3.7	22.2 ± 4.3	0.3199

KEY: PLC = Platelet count, PT= Prothrombin time, APTT =Activated partial thromboplastin time, N = Number of subjects

DISCUSSION

In this study APTT in Diabetic patients was significantly lower than that of control. The result was consistent with Lippi *et al.,* who found reduced APTT in Diabetic patients than in controls.[12] Acang *et al*., also found that there was a significantly lower APTT value, in Diabetic patients, especially in patients with long-term Diabetes with chronic complications, which is also consistent with the results of this study.[16] However, this result was in contrast with the study carried out by Abdurrahman *et al*., which reported that there was a significant elevation in APTT between untreated Diabetic patients and controls but no

significant elevation between treated patients with Diabetics and controls.[2] The result was also not in agreement with the study conducted by Hassan who reported significant elevation of APTT in Diabetic patients compared to control individuals.[17] Reduced APTT in Diabetes mellitus recorded in this study could be a risk factor for hypercoagulability in Diabetic patients following various studies that have demonstrated shortened APTT to be associated with an increased risk of thrombosis and hence hypercoagulability.[18-20] Reduced APTT may result from an accumulation of circulating activated coagulation factors in plasma caused by enhanced coagulation activation in vivo.[12,21] Reduced APTTs are generally considered to be laboratory artefacts arising from problematic venepunctures. However, there is mounting evidence that shortened APTT values in some cases may reflect a hypercoagulable state, which is potentially associated with increased thrombotic risk and adverse cardiovascular events.[12,21]

The result of this study has shown no statistically significant difference ($p>0.05$) for PT of Diabetic patients and control individuals, in contrast with the study conducted by Abdurrahman *et al*., that reported significant elevation of PT between Diabetic patients and controls.[2] It is also not in agreement with research conducted by Lippi *et al*., that reported shortened PT in diabetic patients compared to controls, however, it was in agreement with a study conducted by Abdallah *et al*., that reported no significance different in PT of Diabetic patients and controls.[12,20] The insignificant PT results support the hypothesis that there is less involvement of the extrinsic pathway in hypercoagulability state in Diabetic conditions because injury occurring to the vascular system in Diabetic patients does not involve tissue factor from outside the vascular system.[22]Boekel and Bartels reported that PT and APTT tests are standard screening tests for function of the coagulation system and their utility in monitoring therapeutic anticoagulation is widely accepted.[23]

In this study, it was shown that the mean platelet count was higher in the Diabetic group than in the control group, and the difference was statistically significant ($p< 0.05$). This was similar to other studies.[24,25,26] However, it is in contrast with the study conducted by Hekimsoy *et al*.,[27] that reported an increased platelet count in a group of non-diabetic patients compared with Diabetic patients.[27] This finding may be due to the presence of other factors that may have influenced the platelet count, such as the mean platelet survival, and the platelet production and turnover rate in Diabetes mellitus. This is because hyperglycaemia may lead to shortened red cell lifespan and decreased Erythrocyte deformability and finally results in thrombocythaemia (usually pseudo) during endocrine diseases. In our study there was no statistical difference for PT, APTT and platelet count of males compared to females with Diabetes mellitus, which is not in agreement with research conducted by Abdallah *et al*. that reported significant elevation of PT, APTT and PLC in females than in males diabetic patients.[20]

CONCLUSION

In conclusion, results obtained in this study indicate that patients with Diabetes mellitus were prone to develop a hypercoagulable state. Therefore, routine examinations of APTT and platelet count are necessary to assess coagulation abnormality in Diabetic patients to prevent diabetes-associated thrombosis**.**

RECOMMENDATIONS

1. Patient with Diabetes mellitus should access APTT and PLC during routine checkup.
2. Further research should be done to include bleeding time to determine the vascular integrity of these patients.
3. Diabetes mellitus patients need to be educated on the risk factors, complications and management to improve on glycaemic control to prevent complications.

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Management of Aero-Digestive Tract Foreign Bodies

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ABSTRACT

Aerodigestive tract foreign bodies (FBs) are commonly encountered in medical practice. Presentation could be as elective or life-threatening emergency. Management can be difficult in some cases. The study aims to evaluate institutional experience with the management of aerodigestive tract FBs. Retrospective records of patients who were managed for aerodigestive tract FBs in our hospital between 2008 and 2018 were collated. Extracted data were entered into Microsoft Excel spreadsheet and analyzed using STATA version 10. Two hundred and twenty-three patients were treated for aerodigestive tract FBs during the study period with male: female (M:F) ratio 1:1.1, age range 6 months to 71years and median age of 3 years. There were 59(26.5%) FBs in the digestive tract and 164 (73.5%) FBs in the airway. Common modes of presentations include respiratory distress among patients presenting with foreign body in the airway and dysphagia and odynophagia in those with impacted oesophageal foreign body. Diagnosis and localisation of lower airway FBs were with plain radiograph and occasionally computed tomography while impacted oesophageal dentures were confirmed with dilute barium contrast oesophagogram and rigid oesophagoscopy. All but one FBs were removed, with majority (95%) being via endoscopy. Mortality rate was low (0.45%). The patients in this study presented more commonly with foreign bodies in the airway especially in the paediatric age group. With timely diagnosis and therapeutic interventions including endoscopy and selected open surgeries, successful removal can be achieved with very low mortality.

Keywords: Tracheobronchial, Digestive, Tract, Foreign

INTRODUCTION

Aerodigestive tract foreign bodies (FBs) are common in children and adults. They may present as ingested or aspirated objects impacting in the nose, pharynx, oesophagus and upper or lower airways. Some authors found out that aerodigestive tract FBs resulted in the death of 3000-4100 people per year.[1,2] In the lower airway, location of a foreign body in the right or left main bronchus depends on the patient's age and physical position at the time of inhalation.[3] The same study documented that the angle made by the main stem bronchi with the trachea is similar until the age of 15 years and that up to this age, FBs are found on either side with equal frequency.[3] Growth and development after the age of 15 years make the right and left main stem bronchi to be at different angles,[3] with the right mainstem bronchus becoming larger, wider, shorter and more in line with the trachea.[1-3] Therefore, lower airway FBs are more commonly found in the right than the left side of the bronchial tree.[3,6-9] No age or gender is immune to aerodigestive tract FBs; although tracheobronchial tree FBs are commoner in children while oesophageal FBs are commoner in adults.[10] Both organic and non-organic FBs are often aspirated or swallowed, and may or not be visualised with radiologic images.[4,7,10-12] Utilisation of painstaking diagnostic criteria in the domains of clinical history, symptoms, physical examination and radiological findings as studied by Kiyan *et al.* can help to avoid unnecessary surgery in patients with unsubstantiated FB inhalation.[13]

Endoscopic removal of aerodigestive tract FBs is the preferred means of treatment, however, when it fails, available options include open surgical removals such as oesophagotomy and thoracotomy/ bronchotomy.[7,6,11] Authors have reported

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varying complication rates of endoscopic removal of aerodigestive tract FB to range from 0.4% to 24.7% with such complications including airway oedema and trauma to false cord/laceration of posterior pharyngeal wall.[1,3-6] Mortality figures documented in similar studies also vary from 0-2.4%. Our centre's experience in the management of aerodigestive tract FBs is here reported.

MATERIALS AND METHODS

This was a retrospective descriptive study of 223 patients who were managed for aerodigestive tract FBs in our hospital between 2008 and 2018. Sources of data were records from theatre, ICU and clinic, and patients' case notes. Data were extracted into proforma on the socio-demographic characteristics, mode of presentation and presenting complaint[s], physical examination findings, diagnosis, investigative modalities that assisted the confirmation of diagnosis, treatment modalities and the outcome of treatment.

Extracted data were entered into Microsoft Excel spreadsheet and analyzed using STATA version 10. Continuous data were presented as means with standard deviation, while categorical variables were presented as frequencies and percentages. Chi-square and Fisher's exact tests were utilized to test associations between variables. The level of statistical significance was set at $p<0.05$.

RESULTS

Two hundred and twenty-three patients were treated for aerodigestive tract FBs during the study period with male: female ratio 1:1.1, age range from 6 months to 71 years and median age of 3 years. Patients aged less than 18 years of age constituted about 79%, while adults constituted only 21% (Table 1). According to table 2, 73.5% of FBs were in the airway (with 70.4% in the upper airway) while only 26.5% were in the digestive tract. Table 3 shows that there were 59(26.5%) FBs in the digestive tract which included 34 fishbones (15%), 9 dentures (4%), and 7 coins/metallic objects (3%). Table 4 shows that there were 164(74%) FBs in the airway distributed as 14 (64%) in nose, 3(1.3%) in nasopharynx, 2(0.8%) in hypopharynx, 9(4%) in larynx, 1(0.4%) in trachea, 4(2.2%) in right bronchus and 2(0.8%) in left bronchus. The FBs retrieved from airway included beans, seeds, beads, stones, grain, nuts, coin, steel-ball, nail, thumb pin and toy-part.

One hundred and ten (67%) of 164 patients with FBs in the airway presented with respiratory distress while 57(98%) of 59 patients with impacted oesophageal denture presented with dysphagia and odynophagia. Diagnosis and localisation of FBs in the nose were clinical in all cases, while that of lower airway FBs was with plain radiograph in 87%, computed tomography in 10%, and rigid bronchoscopy in 3%. Impacted oesophageal dentures were confirmed with dilute barium contrast oesophagogram and rigid oesophagoscopy.

As shown in Table 5, about 99% of FBs were removed, with majority (95%) being via endoscopy. Five patients with impacted denture in oesophagus had oesophagotomy for removal via cervical incision (2) and thoracotomy (3). One swallowed office pin was passed out in stool within 34 hours and an impacted piece of meat in oesophagus was pushed into stomach during rigid oesophagoscopy. Of the 6 patients with FBs in bronchus, 5 were successfully removed via rigid bronchoscopy (1) and thoracotomy and bronchotomy (4). One right bronchial FB (steel-ball) slipped back to the carina and into left bronchus intra-operatively. One patient died giving a mortality rate of 0.45%.

As shown in table 5, age group was associated with location of foreign bodies with more children having foreign bodies in the upper (97.5%) and lower (66.7%) while more adults (72.9%) had FB in the digestive tract $P<0.001$). There was no association between sex and location of FBs in this study with $p=0.37$.

Table 1: Age/sex distribution of patients with foreign bodies

Age Group	Male	Female	Frequency	Percent
Children (less than 18 years)	86	90	176	78.9
Adults (18 years and above)	21	26	47	21.1
Total	107	116	223	100
Location of Foreign Bodies				
Upper Airway	70	87	157	70.4
Lower Airway	4	3	7	3.1
Digestive tract (Oesophagus)	33	26	59	26.5
Total	107	116	223	100

The majority (70.4%) of foreign bodies were in the upper airways.

Table 2. Types of foreign bodies in the digestive tract [n=59]

Types of Foreign Body	Frequency	Percent
Fishbone	34	57.6
Denture	9	15.3
Coin/metals	7	11.9
Pin	2	3.4
Meat	1	1.7
Others	6	10.2

The top 3 foreign bodies in the digestive system were fishbone (57.6%), denture (15.3%) and coin/metals (11.9%)

Table 3. Location of foreign body in the upper airway (n=157)

Position	Frequency	Percent
Nose	146	92.8
Larynx	6	3.8
Nasopharynx	3	1.9
Hypopharynx	2	1.3
Which nostril (n=146)		
Right	80	54.8
Left	53	36.2
Both	2	1.4
Not specified	11	7.6

Most (92.8%) of the foreign bodies were lodged in the nostrils. Majority (54.8%) of the FBs are located in the Right nostril

Table 4: Treatment modalities used in patients with aerodigestive tract foreign bodies

Modality	Frequency	Percent
Nasoendoscopy	149	66.8
Laryngoscopy	8	3.6
Oesophagoscopy	54	24.2
Bronchoscopy	2	0.9
Oesophagotomy	Cervical (2) Transthoracic (3)	2.2
Bronchotomy	5 (one failed)	2.2
Total	223 (one patient died after failed removal of right bronchial FB)	100

Table 5: Association between selected factors and location of foreign bodies in the Aerodigestive tracts

Variable	Location of foreign bodies			Total	Statistical test and values
	Upper Airway n (%)	Lower Airway n(%)	Digestive Tract n(%)		
Age groups					
Less than 18	153(97.5)	6(66.7)	16(27.1)	175	P=0.00+
18 and above	4(2.5)	1(33.3)	43(72.9)	48	
Sex					
Males	70(44.6)	4(42.9)	33(55.9)	107	P=0.37+
Females	87(55.4)	3(57.1)	26(44.1)	116	

+ Fishers exact

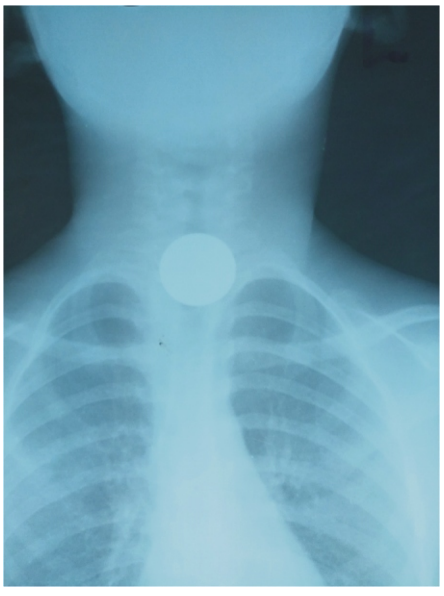

Figure 1: Antero-postero neck radiograph showing FB in oesophagus

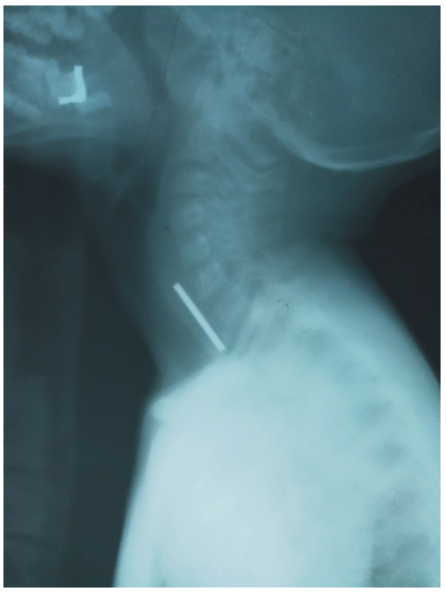

Figure 2: Lateral neck radiograph showing FB in oesophagus

Figure 3: Coin removed from oesophagus

DISCUSSION

The index study has shown aerodigestive tract foreign bodies to be a common presentation to cardiothoracic and otorhinolaryngologic units as previously documented.[14,15] Children and adults were affected in the present study which also shows that children are much more prone to inhalation of foreign bodies into the airway than adults with a ratio of 32:1. This corroborated the finding in other related studies.[10-12] The median age is 3years, which is still similar to findings in other studies.[5-10] A similar study found that 96% of airway FBs occurred in children while 67% of oesophageal FBs occurred in adults.[4] The cases of ingestion of denture all occurred in adults. A common observation was that the dentures were poorly fitted on the alveolus before dislodgment, having been in use for many years. The bronchial FBs in this cohort were predominantly on the right which may be explained by the lower airway anatomy. The right bronchus is wider, shorter and almost in a straight line with trachea at the carina, thereby favouring reception of more FB. Similar findings were made by other researchers.[3,6,7,9] The physical position of the patient at the time of aspiration can also determine the bronchus of FB lodgement.[3] A foreign body aspirated while in the lateral decubitus position is more likely to lodge in the bronchus that is dependent if the FB gets down to the bronchus.

The different objects such as bean, nut, bead, toy part, coin, thumb pin, etc, found variously in the nose and other parts of the airway in children are among the objects commonly available in homes. To prevent their aspiration, care-givers have to ensure that these objects are kept out of the reach of toddlers. Oesophageal FBs such as dentures can be prevented by not wearing any loose-fitted denture. Others like pieces of meat and bone can be prevented through proper eating culture. The findings with regarding the types of FBs corroborated with those of other studies.[4-7,10-12,16,17] There was however no case of aspiration of live insect as was reported by Liu et al.[16] In most patients who presented in emergency with respiratory distress and had a clear clinical history to support the diagnosis of aerodigestive tract FB, endoscopy served both the functions of confirmation of diagnosis and treatment when the FB was successfully removed. Metallic FBs were easily diagnosed with plain radiographs and computed tomographic scan was rarely needed for localisation of FBs. However, non-radiopaque FBs in the oesophagus were diagnosed with the use of dilute barium oesophagogram. Dilute barium sulphate was used because of the potential for mediastinitis associated with concentrated barium sulphate in the event of oesophageal perforation. Fishbones were not seen as radio-opaque FBs in all instances. The study of Hariga, *et al.* reported accuracy of plain radiograph diagnosis of only 48.7%.[4]

Successful removal with rigid endoscope was reported in about 95% with <2% procedural complication rate.[4] The same study also noted that in up to 12% of cases of suspected FB ingestion, no FB was found after investigation and endoscopy.[4] In the index study, 5 patients had failure of bronchoscopic localisation and were then operated on via thoracotomy. In the study of Asif, et al, rigid bronchoscopy had a success rate of 97.5% for removal of airway FBs while the remaining patients were referred for thoracotomy.[3] In that study, though there was no mortality, the complication rate was rather high at 24.7% and included airway oedema and trauma to false cord/ laceration of posterior pharyngeal wall. In the index study,

one FB in the right bronchus in a 6-year-old fell back to the carina and dropped into the left bronchus during right thoracotomy in the left lateral position. This was discovered with immediate post-operative chest radiograph after the thoracotomy wound was closed following non-localisation of the FB in the right bronchus intra-operatively. The patient died before repeat attempt at removal of FB, and constituted the only mortality in the study resulting in 0.45% mortality rate. There were no cases of FB removal via tracheostomy though this method has been reported.[18]

Oesophageal FBs were successfully removed endoscopically except in the cases of impacted denture where oesophagotomy was done for 5 patients; 2 via left cervical incision and 3 via right thoracotomy. and there was no case of sudden death which can occur from airway FB.[11,17]

Analysis showed that age group was associated with location of foreign bodies with children (less than 18 years) having foreign bodies in the upper (97.5%) and lower (66.7%) airways, while more adults (72.9%) had FBs in the digestive tract (P=<0.001). There was no association between sex and location of FBs in the study. The overall mortality rate was 0.45%**.** We recommend that if toddlers who explore their environment extensively are closely monitored by adult care-givers, the incidence of aerodigestive tract FBs could reduce significantly.

CONCLUSION

The patients in this study presented more commonly with foreign bodies in the airway, especially in the paediatric age group. With timely diagnosis and therapeutic interventions including endoscopy and selected open surgeries, successful removal can be achieved with very low mortality.

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An Array of Accidental Deaths; a Retrospective Hospital-Based Study

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ABSTRACT

An accidental death can be defined as an unnatural death that results from. An unforeseen or an unintentional event which may be preventable. The determination of the causes and magnitude of accidental death are invaluable in appreciating its public health burden on the one hand and assist in policy formulation that would result in its prevention on the other. The aim of this study was to determine the frequency and causes of accidental deaths, their age and sex distribution. This study was a retrospective post mortem study carried out in the Department of Morbid Anatomy, UBTH from January 1st, 2013 to December 31,st 2014. The study population were those from accident-related fatalities. Data (age, sex and various causes of accidental deaths) obtained were analysed using statistical package for social sciences version 20. Accidental deaths were attributed to road traffic accident (RTA); burns; fall from height; drowning and choking from foreign body aspiration. RTA was the most common cause of accidental deaths accounting for 75.1% of cases. RTA involving vehicles (99.62%) were the most common. Burns, choking from foreign body aspiration; fall from height and drowning accounted for 23.4%, 0.9%, 0.3% and 0.3% of cases respectively in decreasing order of frequency. More males (72%) died unintentionally and the majority of deaths fell within the young age group (20-39 years). RTA accounted for most cases of accidental deaths. Others were burns, choking secondary to foreign body aspiration, drowning and fall from a height in decreasing order of occurrence. Most cases of accidental deaths occurred in the young.

Keywords: Accidental death, road traffic accident, burns, choking, drowning

INTRODUCTION

The manner of death is the elucidation of how death results based on the circumstances surrounding death and it includes natural, accident, suicide, homicide, undetermined and pending.[1-3] Accidental deaths, on the other hand, includes transport associated mortalities, on the job-related demise, otherwise known as an industrial accident, fall, fires/burns/smoke, forces of nature (lightning, flood, thunderstorms), death due to animal attack, death from electrocution, aspiration of foreign bodies, deaths from illegal drug consumption or too much medication use provided homicide and suicide are not implicated, and death from complication of therapy.[1-4] The causes of accidental death are to a large extent preventable and hence the pattern of its magnitude is important to ascertain its public health burden. Although previous studies from this same environment by Akhiwu *et al.* and Nwafor *et al.* at different times had described the pattern of accidental death, the importance of periodic data collection and analyses has been brought to fore by Azeke *et al.* who recommended it in elucidating the current trend of a particular research work especially when compared with the pre-existing baseline data in that environment.[5-7] The average life expectancy of Nigerians as documented by the World Health Organization is 54.5 years, a far cry from what is obtainable in the western world,[8,9] perhaps an insight to the causes and magnitude of accidental deaths may be invaluable in the long run in improving the life expectancy of Nigerians. The aim of this study is, therefore, to determine the pattern of accidental death at the University of Benin Teaching Hospital (UBTH) while the objectives are to determine the frequency and causes of accidental deaths, their age and sex distribution.

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MATERIALS AND METHODS

This was a retrospective post-mortem study that was carried out in the Department of Morbid Anatomy, UBTH, Benin City, Nigeria. The University of Benin Teaching Hospital is a tertiary referral hospital for

diverse and varied disease conditions in Edo, Delta, parts of Kogi and Ondo states which largely forms its catchment area and sometimes outside these areas.[10] It has a bed capacity of over 860 beds with potentials for an increase.[10] It has several departments of which the Department of Morbid Anatomy is one. This research work was carried out over a 2 year period from 1st January 2013 to 31st December 2014. From a pool of all cases of post-mortem performed during the period under review, the study population were those who died from accident-related causes. The biodata and other relevant information such as age, sex and the precise cause of accidental death were extracted from clinical case note and mortuary/autopsy register of each case in the study population. Cases with complete demographic data and post-mortem cause of accidental death were included in this study while those with incomplete demographic data were excluded from this study.

Data analysis was done using the Statistical Package for Social Sciences, version 20 (SPSS 20, IBM Corp. Armonk, NY, United States of America). For categorical variables (sex and causes of accidental deaths) the frequency and corresponding rates in percentages were analysed while for the continuous variable (age), the age range, mean age, standard deviation and peak age were analysed.

RESULTS

Three hundred fifty (350) cases of accidental deaths were recorded during the study period and these accounted for 43% of medicolegal post-mortems during the study period. Two hundred fifty-three (72%) were males while 97(28%) were females giving a male to female ratio of 2.6:1. Their age ranged from 1 to 85 years with mean age and standard deviation of 37.47 years (SD=16.78). Road traffic accident (RTA) was the most common cause of accidental death and accounted for 263(75.1%) of the cases as shown in table 1. Of these, motor vehicular RTA was far more common and it represented 263(99.62%) of the cases while a case (0.38%) of pedestrian RTA was also noted. The age range for RTA was from 1 to 85 years with a mean age and standard deviation (SD) of 38.66 ± 16.3 years, median and modal ages of 36.00 and 22.00 years respectively. The peak age for RTA was in the 4th decade as shown in table 2. The males were more and accounted for 205 (78%) cases of RTA while the females were 58(22%) with a male to female ratio of 3.5:1 as shown in table 1. The age range in males was from 6 to 80 years with a mean age and SD of 39.06 ± 14.65 years while the females had an age range from 1 to 85 years with a mean age and SD of 37.26 ± 21.24 years. The peak age for RTA related deaths in males and females were in 4th and 3rd decades respectively as shown in table 2.

Death from burns was the next in frequency after RTA and it accounted for 82(23.4%) cases of accidental deaths as shown in table 1. Their age range from 1 to 84 years with a mean age and SD of 33.92 ± 18.15 years, median and modal ages were 31.50 and 28.00 years respectively. The peak age for death that resulted from burns was in the 4th decade as shown in table 2. There were 44 (54%) males and 38(46%) females giving male to female ratio of 1.2:1. The males had their age that ranged from 2 to 84 years with a mean age and SD of 38.59 ± 18.09 years while the females had an age ranged from 1 to 85 years with a mean age and SD of 28.50 ± 16.86 years. The peak age for burns related deaths in males and females were in 4th and 3rd decades respectively as shown in table 2.

Death from choking following foreign body aspiration came up a distant 3rd in frequency with 3(0.9%) cases of accidental deaths. Their age ranged from 22 to 42 years with a mean age and SD of 31.33 ± 10.07 years. There were 2(67%) males and a female (33%) giving a male to female ratio of 2:1 as shown in table 1. The age ranged in males was from 30 to 42 years with a mean age and SD of 36.00 ± 8.49 years. The only female in this category died at 22 years of age.

Death from drowning and fall from a height each accounted for a (0.3%) case of accidental death as shown in table 1, the former died at 23 years of age while the latter died at 42 years of age. Both were males as shown in table 2.

Table 1, frequency and causes of accidental death with sex distribution

Causes of accidental death	Sex		
	Male	Female	Total
Road traffic accident	205	58	263
Burns	44	38	82
Fall from height	1	0	1
Drowning	1	0	1
Choking with asphyxia from foreign body aspiration	2	1	3
Total	253	97	350

Table 2, age group and sex distribution of causes of accidental death

Causes of accidental deaths	Age group	Sex		
		Male	Female	Total
Road traffic accident	0-9	3	4	7
	10-19	6	6	12
	20-29	46	16	62
	30-39	67	10	77
	40-49	36	5	41
	50-59	26	6	32
	60-69	12	4	16
	70-79	8	5	13
	80-89	1	2	3
	Total	205	58	263
Burns	0-9	3	5	8
	10-19	2	7	9
	20-29	7	10	17
	30-39	12	7	19
	40-49	10	3	13
	50-59	5	4	9
	60-69	2	2	4
	70-79	2	0	2
	80-89	1	0	1
	Total	44	38	82
Fall from height	40-49	1		1
	Total	1		1
Drowning	20-29	1		1
	Total	1		1
Choking with asphyxia from foreign body aspiration	20-29	0	1	1
	30-39	1	0	1
	40-49	1	0	1
	Total	2	1	3

DISCUSSION

Accidental death had been categorized as one of the manner of deaths.[1-3] It ranks amongst the most frequent manner of death in most previous medicolegal autopsies in Nigeria and Qatar.[3,5,7,11,12] This is consistent with the observation of this study where it accounted for more than two-fifth but less than half of the medicolegal deaths.

An accident has been described as an unintentional, unexpected, unforeseen and undesirable event which can occur at home, on highways, schools, workplace and recreational centres resulting in injury that may or may not be as a result of carelessness or ignorance on the part of the person(s) injured.[5,13] It therefore follows that this unexpected event can affect all age groups as depicted in the observation of this study where it has an age range that span from the 1st to 8th decade. This is consistent with the observation of previous studies.[5,7]

The mean age for those who died from accident-related fatalities was in the 4th decades as reported by Nwafor et al and Uchendu *et al*.[7,14] This is comparatively similar to a mean age in the 4rd decade as observed in this study.

The unintentional, unforeseen, unexpected and undesirable nature of an accident that may lead to accidental death brings to fore the importance of knowing its causes with the sole aim of minimizing or eliminating it. Globally, road traffic accidents (RTAs) are common cause of morbidity and mortality with particular reference to the developin g world including Nigeria.[15,16] Giving credence to this observation, it was observed to be the major cause of accidental death in this study where it accounted for two-thirds of the mortalities recorded. This observation is also in keeping with those of previous studies where RTAs accounted for 63.6% to 88.7%.[3,5,7,11,17-19] Road traffic accidents involving vehicles were overwhelmingly more prevalent in comparison to pedestrian RTAs in this study. This is consistent with previous studies from the same environment that had observed that motor vehicular RTAs are the most common cause of RTAs although to a much lower extent of 41.3% to 48% in comparison a far higher percentage (99.62%) as observed in our own study.[3,7,20] In this study, less than 1% of RTAs victims were pedestrians which is a far cry from what previous studies in the same environment had observed i.e. 27.6% to 37.1%.[3,7,20] The reasons for this wide disparity is not readily discernable, however, it gives an insight into the presence of a possible factor or factors that have brought about this observation. This is not only a window for future research work, but it also brings to fore that accidental death can either be reduced or eliminated. Previous studies from Karachi (Pakistan), Yazd (Iran), Chandigarh (Nothern India) and Singh Guwahati, Assam (Indian) contrary to the findings of this study reported that pedestrian RTAs accounted for 39 to 67% of mortalities.[21-24] Singh et al attributed this observation as a reflection of the ignorance of traffic rules and also on the speed of the vehicles.[24]

Death from RTAs virtually affects all age group in this study. This is consistent with the documentation of the World Health Organization and also in keeping with previous medicolegal post-mortem studies that looked at RTA fatalities.[23-26]

Moharamzad *et al.* over a year carried out a post mortem study on the mortality pattern amongst traffic accident victims in Yazd, Iran.[22] They reported that the mean age of fatalities in their 251 study population was in the 4th decade.[22] This mean age is consistent with that observed in this study. The peak age observed in this study was in the 4th decade. This is comparatively similar to findings of previous studies that reported more RTAs related fatalities in the young productive age group.[24,27]

The World Health Organization had documented that males are more likely to be involved in RTAs than females. This is in keeping with the observations of this study and previous studies on RTAs fatalities at autopsies.[23-25, 29] The reason for this male preponderance is due to the nature of work that exposes them to RTAs.[24]

Unintentional deaths from burns had been previously reported by various studies

in Nigeria to account for 0.6% to 8.9 % of accidental deaths.[3,7,11,14,17,18,30,31] This study reported a much higher frequency of burns related deaths. Victims of petroleum products related fire explosion in the Edo-Delta region are most likely to be referred to the UBTH for expert management and this may account for this observation.[7,17] More males died from burns related accidental deaths in this study. This is in keeping with the observations of previous studies in this same environment.[3,7,17] This is however contrary to IIiopoulou *et al.* from General District Hospital of Attica, Kat-Kiffissia, Greece who reported that more females died from burns related fatalities.[32]

Choking characteristically delineates an aero-digestive foreign body causing unpredictable amounts of obstruction to the airways,[33] while asphyxia, on the other hand, is a mode of death that is typified by respiratory disorder owing to decrease oxygen saturation in the blood or tissue level.[34] Unforeseen death from choking with asphyxia secondary to foreign body aspiration accounted for less than 1% of accidental deaths in this study. This is comparatively similar to the observation of a previous study by Akhiwu *et al.*[17]

Drowning characteristically encompasses a watery milieu and remains a serious public health concern, claiming an estimated 362000 lives per year worldwide across all socioeconomic groupings and has remained under close surveillance by the WHO and its signatories.[35] To this end, the definition of drowning involves suffocating by partial or complete submersion especially in water.[36] This study observed a very low occurrence rate (0.3%) of accidental drowning. This may be related to the few water bodies and its related activities in this environment.[7] Comparatively similar findings were observed by previous studies in the same locality,[7,17] while much higher occurrence rate of accidental drowning was also observed in other studies.[3,14,18]

Most accidental falls are seen in the elderly.[7] This is contrary to the observation of our own study that noted the age of fall as 42 years for the only case (0.3%) seen during the study period. This finding is comparatively similar to that of a previous study in the same locality,[7] unlike Uchendu (8%) and Amakiri *et al.* (13%) that reported a much higher frequency of occurrence of accidental drowning.[11,14]

CONCLUSION

RTA accounted for most cases of accidental deaths. Others were burns, choking secondary to foreign body aspiration, drowning and fall from a height in decreasing order of occurrence. In comparison to all previous accidental deaths in our own locality, the percentage of deaths due to burns has increased as seen in this study. Males are more commonly affected by accidental deaths and the young age subjects in this study had the highest frequency of accidental deaths. It is our expectation that the data thus generated from this study would re-enforce the findings of previous studies in our environment in particular and other parts of Nigeria in general that had reported that accidental deaths accounted for a high proportion of medicolegal postmortems, thus bringing to fore preventive measures as a veritable means of eliminating or reducing needless deaths.

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Influences of Glycemic Index and Glycemic Load of Two Mixed Diets on Postprandial Responses among Healthy Young Adults in Benin City, Nigeria

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ABSTRACT

There is scarce literature on the glycemic indices and glycemic loads of most Nigerian foods. Diseases and disorders associated with the consumption of carbohydrate foods are on the increase. This study aimed to provide insights into the dietary management of metabolic disorders linked to carbohydrate foods, such as diabetes mellitus, by providing glycemic index and glycemic load data on two commonly consumed Nigerian foods using standard documented methods. Healthy volunteer subjects were selected from among the undergraduate students of the Faculty of Life Sciences, University of Benin, Benin City, to participate in the study. Glucose was served as the control food while Titus sardine with bread and Titus sardine with Indomie noodles were the test foods. All the participants were subjected to an overnight fast of at least 12 hours. The postprandial responses were measured with a standardized glucometer. Hitherto, the proximate analyses of the foods were all determined by standard methods. The results obtained indicated that the glycemic index and the glycemic load of the test foods were low: 23 and 47 for Titus sardine with bread, and Titus sardine with Indomie noodles respectively, indicating that the mixed foods could be consumed by both diabetic and non-diabetic individuals. Consumption of single foods like white bread alone indicated a high glycemic index which is not healthy for diabetic individuals. However, in view of the demonstrated lowering of glycaemic index, the mixed diets evaluated in this study could be recommended for diabetic individuals.

Keywords: Diets, Postprandial, Response, Glycemic, Index, Load

INTRODUCTION

The word "glycemic" is coined from "glycaemia", which has to do with the presence of glucose in the blood. The glycemic index (GI) has drawn broad interests worldwide for its implications in health and disease. GI refers to the glycemic effect of available carbohydrate in food relative to the effect of an equal amount of glucose. Simply put, glycemic index is a measure of the rate at which ingested food causes the level of glucose in the blood to rise. The GI concept is based on the differences in blood glucose response after ingestion of the same amount of carbohydrates from different foods and possible implications of these differences for health, performance and wellbeing. Although GI is tested with individual foods, this data has been used to obtain the GI of a whole diet in which each food's GI is weighted according to its carbohydrate contribution.[1] Differences in the glycemic response to various carbohydrate-containing foods were first investigated by Otto.[2] These discoveries led to the development of the glycemic index, a concept that ranks carbohydrate-containing foods based on their effect on blood glucose levels.[3]

GI is usually tested with individual foods, but as very few foods are consumed solely as a meal GI needs to apply to mixed meals also. The GI of mixed meals can be determined according to available carbohydrate contribution in the meal. Carbohydrates that are rapidly digested release glucose quickly into the blood and thus have a high GI. The rapid digestion and absorption cause marked fluctuations in blood glucose levels. Therefore, they are marked as dietary factors that favour the development of chronic diseases.[4] Carbohydrates that are digested slowly, releasing glucose into the blood gradually, have low GI. These foods produce a gradual increase in glucose and insulin level, and are proven to be beneficial health-wise, such as in weight control because they help control appetite and delay hunger.[5]

Glycemic load (GL) is the theoretical cumulative exposure to glycemia over some

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time and is derived from GI. GL appears to be a significant factor in dietary programs targeting metabolic syndrome, insulin resistance, and weight loss; studies have shown that sustained spikes in blood glucose and insulin levels may lead to increased diabetes risk.[6] Because some foods typically have a low carbohydrate content, Harvard researchers created the GL, which takes into account the quantity of carbohydrates in a given serving of food and so provides a more useful measure.[6] Liu *et al.* were the first to show that based on their calculation, the glycemic load of a specific food-calculated as the product of that food's carbohydrate content and its glycemic index value-has direct physiologic meaning in that each unit can be interpreted as the equivalent of 1g carbohydrate from white bread or glucose depending on the reference used in determining the glycemic index.[7] It became immediately apparent that such direct physiological quantification of glycemic load would allow patients with diabetes to do "glycemic load" counting as opposed to the conventional "carbohydrate counting" for monitoring the glycemic effect of foods.[8]

The aims of this study were as follows:

1. To determine the GI and GL of two Nigerian mixed diets: *Titus* sardine mixed with bread, and *Titus* sardine mixed with *Indomie* noodles.
2. To examine the influence of the components of the mixed diets on the glycemic response in non-diabetic subjects.

MATERIALS AND METHODS

Food Samples Collection

The *Titus* sardine was bought from the same batch of production in a carton from a shopping mall. The white bread was purchased from Nadia Bakery in Benin City. The *Indomie* noodles were bought from the same batch of production in a carton from a shopping mall.

Experimental Design and Subjects

Twenty-two subjects aged between 18 and 23 years were selected from the Faculty of Life Sciences of the University of Benin, Benin City, Nigeria. Eleven of the subjects were served bread and *Titus* sardine while the other eleven were served *Indomie* noodles and *Titus* sardine, with one control. They were all clinically normal, non-smokers and non-diabetic. The subjects were appraised verbally and they gave their informed consent one week before the commencement of the exercise. They also all agreed to observe a twelve-hour overnight fast. The study was commenced after due approval by the approving body, the Academic Board of the Faculty of Life Sciences of the University of Benin.

Proximate Analysis

The standard methods of the Association of Official Analytical Chemists, AOAC (2004) for the determination of proximate analysis were adopted.[9] The moisture content of each mixed food (in the form in which it would be eaten) was determined by the heating and weighing method until a constant weight was achieved. The semi-micro Kjeldahl procedure was used for crude protein determination.[10] The lipid content was determined by the Soxhlet extraction method.[11] The crude fibre was determined by exhaustive extraction of soluble substances in a sample using 5% H_2SO_4 and 5% NaOH and thereafter the residue was ashed for 6 hours at 600^{o}c. The loss in weight was recorded as the fibre.

The ash content was determined by taking a known weight of the sample tarred in a porcelain crucible and ashed in a muffle furnace for 4hours at 600^{o}c.[9] The difference in weight was recorded as the weight of the ash. The percentage carbohydrate content was established by subtracting the sum of the percentages of the other constituents from 100.

Feeding of Subjects

The control subjects were each fed with 50g glucose D dissolved in 200ml of distilled water while the test subjects were fed with 50g available carbohydrate calculated from the proximate analysis result of the test

foods.[12] Thereafter the subjects rinsed the particles of food in their mouths down into their stomachs each with 200ml of distilled water.

Determination of postprandial response

Standard materials and Trinder's glucose oxidase method were used for this exercise.[10,11] The materials used included lancet, test strips, glucometer (*Accu-Check/One-touch*), stopwatch, cotton wool, methylated spirit and latex gloves. Capillary blood samples were obtained via thumb pricks using lancets. Each blood sample was placed on a test strip which was inserted into a calibrated glucometer (*Accu-Check/One-touch*) which gave direct readings after 45 seconds based on the glucose oxidase assay method. The determination of glucose level was done at intervals of thirty minutes within three hours. The relative glycemic index of each food was calculated as a percentage of the mean of individual areas under the glucose response curves.[14] The data obtained were used in plotting the postprandial response curves.

Statistical Analysis

The data collected from this work were analyzed by using ANOVA and all results were expressed as the mean of ±SEM of duplicate determinations.

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GI and GL Calculations

The blood glucose values were used in the construction of curves for the individual control subjects and the test subjects. The trapezoidal rule described by Jenkins *et al.*[15] was used in the calculation of the incremental area under the blood glucose response curve (or incremental area under the curve, IAUC) for 50g carbohydrate of the test food and control food (glucose). The GI and GL were calculated with the formulae below by way of ratings with figures (no units) after calculation:

$$GI = \frac{\text{AUC for 50g carbohydrate from test food}}{\text{AUC for 50g carbohydrate from glucose}} \times 100$$

$$GL = \frac{\text{Carbohydrate content per serving of food}}{100} \times GI$$

RESULTS

The following nutrients were detected in the test foods; moisture, fat, protein, ash, fibre and carbohydrate. The values of the nutrients were present in varying concentrations. The fat/oil and protein contents had higher values while moisture had the highest value. The available/equivalent carbohydrate of the test food was calculated from the proximate analysis result. These findings are displayed in Table 1.

The results of postprandial responses of the control and test subjects were also in varying concentrations. The mean postprandial blood glucose responses of the control and test subjects are as presented in Table 2 and Table 3. These were used in plotting the glucose response curves shown in Figure 1 and Figure 2.

The calculated glycemic indices for both mixed foods were of low rating, while the glycemic load of bread and sardine, and sardine/*Indomine* noodles were of medium and high rating respectively. The mean glycemic indices and loads for both test foods, as well as their respective ratings, are as shown in Table 4.

Table 1: Mean of Proximate Analysis of the test foods

Test food	% Moisture	% protein	% Fat/Oil	% Fibre	% Ash	% Carbohydrate
Sardine and bread	42.34±0.67	19.86±0.22	28.42±0.28	1.56±0.03	2.67±0.02	47.49±0.55
Sardine and noodles	49.58±0.35	19.40±0.42	32.99±0.21	1.32±0.05	2.52±0.00	43.78±0.16

Table 2: Mean of postprandial responses in blood glucose of subjects after the sardine and bread consumption

Subjects	Baseline	30min	60min	90min	120min	150min	180min
Control	72	95	107	140	131	106	70
Test food	78	81	88	94	93	87	73

Table 3: Mean of postprandial responses in blood glucose in subjects after sardine and *indomie* noodles consumption

Subjects	Baseline	30min	60min	90min	120min	150min	180min
Control	74	103	107	97	94	79	66
Test food	76	82	86	87	89	79	69

Table 4: Mean glycemic index and glycemic load of the test foods

S/N	Test food	GI	GI class	GL	GL class
1	Sardine and bread	23.40±1.29	Low	11.1±0.61	Medium
li2	Sardine and noodles	46.80±5.65	Low	20.49±2.48	High

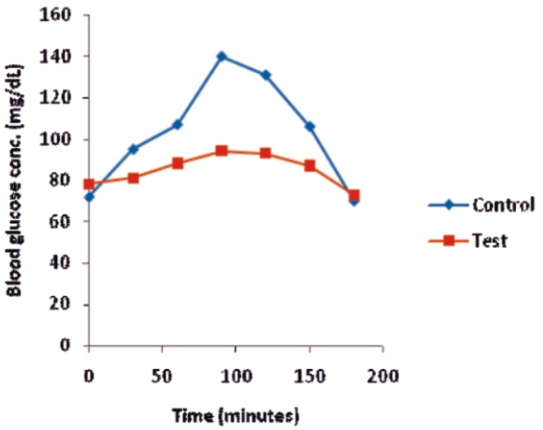

Figure 1: Postprandial response of control and mean postprandial response of test after consumption of bread and sardine.

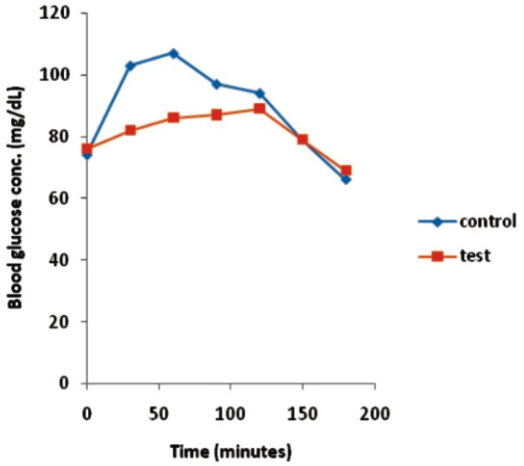

Figure 2: Postprandial response of control and mean postprandial response of test after consumption of sardine and *Indomie* noodles.

DISCUSSION

The composition of the mixed foods studied indicates that they contain good nutrients for healthy living as could be found in a balanced diet. Some factors that could increase or decrease the glycemic index/load besides mode of preparation (roasting methods and time, amount of moisture and heat applied etc.)[16,17] have generated research interests among scientists particularly in the understanding of interactions between food components when they are co-ingested and the overall consequences on postprandial responses. There is however a relative scarcity of studies on the GI and GL of commonly consumed mixed foods in Nigeria, a gap which studies like the index one are intended to fill. For example, to the best of our knowledge and literature search there is no previous study on the effects on human

subjects of the GI and GL of the mixed foods evaluated in this study.

The present work has revealed that the consumption of a single diet with 50g of carbohydrate/glucose D could yield a glycemic index value of 100 (standard value), whereas a mixed diet that contains the same amount of carbohydrate and sardine yielded a glycemic index of 23 (bread and sardine) and 46 (sardine and *Indomie* noodles). The glycemic index of 100 is rated as high while the Glycemic Index of 23 and 46 are rated as low, by international standard.[17] It has been reported that lipid, proteins and fibre play significant roles in the reduction of postprandial responses.[17-20] The drastically reduced GI values were due to the high levels of protein, fat and oil in the mixed food, which was contributed majorly by the sardine. Previous work by Omoregie et al has also shown that the inclusion of fat in meals with high carbohydrate lowers the glycemic response and thus GI by delaying gastric emptying and/or reducing starch gelatinization.[18] Protein may lower the glycemic response and GI by increasing insulin secretion.[18] Otemuyiwa et al reported that the combination of high-GI and GL foods (such as white bread, which many consume alone or with water or soft drinks) with high-protein foods in adequate amounts as a mixed meal results in a significant lowering of the GI and GL compared to when ingested alone.[21] Asinobi and colleagues demonstrated that Nigerian mixed diets rich in dietary fibre contribute significantly to a lower postprandial blood glucose response.[22] Our present work, therefore, complements these earlier findings.

Furthermore, it is noteworthy that although wheat bread is commonly recommended (instead of white bread) for the diabetic diet, depending on the production process, it is also a high-glycemic index food, according to studies done in Europe.[23] Chinese steamed bread is a staple food among the Chinese population, which though made from wheat, has also been reported to have a high glycemic index.[24] In spite of much research in various parts of the world, the demand for low- and moderate-glycemic index bread is currently largely unmet. This demand continues to rise with the rising incidence of chronic metabolic disorders in the population such as diabetes and obesity.[24,25] The pragmatic solution for now appears to reside with the consumption of bread as part of a glycemic index-lowering combination[24] as demonstrated in this work. Although wheat bread was not used in this study it may be deduced from the observed outcome with white bread that the consumption of wheat bread as part of a mixed diet with sardine will improve the postprandial response.

CONCLUSION

This work has revealed that the co-consumption of some food nutrients in mixed foods have the potential of lowering the postprandial response of the high carbohydrate portion in such mixed diets, especially in the case of sardine and bread. White bread if eaten as a single meal produces a glycemic index of 70 but when it was consumed with sardine the glycemic index was reduced to a low value. The consumption of bread should be recommended with sardine for diabetic patients who desire to eat bread. A similar effect was observed when sardine and *Indomie* noodles were eaten together as a mixed diet.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest whatsoever.

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Clinical Profile and Outcome of Patients with Diabetes Mellitus Foot Ulcer in Gusau, Northwestern Nigeria

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ABSTRACT

Diabetes Mellitus foot ulcer (DMFU) is a worrisome chronic complication of diabetes mellitus. This study aimed to evaluate the clinical profile and outcome of patients with DMFU in our setting. This was a 3-year retrospective descriptive study of patients managed with DMFU at two tertiary health facilities in Gusau. Relevant information from the files was extracted such as socio-demographics, duration of Diabetes and ulcer, risk factors and causes of DMFU, Wagner grading, random plasma Glucose at presentation, packed cell volume, duration of hospital stay and outcomes. The data was analyzed using SPSS version 20.0 statistical software. One hundred and nineteen case notes were retrieved. They consisted of 45(37.8%) males and 74(62.2%) females. Their mean age was 56.0±12.8years. The mean duration of Diabetes and foot ulcers before presentation were 4.8±4.29years and 4.02±4.6weeks respectively. The ulcer healed normally in 71(59.6%) patients, 25(21%) had amputations and 15(12.6%) left against medical advice. The overall mortality rate was 6.7% [males 5(62.5%), females 3(37.5%), p < 0.001]. Predictors of ulcer healing were early presentation, female gender and packed cell volume greater than 24% at presentation. The mean duration of admission was 5.4±4.2weeks. Forty-one (43%) patients were on admission for more than 4 weeks. DMFU is a cause of prolonged hospital admission, amputations and mortality in our setting. Sustained health education on foot care will go a long way in taming the tide.

Keywords: Profile, Diabetes mellitus foot ulcer, Outcome

INTRODUCTION:

Diabetes Mellitus is a multisystemic disease with varying acute and chronic complications. One of the worrisome chronic complications is diabetes mellitus foot disease.[1] The diabetes mellitus foot syndrome (DMFS) presents as a combination of neuropathy and peripheral vascular disease that may lead to ulceration and gangrene in a patient with Diabetes Mellitus.[2] Diabetes mellitus foot ulcer (DMFU) is a breach in the continuity of the skin epithelium involving its full thickness or beyond in a person living with Diabetes Mellitus. Neuropathy is the commonest risk factor of DMFU as it causes insensitivity in the feet, reduces proprioception, causes wasting of small muscles of the foot, leads to alteration of normal arches of the foot and peripheral autonomic neuropathy all of which predispose patients with Diabetes Mellitus to trivial foot injuries and subsequent infections.[3]

The prevalence of DMFU is around 5-10% in people living with Diabetes Mellitus A person living with Diabetes Mellitus has about 25% lifetime risk of developing a foot ulcer.[4]

The International Diabetes Federation (IDF) estimated that 40-60 million people globally are living with DMFU. Amputation in people with Diabetes Mellitus is 10 to 20 times more common than in those without Diabetes Mellitus and a lower limb is lost every 30 seconds as a consequence of Diabetes Mellitus globally.[5]

World health organization estimated that more than half of all non-traumatic lower-limb amputations worldwide are due to DMFU.[6] It accounts for over 72% of lower limb amputation in Spain[7] and leads to 73,000 amputations annually in the United States of America.[8] DMFU accounts for up to 20% of Diabetes Mellitus related hospital admissions and leads to prolonged hospital stay and enormous financial burden.[9,10,11]

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A person with DMFU has 2.5 fold increased risk of death compared to other people living with Diabetes Mellitus [12] and the risk of mortality following amputation of DMFU is up to 50% at 2 years which is higher than mortalities of some cancers.[13] Despite the bleak picture of DMFU, 50% of the cases can be prevented by health education and effective identification.[14]

We aimed to determine the clinical profile and outcomes of patients with DMFU in Gusau. To our knowledge, this is the first study of DMFU in Gusau, North-Western Nigeria. This will greatly help in determining peculiarities in our setting and bridge the gap in the aspects of prevention and management.

METHODOLOGY

This was a retrospective descriptive study conducted at the two tertiary health centres in Gusau, North-Western Nigeria. The case files of patients managed with DMFU at Federal Medical Centre Gusau and Ahmad Sani Yariman Bakura Specialist Hospital Gusau from 1st January 2017-31st December 2019 were retrieved. To be included in the study, an individual must have documented history or diagnosis of Diabetes Mellitus at the time of admission and admitted into the adult medical or surgical wards of these hospitals with foot disease. Those excluded were those with foot ulcers in the absence of Diabetes Mellitus.

Relevant information from the files was extracted by a Medical Officer such as Age, Sex, Occupation, duration of diabetes, duration of ulcer, risk factors and causes of Diabetic foot, Wagner grading, random plasma glucose at presentation, Packed cell volume, duration of hospital stay and outcomes such as ulcer healing, amputation, leaving against medical advice (LAMA), discharges or death.

Being a retrospective study, some of our limitations include the inability to determine the glycated haemoglobin of the patients which is a gold standard for glycaemic control, lack of complete microbiological studies of the ulcer, lack of Doppler ultrasound scan and inability to determine the exact reasons why some patients left against medical advice.

The data was analyzed using SPSS version 20.0 statistical software. Frequency distribution tables were constructed and comparison of association between proportions was determined with Chi-square (X^2). Continuous data were presented as means and compared with student's t-test. P-values <0.05 was considered significant at 95% confidence level.

RESULTS

One hundred and nineteen case notes of patients managed for DMFU were retrieved for the study period. They consisted of 45(37.8%) males and 74(62.2%) females. Their mean age was 56±12.8 years; males 57.7±12.7 and females 54.3±12.9; p= 0.12. The mean duration of Diabetes Mellitus was 4.8±4.29 years. Seventeen (14%) patients were diagnosed with Diabetes Mellitus after developing DMFU.

The duration of DMFU before presentation ranged from a day to 20 weeks with a mean of 4.02±4.6 weeks. Ninety-four (79%) patients presented within 4 weeks of developing the ulcer, while the remaining presented after 4 weeks.

The documented risk factors were peripheral neuropathy 65(55%), peripheral arterial disease 39(33%) and visual impairment in 11(9%). The causes of the DMFU identified are shown in Figure 1.

The Wagner grading of the DMFU at presentation is shown in Table 1. Sixty-three (52%) of the patients presented with Wagner grade III and IV; 27 (60%) males, 36(49%) females.

The mean random plasma Glucose at presentation was 18.69 mmol/L. One hundred and one (85%) patients had random plasma Glucose greater than 10mmol/L. Fifty-four (45%) patients had anaemia and 18(15%) of them were transfused with blood.

Figure 2 shows clinical outcome of the patients. Ninety- six (81%) patients were discharged [71 (74%) following normal healing, 25(26%) following amputation].

Fifteen (12.6%) patients left against medical advice (LAMA); 10(67%) males and 5(33%) females; p= 0.001. Eight patients (6.7%) died during admission; 5 males (62.5%) and 3 females (37.5%); p= 0.001.

The mean duration of admission was 5.4(±4.2) weeks. Fifty-five (57%) patients were discharged within a month, while 41(43%) were on admission for more than 4 weeks. Figure 3 shows the duration of hospital stay.

Twenty-five (21%) patients had amputations. The types of amputations done were trans-femoral in 18(72%) patients, trans-tibial in 3(12%) and disarticulation of toes in 4(16%) of the patients.

Predictors of ulcer healing were female gender, early presentation and packed cell volume greater than 24% (Table 2).

Table 1: Wagner grading

Grade	Description	Ma les(%)	Females(%)	Total(%)
0	Foot at risk with deformity or Callosities	0(0)	0(0)	0(0)
I	Superficial ulceration	4(9)	5(7)	9(8)
II	Deep Ulcer to tendons, ligaments or deep fascia	14(31)	33(44)	47(40)
III	Presence of Abscess or Osteomyelitis	12(27)	16(22)	28(23)
IV	Distal gangrene involving toes.	15(33)	20(27)	35(29)
V	Extensive gangrene	0(0)	0	0(0)
		45(100)	74(100)	119(100)

$X^2 = 1.2$ p= 0.3

Table 2: Predictors of ulcer healing

Predictor	DMFU-Healed Normally n=71 (%)	DMFU- Amputation+ Not Healed n=48 (%)	X^2	P-value
Gender				
Males	20(28)	25(52)	12	0.001
Females	51(72)	23(48)		
Duration of ulcer				
< 4 weeks	61(86)	33(69)	8.3	0.004
>4 weeks	10(14)	15(31)		
Wagner Grade				
I	9(13)	0(0)		
II	46(65)	1(1)	140	0.001
III	16(22)	12(25)		
IV	0(0)	35(74)		
RPG at presentation				
< 10mmol/L	10(14)	8(17)	0.8	0.3
>10mmol/L	61(86)	40(73)		
Anaemia (PCV)				
< 24%	4(6)	14(29)	18	0.001
>24%	67(94)	34(71)		

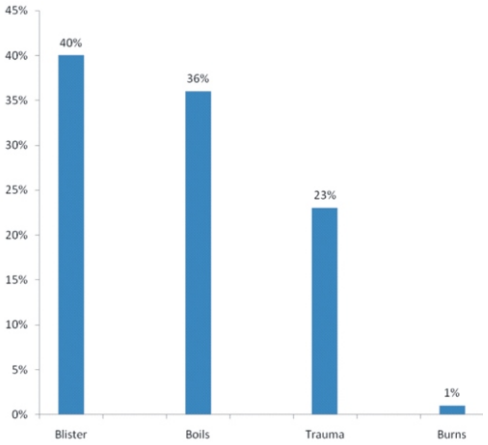

Figure 1: Causes of DMFU.

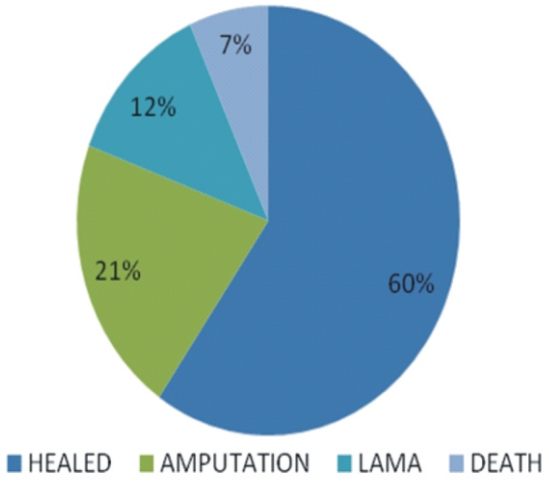

Figure 2: Outcome of DMFU

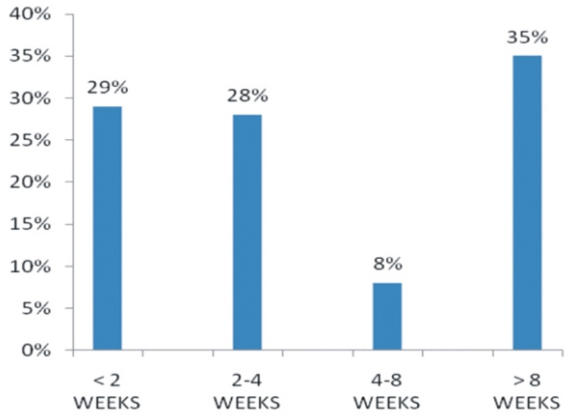

Figure 3: Duration of hospital stay

DISCUSSION

More females were admitted with DMFU in this study which is in keeping with the findings of Odusan *et al.* and Anumah *et al.* - they reported higher female admissions with DMFU of 78.9% and 52.4% in Lagos and Abuja respectively.[15,16] The mean age of our patients was 56 years which is similar to that of Anumah *et al.* whose patients had a mean age of 54.3 years, however, the mean age of patients of Odusan *et al.* was 61.1 years.[16,15]

The preponderance of women may be due to their health-seeking behaviour or the fact that the males who are mostly breadwinners in our society decline admission unless critical and manage their DMFU on an outpatient basis. A study has shown that males have a higher prevalence and severe neuropathy which is a major risk of DMFU compared to female's.[17] The higher prevalence of neuropathy in males is thought to be as a result of height difference between the genders, as males are generally taller and neuropathy affects longer nerve fibres, also, males have more occupational risks such as farming that predispose them to foot injuries.

Our finding that 21% of patients presented 4 weeks after onset of DMFU is similar to the findings of Akaa *et al.* - they reported that 19.6% of their patients with DMFU presented with more than 28 days history of foot ulcer.[18] The late presentation could be due to the trial of native and herbal medications and financial constraints. Late presentation is known to be associated with poor outcome as a result of sepsis.[19]

Aetiological and risk factors in this study were similar to findings from other studies.[16,20] Spontaneous blisters and abscesses were the commonest aetiologies while peripheral neuropathy was the major risk factor. The abscesses indicate an infection which usually occurs secondary to a breach in the skin.[14] Patient education on foot care and the need to visit the hospital immediately they observe a lesion in the foot will go a long way in halting the progression of DMFU and in preventing amputation.[14]

In this study 40% of our subjects presented with Wagner grade II DMFU which is similar to the finding of Jawad *et al.* in India who reported that 34.5% of their patients presented with grade II DMFU.[21] Sixty-three percent (63%) of our patients presented with Wagner grade II-III DMFU, similar to the finding of Anumah et al *et al.* that reported

66%.[16] Presentation with Wagner grade I-III DMFU gives a more favourable outcome than Wagner grade IV-V which often necessitates amputation.[22]

Majority of the patients with DMFU in this study had poor glycaemic control at presentation which could be due to wound infection and sepsis. This is similar to the finding of Salman *et al.* in Saudi Arabia who reported that only 5.6% of their patients with DMFU had good glycaemic control at presentation.[23] The poor glycaemic control seen in patients with wound infection and sepsis is due to the release of cytokines and anti-insulin hormones such as catecholamines which subsequently leads to glycolysis and lipolysis in the muscles and liver and resultant hyperglycaemia.[24]

The 45% prevalence of anaemia observed in this study agrees with the finding of Wright *et al.*, they reported a prevalence of 51.9% in their patients.[25] Gezawa *et al.* also found anaemia in 53.6% of their patients with DMFU and it was also found to significantly predict poor wound healing, amputation and risk of death.[26] The associations with anaemia from their study were nephropathy, osteomyelitis and foot gangrene.

The rate of amputation in this study is lower than that reported from Ibadan and Makurdi, 26.1% and 30.1% respectively, but higher than from Abuja which was 12.7%.[27,18,26] The difference may be attributed to the Wagner grade of the DMFU at presentation.

The 72% choice of trans-femoral amputation compared to other forms of amputation in our patients is higher than the 47.4% reported from Sokoto.[28] Tans-femoral amputation is safer when the extent of vascular compromise is extensive or not ascertained but leads to more challenges in prosthesis compared to trans-tibial amputation.[29] The higher rate of trans-femoral amputations in our patients may be due to late presentation, limited access and high cost of Doppler ultrasound scan that ascertain the extent of good blood supply. Amputation done at sites with impaired blood supply leads to delay in wound healing and may warrant amputation at a proximal site.

The mean duration of hospital stay in this study was about 5 weeks, which was similar to 35 and 38 days reported from Makurdi and Calabar respectively.[18,30] It was, however, shorter than that reported at Ibadan (52.9 days).[27]

Fifteen (12.6%) of our patients left against medical advice mostly due to financial constraints or failure to consent for surgery, this finding is similar to 13.7% reported from Abuja.[16] More males were observed to leave against medical advice because as breadwinners they have to source for their medications and means of livelihood for their families, therefore they could not endure prolonged stay in hospital.

The mortality rate of about 7% in our study is similar to that of Anumah *et al.* who reported 8.7% but lower than that from some centres[16,18,27] The mortality was higher among males (62.5%) in our study, similar to the 62.8% mortality rate among males reported from Australia.[31] The higher mortality rate among males may be explained by late presentation of males compared to their female counterparts.

CONCLUSION

DMFU is a cause of prolonged hospital admissions, amputations and mortalities in our patients with Diabetes Mellitus. Predictors of ulcer healing were early presentation, female gender and packed cell volume >24% at presentation. Sustained health education on foot care will go a long way in taming the tide.

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Ultrasonographic Correlation of Intravesical Prostatic Protrusion with Post-void Residual Urine among Patients with Benign Prostatic Hyperplasia in Calabar, Nigeria-a Pilot Study

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ABSTRACT

Bladder outlet obstruction due to benign prostatic hyperplasia (BPH) is a distressing situation, impacting negatively on patients' quality of life, so early detection is apt. Ultrasonography is a viable alternative to an invasive pressure flow meter for predicting bladder outlet obstruction. There is a dearth of work on the use of intravesical prostatic protrusion (IPP) as an ultrasonographic parameter in Nigeria and there might be racial variations similar to the observation with prostate volume. This study aims to sonographically assess the grade of IPP associated with significant post-void residual (PVR) urine volume. Sixty-three consecutive newly diagnosed BPH patients referred from the general outpatient department were recruited into the study over 18 months. Sonoscape A8 Ultrasound machine was used for the Trans-abdominal pelvic assessment. The measured IPP was graded as <5mm (I), 5-10mm (II) and >10mm (III) and the PVR urine volume as <50ml, 50 -100ml and >100ml. The prostate volumes were also stratified into four before correlating all the parameters. A post-void residual urine volume of 100ml was chosen as the threshold that defines obstruction due to the patients' average age (61.69 years). It was observed that 39.68% of all the patients had significant PVR urine volume. Across all prostate volume groups, only grade III IPP (>10mm) caused a significant mean PVR urine volume (111.76ml). Grade III was responsible for most of the significant PVR urine volume and 96.83% occurred at a prostate volume greater than 40ml.

Keywords: Ultrasonography, Benign Prostatic Hypertrophy, Prostatic Protrusion, Post-Void Urine Volume

INTRODUCTION

Benign prostatic hyperplasia (BPH), usually commences from the age of 40 years and is characterized by the formation of large, fairly discrete nodules in the periurethral region of the prostate gland. BPH results in enlargement and increase in the stromal smooth muscle tone of the gland which subsequently leads to bladder outlet obstruction (BOO). BOO is said to occur when there is a significant residual urine volume in the bladder immediately after voiding. The cut-off value for this significant volume is observed to be age-related and has been debated to be either above 50mls or 100mls. BOO patients may present in the clinic with a complaint of lower urinary tract symptoms (LUTS), haematuria or symptoms of urinary tract infection, bladder calculi and renal failure.[1] BOO significantly affects the quality of life, so early detection and intervention will help to preserve normal bladder function.[2] Most patients with LUTS due to BPH are initially seen by the general practitioners or primary care physicians and a lot of them initiate the medical treatment of the condition.[3-5] Management guidelines have been developed for BPH and all physicians need to be abreast with the protocol. Monitoring of BPH progression includes predicting which of the patients will develop BOO or acute urinary retention. An ideal diagnostic tool for predicting BOO should be non-invasive, cheap, reproducible and give prompt results.[6] Pressure flow studies are the gold standard for BOO assessment but they are invasive and can be complicated by urinary retention and gross haematuria.[7] These necessitated the search for non-invasive options. Ultrasonography is a viable alternative and its various parameters have been assessed for their accuracy mainly in Asia and some parts of Europe and America.[8-10] Though all the ultrasound parameters predict BOO to varying degrees, intra-vesical

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prostatic protrusion (IPP) and detrusor wall thickness (DWT) were found to be better tools than the prostate volume (PV), bladder wall thickness (BWT) and others by a majority of studies.[6,10] Results from other countries might not be applicable in Nigeria, because of the observed ethnic or racial variation in normal prostate volumes.[11,12] This variation might also exist for the grade of IPP associated with significant PVR urine volume. This has made it imperative for different ethnic nations and homogeneous groups to conduct local studies to develop their normal values of measured ultrasound parameters. The trans-abdominal approach will be utilized because it has been reported to be as accurate as the trans-rectal approach in measuring the prostatic volume.[13,14] This approach is also more acceptable by patients with low pain threshold and anal lesions like haemorrhoid, fissure or fistula-in-ano. Furthermore, though catheterization is more accurate in measuring the PVR urine volume, it is not the best option in terms of care and comfort.[15] Again, trans-abdominal ultrasonography has proven to be a reliable, alternative method of measuring PVR urine volume and thankfully it is not intrusive or invasive.[16] The ellipsoid formula for calculating volumes installed in the machine is reputable for estimating PVR urine volume,[17] as it is for prostate volume and the pre-void urine volume. Due to the pre-void volume of urine affecting the ultrasonographic evaluation of the bladder and prostate volumes, IPP and DWT, these parameters were obtained when the bladder was distended with 250-400ml of urine, for an accurate assessment and ease of comparison of results. The lower limit was chosen because the DWT is said to decrease continuously with increasing bladder filling up to 250ml and remains stable thereafter until maximum bladder capacity.[18] The upper limit prevents over distension which may displace and distort the prostate, making it volume assessment inaccurate.[14] In the same vein, measurement of IPP becomes unreliable above the upper limit but its estimation below 400ml correlates well with that obtained through the trans-rectal route.[19] This upper limit also prevents an uncomfortably full bladder which results in false positive, significant PVR urine volume, even in healthy young men. Eriz *et al.* advised that the pre-void volume should not be equal or greater than 540ml.[20] There is a dearth of data on the ultrasound assessment of IPP, particularly in correlation with an elaborate stratification of prostate volume into four groups among Nigerian men. This study aims to sonographically evaluate the IPP, PV and PVR urine volume in BPH and correlate these parameters. The grade of IPP with the propensity to result in BOO will then be determined.

SUBJECTS AND METHODS

This was a prospective observational study at a Secondary health care facility run by the Military in Calabar, Cross River state, Nigeria. The city accommodates a Teaching hospital and two public Secondary health facilities where BPH patients can be treated. The sample size for the pilot study was determined from the mean annual prevalence rate of BPH in a previous study in the city. Four hundred and sixty-three patients had confirmed diagnosis of BPH in 8 years giving an average prevalence rate of approximately 58 patients annually.[21] Five more subjects were added to this to make it 63. The 63 men aged 40 years and above, were newly diagnosed with BPH through a combination of digital rectal examination, PSA levels and sonographic features of the prostate gland. They were recruited from a single centre, over a study period of 18 months, between November 2015 and April 2017. They presented at the general outpatient clinic where the general practice physicians evaluated them. The severity of symptoms was assessed with the international prostate symptom score (IPSS) and digital rectal examination was done to assess the contour, consistency, nodal enlargement and prostate size to make a clinical diagnosis of BPH. They were subsequently sent for laboratory investigations which included prostate-specific antigen (PSA), serum electrolyte, urea and creatinine, full blood count and urinalysis.

Those with PSA levels and findings on digital rectal examination suggestive of BPH were then referred to the Radiology department for routine trans-abdominal ultrasonography. Informed consent was obtained from those who met the inclusion criteria before they were recruited into the study.

Inclusion criteria

Clinical diagnosis of BPH, PSA <4.0 ng/mL, absence of sugar, protein, nitrite or leukocyte esterase on urinalysis, normal values of full blood count and serum electrolyte, urea and creatinine and patients not yet on treatment.

Exclusion criteria

Associated Urethral stricture, Diabetic Mellitus, patients on 5 alpha-reductase inhibitors and alpha-blockers, neurological disorder, chronic renal insufficiency, prior pelvic or urinary tract surgery, prostatic or vesical carcinoma and bladder calculi.

Technique

The trans-abdominal ultrasound scans were carried out in the Radiology department using 3.5Hz curvilinear transducer of a Sonoscape A8 Ultrasound machine. The patients were instructed to drink water and were scanned when they had a moderate urge to void urine to guarantee a reasonable level of bladder filling. The patients laid in the supine position on the couch and were scanned through the supra-pubic region after application of the coupling gel. The pre-void urine volume was first measured to confirm that it was between 250 and 400mls to optimise the evaluation of the ultrasound parameters. The echotexture, outline and volume of the prostate gland were then assessed in transverse and sagittal planes. This was followed by the measurement of the IPP in the mid-sagittal plane. Finally, the patient was allowed to micturate and the PVR was assessed immediately after voiding.

The urine volume were obtained by measuring the length, width and height of the bladder lumen and prostate gland. The lengths of these organs were measured in the sagittal plane, while their width and height were measured in the transverse plane. The IPP was also measured in the midline sagittal plane. IPP is the perpendicular height of the prostate gland, from a line drawn where it adjoins the base of the bladder as shown in figure 1a and 1b. The PVR urine volume was measured immediately after voiding not exceeding 5 minutes to prevent significant refilling of the bladder. The measured IPP and PVR urine volume were put into three groups according to international standards and previous studies. The IPP grades are, I(<5mm), II(5-10mm) and III(>10mm), while the stratification for PVR urine volume was <50ml, 50-100ml and >100ml. Most of the previous studies divided the prostate volume into three or two groups. The three grade systems are <20ml, 20-40ml and >40ml or ≤30ml, 31-80ml and ≥81ml while the common two grading systems are <30ml and ≥30ml or <40ml and ≥40ml. For this study, the measured prostate volume was divided into four; 20-40ml, 41-60ml, 61-80ml and >80ml categories to capture all previous grading. These measured sonographic variables were correlated with each other and the results presented as means, frequencies and percentages.

RESULTS

The mean age of the 63 patients was 61.69 ± 9.82 years, with a range of 49-83 years. The age distribution of participants is shown in table 1. The overall mean PV was 56.18ml but most (36.51%) were between 20-40ml, followed by 41-60ml, which accounted for 33.33%. The grade of IPP increased as the mean PV increased from 38.59 to 64.44ml (table 2). The PV also correlated positively with the PVR urine volume. For the PVR urine volumes less than 50ml, the mean PV was 39.22 ± 11.60ml, for those between 50 -100ml, the mean PV was 55.94 ± 24.79ml and for those greater than 100ml, the mean PV was 74.68 ± 35.47ml. Grades I and II IPP had similar mean PVR urine volume values (between 77.00-78.00ml) which are within normal limits but this was high (111.76ml) for grade III (table

2). Table 3 summarises the number of patients in the 3 categories of PVR urine volume, according to their PV group and IPP grade. The 20-40ml PV was observed in 23 patients, 41-60ml in 21 patients, 61-80ml in nine patients and 10 patients had values greater than 80ml. It was also observed that 39.68% (N=25) had bladder outlet obstruction (PVR >100ml), 19.05% had equivocal PVR urine volume and 41.27% did not have obstruction. Generally, the grade of IPP increases with an increase in the PV and all those greater than 60ml had IPP above 5mm. The detailed frequency distribution of IPP grades amongst the PV's is highlighted in table 4. The frequency of obstruction amongst the IPP grades and PV groups are presented in table 5. Twenty percent of patients with grade I IPP, 25% of grade II and 60.71% of grade III had an obstruction. The rates of obstruction for patients with PV of 20-40ml, 41-60ml, 61-80ml and >80ml are 8.7%, 52.385%, 55.56% and 70% respectively.

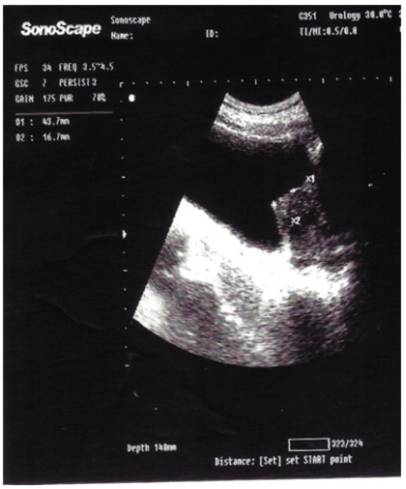

Figure 1a. Midline sagittal sonographic scan image, showing how to measure IPP; perpendicular height (line 2) from the line drawn across the base of the bladder (line 1).

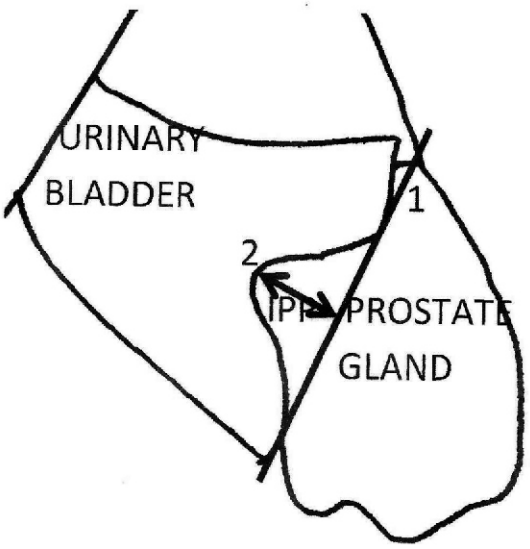

Figure 1b: Diagramatic representation of the ultrasound image showing how IPP (Intravesical prostatic protrusion) is measured.

Table 1. Age distribution of study population

Age group (years)	Frequency (n)
40-49	5
50-59	22
60 - 69	19
70 - 79	14
80 - 89	3
Total	63

Table 2. Mean PV and PVR urine volume in each grade of IPP

IPP (mm)	IPP grade	PV mean (ml)	PV range (ml)	PVR mean (ml)	PVR range (ml)
< 5	I	38.59±13.36	20.46-55.49	77.17±79.5	9.39-204.26
5-10	II	44.08±25.26	26.4-140	77.69±94.3	5.31-305
>10	III	64.44±31.28	26.9 -180	111.76±87.21	0-370

Table 3. Frequency distribution of patients according to their intravesical prostatic protrusion (IPP) grade, Prostatic volume (PV) and Post void residual (PVR) urine volume

IPP grade (mm)	PV group (ml)	Number of patients in the PVR groups (ml)			Total number
		<50	50 -100	>100	
I	20 - 40	2	1	-	3
(<5)	41 - 60	-	1	1	2
	61 - 80	-	-	-	0
	>80	-	-	-	0
II	20 - 40	10	1	-	11
(5-10)	41 - 60	4	-	3	7
	61 - 80	-	-	1	1
	>80	-	-	1	1
III	20 - 40	5	2	2	9
(>10)	41 - 60	2	3	7	12
	61 - 80	2	2	4	8
	>80	1	2	6	9
	Grand total number	26	12	25	63

Table 4. Frequency distribution of IPP grades amongst the prostatic volume

PV (ml)	Frequency distribution of IPP grades % (N)			Total % (N)
	I	II	III	
20-40	13.04(3)	47.83(11)	39.13(9)	100(23)
41-60	9.53(2)	33.33(7)	57.14(12)	100(21)
61-80	0.00(0)	11.11(1)	88.89(8)	100(9)
>80	0.00(0)	10.00(1)	90.00(9)	100(10)

Table 5. Distribution of obstruction amongst the IPP grades and PV groups

Frequency distribution of patients with obstruction in the PV groups and IPP grades % (n/N)				
	Prostate volume			
IPP Grade	20-40ml	41-60ml	61-80ml	>80ml
I	0.00(0/3)	50.00(1/2)	0.00(0/0)	0.00(0/0)
II	0.00(0/11)	42.86(3/7)	100.00(1/1)	100.00(1/1)
III	22.22(2/9)	58.33(7/12)	50.00(4/8)	66.67(6/9)

n= number of obstructed cases. N= total number of patients in the group.

DISCUSSION

A 100ml was chosen as a significant PVR urine volume to define BOO in this study, because of the average age of the patients. Among the three grades of IPP, this study revealed that only those >10mm (grade III) had a significantly high mean PVR urine volume (111.76ml) above the threshold for obstruction. This is higher than the observed cut-off value of 5mm by Reis LO *et al*, 5.5mm by Reddy SVK *et al.*, and 8.5mm by Keqin Z *et al.* who carried out their research in Asia and Latin America.[10,22,23] This study has revealed a racial variation in the IPP grade that is most likely to cause BOO, so 10mm should be used as the cut-off value for Nigerian men. IPP greater than 10mm has found relevance in patient stratification, for managing BPH and projection of its treatment outcomes. BPH patients with this grade of IPP were shown to have three times the probability to use medication than those of lower grades, and they also experience a higher rate of progression, clinically.[24,25]

The index study also shows a positive correlation between PV and IPP which is corroborated by other researchers, though the mean PV varied in the different studies.[22,26,27] Similarly, it was observed that the size of prostate gland affects the PVR; the mean PVR urine volume increased as the mean PV increased. A detailed look at the results showed that obstruction occurred among all grades of IPP but the frequency increased with an increase in PV within each grade. This study showed that 38 patients (60.31%) had grade III IPP which agrees with the 59.5% observed by Reis et al, but higher than the findings of Lee A *et al.* (31.15%), and Topazio L *et al.* (21.54%).[10,27,28] Grades I and II were observed in 7.94% and 31.75% of the patients, respectively. Grade III is responsible for 76% (N=19) of 25 patients who had obstruction, while grades II and I contributed 20% (N=5) and 4% (N=1) respectively. While evaluating each group, it was revealed that, 80% of patients with grade I did not develop obstruction which is similar to the finding of 79% by Chia et al who worked with a sample size of 200 over 30 months study period and 80.49% by Reddy SVK *et al.* who got 164 patients in 32 months.[29,22] Grade III IPP has the highest rate (50%) of obstruction in this index study, similar to, but with a much lower margin than the studies of Chia *et al.* (94%) and Reddy SVK *et al.* (83.3%).[29,22]

This study demonstrated a positive correlation between the mean PV and the degree of IPP; the higher the PV, the higher the grade of the IPP. Patients with low PV (20-40 ml), have the highest frequency (13.04%) of grade I IPP and the lowest rate of grade III IPP (39.13%). Conversely, those with prostate volume >80 ml, have the highest rate of grade III(90%) and no grade I(0%) IPP. It was also observed that PV influenced the possibility of obstruction within each grade of IPP. No obstruction occurred among patients with PV <40ml in grades I and II IPP. This study shows that it was only in grade III, obstruction occurred across all the PV groups, with the lowest rate of 22.22%, seen within 20-40ml group. These findings have shown that correlating the PV and the IPP give a better sonographic evaluation of BOO in BPH.

The limitation of this study is the sample size which might increase the margin of error.

CONCLUSION

Ultrasonographic assessment of the IPP is simple and reliable in patients with BPH having LUTS. Grade III IPP (>10mm) was responsible for most of the significant PVR urine volume (BOO) in men with a mean age of 61.69 years. PVs greater than 40ml, were responsible for most (96.83%) of the obstructions.

RECOMMENDATION

Ultrasonographic assessment of the IPP should be included in the protocol for evaluating patients with BPH presenting with LUTS. Further studies are recommended with larger sample size, possibly multicentre based, to draw more affirmative conclusions and to develop ultrasonographic IPP measurement as a predictive tool for BOO.

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