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Editorial comment

Ageing and Disability

The world's population is ageing and the low and middle income countries are not left out of this graying epidemic. The World Health Organization estimates that the world's population of persons aged 60 years and above will nearly double; with the proportion increasing from 12% to 22% between 2015 and 2050 [1]. The latest Global Burden of Disease 2015 analysis showed that life expectancy from birth has increased by more than one decade in many countries [2]. The gains were attributed to decreases in deaths from HIV/AIDS, malaria, neonatal preterm birth complications, and maternal disorders particularly in sub-Saharan Africa [2]. The longevity trend is a welcome development and indeed a good thing because nations can benefit from the wealth of experience of the older individuals, who can serve as custodians of tradition and culture as well as repositories of knowledge, provided they are cognitively intact. What matters therefore in old age is good quality of life.

Old age is characterized by infirmities and frailty. These are consequent upon immune senescence, accumulation of "wear and tear" or past insults to the body, sensory impairment and degeneration involving many organs. A German proverb likened old age to a hospital that takes in all diseases. Disability is assessed in terms of years lived with disability (YLD) and years of life lost (YLL) from which Disability Adjusted Life Years (DALY) is calculated. This has been the standard measure for the GBD studies and for international comparison.

This issue of the journal features a review paper on the assessment of disability in older adults living in low and middle income countries and highlights the importance of chronic diseases. The paucity of published data on the measurement of disability in older persons in sub-Saharan Africa was evident from this publication by Dr. Ojagbemi. The seven papers used for the systematic review were derived from studies in South and Central America and South East Asia. The review showed that sensory impairment in old age (visual and hearing) and dementia were the highest ranking diseases associated with disability in this old spectrum. However, since the geographic coverage is limited, more studies are needed in other low and middle income countries to add to the list of disability-causing chronic diseases. The publication is considered timely and a shot in the arm for researchers in SSA to focus on causes and impact of disability in older persons so that appropriate health policy changes can follow.

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Effects of trunk rotation and limb activation in the management of unilateral spatial neglect in adult stroke survivors

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Abstract

Background: Unilateral Spatial Neglect (USN) is a disabling feature and a frequent behavioural syndrome in stroke survivors. This study was designed to determine the effects of trunk rotation and limb activation in the management of USN in adult stroke survivors.

Method: Participants were 19 stroke survivors with USN. They were randomly assigned to an intervention group (n=10) and a control group (n=9). All participants took part in conventional physiotherapy protocol thrice a week for four weeks. During the same period, participants in the intervention group also received trunk rotation and limb activation treatment. Cognition, Functional Independence in Activities of Daily Living (ADLs) and severity of USN were assessed using Mini-Mental State Examination (MMSE), Barthel Index (BI) and Behavioural Inattention Test (BIT) respectively.

Results: In the Intervention group, the mean BIT scores increased from 111.20±44.87 to 209.60±13.48, mean BI scores increased from 42.50±29.74 to 74.00±18.07, while MMSE scores increased from 26.60±1.71 to 28.50±1.51. The changes were significant ($p \leq 0.05$). In the Control group, the mean BIT scores increased from 130.56±32.99 to 195.89±14.59, mean BI scores increased from 81.11±26.67 to 91.67±11.18, while MMSE scores increased from 27.33±1.23 to 28.56±0.53. The changes were significant ($p \leq 0.05$) except for the BI score. Between-group comparison showed significant post-intervention differences in BIT and BI ($p < 0.05$) scores, but not in MMSE score.

Conclusion: It was concluded that conventional physiotherapy, trunk rotation and limb activation were efficacious in the management of USN in stroke survivors.

Keywords: *Stroke, physiotherapy, unilateral spatial neglect, trunk rotation, limb activation.*

Résumé

Contexte: La Négligence Spatiale Unilatérale (NSU) est une caractéristique handicapante et un syndrome comportemental fréquent chez les survivants d'attaque paralytique. Cette étude a été conçue pour déterminer les effets de la rotation du tronc et de l'activation des membres dans la prise en charge de l'NSU chez les survivants adultesd'attaque paralytique.

Méthode: Les participants étaient 19 survivants d'attaque paralytique avec NSU. Ils ont été répartis au hasard entre un groupe d'intervention (n = 10) et un groupe témoin (n = 9). Tous les participants ont pris part au protocole de physiothérapie conventionnelle trois fois par semaine pendant quatre semaines. Au cours de la même période, les participants au groupe d'intervention ont également reçu une rotation du tronc et un traitement d'activation des membres. La cognition, l'indépendance fonctionnelle dans les activités de la vie quotidienne (AVQ) et la gravité de l'NSU ont été évalués à l'aide du Mini- Examen de l'Etat Mental (MEEM), l'IndexBarthel (IB) et du Test d'InattentionComportemental (TIC) respectivement.

Résultats: Dans le groupe d'Intervention, les scores moyens de TIC ont augmenté de 111.20 ± 44.87 à 209.60 ± 13.48, les scores moyens d'IB ont augmenté de 42.50 ± 29.74 à 74.00 ± 18.07, tandis que les scores de MEEM sont passés de 26.60 ± 1.71 à 28.50 ± 1.51. Les changements étaient significatifs (pd"0,05). Dans le groupe témoin, les scores moyens de BIT ont augmenté de 130,56 ± 32,99 à 195,89 ± 14,59, les scores moyens d'IB ont augmenté de 81,11 ± 26,67 à 91,67 ± 11,18, tandis que les scores de MEEM ont augmenté de 27,33 ± 1,23 à 28,56 ± 0,53. Les changements étaient significatifs (pd"0,05), sauf pour le score IB. La comparaison entre les groupes a montré des différences significatives après l'intervention dans les scores TIC et IB ($p < 0,05$), mais pas dans le score MEEM.

Conclusion: Il a été conclu que la physiothérapie conventionnelle, la rotation du tronc et l'activation des membres étaient efficaces dans la prise en charge de l'NSU chez les survivants d'attaque paralytique.

Mots-clés: *Attaque paralytique, physiothérapie, négligence spatiale unilatérale, rotation du tronc, activation des membres.*

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Introduction

Unilateral Spatial Neglect (USN) is one of the disabling features and a common behavioural syndrome in patients with stroke [1,2]. It is a neuropsychological disorder characterized by the inability to orient, explore, report or respond to stimuli appearing on the side contralateral to the brain lesion i.e. patients with USN fail to be aware of or acknowledge items on the contra lesional side (the left side for patients with right brain lesion) and attend instead to items towards the same side as the brain damage (the ipsi lesional side) [3,4]. Unilateral spatial neglect may be so profound that patients are unaware of large objects or even people in extra personal space and the neglect may also extend or be confined to personal space with patients failing to acknowledge their own contra lesional body parts in Activities of Daily Living (ADLs) [3,5].

Among stroke associated impairments that result in clinical deficit, the presence of USN has been consistently associated with slower functional progress during rehabilitation (longer rehabilitation and longer length of stay in the hospital), reduced ability to function in ADLs (most especially self-care activities), a greater risk for falls, poor functional recovery, and degrading Quality of Life (QoL) [6-9]. The reported prevalence of USN varies widely from 10% to 82% following right hemispheric stroke and from 15% to 65% following left hemispheric stroke [10,11]. Unilateral spatial neglect is frequently observed in right-handed patients following right hemispheric brain damage [13,14] and may also result from damage to the following parts of the brain: posterior parietal cortex, frontal lobe, cingulate gyrus, striatum and thalamus [10,13,14].

The presence of USN may be determined on the basis of a left-right asymmetry in performance of a variety of measures including line and letter cancellation, reading, drawing, mental imagery, attention to the body and naturalistic action tasks [5]. Different assessment tools have been developed for assessing USN in people who have suffered stroke. These instruments range from paper and pencil tests e.g. Albert's Test [15], Diller's Test [16], Line Bisection test [17], figure copying [18], Bells test [19], writing tests to behavioural tests e.g. the Behavioural Inattention Test (BIT), the Catherine Bergego Scale (CBS) and the Perceptual Assessment Battery [20-23].

Spontaneous recovery usually occurs in the majority of USN but symptoms remain severe in some patients [24]. Different treatment approaches have been developed to manage USN [25,26]. The treatments for USN fall under two types of behavioural approaches [2]. They are either recruiting the hemiplegic limbs to reduce a spatial preference over the ipsilesional space or improving awareness of contra lesional space to promote patients' attention [2,27]. Some of the approaches used in the management of USN include constraint-induced therapy [28], limb activation [29], neck muscle vibration [30], Functional Electrical Stimulation (FES) [31], trunk rotation [32], Transcutaneous Electrical Nerve Stimulation (TENS) [33], ipsilateral eye patching [34], spatial cueing [35] and visual scanning therapy [36].

It has been reported that trunk rotation therapy elicited improvement in patients with USN and it has been proposed that this effect is based on the relationship of the trunk position to the neck position [37]. Limb activation treatment consists of the joint activation of spatio-motor brain maps that enhance conscious representation of specific spatial sectors and may also facilitate multisensory integration [29,38]. Limb activation is based on the idea that any movement of the contra lesional side may function as a motor stimulus activating the brain and improving USN [37]. Empirical evidence which would be included in treatment approaches in the management of USN in stroke survivors would be of immense importance to clinical practice. Hence, this study was designed to evaluate the effects of trunk rotation and limb activation in the management of USN in adult stroke survivors.

Method

The study participants were drawn from a population of patients with stroke referred for outpatient management in two tertiary hospitals in Lagos metropolis. Inclusion criteria were first-episode single stroke with USN, stroke duration of less than six months, scoring less than 196 for the total Behavioural Inattention Test (BIT) and more than 23 points on the Mini-Mental State Examination (MMSE). Random assignment of participants to an intervention group or a control group was done by asking them to blindly draw one of two crushed pieces of paper from a can. Prior to the commencement of the study, ethical approval was sought and obtained from the Health Research and Ethics Committees of the two hospitals (ADM/DCST/HREC/2070 and LREC/10/06/455). Participants also gave written informed consent to take part in the study. A flowchart of the recruitment and allocation of subjects is presented in Figure 1.

On each day of treatment / training, participants observed a pre-exercise rest period of

10 minutes. Thereafter, participants in the intervention group received conventional physiotherapy protocol followed by counselling on USN and half an hour trunk rotation and limb activation treatment. Those in the control group took part in conventional physiotherapy protocol followed by counselling on USN. The conventional physiotherapy protocol consisted of active and passive range of motion (ROM) exercises, strength training, balance training, motor learning techniques and proprioceptive neuromuscular facilitation techniques. These procedures were carried out thrice a week; and for a total duration of four weeks.

Trunk rotation was performed by assisting or actively rotating the trunk 15–35 degrees from the vertical midline toward the neglected side within the peri-personal space. The important element is that the upper trunk initiates the rotation by activating the ipsilesional upper extremity which moves across the midline of the body to the contra lesional space by visual spatial motor cueing. The trunk rotation was performed in three different positions: supine lying on a mat, sitting unsupported on a plinth and standing in a standing frame with feet together. Limb activation is the active or assisted movement of the left upper and lower limbs along the left hemispace. The essentials of the method involve encouraging the participants to actively move the left extremities even in a small range during exploration of space. The movements were performed grossly for both upper and lower limbs and in three different positions: supine lying on a mat, sitting unsupported on a plinth, and standing in a standing frame.

The assessment protocol followed this sequence: Mini-Mental State Examination (MMSE), Barthel Index (BI) assessment and Behavioural Inattention Test (BIT). The MMSE is a brief screening tool that provides a quantitative assessment of cognitive impairment. It consists of 11 simple questions or tasks, typically grouped into 7 cognitive domains: orientation to time, orientation to place, registration of three words, attention and calculation, recall of three words, language and visual construction. The test yields a total score of 30; and levels of impairment are classified as: none (24-30); mild (18-23) and severe (0-17) [39]. The Barthel Index consists of ten common functional ADLs and administered through direct observation. Eight of the items represent activities related to personal care: feeding, bathing, grooming, dressing, bowels continent, bladder continent, toilet use and transfer (bed to chair and back); the remaining two are related to mobility on level surfaces and stairs. The index yields a total score out of 100, the higher the score, the greater the degree of functional independence [40].

The BIT was assessed by sitting the patient on a chair and a table placed in front of the patient. The BIT is a 15-item standardized test battery for assessing USN. It is divided into two major sections, each of which has its own set of subtests. The conventional section of the BIT (BITC) comprised the following 6 subtests: line crossing, letter cancellation, star cancellation, figure and shape copying, line bisection, and representational drawing. The behavioural section of BIT (BITB) comprised the following 9 subtests: picture scanning, phone dialling, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation, and card sorting [41]. The BIT yields a total score of 227 with lower scores indicating greater degrees of USN [42]. Cut-offs have been established for the total BIT as well as for each of the subsections such that a diagnosis of USN is suggested if a patients' score is lower than the cut-off [7,43]. The cut-off for the total BIT is 196 out of 227, 129 out of 146 for the BITC, and 67 out of 81 for the BITB [44]. The severity of USN can also be ranged as severe (BITC score 1–65) and less severe (BITC score 66–128).

Participants in both groups were assessed on the outcome measures pre- and post-intervention. Treatment administration and assessment of outcomes were done by different therapists. Scores from the subsets of MMSE, BI and BIT were summed together to provide the total score for each specific assessment at baseline and post-intervention.

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 17.0. Mann-Whitney *U* test and Wilcoxon signed-rank test were used for comparisons between the baseline and post-intervention assessment scores between groups and within groups respectively. Spearman's rank correlation coefficient (r) was used to determine relationship between functional recovery of ADLs, cognition and severity of USN at baseline. The level of significance was $p \leq 0.05$.

Results

A total of 59 patients with right hemispheric stroke were screened for inclusion in the study. Nineteen (19) subjects comprising 13 males and 6 females satisfied the inclusion criteria. There were ten (10) patients in the Intervention group and nine (9) in the Control group. The socio-demographic and clinical profile of the patients is presented in Table 1.

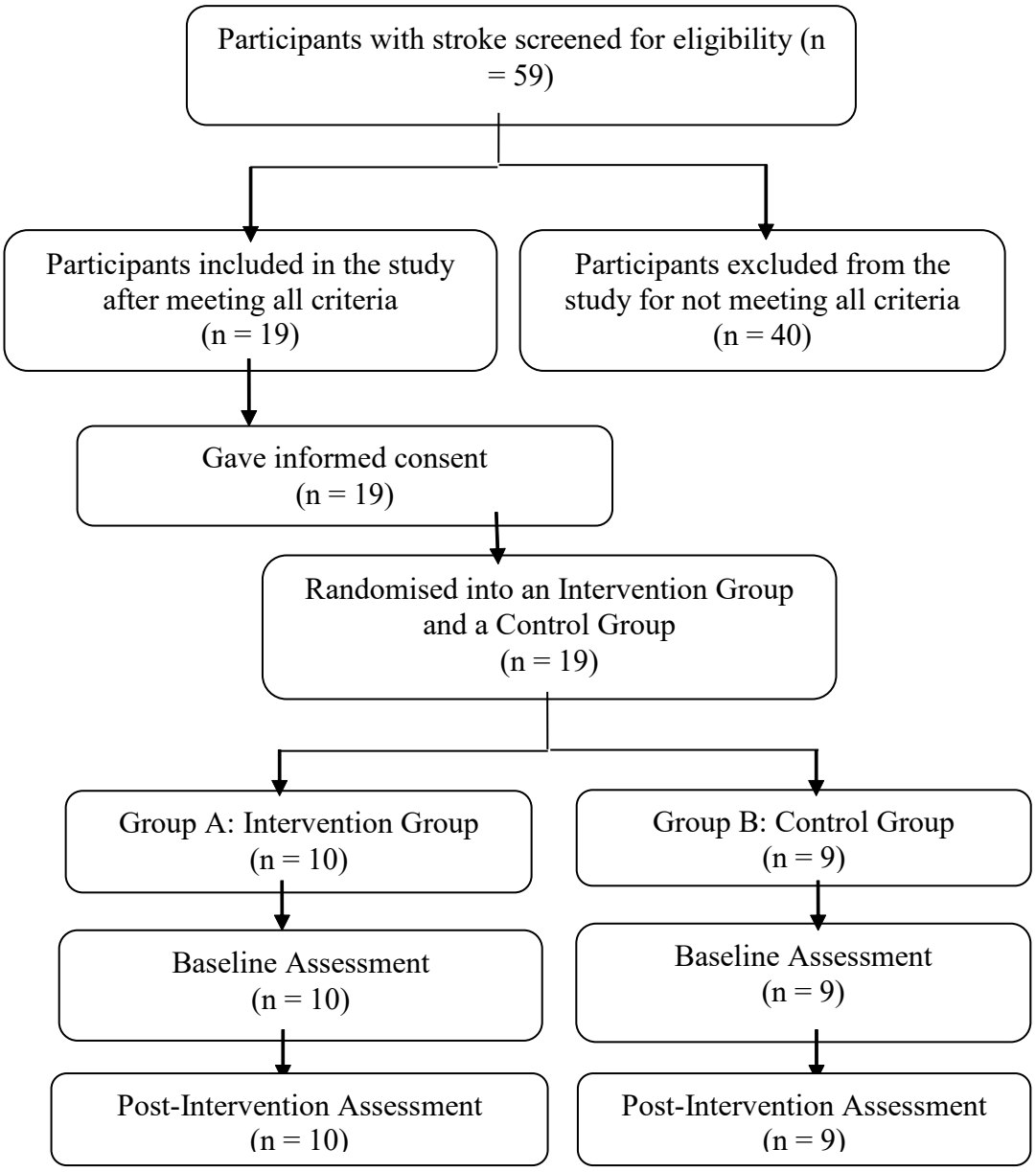
Participants with stroke screened for eligibility (n = 59)
Participants included in the study after meeting all criteria (n = 19)
Participants excluded from the study for not meeting all criteria (n = 40)
Gave informed consent (n = 19)
Randomised into an Intervention Group and a Control Group (n = 19)
Group A: Intervention Group (n = 10)
Group B: Control Group (n = 9)
Baseline Assessment (n = 10)
Baseline Assessment (n = 9)
Post-Intervention Assessment (n = 10)
Post-Intervention Assessment (n = 9)

Table 1: Socio-demographic and clinical profile of participants at baseline

Characteristics	Parameters	Intervention Group Mean±SD	Control Group Mean±SD	*z*-value	*p*-value
BaselineAssessment	Age (years)	52.50±8.48	55.67±8.31	-0.777	0.437
	Weeks post stroke	5.30±4.30	9.11±5.82	-1.521	0.128
	Length of hospital stay (days)	3.10±1.10	3.44±1.13	-0.907	0.365
	Days of unconsciousness	0.70±2.21	0.00±0.00	0.949	0.343
	Pre-BIT	111.20±44.87	130.56±32.99	-1.143	0.253
	Pre-BI	42.50±29.74	81.11±26.67	-2.711	0.007*
	Pre-MMSE	26.60±1.71	27.33±1.22	-0.930	0.352

*Significant at $p \leq 0.05$

Key
z-value: Wilcoxon rank-sum test value
SD: Standard Deviation
Pre-MMSE: Pre-Intervention Mini-Mental State Examination
Pre-BI: Pre-Intervention Barthel Index
Pre-BIT: Pre-Intervention Behavioural Inattention Test

Table 2: Changes in outcome measures within the groups

Groups	Outcome Measures	Pre-Intervention Mean±SD	Post-Intervention Mean±SD	*z*-value	*p*-value
Intervention Group					
	BIT	111.20±44.87	209.60±13.48	-2.803	0.005*
	BI	42.50±29.74	74.00±18.07	-2.680	0.007*
	MMSE	26.60±1.71	28.50±1.51	-2.699	0.007*
Control Group					
	BIT	130.56±32.99	195.89±14.59	-2.668	0.008*
	BI	81.11±26.67	91.67±11.18	-1.826	0.068
	MMSE	27.33±1.23	28.56±0.53	-2.414	0.016*

**Significant at $p \leq 0.05$*

Key
z-value: Wilcoxon signed-rank test
SD: Standard Deviation
MMSE: Mini-Mental State Examination
BI: Barthel Index
BIT: Behavioural Inattention Test

Changes in outcome measures

The changes in outcome measures for the two groups are shown in Table 2. In the Intervention group, the mean BIT scores increased from 111.20±44.87 to 209.60±13.48, mean BI scores increased from 42.50±29.74 to 74.00±18.07, while MMSE scores increased from 26.60±1.71 to 28.50±1.51 after 4 weeks of rehabilitation. The changes were significant ($p \leq 0.05$). In the Control group, the mean BIT scores increased from 130.56±32.99 to 195.89±14.59, mean BI scores increased from 81.11±26.67 to 91.67±11.18, while MMSE scores increased from 27.33±1.23 to 28.56±0.53 after 4 weeks of rehabilitation. The changes in BIT and MMSE scores were significant ($p \leq 0.05$).

Table 3: Between group comparison of changes in outcome measures

Outcome Measure	Intervention group Mean±SD	Control group Mean±SD	*U*-value	*z*-value	*p*-value
BIT	-98.40±38.83	-65.33±22.42	21.00	-1.960	0.050*
BI	-31.50±23.58	10.56±17.76	18.50	-2.207	0.027*
MMSE	-1.90±1.52	-1.22±0.97	34.00	-0.944	0.345

**Significant at $p \leq 0.05$*

Key
U-value: Mann-Whitney U value
z-value: Wilcoxon rank-sum test value
SD: Standard Deviation
MMSE: Mini-Mental State Examination
BI: Barthel Index
BIT: Behavioural Inattention Test

Between-group comparison of mean changes in outcome measures

The mean changes in the pre-intervention and post-intervention scores of MMSE, BI and BIT scores of the participants in both groups were compared. The comparisons are shown in Table 3. There was a significant difference ($p \leq 0.05$) in changes of BI and BIT scores between the intervention and control groups but there was no significant difference in MMSE scores ($p > 0.05$).

Discussion

This study was conducted to evaluate the effects of trunk rotation and limb activation in the management of unilateral spatial neglect (USN) in adult stroke survivors. Significant differences were observed between the baseline and post-intervention scores of Behavioural Inattention Test (BIT), Barthel Index (BI) and Mini-Mental State Examination (MMSE) in participants treated with conventional physiotherapy protocol combined with trunk rotation and limb activation. This means that the severity of USN reduced, functional recovery of ADLs increased and cognition increased. Also, changes in BIT and BI scores between the intervention and control groups were significant at the end of four weeks of intervention.

The small sample size was one of the limitations of this study. A larger number of patients would probably have yielded more robust and comparable results. Also, subjects for the study were heterogeneous (i.e. ischaemic and haemorrhagic) in terms of nature of stroke. Functional outcomes of rehabilitation in such patients are more difficult to elicit than in a homogeneous group of patients with stroke. The results of the study might also have been weakened by the fact that different physiotherapists conducted the treatments and assessments. Patient management was also limited to 3 sessions per week and the total duration was four weeks.

Patients in the two groups recorded significant changes in BIT scores after four weeks of rehabilitation; but changes observed in the intervention group were higher. Similar results have been reported in other studies. In a study [45] it was reported that stroke survivors with USN in the limb activation group recovered signiûcantly in the Conventional section of Behavioural Inattention Test (BITC) scores after rehabilitation. Reduction in severity of USN had also been reported in patients who had conventional physiotherapy protocol combined with trunk rotation and visual scanning [46]. In another study, subjects who were treated using the limb activation approach demonstrated reduction in USN in a single-subject series using either a scanning and cueing strategy or a left-limb activation strategy [47].

The outcome of this study also showed that there was significant difference between the baseline and post-treatment scores of BIT and MMSE in participants treated with conventional physiotherapy protocol. This indicates a reduction in severity of USN and increase in cognition in stroke survivors treated with conventional physiotherapy protocol. In some studies [2,32,46], conventional physiotherapy protocol was reported to have yielded results similar to those of the present study. There was no significant difference between the baseline and post-treatment scores of BI in participants treated with conventional physiotherapy protocol. This means that there was no significant change in the functional recovery of

ADLs. Hence, the outcome of this study did not demonstrate any beneficial effect of conventional physiotherapy protocol on functional recovery of ADLs.

The results of the study also showed reduction in the severity of USN and increase in functional recovery of ADLs in the intervention group compared with the control group. This finding is different from the reports of another study where it was reported that there was no significant difference among voluntary trunk rotation, voluntary trunk rotation and half-field eye-patching and controls in functional performance and severity of USN after 30 days of intervention [32]. In the same study [32], it was reported that voluntary trunk rotation was initiated by the ipsilesional (right) hand and this might abolish the advantage of left limb activation, and therefore might provide an explanation as to why the trunk rotation group had resulted in improvements in mobility rather than unilateral neglect. Another study [2] reported that participants who had sensory cueing and limb activation treatment were not different from those that did not receive sensory cueing and limb activation treatment to reduce USN.

The outcome of this study also showed that there was significant relationship between severity of USN, functional recovery of ADLs and cognition in right hemispheric stroke survivors with USN at baseline. This observation is similar to that made in an earlier study [47] where it was reported that patients with USN have greater functional disabilities. In another study [7] it was reported that there was correlation and significant association between severity of USN and functional recovery of ADLs measured with FIM at admission. Also, it has been stated that patients with USN have lower FIM scores than patients without USN, and USN is a major predictor of func-tional outcome from admission to follow up in patients with left hemiplegic stroke [2].

Conclusion

Based on the findings of this study, it was concluded that conventional physiotherapy and conventional physiotherapy protocol combined with trunk rotation and limb activation were efficacious in the management of USN in stroke survivors. The present study did not examine the influence of premorbid hand dominance/laterality on recovery of USN and this is recommended for further studies.

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Predictive value of the Edinburgh claudication questionnaire in diagnosing peripheral arterial disease among Nigerian adults

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Abstract
*Background***:** Although Peripheral arterial disease (PAD) is a strong predictor of adverse cardiovascular events, it is frequently unrecognized and under diagnosed. When the diagnosis is considered, it is often made by eliciting the presence of intermittent claudication using the Edinburgh Claudication Questionnaire (ECQ) whereas the Ankle Brachial Index (ABI) is a simpler and more objective means of making the diagnosis with a sensitivity and specificity of > 90%.
Objective : To determine the predictive values of Edinburgh Claudication Questionnaire in the diagnosis of PAD among adult patients in Sagamu, south western Nigeria.
*Methods***:** A cross-sectional study of 400 patients aged ≥ 50 years attending the General Out- Patients Clinic of Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria was carried out. ECQ was administered on all the subjects to determine the presence of intermittent claudication (IC) and their ABI were also measured. A value of ABI d" 0.9 was taken as diagnostic of PAD. The prevalence of PAD, the sensitivity, specificity, positive and negative predictive values of ECQ against ABI were evaluated.
Results: Using ECQ 25 (6.3%) of the patients had PAD while 99 (24.8%) had PAD when ABI was used. Among these 99 patients, 17 (17.2%) had symptoms consistent with IC based on ECQ. The presence of IC was significantly associated with ABI values d"0.9 (p = 0.000).The sensitivity of ECQ was 17.2% while the specificity was 99% with a positive predictive value of 85% and a negative predictive value of 77.7%.
Conclusion: The ECQ is not a useful tool for the screening of PAD given its low sensitivity. Its use would result in missing a large number of patients with asymptomatic PAD who would have benefitted from interventions.

Keywords: *Intermittent Claudication, Peripheral arterial disease, Ankle brachial index, Edinburgh Claudication Questionnaire, sensitivity, specificity*.

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Résumé
Contexte: Bien que la maladie artérielle périphérique (MAP) soit un prédicteur puissant des événements cardiovasculaires indésirables, elle est souvent méconnue et sous-diagnostiquée. Lorsque le diagnostic est pris en considération, on le fait souvent en provoquant la présence d'une claudication intermittente en utilisant l'Edinburgh Claudication Questionnaire (ECQ), alors que l'index Brachial de la cheville (ABI)est un moyen plus simple et plus objectif de faire le diagnostic avec une sensibilité et une spécificité de > 90%.
Objectif: Déterminer les valeurs prédictives d'Edinburgh Claudication Questionnaire dans le diagnostic de MAP chez des patients adultes à Sagamu, sud-ouest du Nigeria.
Méthodes: Une étude transversale de 400 patients âgés de e" 50 ans fréquentant la Clinique Générale pour Patients Non-Hospitalisés de l'Hôpital d'Enseignement Universitaire OlabisiOnabanjo, Sagamu, Nigéria, a été réalisée. ECQ a été administré sur tous les sujets pour déterminer la présence de claudication intermittente (IC) et leur ABI ont également été mesurés. Une valeur d'ABI d" 0,9 a été prise comme diagnostic de MAP. On a évalué la prévalence de la MAP, la sensibilité, la spécificité, les valeurs prédictives positives et négatives de l'ECQ par rapport à ABI.
Résultats: En utilisant l'ECQ, 25 (6,3%) des patients avaient MAPcependant 99 (24,8%) avaient MAP quand ABI a été utilisé. Parmi ces 99 patients, 17 (17,2%) avaient des symptômes compatibles avec l'IC basée sur l'ECQ. La présence de l'IC était significativement associée aux valeurs d'ABI d"0,9 (p = 0,000).La sensibilité de l'ECQ était de 17,2% alors que la spécificité était de 99% avec une valeur prédictive positive de 85% et une valeur prédictive négative de 77,7%.
Conclusion: L'ECQ n'est pas un outil utile pour le dépistage du MAPétant donné sa faible sensibilité. Son utilisation entraînerait la disparition d'un grand nombre de patients atteints de MAP asymptomatique qui auraient bénéficié d'interventions.

Mots-clés: *Claudication intermittente, Maladie artérielle périphérique, Index brachialde la cheville, Edinburgh Claudication Questionnaire, sensibilité, spécificité.*

Introduction

Peripheral arterial disease (PAD) is frequently associated with increased cardiovascular morbidity and mortality because the underlying pathological process, atherosclerosis, is a systemic one. Atherosclerosis, if present in the peripheral vessels, is also likely to be present in the coronary and cerebral vasculature [1]. Therefore, individuals with PAD have a high chance of suffering angina, acute myocardial infarction, transient ischaemic attack and stroke [2]. PAD is thus considered an independent biomarker of cardiovascular disease [3]. The gold standard in the diagnosis of PAD is the Ankle Brachial Index (ABI), which is the ratio of Doppler recorded systolic arterial blood pressure at the ankle, usually dorsalis pedis artery, to brachial systolic blood pressure [4,5]. Values of ABI $\leq$ 0.9 predicts the diagnosis of PAD in both symptomatic as well as asymptomatic patients with a sensitivity and specificity of > 90% for detecting angiographically confirmed PAD [4-6]. However, despite the simplicity of this procedure, ABI is not widely used by clinicians because of poor awareness that a low ABI is a marker of cardiovascular risk, the misconception that it is a specialist test for use only by vascular surgeons and physicians and the lack of familiarity with the procedure [7]. As a result of this, the diagnosis of PAD tends to be made based on the presence of intermittent claudication (IC) which is the classical symptom of PAD.

Intermittent claudication is defined as exertional calf pain that is relieved within 10 minutes of resting and is usually assessed by the Edinburgh Claudication Questionnaire (ECQ), which is an improved version of WHO/Rose Claudication Questionnaire [8]. Compared with the diagnosis of PAD made by clinical examination, ECQ had been shown to be 91.3% sensitive and 99.3% specific in detecting IC in the general population [8,9] . Given that the diagnosis of PAD is often made based on the presence of IC, this study was conducted to look at the predictability of ECQ as a screening tool for the diagnosis of PAD compared with ABI as a gold standard in a general practice setting.

Materials and methods

The study formed part of a cross-sectional study on the profile of ABI of adult patients attending the General Out-Patient clinic of Olabisi Onabanjo University Teaching hospital (OOUTH), Sagamu, south west of Nigeria and was carried out on consecutive working days from January to May 2011. The target population was adult patients attending the clinic and aged $\geq$ 50 years. The study population was determined using the sample size calculation for prevalence studies [10]. This gave a sample size of 376 which was approximated to 400. The recruitment was done by systematic random sampling in which every fourth patient was selected. Excluded from the study were those with respiratory distress and clinical features suggestive of deep vein thrombosis, to prevent embolism which may occur while measuring ABI. The presence of IC among the patients was determined using ECQ as shown in Table 1.

The ABI of the participants were measured using *Accoson*® sphygmomanometer with appropriate cuff and hand-held 10-MHz Doppler device with vascular probe (*Huntleigh Healthcare Mini Dopplex Model No 0900*). Each patient was allowed to rest for 10 minutes in the supine position on the examination couch. The brachial systolic pressure was measured by applying the cuff of the sphygmomanometer on the upper arm of the patient with the lower edge approximately 1 inch above the antecubital fossa. The brachial artery was localized by palpation and conductivity gel applied over it. The tip of the probe of Doppler device was placed on the gel at 45-60 degree angle until clear arterial pulse sounds were heard. The cuff was inflated

Table 1: The Edinburgh Claudication Questionnaire for detecting intermittent claudication [8].

If a patient describes pain or discomfort in the legs when they walk, ask **Question**	**Interpretation**
Does the pain ever begin when you are standing still or sitting?	No = IC
Do you get pain if you walk uphill or hurry?Yes = IC	
Do you get pain if you walk at an ordinary pace on the level?	No = mild IC Yes = moderate/severe IC
What happen if you stand still?	Pain goes away = IC
Does pain disappear within 10 minutes or less when you stand still	Yes = IC
Where do you get the pain or discomfort?	IC is present if patient indicates pain in the calf irrespective of whether pain is indicated in any other part of the body

progressively up to 20 mmHg above the level of flow signal disappearance and then deflated slowly to detect the pressure of flow signal reappearance. The corresponding cuff pressure is the systolic pressure. This procedure was repeated in the other arm. The ankle systolic pressure was measured by applying the cuff on the patient's leg just above the medial malleolus. The dorsalis pedis pulse was palpated and the gel applied. The tip of the Doppler probe was applied to the gel and the systolic pressure measured following the same step described for the arm. The systolic pressure from the posterior tibial artery was similarly measured. The same procedure was repeated for the other leg. The ABI was calculated for each leg by dividing the higher of the systolic blood pressure in the ankle by the higher systolic blood pressure in the arm [4]. The diagnosis of PAD was made if the ABI in either of the leg was d" 0.9.Normal ABI was taken as >0.9 while ABI of > 1.3 indicated incompressibility of the artery as a result of calcification [4]. Due to poor correlation between calcification and severity of atherosclerosis, the ABI is generally unreliable in this situation (i.e.>1.3) and was excluded from the analysis.

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 16 and descriptive statistics was used to present the results. The Chi-square test was used to determine the association between categorical variables with the level of significance set at $p< 0.05$.

The study was approved by the Health Research and Ethical Committee of the Olabisi Onabanjo University Teaching Hospital, Sagamu. Informed written consent was obtained from each of the participants.

Results

Table 2 shows the demographic data and results of investigation with ECQ and ABI. The mean age was 62.5 ± 9.29 years and there were 244 (36%) males and 256 (64%) females. The prevalence of PAD using both ABI and ECQ were also shown. With the value of ABI of ≤0.9 for the diagnosis of PAD, 99 (24.8%) had PAD while with ECQ only 25 (6.2%) were diagnosed as having PAD. 13 (3.3%) of the patients had arterial calcification and so could not have a successful ABI. Table 3 is a cross-tabulation of ABI and IC showing that of the 99 patients who were found to have PAD using ABI, only 17 (17.2%) had IC while the majority (82.8%) did not have. The presence of IC was significantly associated with ABI values ≤0.9 ($p = 0.000$). The sensitivity, specificity, positive and negative predictive values of ECQ in the diagnosis of PAD are shown in Table 4.

Table 2: Demographic data and results of ankle brachial index and Edinburgh Claudication Questionnaire in all patients

Parameters	Frequency n=400	%
Age group (yrs)		
50-59	162	40.5
60-69	146	36.5
≥70	92	23.0
Gender		
Male	244	36
Female	256	64
ABI		
PAD present	99	24.8
PAD absent	288	72.0
Arterial calcification	13	3.3
ECQ		
PAD present	25	6.2
PAD absent	375	93.8

Table 3: Cross-tabulation of Ankle brachial index and Intermittent Claudication

ABI	IC		Total	Chi-square
	Yes	No		
High ABI	5 (38.5%)	8 (61.5%)	13	0.000
Low ABI	17 (17.2%)	82 (82.8%)	99	
Normal ABI	3 (1.0%)	285 (99.0%)	288	

Table 4: Predictive values of Edinburgh Claudication Questionnaire for Peripheral arterial disease

ECQ	Low ABI (PAD present)	Normal ABI (PAD absent)
IC present	17 (true positive)	3 (false positive)
IC absent	82 (false negative)	285 (true negative)

Sensitivity (17.1%), Specificity (99%), Positive predictive value (85%), Negative predictive value (77.7%).

Discussion

Reports on the prevalence of PAD varied depending on the methods used and the population studied. It had been found to be between 1.6%-6.4% based on Rose Questionnaire/ECQ and 8%-52.5% based on ABI [11-14]. In this study, similar prevalence of PAD was found as the use of ABI and ECQ gave a prevalence of 24.8% and 6.3% respectively. While the asymptomatic nature of PAD had been shown in many studies mainly in high risk group such as the cigarette smokers and diabetics[1,2,12] , the finding from this study showed that even among unselected group of patients in general practice, PAD is largely asymptomatic as only 17 (17.2%) of the 99 patients with low ABI reported intermittent claudication. Similarly, Bernstein *et al.* found out that 20% of patients referred by primary care physicians for evaluation of lower extremity pain have asymptomatic PAD irrespective of the cardiovascular risk status [15]. The ECQ showed a low sensitivity of 17.2% and a high specificity of 99% with a positive predictive value of 85% and a negative predictive value of 77.7% for an ABI of **d"**0.9 for PAD. Even among high risk patients the sensitivity and specificity of ECQ range between 25% - 28.6% and 90.0%-99.4% respectively [9,16] . The implication of this is that ECQ is not a very reliable screening tool for PAD given its low sensitivity. This is due to the fact that ECQ evaluates PAD symptoms and so cannot be expected to detect asymptomatic disease, which represents a large proportion of the total PAD burden [17] .However, its high positive and negative predictive values make it a good diagnostic tool for PAD.

Many studies have shown that using the presence of IC as screening for PAD, would result in missing large number of patients who would have benefitted from early interventions to prevent adverse effects of atherosclerosis [6,7,9]. It has also been shown that a history of IC, underestimated the presence of PAD by a factor of two to five and screening for PAD on the basis of finding a complaint of IC will miss up to 90% of high risk patients with the disease [7]. While the previous studies were done on high risk groups such as diabetic patients in which the presence of peripheral neuropathy may mask IC, the present study was carried out on an undifferentiated group of patients frequently encountered in general practice. Yet the results are similar, implying that even among patients considered as low risk, ECQ is not a very useful screening tool for PAD. In this group of patients other causes of leg pain such as neurological, musculoskeletal and venous pathology may exist or coexist with leg pain from PAD, confounding the diagnosis of PAD by ECQ. Additionally, IC may be atypical in its presentation with potential of ECQ missing the diagnosis of PAD [16,18]. These may limit the ability of ECQ to detect PAD to an appreciable extent.

A limitation of this study is that more than half of the study population (59.5%) were aged 60 years and above. This group of patients may be less active thereby not generating enough exertion to provoke calf pain and may even take the pain as part of normal ageing process [18].

Conclusion

The prevalence of PAD using ABI was 24.8% while it was 6.3% based on ECQ. This means that just about a quarter of patients with PAD have symptoms of IC. While the ECQ was demonstrated to have high positive and negative predictive values, its low sensitivity renders it a poor screening tool for screening for PAD even among patients considered as low risk. It is suggested that primary care physicians should be familiar with the procedure for ABI assessment in order to detect PAD early and institute appropriate strategies to prevent adverse cardiovascular events.

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Pattern and outcome of radiotherapy management of oral cancers in a Nigerian Teaching Hospital: a twenty four year experience

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Abstract
Introduction: The incidence of oral cavity cancer is on the increase. Most cases present late resulting in poor prognosis of the disease. In the last few decades there has been an increasing trend of use of radiotherapy to treat oral cancers with improvement in survival. This retrospective study was aimed at determining the pattern of oral cancers seen at Radiotherapy Department of University College Hospital Ibadan and also to assess outcome of treatments offered over a period of 24 years.
*Methodology***:** Data extraction form was designed to obtain information from case notes and treatment records of patients with histologically diagnosed oral cavity cancer from 1987 to 2011 at the Radiotherapy clinic. The outcome of treatment at 6 months follow up was determined as either complete or partial/ no clinical response. Symptom free interval was also determined for each patient.
*Results***:** A total of 88 patients with histologically diagnosed oral cavity cancer were analysed. The mean age of presentation was 51.8 years with M: F ratio 1.8: 1. The mean duration of symptoms was 13.4 months. All the patients in this study had radiotherapy. Complete clinical response was seen in 35 patients (39.8%) while partial and no response was observed in 53 (60.2%) patients. Patients who had radical doses of radiotherapy, early stage at presentation and multimodality treatment were found to have better outcome.
*Conclusion***:** Oral cancer patients present late in our environment, Radiotherapy in combination with other modalities of treatment have been found to have better outcome.

Keywords - *Radiotherapy Management, clinical response, symptom free interval*

Résumé
Contexte : L'incidence du cancer de la cavité buccale est en augmentation. La plupart des cas se présentent tardivement, ce qui entraîne un mauvais pronostic de la maladie. Dans les dernières décennies il ya eu une tendance croissante de l'utilisation de la radiothérapie pour traiter les cancers oraux avec une amélioration de survie. Cette étude rétrospective visait à déterminer le schéma des cancers oraux observés au département de radiothérapie du Collège Hospitalier Universitaire d'Ibadan et aussi évaluer les résultats des traitements offerts sur une période de 24 ans.
Méthodologie: Le formulaire d'extraction de données a été conçu pour obtenir des informations à partir des notes de cas et des dossiers de traitement des patients atteints d'un cancer histologique de la cavité buccale de 1987 à 2011 à la clinique de radiothérapie. L'issue du traitement à 6 mois de suivi a été déterminée comme complète ou partielle / pas de réponse clinique. L'intervalle libre de symptômes a également été déterminé pour chaque patient.
Résultats: Un total de 88 patients ayant un cancer histologique de la cavité buccale ont été analysés. L'âge moyen de présentation était de 51,8 ans avec un rapport M:F de 1,8:1. La durée moyenne des symptômes était de 13,4 mois. Tous les patients de cette étude avaient une radiothérapie. Une réponse clinique complète a été observée chez 35 patients (39,8%) alors que la réponse partielle et aucune réponse n'a été observée chez 53 (60,2%) patients. Les patients qui ont reçu des doses radicales de radiothérapie, au stade précoce de la présentation et au traitement multimodal ont été jugés à avoir de meilleurs résultats.
Conclusion: Les patients atteints d'un cancer buccal se présentent tardivement dans notre environnement, la radiothérapie en association avec d'autres modalités de traitement s'est révélée avoir de meilleurs résultats.

Mots-clés - *Gestion de la radiothérapie, Cancer buccal, survie*

Introduction

According to the American joint committee on cancer (AJCC) the oral cavity is defined as the region extending from the mucocutaneous border of the lips to the junction of the hard and soft palate superiorly and inferiorly to the line of the circumvallate papillae

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of the tongue [1]. The oral cavity consists of the lips, buccal mucosa, alveolar gingivae, oral tongue, and floor of the mouth (FOM), hard palate, and retromolar region.

Cancer of the oral cavity is said to be uncommon, it is the sixth most common cancer worldwide [2] with over 274,000 new oral cavity cancers diagnosed annually, out of which two-thirds occur in developing countries [3]. There is a worldwide geographic variation in the prevalence of oral cancers ranging from only a few percent in most Western countries to over 40% in South and South-East Asia [4]. Data from Africa are limited to a few hospital cancer registries. It is therefore difficult to extrapolate the true incidence in these countries; however reported rates do not show evidence that oral cancer is a serious problem in the African continent [5]. Elumelu et al (2011) [6] at the Radiotherapy department University College Hospital (UCH), Ibadan found that oral cavity cancer consists about 12% of all head and neck cancers and squamous cell carcinoma is the most common histology.

Surgery, radiotherapy, chemotherapy, or combination of these modalities are classical treatment options for patients with cancers of the oral cavity. The choice of treatment modality depends on the stage of the disease and patient factors such as toxicity, performance status, co morbid disease, and convenience. Broadly speaking, single modality treatment is preferred for early stage lesions and combined modality for more advanced lesions [7].

The change in trend in the management and outcome of oral cancers over the years was demonstrated in a study by Carvalho et al (2004) [8]; in the 1950s only 29.1% of oral cancer patients were treated by surgery alone, 54.5% by radiotherapy and 16.4% by combined treatment; while in the 1990s there was increased use of multimodality treatment with 39.7% treated with surgery alone, 9.7% with radiotherapy alone and 50.6% by combined treatment. They also reported a significant increase in the 5-year survival rates from 28.7% for patients treated in the 1950s to 43.2% in the 1990s.

This study was therefore designed to determine the pattern of oral cancer in our environment, evaluate the role of radiotherapy in its management and outcome.

Materials and methods

This was a retrospective study of all patients with histologically diagnosed oral cavity cancer who received external beam radiotherapy at the Department of Radiotherapy, University College Hospital (UCH), Ibadan, from November 1987 to December 2011. Patients with tumours of the jaw bones, facial skin, major salivary gland tumours, tonsils and oropharynx, children (age d”15years) with oral cancer and patients who did not receive radiotherapy in Ibadan were excluded. All available records of oral cavity cancer patients treated during the study period were retrieved and analysed. Information obtained include patients’ bio-data (age, gender and occupation), duration of illness prior to presentation, stage at presentation and histology. Socioeconomic class was classified according to Boroffka and Olatawura (1976) [9]. The details of treatment received were also taken into consideration e.g. dose and mode of radiotherapy, surgery, chemotherapy regimen. Lesions were classified according to primary site as described in the WHO International Classification of Diseases+ for Oncology ICD-10 2010 [10]. Tumour involving more than one site or multiple simultaneous primary tumours was classified as multiple sites. The patients were retrospectively restaged using the 2010 edition of the American Joint Committee on Cancer (AJCC).

The role of radiotherapy was assessed using the number of patients that received radiotherapy as part of their treatment, the mode of radiotherapy (adjuvant, neo adjuvant or radical), the intent of radiotherapy as either curative or palliative, and the outcome between radical radiotherapy with adjuvant radiotherapy. The outcome of radiotherapy was also compared between radiotherapy alone or in combination with surgery and/or chemotherapy. Response to treatment was documented from 6 months’ follow-up clinic as either complete, partial or no remission. Complete response (CR) was considered as disappearance of irradiated tumour on clinical examination within 6 months of completion of prescribed treatment, while partial response (PR) is greater than 50% reduction in size of the tumour at 6 months of completion of prescribed treatment and no response (NR) when there is no reduction in size or a reduction in size of less than 50% of the irradiated tumour or disease progression at 6 months of completion of prescribed treatment. The symptom free interval at 6 months, 12 months and beyond 12 months were used for assessing response to treatment as a result of high default rate during follow ups. Symptom free interval (SFI) was defined as the duration that the patient stayed clinically free of signs and symptoms associated with the disease after treatment. Patients who had partial or no remission were considered to have SFI of zero (0) months. The

above information was extracted using a data extraction form. The data were carefully entered and analysed using SPSS version 17.0.

Results

A total of 117 oral cavity cancer patients were seen over the study period out of which 88 patients met the selection criteria and were analysed. The other 29 patients were not analysed due to scanty records and/or did not receive radiotherapy as part of their treatment, and/or had radiotherapy outside Ibadan. This formed 0.4% of the 32,009 patients seen at the UCH cancer registry and 0.8% of the estimated 13,979 patients seen at the Radiotherapy Department over the same period. The mean age of the patients was 51.8 years (SD±16.5), ages ranged from 18-98 years. The peak age range was 40-49 (22.7%) years. There were 56 males (63.6%) and 32 (36.4%) females giving a male to female ratio of approximately 1.8: 1. The distribution according to the social classes were class I- 4 (4.5%), class II- 11(12.5%), class III- 11(12.5%), class IV- 9(10.2%), class V- 20(22.7%), class VI- 21(23.9%) and retired- 12 (13.6%). The yearly distribution of patients is shown in table 1.

Table 1: Yearly distribution of the 88 patients with oral cavity cancer that had radiotherapy from 1987-2011

Years	Number of cases	Percent
1987	1	1.1
1988	6	6.8
1989	8	9.1
1990	6	6.8
1991	0	0.0
1992	5	5.7
1993	0	0.0
1994	5	5.7
1995	3	3.4
1996	4	4.5
1997	1	1.1
1998	7	8.0
1999	1	1.1
2000	2	2.3
2001	1	1.1
2002	3	3.4
2003	1	1.1
2004	3	3.4
2005	1	1.1
2006	3	3.4
2007	4	4.5
2008	12	13.6
2009	3	3.4
2010	3	3.4
2011	5	5.7
Total	88	100.0

Average of 3.5 patients per year.

Twenty patients (22.7%) had complaints of less than 6 months' duration at presentation, while 46 (52.3%) had presenting complaints of 6-12 months and 22 (25.0%) had complaints above 12 months. The commonest site of involvement was hard palate in 32 (36.4%) of the patients. Other sites were; lips-13 (14.8%), buccal mucosa- 4 (4.5%), alveolar gingivae- 3 (3.4%), oral tongue- 22 (25.0%), floor of the mouth- 9 (10.2%), and multiple sites- 5 (5.7%). The most common histological type was squamous cell carcinoma in 64 (72.7%) patients. The other histological types included, minor salivary gland tumours 16 (18.2%) which consisted of adenoid cystic carcinoma [10], mucoepidermoid carcinoma [4] and one each of adenocarcinoma and papillary adenocarcinoma. About 62.5% of the minor salivary gland tumours were adenoid cystic carcinoma. The remaining 8 (9.1%) included basal cell carcinoma [2], melanoma [1], intraepithelial carcinoma [1], lymphoma [1], sarcoma [1], Kaposi sarcoma [1], and adenosquamous carcinoma [1]. Stage distribution is shown in figure 1 below.

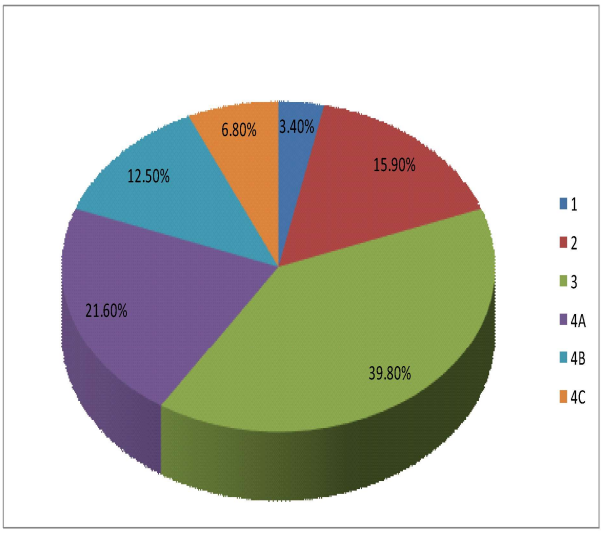

Fig. 1: Distribution of stage at presentation

All patients in this study had radiotherapy. Fifty-four patients (61.4%) received curative doses from a Co-60 teletherapy machine, a dose of 60-66Gy in 30-33 fractions or hypo-fractionated 45Gy in 12 fractions, while 34 patients (38.6%) who had advanced disease received palliative doses of either 15Gy in 5 fractions, 20Gy in 6 fractions or 30Gy in 10 fractions in order to control pain, bleeding and local disease. Twenty-seven (30.7%) had radiotherapy alone, 35 (39.8%) had chemotherapy and radiotherapy, 7 (8.0%) had surgery and radiotherapy, while 19 (21.6%) had all the 3 modalities. The distribution of radiotherapy treatment is shown in table 2.

Table 2: Distribution of radiotherapy treatment

	Number of patients	Percent
Palliative	34	38.6
Radical	54	61.4
Radiotherapy modality		
Combined (+surgery/ chemotherapy)	61	68.2
Alone	27	31.8
Radiotherapy form		
Neoadjuvant	1	1.1
Adjuvant	25	27.3
Radiotherapy alone	27	34.1
Chemo-radiation	35	37.5

Only 54 patients had chemotherapy, the combinations include Cisplatin/5-FU (24) for squamous cell carcinomas, patients with minor salivary gland tumours and adenocarcinomas had Vincristine/Bleomycin/Methotrexate-VBM [9] or Cyclophospomide/Methotrexate/ Vincristine CMV [14] combinations, while others [7] had different regimens depending on the histological type. All the 54 patients had 4-6 courses of chemotherapy. Treatment outcome is shown in figure 2.

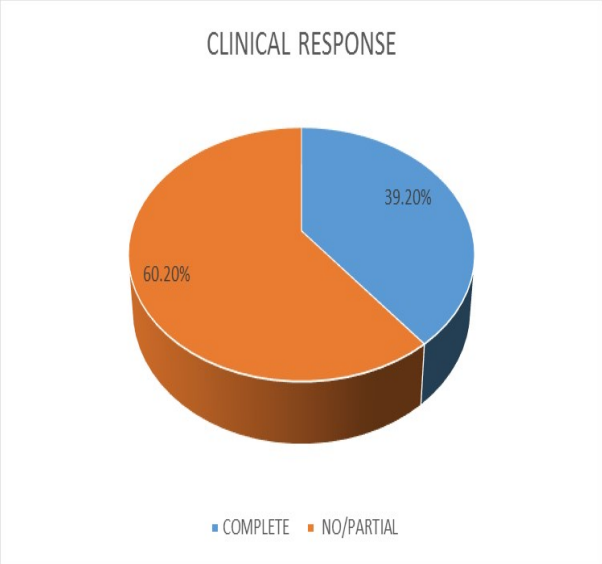

Fig. 2: Clinical outcome at 6 Months

Fifty-three patients (60.2%) had SFI of less than 6 months, while 11 (12.5%) had an SFI of 6-12 months and 24 (27.3%) had SFI of greater than 6 months. About 66.6% of the patients in stage 1 and 71.5% of the patients in stage 2 had SFI of greater than 12 months while 17.2% and 15.8% of patients in stage 3 and 4 respectively had a SFI beyond 12 months. As the dose of radiotherapy increases so also the SFI, it was found that for lower doses of equal to or less than 30Gy none of the patients had an SFI of greater than 12 months while at doses of about 60Gy SFI after 12 months was seen in 40% of the patients. In those that received radical radiotherapy, 40.8% had a SFI greater than 12 months compared to those that received palliative radiotherapy with only 5.9% having an SFI greater than 12 months. Forty eight percent of patients who had adjuvant radiotherapy had an SFI beyond 12 months compared to radiotherapy alone with only 22.2%, neoadjuvant radiotherapy and concurrent chemo-radiation groups had 0.0% and 17.2% of patients with SFI beyond 12 months respectively. However these differences were not statistically significant (table 3; mode of radiotherapy).

Those patients that had all the 3 modalities had the best outcome with 59.7% having SFI of more than 12 months, while it was 22.2%, 17.1% and 14.3% of those who had radiotherapy alone, chemotherapy + radiotherapy, and surgery + radiotherapy respectively. SFI for social class, duration of illness were not statistically significant. The variables and their statics significance in relation to SFI are summarised in table 3.

Table 3: Symptom Free Interval for Socio-demographic and clinical Characteristics

Factor	Pearson's Chisquare (X^2)	P-Value
Social Class	6.099	0.911
Duration of Illness at presentation	5.132	0.274
Stage	27.398	0.002
Dose (Increasing dose)	28.730	0.004
Aim (Radical/Palliative)	22.158	0.000
Treatment Combination	14.672	0.023
Mode of Radiotherapy	10.474	0.106

Discussion

Most studies put the mean age of patients with oral cancer around the 5th or 6th decade. The mean age in this study was 51.8 (SD±16.5) years which is similar to the mean age of 52.8 years reported by Olusanya and colleagues in Ibadan [11]. A lower mean age at presentation of 37.1 years has also been reported in a local study [12] while others found a slightly higher figure [13, 14]. The peak age group was 40-49 years which is a decade or two lower than most local studies [11, 14-16,]. Oral cancers are said to be more common in males than in females. Arotiba and colleagues [17] reported a M: F of 1.5:1, researchers at the Base Hospital Yaba reported M:F of 2:1 [18], in a study in Zimbabwe 1.9:1 was documented [19],

while 2.4:1 was reported in another study from Ibadan [16]. This study found a male to female ratio (M: F) of 1.8:1. Majority of the patients in our study belonged to the low socioeconomic class, this is in line with claims by some authors on the increase risk in those of the low socioeconomic class [20]. There is however uncertainty and limited recognition of the association between socioeconomic class and oral cancer. In a study by Adeyemi and others in Ibadan they failed to demonstrate any significant statistical association between them [14]. The high number of low socioeconomic status in these group studied may also be associated with risk factors such as poor oral hygiene and infections, ignorance, difficulty in accessing care and lack of adequate medical screening to detect premalignant conditions also contribute to increase number of cases in this vulnerable group.

Even though one may think that oral cavity is readily accessible to visual inspection, however most reports from Nigeria had patients presenting late [21, 22]. Most tumours of the oral cavity are not diagnosed until at least T2 stage as initial symptoms may be vague and painless [23]. Patients in this study presented late with 77.3% of the patients presenting at 6 months and beyond. Ignorance, poverty, low socioeconomic class, marital problems, sense of despair and delay in referral has been suggested by the aforementioned studies as reasons for delayed presentation. In this study the characteristics of most patients fit into these. Also the lack of radiotherapy facilities in most states may have also contributed, as patients will have to travel long distances and may require to pay for accommodation and feeding so the patients take a long time to prepare before coming for radiotherapy. Similarly, the incompetence of some primary physicians in detecting early disease and delayed referral by the primary physicians may have contributed. The mean duration of symptoms at presentation in North Central Nigeria for tongue cancers is 13±13.3 months and lips 23±22.9 months [24].

The commonest site for oral cancer varies from region to region, Olusanya and colleagues in Ibadan found hard palate to be the most common site over a 25 year period [11]. At the Ahmadu Bello University Zaria floor of the mouth was reported as the commonest [15], in another report from Zimbabwe it was the gingivae [19], in the US at the M.D Anderson Cancer Centre it was oral tongue [25] and in most studies in Southeast Asia the buccal mucosa [5, 25]. This suggests that there may be difference in risk factors according to region, for instance cancer of the floor of the mouth is more strongly associated with smoking than cancer of the gingivae [26], and practice of reverse smoking (smoking with the light end of cigar in the mouth) in India has been associated with increased risk of cancer of the hard palate [27].

Over 80% of the patients presented at late stages 3 and 4. It is well documented that oral cavity cancer in most cases remain localised until late in the course of the illness. Late stage at presentation may be as a result of the fact that most of the patients are of low socioeconomic class with high level of poverty and ignorance which may hinder accessing care at early stages. The most common histology in this study and in most local and international studies [19, 24, 28, 29] is squamous cell carcinoma. It is reported that adenoid cystic carcinoma accounts for 30-40% of minor salivary gland tumours in the oral cavity [30]. The relative high occurrence of minor salivary gland tumours in this study can be explained by the fact that most minor salivary glands tumours arise in the hard palate and the commonest site in this study was the hard palate.

SFI was used to assess the outcome as a result of high default rate and late presentation of the patients. The patients presented with late stage disease whereby the prognosis is already poor, most of the patients were from low socioeconomic position and had delay in presentation, all of which may contribute to the poor outcome in these patients. The study found a significant association between stage and SFI (P value=0.002). Patients with early stage disease have a higher proportion of patients that were symptom free beyond 12 months than those in late stage. Staging has also been found to be vital on prognosis of patients with oral cancer by Guerra and colleagues [31], Gonzales-Moles and others [32], and Nguyen and Yueh [33] which all demonstrated a better outcome at early stages than late stages. The lower SFI in stage 1 compared to stage 2 in this study may be attributed to the few number of patients in stage 1 compared to stage 2 (3 vs 14 patients). However from the analysis no patient in stage 1 (0.0%) had an SFI less than 6 months while three (21.4%) patients in stage 2 had a lower SFI of 6 months which still points to a better outcome in the patients in stage 1. Other factors that may have contributed in this variation include the site of the tumour and the histological type as these are also known to affect prognosis in oral cavity cancer.

The advanced nature of the disease in most patients require multimodality treatment. This may have contributed to better outcome in patients who had all the 3 modalities. This is further buttressed

by the findings of Carvalho and colleagues [8]. They showed that with increased use of multimodality treatment over 5 decades brought about a significant increase in the 5-year survival rates from 28.7% for patients treated in the 1950s to 43.2% in the 1990s. This study did not suggest any statistically significant improve outcome of in patients that had adjuvant radiotherapy over those that had radiotherapy alone or vice versa, but only showed improved outcome if radiotherapy is combined with chemotherapy and surgery.

Conclusion

Patients with oral cavity cancer present with advanced disease. Adjuvant radiotherapy is not superior to radiotherapy alone, however radiotherapy in combination with surgery and chemotherapy has been found to have better outcome.

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Contributions of chronic diseases to measured disability in older adults living in Low/middle income countries: a systematic review with syntheses

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Abstract

Background: Due to rapid socio-economic transition and demographic aging, the number of older persons living with chronic diseases is set to increase in low and middle income countries (LMICs). The identification of conditions that may be associated with greater disability burden may help in the prioritization of health policies and allocation of limited resources. However, existing information about the contributions of chronic diseases to disability in older persons living in many LMICs is based on projections from studies conducted in mostly higher income countries. The present systematic review aims to determine the relative contribution of chronic diseases to directly-measured disability in older persons living in LMICs.

Methods: The present systematic review used a simple methodology to estimate the proportions of community-dwelling older persons with a specific chronic disease-disability among all persons with the relevant disease who were participants in studies drawn across LMICs wherein disability was directly measured, rather than implied. Records in the African Journals Online, Medline, EMBASE, PsychINFO, and the Cumulative Index to Nursing and Allied health Literature were searched for relevant citations, and the Pubmed for in-process articles.

Results: Seven cross-sectional surveys including a total of 42,581 community-dwelling older persons met criteria for syntheses. None of the identified studies was based on samples derived from countries in sub-Saharan Africa. Observations are made suggesting that implicit data derived from a global pool of studies may have the potential to mask the true state of the experience of older persons living with chronic diseases in countries with lower research mileages.

Conclusion: Recommendations are made for future designs of studies investigating the impact of chronic diseases on directly-measured disability in LMICs, especially those in sub-Saharan Africa.

Keywords: *Global burden of disease; Population attributable prevalence fractions; Disability adjusted life years; Developing countries*

Résumé

Contexte: En raison de la transition socioéconomique rapide et du vieillissement démographique, le nombre de personnes âgées vivant avec des maladies chroniques devrait augmenter dans les pays à revenu faible ou intermédiaire (PRFI). L'identification des conditions qui peuvent être associées à une plus grande charge d'infirmité peut aider à établir des priorités dans les politiques de santé et à allouer des ressources limitées. Cependant, les informations existantes sur les contributions des maladies chroniques aux handicaps chez les personnes âgées vivant dans de nombreux pays à revenu faible sont basées sur des projections d'études menées dans des pays à revenu plus élevé. La présente étude systématique vise à déterminer la contribution relative des maladies chroniques au handicap mesuré directement chez les personnes âgées vivant dans des pays à faible revenu.

Méthodes: La présente revue systématique a utilisé une méthodologie simple pour estimer les proportions de personnes âgées vivant dans la communauté atteintes d'une maladie-handicap chronique spécifique parmi toutes les personnes atteintes de la maladie concernée qui ont participé aux études menées dans les pays à faible revenu où l'incapacité était mesurée directement plutôt que implicite. Les registres des Revues Africaines en Ligne, Medline, EMBASE, PsychINFO et l'Index Cumulatif de la Littérature sur les soins Infirmiers et connexes ont été recherché pour des citations pertinentes et le Pubmed pour les articles en cours.

Résultats: Sept sondages transversaux, dont un total de 42.581 personnes âgées vivant en communauté, ont satisfait aux critères de synthèse. Aucune des études identifiées n'a été basée sur des échantillons

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provenant de pays d'Afrique subsaharienne. Des observations font ressortir que les données implicites tirées d'une série d'études mondiales risquent de masquer l'état réel de l'expérience des personnes âgées vivant avec des maladies chroniques dans les pays à moindres cadences de recherche.
Conclusion: Des recommandations sont formulées pour la conception future d'études sur l'impact des maladies chroniques sur la déficience mesurée directement dans les pays à faible revenu, en particulier en Afrique subsaharienne.

Mots-clés: *Charge mondiale de maladie; Fractions de prévalence attribuables à la population; Années de vie ajustées d'handicap; Pays en voie de développement*

Introduction

Projections from the World Health Organisation (WHO) Global Burden of Disease (GBD) studies [1-3] suggest that an older person living in Low and Middle Income Countries (LMICs) can expect to spend about half of their remaining life in disability. A substantial portion of this disability will result from chronic diseases such as sensory impairments (vision and hearing), dementia, depression, and many causes of musculoskeletal pain [4].

Currently, demographic aging is increasing rapidly in LMICs. For example, it is estimated that by 2050 the population older than 60 years in countries in the region is expected to have increased from approximately 490 million to nearly 1.6 billion persons [5-7]. The estimated population growth may be explained in part by the global increase in life expectancy and decrease in mortality [8]. In Nigeria, as an example, estimates suggest that despite an average life expectancy at birth of about 52 years [9], the population surviving to the age of 65 years in the country may have the prospect of an additional 15 years of life [10, 11]. As rates of chronic diseases are known to increase with aging [12], the expectation is that the number of persons living with these conditions in LMICs will increase in the coming few years.

Compared with more developed countries, rates of many chronic diseases may also be higher in less developed regions of the world. As an example, age specific stroke rates in a country like Tanzania have been estimated to reach nearly six times the rates in some countries in Western Europe [13]. Perhaps, this is a reflection of differences in access to quality healthcare. Even within LMICs, access to quality healthcare is generally known to be dictated by levels of financial resources [14].

Globally, an important approach to reduce the disability engendered by chronic diseases is the development of effective strategies for their prevention. In this regard, the identification of chronic diseases that may be more associated with disability in older adults is a logical step in the effort at reducing overall burden. This approach may also help in the prioritization of health policies, planning, and allocation of available resource. This is especially important in LMICs where resources for healthcare are limited. However, currently available information about the contributions of chronic diseases to disability in older persons living in LMICs have been based on data extrapolated from a global pool of studies collated in the WHO GBD collaborations.

The GBD estimates are implied, rather than measured, disability indicators extrapolated mostly from studies of incidence and duration of the relevant diseases from across many countries [1]. In the GBD methodology, expert judgements about the global and regional impact of several chronic diseases on disability were made by allocating disorder-specific disability weights, also called the 'implicit societal weighting', to each chronic disease after an 'in-depth' review of all available epidemiological studies of the relevant disease. In this way, projections about the impact of the diseases from higher income countries or those with higher volumes of relevant research are extrapolated to other countries. Not accounted for in these projections are factors such as the rapid epidemiological transition in many developing LMICs relative to more stable dynamics in higher income countries. Also, the natural trajectory of onset and course of some chronic diseases, for example cardiovascular diseases, may differ between developed and less developed countries [13]. The GBD estimates are also limited by the assignment of disability portions to individual chronic diseases independently, and without accounting for the effect of co-occuring conditions. Where as co-morbidities are generally commoner in old age [12].

The present systematic review aims to determine the relative contribution of several chronic diseases to directly-measured, rather than implied, disability in older persons living in LMICs. The review uses a simple methodology of proportions of older persons with a specific chronic disease-disability among all persons with the relevant disease who were participants in studies where disability was directly measured, rather than implied or self-reported.

Materials and methods

Search strategy

This review followed conventional recommendations for the methodology and reporting of systematic reviews [15, 16]. A systematic search of the Medline (Ovid SP-1946-25th November 2015), PsychInfo (Ovid SP 1806-7th October, 2015) EMBASE (Ovid SP 1974-25TH November, 2015), and CINHAL (EBSCO host, 7th October, 2015) databases was conducted using the following keywords with the .mp. and explode operators: 'old age'/ elderly/ aged and 'Chronic diseases'/ 'chronic conditions' and disability/ 'Activities of daily living'/ 'daily life activities'.

Inclusion criteria

Studies were included if; 1), they were peer reviewed, 2), reporting on participants who were 60 years or older, 3), participants were drawn from a country grouped as belonging to LMICs in the WHO and World Bank income categories [17], and 4), included a validated measurement of disability. For the purpose of inclusion, disability was defined as the inability to cope with activities of daily life without assistance.

Exclusion criteria

Studies were excluded if they relied on participants' self-report of disability. An additional exclusion criterion was failure to provide data on the association between individual chronic conditions and disability.

A search of the Pubmed database (1966-2nd October, 2015, repeated for updates on the 4th of January, 2015) was also conducted to retrieve 'in-process' and 'ahead of print' citations. For this, the following key words were combined: ('old age' or elderly or aged) and ('Chronic diseases' or 'chronic conditions') and (disability or 'Activities of daily living' or 'daily life activities'). The same key words were entered into 'advanced search' in the African Journals Online (AJOL) database on the 10th of September, 2016. The database searches were limited to English language and human literature. Limits on publication dates were not imposed. The search strategies for the databases are available from the author.

Ascertainment of risk of bias

A standard framework for assessing biases in studies showing associations between variables [15, 18] was used for judgements about the risk of bias in the selected trials. All 5 steps in the modified Graphical Appraisal Tool for Epidemiologic Studies (GATE) [15, 18] were used for the determination of the risk of bias in each of the identified studies. Step 1 in the modified GATE criteria seeks to determine the external validity of the selected study. For this, key characteristics of the eligible sample in the relevant studies were assessed to determine the level of representativeness of the source population. Steps 2 to 4 of the modified GATE criteria seek to determine the internal validity of the selected study. An assessment of the methods of selection of exposure, outcome measurements, and analytical strategies was conducted. These steps were undertaken to ensure that the associations identified by the respective studies are valid and are not due to unidentified factors that may be related to both exposure and outcome.

Risk of bias was classified as low, unclear/ unknown, and high [15]. Points were allocated to each component of the study as follows: 2 points when the risk of bias was low, 1 point when this was unclear /unknown and no points when the risk of bias was clearly high. Modified GATE step 5 ascertains the overall risk of bias in the selected study. For this, the average risk of bias for a particular study was calculated by summing up the total points accrued by that study and dividing the result by the total number of components assessed. Finally, we classified the overall risk of bias for a particular study as high (when the average risk of bias scores for that study is less than 1), moderate (when this is between 1 and 1.5), and low (when the score is greater than 1.5).

Quantitative syntheses

Previous studies, for example Sousa and colleagues [4], have used the method of Population Attributed Prevalence Fractions (PAPF) or meta-analyses in quantifying disability attributable to individual chronic diseases. These methods rely on the availability of outcome data in both the exposed and unexposed. In the present study, the disability-outcome data for unexposed (i.e., participants not reporting the relevant chronic diseases) were not available from the studies under review. This limitation prevented the calculation of PAPFs of disability by individual chronic disease, or the overall quantitative effect of individual chronic diseases on disability as synthesised across included studies (i.e., those investigating such diseases) using meta-analysis. Given the limitations around the quality of available data, judgement about the contributions of individual chronic disease to disability was made using the proportion of participants with the relevant disease-disability in studies providing data for that disease. Data on the number of participants with individual chronic diseases-disability were first extracted for each study. The proportion of participants who had a named chronic disease-disability was then calculated by dividing the total number of participants with the relevant disease-disability across the relevant studies by the total number of participants with disability, also across

studies. These proportions are presented along with PAPFs generated in a previous study conducted across 7 LMIC [4].

Results

Search results

The combined database searches identified a total of 3,260 records. Notably, the keywords search of the AJOL database produced 'no results'. After removing duplicates in either databases (N=2,101 articles), the titles and abstract of 1,159 articles were screened. A total of 19 articles that might have contained relevant information were retrieved. After reading through their full texts, a further 12 articles were excluded. Four studies [14, 19-21] relied on self report, rather than direct measurement of disability as required for inclusion. The study by Tyrovolas *et al* [22] used a general population sample older than 18 years, rather than 60 years or older as required for inclusion. The remaining 7 studies [10, 23-28] were excluded because they failed to provide appropriate data for the association of individual chronic diseases on disability. Details of included and excluded studies are shown on the flow chart in Figure 1 [16].

Appraisal of studies meeting inclusion criteria

In all, 7 studies [4, 29-34] met criteria for syntheses. The studies were drawn from across 8 LMICs. They included a total of 42,581 mostly female participants with an average age of 73 years (Table 1).

Key information about the studies is presented in Table 2. They were all cross-sectional surveys. In studies where a variety of conditions were investigated in the same survey [4, 29, 30, 32], self report of clinician diagnoses was used in the ascertainment of the presence of a chronic disease. Dementia and depression were often measured using validated tools, rather than self report. All studies in the present review relied on standardized measurements of disability using a variety of methods.

The studies clearly described the source population and sampling frame. Appropriate analytical techniques were used. Most studies derived relative risks or odds ratios for associations between the chronic diseases and disability. However, the study by Hairi et al [31] derived prevalence ratios. That study [31] also made judgements about functional disability relying on a measure of gait and balance [35]. Overall, the combined risk of bias as assessed using the modified GATE criteria was low.

Figure 1: Flow chart for included and excluded studies

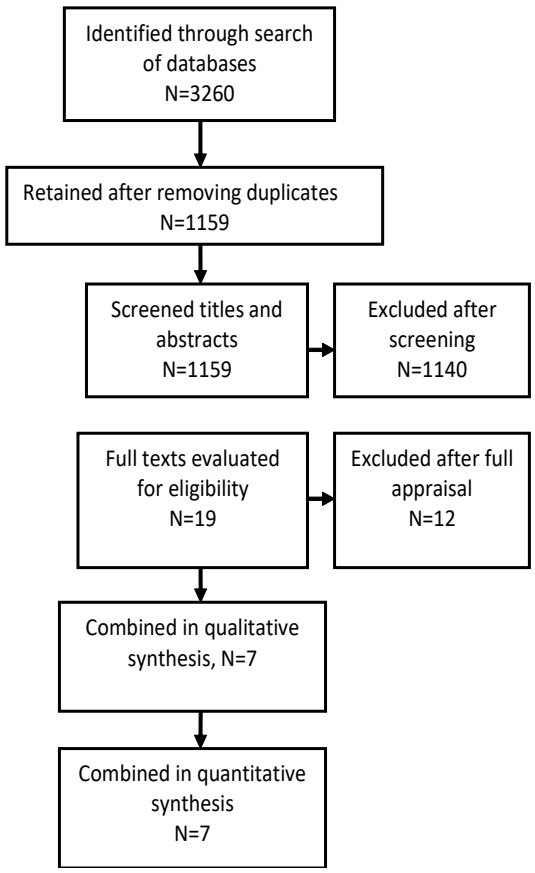

Table 1: Participant characteristics

Reference	Sample sizes	Country	Setting	Female (%)	Average ages
Patel *et al* 2006	15,186	Mexico	Community	54.7	73.0
Sousa et al 2009	15,022	China, India, Cuba, Dominican republic, Venezuela, Mexico, Peru	Community	59.5	73.3
Acosta *et al* 2010	2,111	Dominican republic	Community	65.9	74*
Hairi *et al* 2011	765	Malaysia	Community	62.6	74
Llibre-Rodriguez *et al*, 2011	2,944	Cuba	Community	64.7	74
Duba *et al* 2012	1,000	Rural India	Community	54.6	72.5
Arias-Merino *et al* 2012	5,553	Mexico	Community	61.2	71.6

**Median*

Quantitative estimates of the contributions of chronic diseases to disability in LMICs

The relative contributions of individual chronic disease to directly-measured disability in LMICs as assessed using the proportion of participants who had a named chronic disease-disability is presented in table 3 along with PAPFs calculated for disability due to several diseases in a previous study conducted across 7 LMICs [4]. Also presented in Table 3 are the projected contributions of individual chronic disease to disability according to the GBD estimations [1-3].

Some chronic diseases that were ranked as disability-associated by the GBD estimates, for example malignancies [odds ratio=1.5, 95% C.I=0.9-2.6 [29]] and hypertension [relative risk= 1.0, 95% C.I=0.9-1.1 [30, 32] and relative risk=1.0, 95% C.I=1.0-1.1 [4]] were not found to be statistically associated with functional disability when considering relevant studies using direct measurements. However, there was a consensus on the impact of eye disease and dementia as the highest ranking disability-associated chronic diseases, while cerebrovascular (mostly stroke) and respiratory diseases were lower ranking disability-associated diseases according to direct measurements in studies reporting on samples from LMICs (Table 3).

Discussion

In reviewing existing evidence for the relative contributions of chronic diseases to directly-measured disability in LMICs, some important observations have been made. First, none of the studies meeting inclusion criteria of the present review was based on samples derived from countries or regions in sub-Saharan Africa. It is important to note that two studies from Nigeria [14, 20] were excluded from the final syntheses because they relied on self-report of disability, rather than direct measurement as indicated in the criteria for the present study. The second observation is that some chronic diseases ranked as disability-associated by the GBD estimates were not found to be statistically associated with functional disability when considering relevant studies using direct measurements. Third, there was consensus across studies about the impact of many diseases on disability in older persons living in LMICs. For example, and as estimated by the GBD studies, sensory impairments (especially eye diseases) and dementia were found to be among the highest ranked disability-associated chronic diseases according to direct measurements in studies reporting on samples from the region. Also, across methods (direct measurements or GBD estimations), cerebrovascular (mostly stroke) and respiratory diseases appear to be lower ranking disability-associated diseases in the region.

The first and second observations in the present systematic review would suggest that implicit data derived from a global pool of studies may have the potential to mask the true state of the experience of older persons living with chronic diseases in countries with lower research mileages. In line with this idea, improved data in 2012 [2] and 2014 [36] suggest that the global and regional impact of some conditions on disability in older adults, for example dementia, may have been underestimated previously by the GBD studies. Another important example of the limitation of implicit data in the context of LMICs is the ranking of depression in the GBD studies compared with the status when considering studies

Table 2: Study characteristics

Reference	Study types	Chronic diseases investigated	Outcome measure	Measure of study effect	Strongest association with disability
Patel *et al* 2006	Cross-sectional	Self report of physician diagnoses: Diabetes, cancer, respiratory diseases, heart attack, stroke, and arthritis.	Activities of Daily living (Katz index)	Odds ratio	Stroke
Sousa *et al* 2009	Cross-sectional	Self report of clinician diagnoses: diabetes, stroke, heart disease, vision and hearing impairments, arthritis, respiratory, and skin diseases; dementia (DSM IV), depression (ICD-10), Hypertension (sphygmomanometer)	WHO Disability assessment schedule (WHO-DAS 2.0)	Relative risk	Angina, Dementia
Acosta *et al* 2010	Cross-sectional	Self report of physician diagnoses: Dementia, stroke, myocardial infarction, angina, hypertension, COPD, depression	WHO Disability assessment schedule (WHO-DAS 2.0)	Relative risk	Dementia
Hairi *et al* 2011	Cross-sectional	Depression (Geriatric depression scale)	Tinetti performance oriented mobility assessment tool	Prevalence ratio	Depression*
Llibre-Rodriguez *et al*, 2011	Cross-sectional	Self report of clinician diagnoses of stroke, heart disease, and diabetes. Dementia (Community screening interview for dementia), and Hypertension (sphygmomanometer)	WHO Disability assessment schedule (WHO-DAS 2.0)	Relative risk	Dementia
Duba *et al* 2012	Cross-sectional	Self report of clinician diagnoses of respiratory diseases, hypertension, diabetes, heart diseases, arthritis, vision impairment, stroke, hearing impairments, and skin diseases. DSM IV Dementia, and depression using computer algorithm	WHO Disability assessment schedule (WHO-DAS 2.0)	Odds ratio	Arthritis
Arias-Merino et al 2012	Cross-sectional	Depression (The geriatric depression state)	Activities of Daily living (Katz index)	Odds ratio	Depression*

*COPD= Chronic obstructive pulmonary diseases, WHO= World health organization, DSM IV= Fourth edition of the Diagnostic and Statistical manual of mental disorders, I CD 10= 10TH revision of the International Classification of diseases, *No other chronic condition was investigated*

Table 3: Quantitative syntheses- contributions of chronic diseases to disability in LMICs

Diseases	Proportions with measured-disability among study participants with disease (%)	Ranks	PAPF of disease-disability from 7 LMICs (%)	Ranks	GBD estimates of contributions to total chronic disease-disability (%)	Ranks
Angina	1.2[ab]	Not applicable	Not assessed	Not applicable	Not applicable	Not applicable
Musculoskeletal	33.1	2	9.9	3	8.9	4
Cancers	2.9[ab]	Not applicable	Not assessed	Not applicable	1.1	12
Dementia	11.3	6	25.1	1	10.2	3
Depression	22.5	3	8.3	4	7.3	6
Diabetes	22.5	3	4.1	7	2.6	10
Hearing impairment	13.5	4	2.2	9	11.3	2
Heart disease	11.8	5	0.8	11	7.6	5
Hypertension	74.2[b]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Respiratory diseases	9.9	7	3.3	8	5.3	7
Cerebrovascular	9.1	8	11.4	2	4.3	8
Eye diseases	39.6[a]	1	6.8	5	33.9	1

PAPF= Population attributable Prevalence Fraction, GBD= Global burden of disease, [a]Reported by one study, [b]Not statistically associated with disability

including samples drawn directly from the region. While primary data suggests that depression may be among the top 3 or 4 disability-associated chronic conditions in LMICs, the ranking in the GBD estimation is 6th. Other studies have also found that some of the highest rates of late-life depression in the world can be found in a countries like Nigeria [37]. In one of the two Nigerian studies excluded from our final syntheses, participants with depression reported themselves as having the most severe disability. It is important to note that in the context of depression people are more likely to have a negative self-perception, and therefore likely to report themselves as having the worse forms of impairments in daily life activities. In the present systematic review, we have focused on studies using directly-measured, rather than self-reported, disability.

Lower ranking diseases (i.e., by relative contributions to directly-measured disability) and conditions not statistically associated with disability in individual studies included in the present systematic review were observed to be those reported to be associated with higher mortality burden in LMICs. Stroke and malignancies, as examples, are known to be associated with relatively higher levels of mortality in LMICs compared with higher income countries [38-40]. Similarly, systemic hypertension which is now one of the leading causes of disease in LMICs [41] has been associated with a high global and regional mortality burden [42]. In circumstances of diseases with relatively high mortality weights, it can be expected that only those with less severe disease, which may or may not be associated with high levels of functional disability, may be available to provide self report of such diseases in surveys conducted in LMICs.

The observations in the present review are made within limitations of the quality of available data. Judgments about the quantitative contributions of the different diseases to disability using the proportion of participants with the relevant disease-disability is unlikely to be as accurate as those derived from more sophisticated methodologies, for example meta-analysis or PAPFs. However, because data for unexposed participants were not provided by individual studies, a formal meta-analysis or the calculation of PAPFs based on each chronic disease could not be implemented. Nevertheless, the qualitative similarities in the overall judgments of the relative contributions of a majority of the diseases to disability across methods of ranking would provide some measure of validity to the simple methodology based on proportion of disease-disability. Similar to the GBD estimates, portions of disability has been allocated to different chronic diseases in the present systematic review without factoring the effect of comorbidities. Whereas the number of co-occuring chronic diseases can be expected to increase with ageing [12]. This can be expected to have additional impact on functional disability over time [43]. Also, while the GBD estimates assume disability occurring overtime all the studies identified for the present systematic review relied on cross-sectional methodologies. Cross-sectional analyses are inadequate in providing strong evidence for the direction of associations between events occurring overtime. The plausible effect of reverse causality between depression and disability, as an example, in cross-sectional surveys may result in larger sizes of association between the two conditions. Similarly, the impact of conditions which may be associated with cummulative disability overtime, for example systemic hypertension, may be under-estimated in cross-sectional analyses. Furthermore, short term relapse and remitting disability, which occurs in some categories of depression [44], may be qualitatively different from the chronically unremitting disability that may be associated with many types of musculoskeletal diseases. In this way, longitudinal investigations of measured disability, conducted in multiple waves may better provide a measure of disease-disability that is qualitatively similar to the conceptual framework of 'years lived with disability' as approximated in the GBD studies.

The present systematic review has strengths and limitations. The search strategy had been designed to be meaningfully sensitive. In this regard, the searches have focused on some of the largest repository of biomedical literature with additional strategy to cover recent citations that might not have been included in the Medline and EMBASE databases, as well as citations of African studies in the AJOL database. On the other hand, manual searches of the references of the appraised articles were not undertaken. An additional limitation of the present review is that the search strategy did not cover grey literature which may be another valuable source of materials dealing with the specific review question.

In concluding, health care resources are limited in many LMICs, especially those in sub-Saharan Africa. Accurate information about the contribution of chronic diseases to disability will help in the planning and prioritization of policies and allocation of scarce resources. Therefore, epidemiological studies estimating the impact of several chronic diseases on directly-measured disability in the older person living in resource poor

countries, such as those located in most of sub-Saharan Africa are urgently needed. Cross-sectional surveys are important. However, the plausible effect of reverse causality between some of the chronic diseases and disability in cross-sectional analyses may result in inaccurate estimates of the impact of the diseases investigated. Thus, longitudinal investigations of the impact of chronic diseases on measured disability will provide better information about the contributions of the conditions to disability in the older person living in LMICs. Apart from the impact of these diseases on incident disability, the possibility of investigating persistence of disability engendered by the different conditions may enable the identification of diseases which may be directly associated with a longer duration of disability, in years. Such longitudinal studies should also investigate the impact of co-occuring chronic diseases on disability over time.

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Bilateral tubal ligation in a nulliparous woman – a case report

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Abstract
Infertility is viewed in diverse ways in our environment with couples often attempting various options of treatment. Thus, voluntarily opting to remain childless has little or no socio-cultural approval and is often perceived to be an indication of covert disability. Commonest indication for bilateral tubal ligation (BTL) in our environment is completion of family size and in situations where further pregnancies will jeopardize maternal health. We present a case of a married 41 year old nulliparous woman who requested for BTL on religious ground. The couple had opted for voluntary childlessness and had been on other forms of contraceptives all through their twelve years of marriage. This is to highlight the fact that there exist in our society a small number of couples who wish to be childless and should not be denied that right after thorough counseling.

Keywords: *Infertility, disability, pregnancy, nulliparous, childless.*

Résumé
L'infertilité est considérée de manièresdiverses dans notre environnement avec des couples essayant souvent divers options de traitement. Ainsi, le fait de choisir volontairement de rester sans enfant a peu ou pas d'approbation socioculturelle et est souvent perçu comme une indication d'incapacité cachée. L'indication la plus courante pour la ligature des trompes bilatérale (LTB) dans notre environnement est la terminaison de la grandeur de la famille et dans les situations où d'autres grossesses mettent en danger la santé maternelle.
Nous présentons un cas d'une femme nullipare casée de 41 ans qui a demandé pour LTB sur un fondement religieux. Le couple avait opté pour l'absence volontaire d'enfants et avait été sur d'autres formes de contraceptifs tout au long de leurs douze années de mariage. Il s'agit de souligner le fait qu'il existe dans notre société un petit nombre de couples qui souhaitent être sans enfants et ne doivent pas être nié de ce droit après un conseil approfondi.

Mots-clés: *Infertilité, impotence, grossesse, nullipares, sans enfant.*

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Introduction

Childlessness is regarded in many different ways in our society, at best as a misfortune, at worst as irresponsibility or deviance. Voluntary childlessness has yet to gain wholehearted social approval, and is often acknowledged as indicative of covert disability [1]. However, over the past few decades, public attitudes toward childlessness appeared to have become more accepting in some cultures [2].

Demographic characteristics, cultural and religious beliefs, and economic and education levels of the female population have been demonstrated to affect the choice of a contraceptive method [3]. Barrier methods are common with younger age group while tubal sterilization was preferred by the elderly population [3,4].In addition, high parity is an important factor choosing sterilization as nearly 90% of the sterilized women were found to have had more than 3 parous experiences [5,6]. This implied that most women had 2 reasons for wanting sterilization – no desire to have children and dislike for other contraceptives as either unsafe or ineffective [7,8].

Voluntary childlessness, on the other hand, refers to a couple's decision to delay child-bearing or not to have any children at all. There are various factors associated with a woman's likelihood of being voluntarily childless. Education, race, ethnic group and marital status have been implicated as plausible reasons for choosing voluntary childlessness. Citing religious ground as the main reason for opting to be voluntarily childless despite being married is alien to our environment.

The aim of this report is therefore to make practitioners aware of this indication for sterilization.

Case presentation

A 41 year-old nulliparous married lady presented in our facility, accompanied by her husband, with a request for bilateral tubal ligation. She is a pharmacist who had been married for 12 years but was never interested in getting pregnant. She had experienced adverse effects from some of the contraceptives used in the past including oral contraceptive pills and IUDs. As at the time of presentation, she was inconsistently using barrier methods of contraception. The couple had opted to be childless voluntarily and requested for the procedure on religious grounds (they were going to

live in the seminary for the rest of their lives). They were counseled on the implication of their choice including irreversibility and possible complications of the procedure while available options such as long acting reversible contraceptives and vasectomy as well as possibility of regrets were also discussed. The coupled were advised to take some time and consider their decision but returned to the clinic after a week and insisted on proceeding with BTL as they did not want other forms of contraception. In the presence of a second gynaecologist and a public health nurse, they both signed the consent form for the operation. She subsequently had minilaparotomy bilateral tubal ligation, using the modified Pomeroy technique, under local anaesthesia. Procedure was well tolerated and subsequent follow up was uneventful.

Discussion

The state of being childfree has been described as one borne out of a conscious decision not to have children. It has also been described as voluntary infertility implying that the couple chose to remain childless for reasons best known to them. Some couples deliberately delay child-bearing and remain childless for a certain period of time after which they proceed to have or adopt a limited number of children. On the contrary, some other couples voluntarily remain childless all through their marriage.

Different socio-demographic factors have been associated with voluntary childlessness with significant ones being education, race and marital status. Although a stable career increases the likelihood of remaining childless among women, it increases the likelihood of entering fatherhood [9,10]. Educational attainment increases the likelihood of remaining childless among women only and well–educated women are still among the most likely never to have had a child. According to a report by Livingston et al, a notable exception to the overall rising trend was observed in 2008 when only 24% of women ages 40-44 with a master's, doctoral or professional degree had not had children, a decline from 31% in 1994 [2].

When race and ethnicity are considered, white women are least likely to have borne a child and more likely to choose voluntary childlessness. However, over the past decade, childless rates have also risen more rapidly for black, Hispanic and Asian women thereby narrowing the racial gap [11]. In terms of marital status, women who were never married are most likely to be childless as would be expected but their rates have declined over the past decade, while the rate of childlessness has risen for the so-called ever-married — those who are currently married or were married at a point in time [3,11].

There are no absolute contraindications to sterilization of men or women, provided that they make the request themselves, are of sound mind and are not acting under external duress [12]. A comprehensive history should be taken and an examination should be conducted on all patients requesting sterilization. Counseling and advice on sterilization procedures should be provided to women and men within the context of a service providing a full range of information about and access to other long-term reversible methods of contraception. This should include information on the advantages, disadvantages and relative failure rates of each method. All verbal counselling must be supported by accurate, impartial, printed or recorded information (in translation, where appropriate and possible), which the person requesting sterilization may take away and read before the operation [12]. Post tubal ligation regrets are uncommon in carefully selected patients [6] and a review of 35 women showed that there was no significantly higher rate of regret in nulliparous women undergoing tubal ligation than that seen in studies of parous women [13].

In this case, the couple never wanted to have any child and hence resorted to using different types of contraceptive devices with unsatisfactory experiences, thereby necessitating her request for sterilization. After due counseling on the implication of her request and the possible alternatives especially vasectomy, she remained adamant on her choice for sterilization. Post-operatively, she was followed up for one year with no evidence of regret. It is thus pertinent to note that previously unidentified factors such as religious obligations can play a significant role in taking decisions for permanent sterilization.

However, there are certain communities and individuals with long established religious, cultural and sometimes emotional objections to sterilization and other forms of contraception [12]. Involving a mental health expert or a clinical psychologist in the counseling process will go a long way in ensuring that the patient is in the best frame of mind, thereby reducing the incidence of post BTL regrets. Even though we were unable to adopt this approach, our patient remained free of regrets one year after the procedure. Psychosocial and religious issues should, therefore, not be overlooked or given less consideration than medical issues and should constitute part of comprehensive pre-sterilization counseling.

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Neuroprotective effects of aqueous extract of *Carica papaya*, vitamin E and dexamethasone on traumatic brain injury-induced oxidative damage in adult male Wistar rats.

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Abstract
*Background***:** Traumatic brain injury, TBI (blunt or penetrating) induces oxidative stress by generation of free radicals which triggers a cascade of events resulting in cellular dysfunctions and death. The neuroprotective effects of ripe aqueous extract of *Carica papaya* (paw-paw) (CP) fruit, vitamin E and dexamethasone, respectively, on traumatized cerebral cortex of Wistar rats was studied.
Method: Fifty adult male Wistar rats were divided into six groups; control, trauma control (TC), Carica papaya control (CPC), *Carica papaya*+trauma (CPT), vitamin E+ trauma (VET) and dexamethasone+trauma (DET) groups. Two hundred (200) mg/kg body weight of CP and vitamin E were administered orally, while dexamethasone was administered at 0.005 ml of 4 mg/ml intraperitoneally. Rats were treated for 14 days pre-trauma induction and sacrificed 7 days post-trauma. Body, brain and cerebral weights as well as the behaviour of the rats were studied. Blood and brain tissues were processed for haematological parameters, oxidative stress markers and histomorphological evaluations.
Results: A decreased body weight was seen in all the traumatized rats compared with the control rats ($p<0.05$). Increased body weight was observed in the CPC, CPT and VET rats, respectively, compared with the TC rats ($p<0.05$). An increased brain weight was observed in the TC and VET rats compared with the control rats at $p<0.05$. In behavioural studies, trauma significantly ($p<0.05$) reduced the hang time (forelimb grip) and delayed time of re-orientation (negative geotaxis). *Carica papaya* and DET increased the time of re-orientation. A decreased percentage lymphocyte in the DET rats and an increased percentage neutrophil was seen in the TC and DET rats compared with the control rats at $p<0.05$. An increased levels of hydrogen peroxide (H_2O_2) and lipid peroxidation (LPO) were seen in the TC and DET rats at $p<0.05$. *Carica papaya* extracts and VET significantly increased the percentage lymphocytes and decreased neutrophil accumulation; they also increased H_2O_2 levels and LPO compared with the control rats at $p<0.05$. Cerebral cortical thickness was reduced in the TC and DET groups compared with the control rats at $p<0.05$. *Carica papaya* improved cortical thickness. Dexamethasone-treated rats showed severe distortion of the cerebral cortical layers, while the TC rats (penetrating) showed haemorrhage, vascular infiltration and congestion, and darkly stained (pyknotic) bodies.
Conclusion: Carica papaya fruit extracts and vitamin E appeared to protect the brain against TBI-induced oxidative stress. Dexamethasone however, aggravated the oxidative stress when compared to the TC group as such may not be neuroprotective.

Keywords: *Traumatic brain injury, Oxidative stress, Cerebral cortex, Carica papaya, vitamin E, Dexamethasone*

Résumé
Contexte: La lésion cérébrale traumatique, LCT (émoussée ou pénétrante) induit un stress oxydatif par la génération de radicaux libres qui déclenche une cascade d'événements entraînant des dysfonctionnements cellulaires et la mort. On a étudié les effets neuro-protecteurs de l'extrait aqueux mûr de fruits de Carica papaya (papaye) (CP), de vitamine E et de dexamethasone, respectivement, sur le cortex cérébral traumatique des rats Wistar.
Méthode: Cinquante rats Wistar mâles adultes ont été divisés en six groupes; le contrôle, contrôle de trauma (CT), le contrôle de carica papaya (CCP), carica papaya + trauma (CPT), la vitamine E + traumatisme (VET) et les groupes dexaméthasone + trauma (DET). Deux cent (200) mg / kg de poids corporel de CP et de vitamine E ont été administrés par voie orale, tandis que la dexaméthasone a été administrée à 0,005 ml de 4 mg / ml par voie intra-péritonéale. Les rats ont été traités pendant 14 jours d'induction pré-traumatique et sacrifiés 7 jours après le traumatisme. Lespoids corporels, cervicaux et

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cérébraux ainsi que le comportement des rats ont été étudiés. Le sang et les tissus cérébraux ont été traités pour des paramètres hématologiques, des marqueurs de stress oxydatif et des évaluations histomorphologiques.

Résultats: Une diminution du poids corporel a été observée chez tous les rats traumatisés par rapport aux rats témoins ($p < 0,05$). On a observé une augmentation du poids corporel chez les rats CCP, CPT et VET, respectivement, comparativement aux rats CT ($p < 0,05$). Une augmentation du poids du cerveau a été observée chez les rats CT et VET comparativement aux rats témoins à $p < 0,05$. Dans les études comportementales, le traumatisme a significativement diminué ($p < 0,05$) le temps de suspension (prise d'avant-bras) et le délai de réorientation (géotaxie négative). Carica papaya et DET augmentent le temps de réorientation. Une diminution du pourcentage de lymphocytes chez les rats DET et une augmentation du pourcentage de neutrophiles ont été observées chez les rats CT et DET par rapport aux rats témoins à $p < 0,05$. Des concentrations accrues de peroxyde d'hydrogène (H_2O_2) et de peroxydation lipidique (POL) ont été observées chez les rats CT et DET à $p < 0,05$. Les extraits de carica papaya et le VET ont significativement augmenté le pourcentage de lymphocytes et diminué l'accumulation de neutrophiles; Ils ont également augmenté les niveaux de H_2O_2 et POL par rapport aux rats de contrôle à pÂ0,05. L'épaisseur corticale cérébrale a été réduite dans les groupes CT et DET par rapport aux rats témoins à $p < 0,05$. Carica papaya a amélioré l'épaisseur corticale. Les rats traités par la dexaméthasone présentaient une distorsion sévère des couches corticales cérébrales, alors que les rats CT (pénétrants) présentaient une hémorragie, une infiltration vasculaire et une congestion, et des corps sombres (pycnotiques).

Conclusion: Les extraits de fruits de carica papaya et de vitamine E ont paru protéger le cerveau contre le stress oxydatif induit par les LCT. Cependant, la dexaméthasone a aggravé le stress oxydatif par rapport au groupe CT, car elle peut ne pas être neuro-protectrice.

Mots-clés: *Lésion cérébrale traumatique, stress oxydatif, cortex cérébral, carica papaya, vitamine E, dexaméthasone*

Introduction

Traumatic brain injury (TBI) is a result of a mechanical force (blunt or penetrating) causing immediate injury to brain tissue and delayed pathogenic events which collectively mediate widespread neurodegeneration [1]**.** Brain injury tends to produce varying degrees of alterations in levels of consciousness as well as temporary or permanent impairment of cognitive, physical and psychosocial functions and even death [2]. It is a heterogeneous disorder that varies with mechanisms, nature, severity and distribution of parenchymal damage. TBI, apart from gross mechanical injuries, also triggers biochemical changes that lead to delayed neural cell loss [3].

In Nigeria, TBIs follow the global pattern occurring mostly in urban areas. Adeolu *et al.*, [4] conducted a retrospective study of head injury emergencies in hospitals in the South-Western Nigeria between July 1993 and June 1998 and recorded that Motor Vehicle Accidents (MVA) accounted for 65.3% of all cases, followed by falls and pedestrian Motor Vehicle Accidents (MVA) which account for 16.4% and 8.1% respectively. In another study, Shokunbi and Solagberu [5] documented that high mortality occurred among head injured children attending the University College Hospital (UCH), Ibadan. Furthermore, Adeolu *et al*., [4] reported that most head injuries occur frequently around the age of 30 and Umoh *et al.*, [6] documented that males are more affected than females. Other workers found that TBI could result from, automobile accidents (36%), falls (29%), assaults/blows (11%), sports-related injuries (10%), and explosive blasts (14%) [7]. TBIs are known leading causes of disability and death both in the industrialized and developing world, with an incidence of 200-400 cases per 100,000, and so, constitute a major contributor to socio-economic loss [8].

The severity of the injury depends on various characteristics of causative forces. In the last decade, accumulating evidence has shown that the central nervous system (CNS) can mount a well-defined inflammatory reaction to a variety of insults such as trauma, ischemia, various infections as well as neurodegenerative changes [9].

Extensive research has indicated that cellular and humoral inflammation after TBI play a key role in the extent of brain injury and repair processes [10]. The initiation, progression and resolution of inflammation in TBI is multifaceted involving secretion of inflammatory mediators such as pro- and anti-inflammatory cytokines and chemokines, activation of resident immune cells, and leukocyte infiltration [10]. Traumatic brain injury thus triggers a cascade of events resulting in delayed oedema, impaired function and necrosis due to accumulation

of harmful mediators in the brain after injury [11].

TBI is the most common cause of death and disability in young people [12]. The Glasgow Coma Scale (GCS) is the most common scoring system used to describe the level of consciousness in a person following a traumatic brain injury. Every brain injury is different, but generally, brain injury is classified as: Severe: GCS 3-8 (a score lower than 3, cannot be scored) Moderate: **GCS** 9-12. Mild: GCS 13-15.Basically, it is used to help gauge the severity of an acute brain injury. The test is simple, reliable, and correlates well with outcome following severe brain injury [13]. Following a head trauma or other pathological states, disruption of the BBB can be a relatively major part of the pathology. Breakdown of blood-brain-barrier (BBB) and infiltration of peripheral immune cells (neutrophils and macrophages) into the brain parenchyma have been reported previously in fluid-percussion brain injury in rats and recently in human brain contusion [14].

TBI has been reported to induce oxidative stress by generation of free radicals leading to cellular dysfunctions and death. Traumatic brain injury (TBI) leads to massive production of reactive oxygen species (ROS) [15], an important component of the secondary injury cascade that includes superoxides, hydrogen peroxide, hydroxyl radicals, nitric oxide, and peroxynitrite [16]. ROS mediates further damage via cellular molecular pathways such as damage to cellular components like lipids, proteins and nucleic acids with neuronal death occurring as a result of impairment of cellular calcium homeostasis, tissue acidosis and oxidative stress [17]. More recently, it has become evident that cells produce free radicals positively and utilize them to regulate cellular functions. For example, oxidative stress induces apoptosis to prepare the birth canal for delivery [18, 19].

Under physiologic conditions, endogenous antioxidants—including superoxide dismutase, glutathione peroxidase, and catalase—prevent oxidative damage [20]. Superoxide dismutase catalyses the conversion of superoxide to hydrogen peroxide, which is further degraded by glutathione peroxidase and catalase to molecular oxygen and water. Low-molecular-weight antioxidants—including glutathione, melatonin, and uric acid—and dietary sources of α- tocopherols, ascorbic acid and lipoic acid, are also available in the brain. Antioxidant activities have also been reported in some plants, fruits and vegetables such as Vernonia amygdalina, Occimum gratissimum, Calotropis procera, Carica papaya and Garcinia kola [21], representing the nutritional supplements [22].

Carica papaya, a tropical plant native to Southern Mexico, Central America and Northern South America is now cultivated in most countries with tropical climate such as Malaysia, the West Indies and throughout Africa [23]. In Nigeria, it is commonly known as paw-paw and belongs to the fruits and vegetable class. However, in Nigeria, it is also known by different local names depending on the tribe. For example, among the Yoruba (South-West Nigeria) it is known as "Ibepe" and "sigun", "gwanda" among the Hausa (Northern Nigeria), "ojo" and "okwere" among the Igbo (South-East Nigeria), "etihi-mbakara" among the Efik (South-South Nigeria).Practically, every part of the plant is of economic, nutritional and medicinal values [24]. Carica papaya is the most important species within the Caricaceae, being cultivated widely for consumption as a fresh fruit, for use in drinks, candies, jams and as dried crystallized fruits [25]. Nutritionally, the fruit, leaves and flowers may also be used as cooked vegetable. It is an excellent source of vitamin A and C as well as a good source of calcium [26]. Biochemically, the leaves and fruits of papaya are complex, producing several proteins and alkaloids with important pharmaceutical and industrial applications [27]. However, of particular importance is papain, a proteolytic enzyme that is produced in the milky latex of green, unripe papaya fruits. Papain has various commercial uses industrially (beverage, food and pharmaceutical) that include: production of chewing gums, tenderising meat, drug preparation for various digestive ailments and treatment of gangrenous wounds. It has also been used in the textile industry for softening of wool and in the cosmetic industry, for the making of soaps and shampoos [25].

Vitamin E is a fat-soluble vitamin required by animals and man, and necessary for normal growth maintenance and reproduction. It is a biological antioxidant and detoxifying agent which protects unsaturated fatty acids and membrane structure [28].

Vitamin E is the major lipid soluble chain breaking antioxidant in the body tissues and the most effective lipo-solouble antioxidant found in the human biological system [29, 30]. It interacts with free radicals to prevent lipid peroxidation which is a protective mechanism against oxidative damage in neuronal tissue.

Dexamethasone, a catabolic corticosteroid which breaks down stored fat, sugar and protein used as fuel in times of stress has been reported to have anti-inflammatory and anti-allergic properties. Its anti-inflammatory functions in cancer chemotherapy, treatment of central nervous system disorders, itchy

skin, immune suppression, joint pain, shock and reduction of blood calcium levels in certain medical conditions where calcium level is dangerously high are well documented [31]. The study therefore aimed at evaluating the neuroprotective effects of *Carica papaya* fruit extracts, vitamin E and dexamethasone on traumatic brain injury-induced oxidative damage in adult male Wistar rats.

Materials and methods

Experimental animals

Fifty adult male Wistar rats weighing 160-180 g were purchased from the central animal house of the Faculty of Basic Medical Sciences, University of Ibadan and used for this research. The animals were fed with rat pellet feed obtained from Ladokun Feeds in Ibadan and water provided *ad libitum*. Only male Wistar rats were used for this study in order to avoid bias in gender with respect to inflammatory activity and susceptibility to brain injury, which seems to be greatly influenced by female reproductive hormones [32]. All animals received human care according to criteria outlined in the Guide for the Care and Use of Laboratory Animals [33].

Groupings

Group I: (5 rats) Received distilled water orally only and served as the control group

Group II: (10 rats) Trauma (blunt and penetrating) control animals only

Group III: (5 rats) Received 200 mg/kg body weight of *Carica papaya* extracts (*C. papaya*) orally

Group IV: (10 rats) Received 200 mg/kg body weight *C. Papaya* orally + trauma (blunt and penetrating) .

Group V: (10 rats) Received 200 mg/kg body weight Vitamin E orally + trauma (blunt and penetrating)

Group VI: (10 rats) Received 0.005 ml of 4 mg/ml body weight of dexamethasone intraperitoneally + trauma (blunt and penetrating).

The interventions were administered for 14 days pre-induction of trauma and continued for 7 days post-sham trauma before sacrifice.

Collection and identification of plant materials

Fresh, ripe mature fruits of *Carica papaya* were purchased from Bodija market in Ibadan North Local Government Area of Oyo State, Nigeria. The fruits were identified and authenticated at the Forestry Research Institute of Nigeria (FRIN) Ibadan; Oyo State Nigeria, by Shasarya O.S and given the Forest Herbarium Identification Number (FHI): 109722.

Preparation of the extracts

Fresh fruit of ripe *Carica papaya* was peeled, seeds were removed and the pulp then cut into pieces. 500 g of the fruits was weighed and blended into a beaker and 1.5 L of water was used to soak the peeled and diced Carica papaya overnight. The juice was filtered using a Whatmann filter paper 125 mm and concentrated using a rotary evaporator [34]. The filtrate was then oven-dried at 40^{o}C. The dried extract (flakes) was used for the study [35].

Administration of interventions

This was done for 14 days pre-induction of trauma and continued for 7 days post-sham trauma. Animals in group I received distilled water only and served as the control. Group II: TBI model control group received distilled water. Group III: C. Papaya only (200 mg/kg body weight). Group IV: C. Papaya (200 mg/kg body weight) and trauma. Group V: Vitamin E (200 mg/kg) and trauma. Group VI: 0.005 ml of 4mg / ml Dexamethasone and trauma. The chosen dose of papaya fruit extract was based on the active pharmacological dose range obtained from the (preliminary) orientation study earlier conducted.

Experimental induction of traumatic brain injury (TBI)

The following steps were followed in the experimental procedure

Step 1: The animals were anaesthetized with 10 mg of Ketamine Hydrochloride injection (by Rotexmedica Trittan, Germany) and 0.5 g of Diazepam- Tranzite injection (by Sirochem Ningbo Limited, China). Anaesthesia was active between 3-5 minutes.

Step 2: The skin on the head was shaved with a pair of scissors.

Step 3: Dettol antiseptic lotion was applied to the shaved region

Step 4: Animal was placed on the levered table, provided on a flat surface for the study.

Step 5: A spot 2.5 mm posterolateral to the Bregma was marked [36].

Step 6: A round metallic ball for non-penetrating trauma was moulded to the tip of Steinmann's pin for blunt trauma and a normal Steinmann's pin was used for penetrating injury.

Step 7: The levered table was adjusted to accommodate 2 mm traumatic distance of each animal with a steel ruler.

A weight of 425 mg was dropped from a uniform height of 5 cm to inflict trauma. The cortical injury device as described by Stahel *et al*., [37] and

employed by Leinhase *et al;* [32] was used using a standardized weight drop device.

Step 9: Topical application of cotton wool to bleeding spot was done.

Step 10: Animals were removed from the levered table to recover.

Trauma method

After induction of anaesthesia for about 1 min, a weight of 425 mg was dropped on the skull from a height of 5 cm for both penetrating and blunt injuries. The equipment (modified weight-drop device) was made of a levered table with slide retort stand holding two clamps at a distance of 5 cm interval. The upper clamp holds the Steinmann's pin with the help of a perforated wood, which serves as a stopper. The lower clamp with the perforated wood helps to appropriate the pathway of the pin over the rat's skull.

Sham-operated gontrol group p and subjected to the same procedures except that no head trauma was applied.

Baseline control group

For assessment of baseline characteristics in untreated animals, these rats were kept under identical conditions as the head-injured and sham-operated animals, but no experimental procedures were performed [32]. They were subjected to identical neurological assessment and brain tissue analysis as the experimental groups.

After the induction of the traumatic brain injury, the animals were allowed to recover under close supervision till the time of sacrifice.

Body weight of the animals

This was done using a Swiss Microwa balance (type 7720).

Determination of relative cerebral weight

$$\text{Relative cerebral weight: } \frac{\text{Cerebral weight}}{\text{Total brain weight}} \times 100$$

$$\text{Organ (brain) to body weight index (\%): } \frac{\text{Total brain weight}}{\text{Body weight}} \times 100$$

Behavioural tests

Behavioural tests were performed on the rats on the 5th day after the induction of trauma on recovery to evaluate motor function and equilibrium.

Forelimb grip strength test

This test involves the forepaws of the rats being placed on a horizontally suspended metal wire (measuring 2mm in diameter and 1m in length), placed one meter above a landing area filled with soft bedding. The length of time each rat was able to stay suspended before falling off the wire is recorded. A maximum time of 2 minutes is given to each rat after which it will be removed. This test reflects muscle strength in the animals [39].

Negative geotaxis

This test, which is believed to test reflex development, motor skills, vestibular labyrinth and cerebellar integration, is a modification of Hermans *et al.* (1992) method [39]. A wooden plank with a rough surface was put at an angle 45^0 to the wall on a levelled ground, the rat placed at a particular point facing downwards, alongside the gravity. The time it took for the rat to re-orientate itself against the gravity was measured.

Haematological analysis

Blood samples were collected from the retro-ocular plexus of five animals in each group on the 5th day post sham-trauma using heparinized capillary tubes into Ethylene Di-amine Tetra Acetic (EDTA) acid-treated sample bottles for the determination of white blood cell count as well as the differential cell count (lymphocytes, monocytes, neutrophils, eosinophils). The procedure was done at the Veterinary Pathology Laboratory of the University of Ibadan.

Collection of brain tissues for biochemical assays

The brains of rats were dissected out on the 7th day post-TBI and preserved in phosphate buffered solution at a temperature of 4^oC and a pH 7.4. These brains were homogenized, centrifuged at 12,000 rpm for 10 minutes at -4^oC. The supernatant was collected and the following oxidative stress markers were assayed; superoxide dismutase (SOD), hydrogen peroxide (H_2O_2), glutathione peroxidase (GSH-Px), lipid peroxidase (LPO) and reduced glutathione (GSH).

Tissue processing for Histological evaluations

The rat brains were dissected out on the 7th day post-TBI and weighed. The cerebrum was dissected out, weighed and fixed in 10% formol-saline for histological and histomorphometric studies employing routine paraffin embedding technique and stained in Haematoxylin and Eosin (H and E). Histological changes in the cerebral cortex was observed by an Olympus binocular microscope (XBS series, Zhangqui Meihua Ltd. China), while cerebral cortical thickness was done on the frontal lobe using

a graticle (calibrated eye piece attached to the microscope).

Statistical analysis

The data obtained were further subjected to statistical analyses employing the unpaired students't-test and one-way Analysis of variance (ANOVA), using the statistical software package Microsoft Excel for Windows 2007. The mean, Standard error of mean (SEM) and level of significance at $p < 0.05$ were calculated.

Results

Body weight

A decreased body weight was observed in the traumatized rats but most severe in the dexamethasone group compared with the control at $p < 0.05$. *Carica papaya* fruit extract improved the body weight when compared with the trauma control and dexamethasone groups at $p < 0.05$. There was no increased body weight in the VET group. There was no observable change in the cerebral weight of all groups at $p>0.05$. An increased brain to body weight index was observed in the trauma control, vitamin E and dexamethasone (blunt) groups compared with the control group at $p < 0.05$. *Carica papaya* fruit extract decreased brain weight when compared with the trauma control rats at $p < 0.05$ (Table 1).

Neurobehavioural studies

Trauma significantly reduced the hang time (forelimb grip) and delayed the time of re-orientation (negative geotaxis) in the trauma control and vitamin E groups at $p < 0.05$. Carica papaya and dexamethasone reduced the time of re-orientation (Table 2).

Haematological studies

Haematological studies revealed no significant difference in white blood cell (WBC) count in the control and trauma control animals at $p > 0.05$ but elevated in the penetrating trauma + *Carica papaya* and dexamethasone + trauma animals when compared with the control group at $p < 0.05$. There was no significant difference in the percentage monocytes count between the treated and control groups at $p > 0.05$. The percentage neutrophil was significantly increased in the trauma control, dexamethasone + trauma (penetrating and blunt) and *C. papaya* + penetrating trauma groups compared with the control at $p < 0.05$. There was a significant reduction in the percentage of lymphocytes in the trauma control, dexamethasone + trauma groups (penetrating and blunt) and *C. papaya* + trauma (penetrating) compared with the control group at $p < 0.05$ (Tables 3).

Oxidative stress markers

Elevated levels of SOD were seen in the treated rats compared with the control at $p< 0.05$. A significant increase in hydrogen peroxide levels and lipid peroxidation was seen in trauma control and dexamethasone with trauma treated rats in penetrating and blunt animals at $p< 0.05$. *C.papaya* and vitamin E tend to decrease these levels of oxidative markers (Tables 4).

Histomorphometric evaluations

Thickness of the cerebral cortex

A decreased cerebral cortical thickness was observed in the traumatized rats but significantly in the trauma

Table 1: Body weight, relative cerebral weight and brain to body weight index of control and traumatized (penetrating and blunt) rats

\	Body weight of rats (g)		Relative cerebral weight (%)		Brain to body weight index	
Group	Penetrating	Blunt	Penetrating	Blunt	Penetrating	Blunt
CTRL	174.24 ± 1.81	174.24±1.81	71.89±1.00	71.89 ± 1.00	1.14±0.05	1.14±0.05
TC	156.67 ±2.90[a]	150.63±0.84[a]	74.00±1.36	73.19±1.59	1.41±0.05[a]	1.34±0.03[a]
CPC	168.20±2.12[b]	168.20±2.12[b]	72.82±1.10	72.82 ± 1.10	1.14±0.04[b]	1.14±0.04[b]
CPT	165.86±0.93[a,b]	162.74±0.71[a,b]	72.73±0.83	70.14±1.02	1.13±0.02[b]	1.21±0.04[b]
VET	155.64±3.80[a]	156.44±2.15[a]	73.07±0.90	69.78±0.80	1.37±0.07[a]	1.27±0.02[b]
DET	142.70±0.91[a,b]	136.18±2.85[a,b]	71.93±0.89	70.47±1.02	1.25±0.03	1.32±0.04[a]

Values are expressed as Mean ± SEM. (n=5) CTRL: Control, TC: Trauma Control CPC: *Carica papaya* Control, CPT:*Carica papaya* + Trauma, VET: Vitamin E + Trauma, DET: Dexamethasone + Trauma. [a]$p < 0.05$ versus control [b]$p < 0.05$ versus trauma control

Table 2: Neurobehavioral assessment of control and traumatized (penetrating and blunt) rats.

Group	Forelimb grip test (second)		Negative geotaxis (second)	
	Penetrating	Blunt	Penetrating	Blunt
CTRL	20.02 ± 0.41	20.02 ± 0.41	3.06 ± 0.26	3.06 ± 0.26
TC	6.19 ± 0.31[a]	3.93 ± 0.54[a]	4.50 ± 0.12[a]	4.18 ± 0.19[a]
CPC	4.88 ± 0.12[a,b]	4.88 ± 0.12[a,b]	2.99 ± 0.25[b]	2.99 ± 0.25[b]
CPT	5.00 ± 0.65[a]	4.04 ± 0.33[a]	3.52 ± 0.19[b]	3.34 ± 0.05[b]
VET	6.06 ± 0.52[a]	4.48 ± 0.76[a]	4.26 ± 0.03[a]	4.39 ± 0.08[a]
DET	5.57±0.67[a]	6.48±0.10[a,b]	2.24±0.12[b]	3.29±0.18[b]

Values are expressed as Mean ± SEM. (n = 5) CTRL: Control, TC: Trauma Control CPC: Carica papaya Control, CPT: Carica papaya + Trauma, VET: Vitamin E + Trauma, DET: Dexamethasone + Trauma. [a]p < 0.05 versus control [b]p < 0.05 versus trauma control.

Table 3: Haematological assessment of control and traumatized (Penetrating and blunt) Rats

Groups		CTRL	TC	CPC	CPT	VET	DET
Neu	Pen	22.60±2.24	32.00±2.14[a]	30.20±1.88	32.20±1.93[a]	25.80±2.80	37.68±3.67[a]
%	Blu	22.60±2.24	32.20±1.51[a]	30.20±1.88	27.25±2.03	25.20±3.74	33.07±1.71[a]
Lym	Pen	75.40±2.38	66.75±3.36[a]	67.00±1.39[a]	63.20±1.31[a]	73.75±1.11[b]	32.80±3.74[a,b]
%	Blu	75.40±2.38	64.20±1.45[a]	67.00±1.39[a]	70.00±2.35	69.00±2.61	31.33±2.23[a,b]
Mono	Pen	1.80±0.33	2.00±0.49	1.20±0.52	1.60±0.22	1.00±0.28	2.10±0.38
%	Blu	1.80±0.33	1.00±0.28	1.20±0.52	0.60±0.22	1.60±0.22	2.60±0.21
Wbc	Pen	6.42±0.33	5.48±0.66	5.35±1.04	8.11±0.83[a]	5.17±0.59	7.68±0.63[a]
x109/L	Blu	6.42±0.33	7.28±0,98	5.35±1.04	6.44±0.80	6.30±1.10	5.70±0.46

Values are expressed as Mean ± SEM. (n=5) CTRL: Control, TC: Trauma Control CPC: Carica papaya Control, CPT: Carica papaya+Trauma, VET: Vitamin E+Trauma, DET: Dexamethasone+Trauma. Neu: Neutrophil, Lym: Lymphocyte, Mono: Monocyte, Wbc: White blood cell. Pen: Penetrating, Blu: Blunt. [a]p< 0.05 versus control [b]p< 0.05 versus trauma control.

Table 4: Biochemical assessment of control and traumatized (penetrating and blunt) rats

Groups		CTRL	TC	CPC	CPT	VET	DET
SOD	P	0.38±0.03	0.83±0.07[a]	0.71±0.06[a]	0.78±0.04[a]	0.75±0.04[a]	0.87±0.06[a]
µ/mg	B	0.38±0.03	0.71±0.03[a]	0.71±0.06[a]	0.42±0.06[b]	0.67±0.05[a]	0.92±0.04[a,b]
H_2O_2	P	11.54±0.42	14.92±0.81[a]	11.46±0.31[b]	11.77±0.31[b]	11.17±0.27[b]	14.25±0.23[a]
µmol/mg	B	11.54±0.42	14.58±0.51[a]	11.46±0.31[b]	12.55±0.46	12.92±0.92	14.95±0.31[a]
GSH	P	35.96±0.13	34.73±0.28	36.49±0.39	36.49±0.08	34.73±0.36	34.95±0.31
µg/ml/mg	B	35.96±0.13	37.66±0.28[a]	36.49±0.39[b]	34.94±0.20[a,b]	36.33±0.35	37.45±0.81
GSH-Px	P	48.48±1.53	56.71±1.34[a]	48.11±2.62[b]	47.80±3.94	56.26±0.45[a]	52.66±2.32
µ/mg	B	48.48±1.53	44.00±3.72	48.11±2.62[b]	50.08±2.61	45.92±3.62	53.37±0.65
LPO	P	0.57±0.01	0.92±0.03[a]	0.52±0.02[b]	0.70±0.02[a,b]	0.60±0.03	0.93±0.01[a]
µmol/mg	B	0.57±0.01	0.81±0.03[a]	0.52±0.02[b]	0.63±0.04[b]	0.53±0.04[b]	0.86±0.03[a]

Values are expressed as Mean ± SEM. (n=5) CTRL: Control, TC: Trauma Control CPC: Carica papaya Control, CPT: Carica papaya+Trauma, VET: Vitamin E+Trauma, DET: Dexamethasone+Trauma, P: Penetrating, B: Blunt. [a]p< 0.05 versus control [b]p< 0.05 versus trauma control.

control, vitamin E and dexamethasone groups compared with the control rats at $p < 0.05$. Treatment with *Carica papaya* fruit extract improved the thickness of the cerebral cortex when compared with the trauma control rats at $p < 0.05$ (Table 5).

Histological observation

Altered leptomeninges, oedema, astrocytic gliosis and tissue injury were seen in the tissues of trauma (penetrating) rats compared with the control rats.

Table 5: Thickness of the cerebral cortex of control and traumatized (penetrating and blunt) rats in millimetres

Group	Penetrating (mm)	Blunt (mm)
CTRL	4.04 ± 0.01	4.04 ± 0.01
TC	2.48 ± 0.02[a]	3.04 ± 0.00[a]
CPC	3.66 ± 0.04[b]	3.66 ± 0.04
CPT	3.11 ± 0.05[b]	3.39 ± 0.02
VET	2.72 ± 0.06[a]	3.60 ± 0.03
DET	2.23 ± 0.00[a]	3.13 ± 0.00[a]

Values are expressed as Mean ± SEM. CTRL: Control, TC: Trauma Control, CPC:*Carica papaya* Control, CPT:*Carica papaya* + Trauma, VET: Vitamin E + Trauma, DET: Dexamethasone + Trauma. [a]$p < 0.05$versus control, [b]$p < 0.05$ versus trauma control.

Carica papaya fruit extract and vitamin E did not distort the cortical layer of the cerebral cortex compared with the trauma rats. Dexamethasone + penetrating trauma showed altered dura matter, oedema and tissue injury and distorted cortical cytoarchitecture compared with the control rats (Fig 2). Only minor leptomeningeal and parenchymal damages were seen in the blunt trauma group compared with the control rats (Fig 3).

Discussion and conclusion

The brain is particularly vulnerable to oxidative injury because of its high rate of oxygen consumption, intense production of reactive radicals and high levels of transition metals, such as iron, which can catalyse the production of reactive radicals leading to oxidative stress. When the tissues are exposed to oxidative stress they increase the activity and expression of antioxidant enzymes as a compensatory mechanism against free radical-mediated damage [40].

The general results in this study revealed a significant reduction in the body weight of the trauma groups; this however may be due to the fact that the animals ate less after the trauma and were also generally less active.

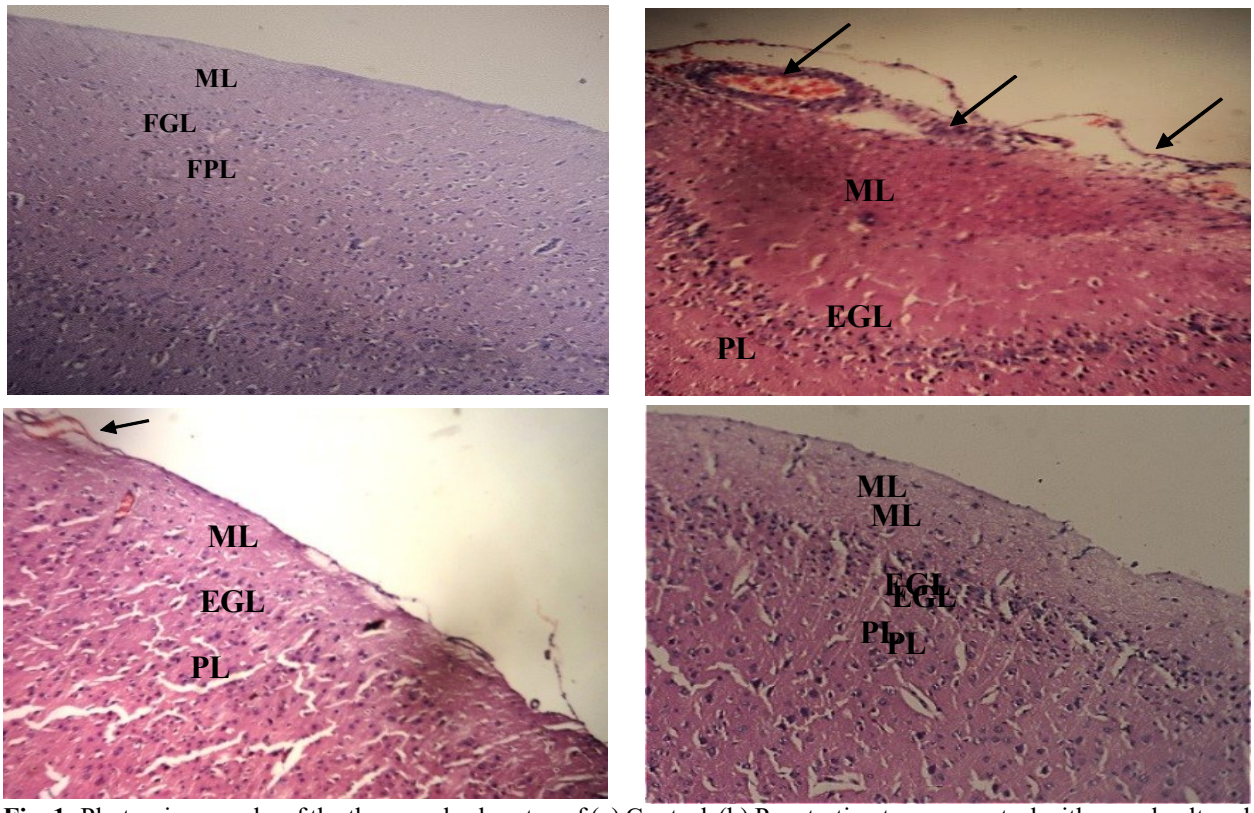

Fig. 1: Photomicrographs of the the cerexbral cortex of (a) Control (b) Penetrating trauma control with severly altered dura matter, oedema and tissue injury (arrows) (c) Blunt trauma control with midly altered dura matter (arrow) (d) *Carica papaya* alone with normal cortical cytoarchitecture. Molecular layer, ML, External granular layer, EGL, Pyramidal layer, PL. Bar, 100 µm . X100.

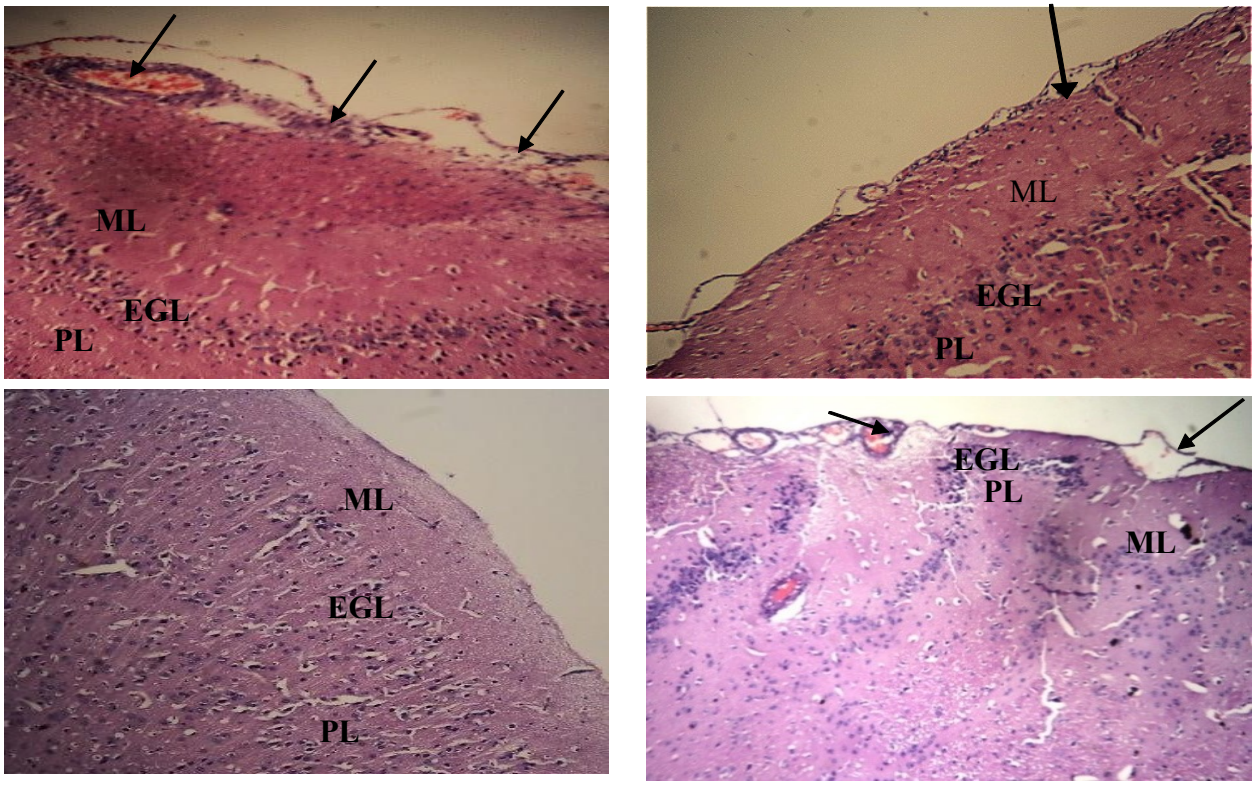

Fig. 2: Photomicrographs of the cerexbral cortex of (a) Penetrating trauma control with altered dura matter, oedema and tissue injury (arrows) (b) *Carica papaya* and penetrating trauma with midly altered dura matter (arrow) (c) Vitamin E and penetrating trauma with normal cortical cytoarchitecture (d) Dexamethasone and penetrating trauma with altered dura matter, oedema and tissue injury (arrows) and distorted cortical cytoarchitecture. Molecular layer, ML, External granular layer, EGL, Pyramidal layer, PL. Bar, 100 µm . X100.

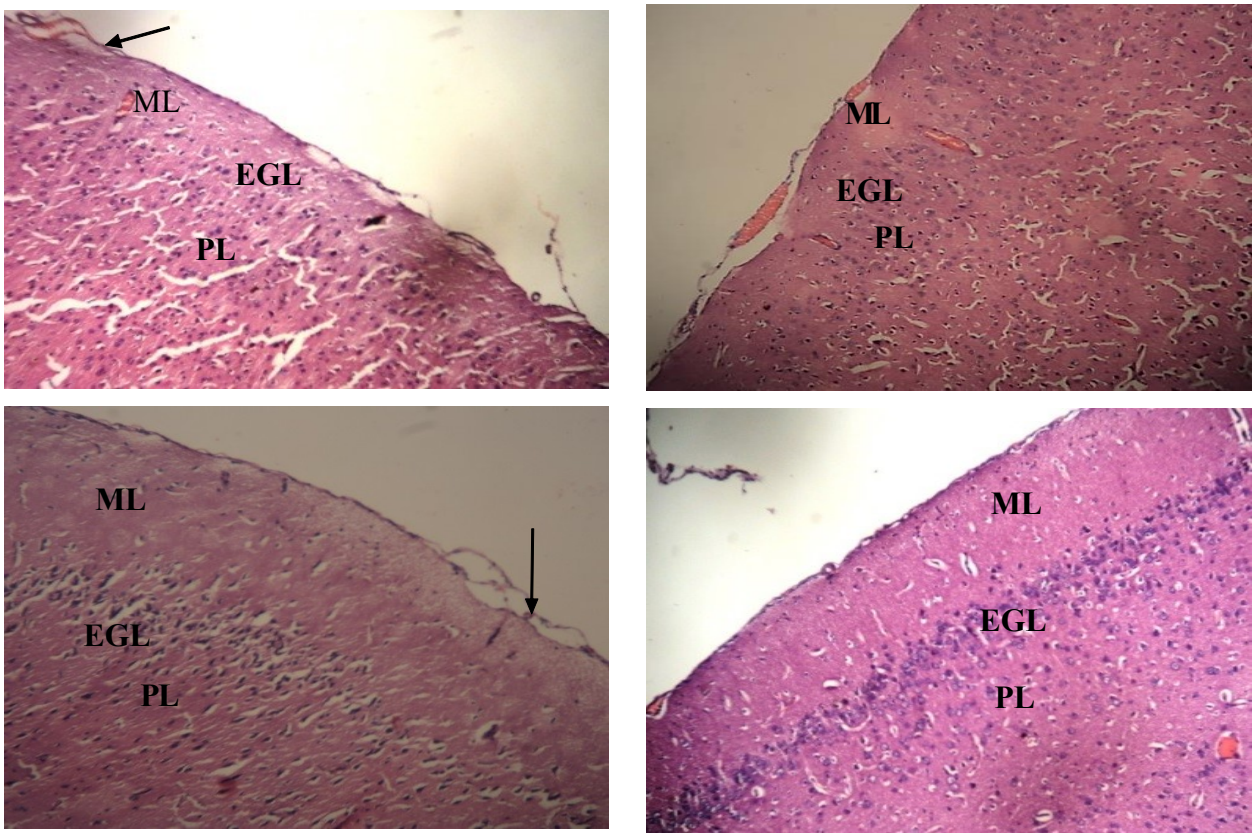

Fig.3: Photomicrograph the cerexbral cortex of (a) Blunt trauma control with midly altered dura matter (arrow) (b) *Carica papaya* and blunt trauma (c) Vitamin E and blunt trauma with altered dura matter (arrow) (d) Dexamethasone and blunt trauma. Molecular layer, ML, External granular layer, EGL, Pyramidal layer, PL. Bar, 100 µm . X100

Trauma has been reported to cause the release of inflammatory cytokines which induce anorexia and weight loss [41-43].

Carica papaya fruit extract was able to improve the body weight after trauma compared with the trauma control rats. Administration of dexamethasone to traumatized rats significantly reduced the body weight compared with the trauma control rats. This result is consistent with the results of Lingaiah *et al* [44] and Sekita-Krzak *et al* [45]. Increased brain and cerebral weight observed in the trauma control rats could be as a result of brain tissue swelling (oedema) which is in line with the works of Onose *et al* [46] and Ijomone *et al* [22]. The oedema observed in this study, may be due to intracellular water accumulation of neurons, astrocytes and microglia in spite of an intact vascular endothelial wall. The above feature is caused by increase cell membrane permeability for ions and failure of ionic pump due to energy depletion [47, 48]. *Carica papaya* extract effectively reduced the effect of trauma on the weight of the brain probably by reducing the oedema through its anti-inflammatory activitiy. This is consistent with the works of Owoyele *et al*. [49]. Vitamin E and dexamethasone though reduced the weight of the brain but not effectively.

Neurobehavioral studies revealed that the forelimb grip test (Fore limb motor control), a measure of the muscle strength of the rats showed a statistically significant difference among the groups. The traumatized rats had reduced muscular strength with a shorter drop-off time when compared to the control. This could be as a result of injury to the frontal lobe, thus causing weakness of the muscles. It is consistent with the works of Alvarez and Emory [50]. The reduced drop-off time observed in the traumatized rats was statistically significant. The interventions administered had no effect on the drop-off time of the traumatized rats. The negative geotaxis showed a delayed time of re-orientation (in-coordination) of the rats in the trauma control which may have resulted from secondary injury to the frontal lobe. This however, may have impaired vestibular or proprioceptive receptor function sufficient to detect a geo-gravitational stimulus, central organization sufficient to process differential inputs that reflect the direction of the substrate angle in relation to the gravity vector, and in addition to decreased cortical thickness, the motor competence to orient and move on the incline. *Carica papaya* and dexamethasone effectively returned the re-orientation time to normal. Vitamin E, however, had no effect on the negative geotaxis of traumatized rats.

Haematological results in this study revealed no significant difference in the monocytes count between the treatment groups and the control. The percentage neutrophil was increased in the trauma control groups (penetrating and blunt) on day 7 post-trauma. Allen *et al* [51] reported that neutrophils appear in the brain within hours of an ischaemic event, adhering to activated blood vessels or migrating to the parenchyma, which is increased under systemic inflammatory conditions. It peaks within 2 days after TBI whereas monocytes accumulate slightly later [52]. There was a significant reduction in the percentage lymphocytes in the trauma control and other treated groups (penetrating and blunt) but severely in the dexamethasone group compared with the control. The mechanism for the reduction of the percentage lymphocytes in this present study is poorly understood, however, research has shown that severe TBI resulted in a significant decrease in percentage and absolute number of circulating T lymphocytes, observed within 24 hours of injury as well as day 4 post injury [53, 54]. And given that TBI results in increased circulating levels of catecholamines [55, 56], then lymphocyte retention in lymph nodes may explain the significant reduction in circulating T cells that has been observed following TBI. Reduction of lymphocytes results in immune suppression and production of cytokines.

The formation of free radicals and reactive species is a significant event after TBI and has been implicated in accentuating other elements of the secondary injury cascades [57]. Biochemical assays for the study of biomarkers of oxidative stress revealed that there was a significant elevation in the production of SOD in the treated rats. This is consistent with the work done by Sangeetha *et al,* [58]. Increase in SOD is indicative of increased generation of superoxide radicals thus inducing oxidative stress. The administration of *Carica papaya* fruit extract was associated with lower levels of SOD when compared with the control rats. Hydrogen peroxide generation and lipid peroxidation in the trauma control and dexamethasone groups (penetrating and blunt) was significantly increased. Slemmer *et al*, [59] showed that superoxide dismutase (SOD) catalyzes the conversion of O^{2-} to H_2O_2. Therefore increased SOD signals increased H_2O_2 generation. *Carica papaya* and vitamin E reduced H_2O_2 generation and lipid peroxidation in penetrating and blunt trauma probably by their antioxidant activity. The reduction in free radical yield and the subsequent decrease in harm and damage to the cell membrane may be due to decrease

in malondialdehyde (MDA) production, an end product of lipid peroxidation [60].

The histological alterations observed in this study are suggestive of inflammation and justifies the fact that mechanically induced neurodegeneration is characterised by different patterns of neuronal cell death, gliosis, swollen or destroyed axons and severely altered dura matter. Reduction in the cortical thickness observed in the trauma control group may be due to neuronal cell death induced by oxidative stress as a result of TBI. This effect leads to ROS formation, astrocytes swelling and thus, increasing the surrounding pressure which could cause a decrease in dendritic spines of the cortical pyramidal neurons with resultant decrease in cortical thickness. Smith *et al* [61] reported that, just as in humans, mild TBI in juvenile rats induced marked cortical atrophy (i.e., decreased cortical thickness) and enlarged ventricles that were most pronounced beneath the impact site. Carica papaya and vitamin E increased the cortical thickness probably by their free radical scavenging activity, preventing the formation of ROS and hence, oxidative stress in the traumatized rats. Parle and Gurditta [62] reported the free radical scavenging property of *Carica papaya* capable of preventing oxidative damage and cellular dysfunction. Dexamethasone however, was associated with a decrease in cortical thickness in the penetrating trauma group, as such may aggravate motor function impairment. This finding is consistent with reports from human studies which have suggested that steroids worsen the clinical outcome of TBI in humans. Duffy *et al*. [63] suggested that dexamethasone can exacerbate the acute cerebral oedema and brain injury resulting in neuronal damage in status epilepticus.

In conclusion therefore, this present study has shown that acute TBI induced oxidative stress, especially in penetrating trauma which severely affected brain morphology and behaviour. Pre-treatment with aqueous extract of *Carica papaya* fruit and vitamin E protected against TBI-induced brain damage and oxidative stress. Dexamethasone however, tends to generate free radicals and induced lipid peroxidation in TBI-induced rats. This research was met with some limitations, as there was no automatic weight drop machine and the amount of the *Carica papaya* extract that crossed the blood brain barrier was not quantified.

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Evaluation of rural posting experience among final year dental students of University of Ibadan, Nigeria

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Abstract

*Background***:** Globally, evidence has shown that rural medical training promotes recruitment and retention of medical personnel translating into an increasing demand for undergraduate medical placements in rural communities.

Aim: The aim of this study was to describe rural posting experience among final year dental students of the University of Ibadan, Nigeria.

*Methods***:** A cross-sectional study was undertaken among 4 sets of 142 final year dental students of the University of Ibadan who had their rural posting at Igboora, Southwest Nigeria using a forty-seven-item questionnaire. Survey sections included demographics, general experience, skill development, supervision and comparison between urban and rural dental postings. Frequencies of relevant variables were generated and chi-square test was used to compare categorical variables at $p < 0.05$.

Results The mean (SD) age of the students was 23.9 (2.4) years, there were more males 51.4% (73/142) than females 48.6%(69/142). The majority 73.9%(105/142) agreed that their educational experience met their expectations of what a rural dental program was. The majority 90.8% (129/142) and 71.1% (101/142) disagreed that there was adequate access to information technology and library facilities respectively. All the students agreed that their research skills were developed and improved. The majority 83.8% (119/142) disagreed that the accommodation provided in the rural posting was better than that provided in the urban posting. All the students agreed that the rural posting provided them the opportunity to observe the various determinants of health. The majority 76.1% (108/142) reported that they will like to go for rural posting again. There was no significant difference between gender and experience of participants about rural and urban posting ($p > 0.05$).

Conclusions: There were both negative and positive feedbacks about rural dental postings from the final year dental students that should be considered to strengthen the programme.

Keywords: *Rural posting, dental students, underprivileged areas*

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Résumé

Contexte: À l'échelle mondiale, des preuves montrent que la formation médicale en milieu rural favorise le recrutement et la rétention du personnel médical, ce qui se traduit par une demande croissante de stages pour les étudiants de premier cycle enmédecine dans les communautés rurales.

Objectif: Le but de cette étude était de décrire l'expérience d'affectation en milieu rural parmi les étudiants en dernière annéede médecine dentaire de l'Université d'Ibadan, au Nigeria.

Méthodes: Une étude transversale a été menée auprès de 4 séries de 142 étudiants en dernière annéedemédecine dentaire de l'Université d'Ibadan qui avaient leur poste rural à Igboora, dans le sud-ouest du Nigeria, à l'aide d'un questionnaire de quarante-sept items. Les sections de l'enquête comprenaient les données démographiques, l'expérience générale, le perfectionnement des compétences, la supervision et la comparaison entre les affectations dentaires urbaines et rurales. Les fréquences des variables pertinentes ont été générées et le test du chi-carré a été utilisé pour comparer les variables catégorielles à $p < 0,05$.

Résultats : L'âge moyen (ET) des étudiants était de 23,9 (2,4) ans, il y avait plus d'hommes 51,4% (73/142) que les femmes 48,6% (69/142). La majorité 73,9% (105/142) ont convenu que leur expérience en éducation satisfaisait à leurs attentes quant à ce qu'était un programme dentaire en milieu rural. La majorité 90,8% (129/142) et 71,1% (101/142) étaientrespectivement en désaccord sur l'accès adéquat aux technologies de l'information et aux bibliothèques. Tous les étudiants ont convenu que leurs compétences en recherche ont été développées et améliorées. La majorité des répondants, soit 83,8% (119/142), était en désaccord sur le fait que le logement offert dans le secteur rural était meilleur que celui offert dans l'affectation urbaine. Tous les étudiants ont convenu que l'affectation en milieu rural leur a permis d'observer les différents déterminants de la santé. La majorité, 76,1% (108/142) ont indiqué qu'ils aimeraient encoreêtre affectés à la campagne. Il n'y avait pas de différence significative entre le sexe et l'expérience des participants sur l'affectation en milieu rural et urbain ($p > 0,05$).

Conclusions: Il y avait des feedbacks négatifs et positifs sur les affectations dentaires en milieu ruraldes étudiants en dernière annéede la médecine dentaire qui devraient être considérés pour renforcer le programme.

Mots-clés: *Affectation en milieu rural, étudiants en médecine dentaire, zones défavorisées*

Introduction

Recruiting and retaining practitioners in rural and remote areas is a challenge for many industries including health and education [1]. In recent years, large investments have resulted in improved health infrastructure and access to care but finding effective ways of encouraging dentists to work in rural and remote health centres remains a problem. This problem is difficult to solve probably due to the unwillingness of dentists like other health workers to work in rural areas. Factors such as disparity in rural-urban living conditions, low socioeconomic background of inhabitants and lack of experience with rural life may be responsible for this pattern [2,3]. Retention of health workers in rural areas appears to be worse with dentists mainly because of dependence of dentistry on technology which is lacking in rural areas especially in developing countries.

Globally, there is an increasing demand for undergraduate medical placements in rural communities due to international evidence that supports the importance of rural exposure on recruitment and retention of rural physicians [4-6]. Immersion experiences for students in the medical, nursing and teaching professions have been used to better prepare professionals for working and to address workforce shortages in cross-cultural and underserved areas [7,8]. Jinadu *et al*. [9] mentioned that students in innovative primary health care medical schools had more experience of rural community settings and had more positive attitudes to community-based Primary Health Care postings which were mainly located in rural settings than traditional medical schools where students were not involved in rural postings. The strengthening of community oriented medical education will motivate doctors to participate in rural health services [10]. Senf and Campos-Outcalt [11] in their study on the effect of a required third-year Family Medicine Clerkship on medical students' attitudes reported that medical students' experiences serve to confirm, clarify and modify their existing values and interests. In the field of dentistry, community-based clinical education programmes have been established in developed countries and positive impact on dental training has been reported. For example, a study on clinical placement programme on the work location of a new dental graduates found that a higher proportion of graduates who participated in a rural dental placement programme were working in a rural locations when compared with those who had not been offered such a placement [12].

In 2007, the Community Oral Health unit of the Department of Periodontology and Community Dentistry, Faculty of Dentistry, University of Ibadan, Nigeria established the Ibarapa Community Oral Health Program at Igboora, a rural community and headquarters of Ibarapa Central Local Government Area of Oyo State, Nigeria [13].This program provided community based rural dental education program for dental students. The purpose of the program was to train dentists with a great sense of service and a strong inclination to broad community oral health care and preventive dentistry. However, this rural posting program has not been evaluated to determine if it meets set objectives. Evaluation of the program especially by students is needed to better inform curriculum developers in dental schools on how to review the curriculum for maximum efficiency. In their report of an innovation in Australian dental education, Bazen et al. [14] mentioned that assessment of students' attitude to rural practice and rural life is an essential part of the program in order to evaluate the impact of the rural experience. Data on professional needs and priorities are essential in determining ways of effectively engaging health practitioners in rural and remote health practices [15]. In rural areas, professional priorities of health personnel to rural service demand investigation so as to improve the distribution and retention of health workers in these areas. Relatively little research has been conducted to find out effective strategies to promote rural practice particularly in low-income countries [16]. Therefore this study provides a description of the experiences of undergraduate dental students during their rural posting. The description of their experience may provide information that will help to continuously improve the rural dental program of the Dental School University of Ibadan, Nigeria. It will also provide information for the effective establishment of such programs by dental schools especially in developing countries and in designing specific strategies to overcome the shortage of rural dentists in Nigeria and other developing countries.

Materials and methods

Ethical review board exemption and permission to undertake the study were obtained from the Dean, Faculty of Dentistry, University of Ibadan, Nigeria

since the study was an evaluation of the rural dental program. This evaluation formed part of the rural posting program to provide information for improving the program. Study was undertaken between 2009 and 2014 in accordance with the ethical standards provided by the Ibarapa Community Oral Health Programme of the University of Ibadan and in accordance with the Declaration of Helsinki. Written informed consent was obtained from the study participants.

Four sets of 142 final year dental students of the Dental School, University of Ibadan, Nigeria completed a six weeks rural posting in the penultimate year of their undergraduate program at Igboora, a rural community and headquarters of Ibarapa Central Local Government Area of Oyo State, Nigeria. Igboora is about 80 kilometres from Ibadan, the capital city of Oyo State and location of the University of Ibadan, Dental School. This rural community is inhabited by about 60,000 people whose main occupations are farming and trading [17]. The dental students carried out both curative and preventive services at the dental clinic located at the General Hospital Igboora and during outreach programmes to various population groups. This dental clinic was established as part of the rural dental education program of the University of Ibadan. The students visited various population groups in market places, schools, antenatal clinics, immunization clinics and artisans' workshops where they screened for oral diseases and provided oral health education under the supervision of community dental health practitioners. Lectures in oral disease epidemiology, research methodology and biostatistics as well as prevention of oral diseases and community oral health care were given to the dental students by lecturers in Community Dentistry. These lectures complemented the structured community observation and investigations.

The students were divided into four groups and given topics relevant to oral health issues in rural communities for weekly presentation. Scores were awarded to each group during the presentation. A representative from each group balloted for the epidemiological survey that was carried out by them. These surveys were on common oral health diseases and problems that are relevant to the needs of the community. After undertaking the surveys and data analysis, the students presented their findings in a community feedback programme in the town hall. Two weeks after their return to the dental school from the rural posting, all the 142 students were asked to anonymously and voluntarily complete a 47-item self-administered semi-structured questionnaire on their experience of the posting after obtaining written informed consent. Prior to administering the questionnaire to the dental students, it was pre-tested among 20 dental house officers who were undergoing their internship at the Dental Centre, University College Hospital, Ibadan, Nigeria and had previously participated in the rural program. The questionnaire was validated by asking experts to assess it to establish that the items were representative of the outcome. The experts also ensured that items and questions cover the full range of the issues or problems being measured and each question or item had a logical link to the objective of the study. In addition, a good background of the study, questionnaire conceptualization and formatting was undertaken before pre-testing the questionnaire. The questionnaire was modified after the pre-test was done to ensure that it was reliable and valid. Survey sections included demographics, general experience, skills development, supervision and comparison between urban and rural dental postings. All the students returned completely filled questionnaires. The students responded to questions on a Likert scale with five possible responses (strongly agree, agree, undecided, disagree and strongly disagree). These five responses were collapsed into two responses namely; agree comprising of strongly agree and agree and disagree comprising of strongly disagree, disagree and undecided. Frequencies of relevant variables were generated using Statistical package for Social Sciences Inc. Chicago Illinois USA (version 21). Chi-square test was used to test categorical variables at $p < 0.05$ level of statistical significance.

Results

All the 142 dental students returned a completed questionnaire. The mean (SD) age of the students was 23.9 (2.4) years and their age ranged between 22 years and 28 years.There were more males 51.4% (73/142) than females 48.6% (69/142). One hundred and twentyeight (90.1%) participants and their parents lived in urban communities while 9.9% (14/142) participants and their parents lived in rural communities. Table 1 shows the distribution of responses to general experience among the dental students during the rural posting. The majority agreed that there was less distractions to learning 81.0% (115/142), their educational experience met expectations of what a rural dental program was 73.9% (105/142), the posting provided the required preparations for examinations in Community Dentistry 69.7% (99/142) and they were able to negotiate learning goals 57.7% (82/142). However,

the majority disagreed that there was access to adequate information technology 90.8% (129/142) and library facilities 71.1% (101/142) or that they were able to attend to many patients 66.2% (94/142).

Table 1: Distribution of responses on general experience of study participants about the rural posting

General experience about rural posting	Agree No. (%)	Disagree No. (%)
Less distraction to learning	115 (81.0)	27 (19.0)
Educational experience met expectation of what rurual dental program was	105 (73.9)	37 (26.1)
Well prepared for examinations in Community Dentistry	99 (69.7)	43 (30.3)
Negotiated learning goals	82 (57.7)	60 (42.3)
Participated actively in patient care	73 (51.4)	69 (42.6)
Attende to many patients	48 (33.8)	94 (66.2)
Access to adequate library facilities	41 (28.9)	101 (71.1)
Access to adequate Information Technology	13 (9.2)	129 (90.8)

Table 2: Distribution of responses on skills development of study participants during the rural posting.

Skills development during the rural posting	Agree No. (%)	Disagree No. (%)
Developed research skills	142(100.0)	0 (0.0)
Developed knowledge base	133 (93.7)	9 (6.3)
Developed presentation skills	131 (92.2)	11 (7.8)
Developed communication skills in local language	(121 (85.2)	21 (14.8)
Developed follow up skills	103 (72.5)	39 (27.5)
Developed writing case histories	96 (67.6)	46 (32.4)
Developed procedural skills	89 (62.7)	53 (37.1)
Developed case presentation skills	87 (61.3)	55 (38.7)

The majority of the students developed many skills during the posting as shown in Table 2. All the participants agreed that they developed research skills.Table 3 shows students' responses to supervision. The majority of the students agreed that the supervisors were approachable and treated them with respect 96.5% (137/142). The majority 64.8% (92/142) of the students agreed that rural posting provided them greater opportunity to observe the various determinants of health compared to urban

Table 3: Distribution of responses on supervision of study participants during the rural posting.

Supervision during the rural posting	Agree No. (%)	Disagree No. (%)
Supervisors were approachable	137 (96.5)	6 (3.8)
Supervisors treated participants with respect.	137 (96.5)	5 (3.8)
Supervisors were enthusiastic to provide information	135 (95.1)	7 (4.9)
Supervisors were facilitated learning environment	132 (93.0)	10 (7.0)
Supervisors were excellent role models	130 (91.5)	12 (12.7)
Supervisors gave participants sufficient autonomy	124 (87.3)	18 (12.7)
Supervisors gave participants adequate help and adivce	119 (83.8)	23 (16.2)
Supervisors facilitated the developmwent of decision making skills	101 (71.1)	41 (19.9)

posting (Table 4). Table 4 also showed that a great number of students agreed that rural posting provided them the opportunity to work as a team 83.8% (119/142) but there was less opportunity for specialist care 82.4%(117/142) and increased socialization compared to urban posting 76.1% (108/142). Many students agreed that rural posting provided better and more teaching in Community Dentistry 54.8% (34/142) than urban posting. The majority disagreed that rural posting provided better accommodation 83.8% (119/142); as well as greater and better patient access 61.3% (87/142) than urban posting. Furthermore Table 4, showed that there was no statistical significance difference between gender and experience of study participants about rural and urban posting ($p > 0.05$). Table 5 showed that 57.1% (8/14) and 86.7% (111/128) of those who lived in rural and urban communities respectively agreed that rural posting provided opportunity to work as a team than urban posting ($p < 0.05$). Table 5 also showed that 50.0% (7/14) and 78.9% (101/128) of those who lived in rural and urban communities respectively agreed that rural posting increased socialization than urban posting ($P < 0.05$).

Table 6 shows that the majority 76.1% (108/142) and 71.1% (101/142) of study participants reported that they would like to go for rural posting again and spend more time in the posting respectively. Sixty (42.3%) participants reported that they would like to practice in a rural community and 53 (37.3%) participants reported that they would like to specialize in Community Dentistry (Table 6).

Table 4: Gender comparison between rural and urban posting experience of study participants

Rural and urban posting experience	Agree No. (%)	Disagree No. (%)	Total No. (%)	P
Rural posting provided opportunity to observe the various determinants of health than urban posting				
Male	52 (71.2)	21 (38.8)	73 (100.0)	0.10
Female	40 (58.0)	29 (42.0)	69 (100.0)	
Total	92 (64.8)	50 (35.2)	142 (100.0)	
Rural posting provided opportunity to work as a team than urban posting				
Male	65 (89.0)	8 (11.0)	73 (100.0)	0.08
Female	54 (78.3)	15 (21.7)	69 (100.0)	
Total	119 (83.8)	23 (16.2)	142 (100.0)	
Rural posting provided less opportunity for specialist care than urban posting				
Male	57 (78.1)	16 (21.9)	73 (100.0)	0.17
Female	60 (87.0)	9 (23.0)	69 (100.0)	
Total	117 (82.4)	25 (17.9)	142 (100.0)	
Rural posting increased socialization than urban posting				
Male	58 (79.5)	15 (20.5)	73 (100.0)	0.34
Female	50 (72.5)	19 (28.5)	69 (100.0)	
Total	108 (76.1)	34 (23.9)	142 (100.0)	
Rural posting provided more experience in Community Dentistry than urban posting				
Male	43 (58.9)	30 (41.1)	73 (100.0)	0.91
Female	40 (58.0)	29 (42.0)	69 (100.0)	
Total	83 (58.5)	59 (41.5)	142 (100.0)	
Rural posting provided better and more teaching in Community Dentistry than urban posting				
Male	43 (58.9)	33 (45.2)	73 (100.0)	0.97
Female	38 (55.1)	31 (44.9)	69 (100.0)	
Total	78 (54.9)	64 (45.1)	142 (100.0)	
Rural posting provided better and more patient access than urban posting				
Male	27 (37.0)	46 (63.0)	73 (100.0)	0.66
Female	28 (40.6)	41 (59.4)	69 (100.0)	
Total	55 (38.7)	87 (61.3)	142 (100.0)	
Rural posting provided better accommodation than urban posting				
Male	12 (16.4)	61 (83.6)	73 (100.0)	0.94
Female	11 (15.9)	58 (84.1)	69 (100.0)	
Total	23 (16.2)	119 (83.8)	142 (100.0)	

Discussion

A study [14] on rural, remote and indigenous pre-graduation placements as an innovation in Australian dental education reported that the placements were optional which is at variance with this present study where rural dental posting was compulsory for the final year dental students. Making the posting compulsory has the advantage of exposing all undergraduate dental students to rural practice. In Nigeria, the majority of newly-graduated physicians and dentists are posted to rural health facilities for one year National Youth Service Corps. However, these physicians and dentists could sometimes not perform according to the expectations of the communities because of inadequate orientation to Primary Health Care. A previous study [9] reported that the majority of graduates of a medical school who had rural posting programme reported that the programme was very relevant to present functions. Similarly, in this present study as in previous studies [9,10], the majority of the dental students in the rural posting agreed that their educational experience met

Table 5: Relationship between locality of study participants and their rural and urban posting experience

Rural and urban posting experience	Agree No. (%)	Disagree No. (%)	Total No. (%)	P
Rural posting provided opportunity to observe the various determinants of health than urban posting				
Lived in rural community	8 (57.1)	6 (42.9)	14 (100.0)	0.53
Lived in urban community	84 (65.6)	44 (34.4)	128 (100.0)	
Total	92 (64.8)	50 (35.2)	142 (100.0)	
Rural posting provided opportunity to work as a team than urban posting				
Lived in rural community	8 (57.1)	6 (42.9)	14 (100.0)	< 0.01
Lived in urban community	111 (86.7)	17 (13.3)	128 (100.0)	
Total	119 (83.8)	23 (16.2)	142 (100.0)	
Rural posting provided less opportunity for specialist care than urban posting				
Lived in rural community	10 (71.4)	4 (28.6)	14 (100.0)	0.26
Lived in urban community	107 (83.6)	21 (16.4)	128 (100.0)	
Total	117 (82.4)	25 (17.6)	142 (100.0)	
Rural posting increased socialization than urban posting				
Lived in rural community	7 (50.0)	7 (50.0)	14 (100.0)	0.02
Lived in urban community	101 (78.9)	27 (21.1)	128 (100.0)	
Total	108 (76.1)	34 (23.9)	142 (100.0)	
Rural posting provided more experience in Community Dentistry than urban posting				
Lived in rural community	8 (57.1)	6 (42.9)	4 (100.0)	0.92
Lived in urban community	75 (58.6)	53 (41.4)	128 (100.0)	
Total	83 (58.5)	59 (41.5)	142 (100.0)	
Rural posting provided better and more teaching in Community Dentistry than urban posting				
Lived in rural community	7 (50.0)	7 (50.0)	14 (100.0)	0.70
Lived in urban community	71 (55.5)	57 (44.5)	128 (100.0)	
Total	78 (54.9)	64 (45.1)	142 (100.0)	
Rural posting provided better and more patient access than urban posting				
Lived in rural community	6 (42.9)	8 (57.1)	14 (100.0)	0.74
Lived in urban community	49 (38.3)	79 (61.7)	128 (100.0)	
Total	55 (38.7)	87 (61.3)	142 (100.0)	
Rural posting provided better accommodation than urban posting				
Lived in rural community	4 (28.6)	10 (71.4)	14 (100.0)	0.19
Lived in urban community	19 (14.8)	109 (75.2	128 (100.0)	
Total	23 (16.2)	119 (83.8)	142 (100.0)	

their expectations of what a rural dental program is. The rural posting helped the students in providing the required preparations for examination in Community Dentistry as agreed by the majority of the students. This might be because the postings were structured with community observations and investigations. This kind of teaching or learning methods might translate into the students being satisfied because it allowed students to apply theoretical concepts into real life situations. A previous report [9] mentioned that medical students were more satisfied with structured observations and investigations than lectures. In this present study, the majority of the students disagreed that they had access to adequate information technology and library facilities. These facilities should be improved upon since they are needed for effective and efficient dental education. These students are used to accessing these facilities in their urban location thereby any inadequacy will be worrisome to them.

Table 6: Distribution of general opinion of study participants about rural posting

General opinion about rural posting	Yes		No		Undecided	
	No.	%	No.	%	No.	%
Would you like to go for rural posting again	108	76.1	24	16.9	10	7.0
Would you like to spend more time in rural posting	101	71.1	30	21.1	11	7.8
Would you like to practice dentistry in a rural community	60	42.3	41	28.9	21	28.8
Would you like to specialize in community dentistry	53	37.3	48	33.8	41	28.9

Rural postings do not have a detrimental impact on skills rather it leads to the development and improvement of all the skills according to this study. All the dental students agreed that their research skills were developed since they were able to initiate, plan, carry out and present findings of their group research. Jinadu et al. [9] mentioned that health surveys were part of the activities performed by medical students at their rural posting while their counterparts who were not involved in such posting but were involved in clinic-based activities could not carry out health surveys. Those who could not carry out surveys may find it difficult to participate in Community-based research in the future. A previous study [18] showed that medical school undergraduate research experience was found to be strongly associated with postgraduate research involvement. Zier and Stagnaro-Green [19], mentioned that introducing medical students to research and relevant support mechanisms early in their education may help to reverse the drop in the number of physicians applying for and receiving grants from the National Institutes of Health (NIH). The majority of students in this study agreed that they were able to develop presentation skills as well as communication skills in local language. Development of communication skills in local language might be due to their interactions with people in the local community.

Supportive supervision was provided by dental officers and resident doctors on rotation in community dentistry to the dental students and this was also complemented by consultants in community dentistry. Dental students agreed that the supervision facilitated learning environment and the development of decision-making skills. Supportive supervision has been noted to improve motivation among health workers and quality of care [20].The supervisors treated them with respect and were approachable and excellent role models. In this study as in a previous study [14], the majority of the dental students disagreed that the accommodation provided in their rural posting was better than that provided in the urban posting. Efforts should be made by the university authority to improve student accommodation during rural posting which will motivate students to participate in the posting. A greater number of students in this study disagreed that rural posting provided better and more patient access than their posting in the urban dental clinic. This might be due higher level of poverty and low level of oral health care awareness among inhabitants of rural communities compared to urban inhabitants. More effort should be instituted by oral health practitioners working in Igboora community to increase their level of oral health awareness. This increase in level of oral health awareness together with the introduction of affordable cost of dental treatment will translate into increase in oral health care utilization. This increase in oral health care utilization will allow students on rural posting to attend to many patients at the dental clinic. This may lead to generation of similar revenue as in the clinic at the dental school. Bean et al. [21] reported that fourth-year dental students completed as many procedures and generated similar revenue-equivalents in community sites as they did in a dental school clinic in half the time during their rural, remote and indigenous pre-graduation placements. In this present study, gender was not related to experience of participants about rural and urban posting but the majority of the students agreed that rural posting provided opportunity to work as a team and increased socialization than urban posting.

In the present study, many students suggested that they would like to go for rural posting again, this is in accordance to another study [11] reported in the literature. Similarly, the majority of dental students requested that they would like to spend more time in rural posting. Allowing dental students to see the wider context of general dental practice in a rural setting might be the reason for this reporting that they would like to go for the posting again or spend more time in rural posting. Some participants reported that they will not want to practice in rural communities which might be mainly due to lack of infrastructure such as regular electricity and non-lucrativeness of dentistry in rural communities. If infrastructure can be improved upon

and dental practice can make much profit in rural communities then many dentists would want to set up their private practice in these communities. On the contrary, a considerable number of students reported that they would like to practice in a rural community despite their urban background. Some students reported that they will like to specialize in community dentistry in future. Opportunity to provide dental care to underserved and underprivileged populations who quite often appreciate such services might be the reason for wanting to practice in rural communities or specialize in community dentistry. It is recommended that further robust studies should be undertaken among final year dental students to explore factors that influence choice of location of practice or specialization.

The limitation in this study is the lack of data about attitudes and preferences of the dental students before their participation in the rural posting and lack of comparison with students who did not participate in the programme. However, the objective of this study was only to describe rural posting experience among dental students. The direction for future research in this area will be to measure the uptake of rural postings that provide incentives so as to identify effective human resource approaches for meeting the oral health needs of inhabitants of underprivileged rural populations. Also the impact of this community-based Primary Oral Health Care (POHC) educational strategy on dental education and practice in Nigeria is needed. In addition, assessment of the impact of the Igboora Oral Health Care programme on oral health of inhabitants of the Ibarapa region is also needed.

Conclusion

There were positive feedbacks about rural dental postings from the final year dental students such as less distraction to learning, development of research and presentation skills, supervisors were approachable and enthusiastic to provide information, observation of the determinants of health and opportunity to work as a team. On the contrary, there were negative feedbacks from these students namely poor access to adequate library and information technology facilities and lower access to patients. These feedbacks should be considered during subsequent rural dental postings and references for future policy on dental education especially in developing countries. In developing, sustaining and expanding undergraduate dental or medical and other health sciences education in rural areas, infrastructure such as accommodation, information technology and library facilities should be properly put in place. Providing these facilities will be an effective intervention for attracting dentists to rural and remote areas.

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Oto-renal syndromes: disorders of shared developmental gene polymorphisms and overlapping physiology

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Abstract

Background: – Although, it has been documented that infants with ear malformations are among the highest-risk cohorts for renal malformations of any studied population with congenital birth defects, however report from meta-analyses have showed an insignificant relationship between minor ear malformations and kidney anomalies. In order to explain the intractable link between kidney and ear syndromes, we discussed the molecular regulation of development of both organs. In addition, the role of shared developmental control gene polymorphisms and dysfunction of shared transport or structural proteins in the ear-kidney syndrome were reviewed.

Methodology and review criteria: – A narrative review of ear and kidney syndrome. Pubmed Medline and Online Library search was conducted for literature/studies in English from their conception until September 2016 (without any date restrictions) using the relevant search words.

Results: – An overview on the development of ear and kidney and their molecular regulation, indicated that ear and kidney develop from primordial cells that arise at different time and grow at dissimilar rate, and the development of both organs is synergistically regulated by PAX-SIX-EYA regulatory cascade.

*Conclusion:*The molecular regulation of development of the ear and the kidney and the presence of some shared developmental control gene polymorphisms and structural/transport proteins are documented in this review. A careful clinical analysis of these pathologies will facilitate better understanding and diagnosis of ear-kidney syndromes in affected patients. Furthermore, there is need for continued research especially among the Nigerian population as part of the global data.

Keywords: *Ear-kidney syndromes, Hearing impairment, Renal dysplasia, Genetic disorders, Nephrotoxicity and Ototoxicity*

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Résumé

Contexte: - Bien qu'il ait été documenté que les nourrissons présentant des malformations auriculaires sont parmi les cohortes les plus à risque pour les malformations rénales de toute population étudiée présentant des anomalies congénitales, cependant les méta-analyses ont montré une relation insignifiante entre les malformations mineures de l'oreille et les anomalies durein. Afin d'expliquer le lien insoluble entre les syndromes du rein et de l'oreille, nous avons discuté de la régulation moléculaire du développement des deux organes. En outre, on a passé en revue un certain nombre de polymorphismes du gène de contrôle du développement et du dysfonctionnement du transport partagé ou des protéines structurales dans le syndrome de l'oreille et du rein.

Méthodologie et critères d'examen: - Examen narratif du syndrome de l'oreille et du rein. PubMed, Medline et la recherche en ligne de bibliothèque a été menée pour la littérature / les études en anglais de leur conception jusqu'à septembre 2016 (sans aucune restriction de date) en utilisant les mots recherchés pertinents.

Résultats: - Fournir une vue d'ensemble sur le développement des oreilles et des reins et leur régulation moléculaire, indiquant que l'oreille et le rein se développent à partir de cellules primordiales qui apparaissent à différents moments et croissent à des taux différents, et le développement des deux organes est de manière synergique régulé par PAX-SIX-EYA cascade réglementaire.

Conclusion: - La régulation moléculaire du développement de l'oreille et du rein et la présence de certains polymorphismes du gène du développement partagés et des protéines structurelles / de transport sont documentées dans cette revue. Une analyse clinique minutieuse de ces pathologies facilitera une meilleure compréhension et un meilleur diagnostic des syndromes auriculo-rénal chez les patients atteints. En outre, il est nécessaire de poursuivre les recherches, en particulier auprès de la population nigériane, dans le cadre des données mondiales.

Mots-clés: *Syndromes auriculo-rénal, Troubles auditifs, Dysplasie rénale, Troubles génétiques, Néphrotoxicité et Ototoxicité.*

Introduction

Edith Louise Potter first described an association between kidney and ear abnormalities in 1946 when she reported occurrence of wrinkled and flattened ears in 20 infants dying in perinatal period with bilateral renal agenesis [1]. Isolated minor ear malformations, with intact inner ear structure and function, occur with a frequency of 5-10/1000 live births [2,4] while the incidence of structural renal anomalies among paediatric population is reported to be 1-3/100 live births [5]. Reports from various studies have documented evidence of significant association between renal and ear abnormalities [6,8]. In studies of children with isolated pre-auricular tags who had renal ultrasonography done, 3-8% of the cohorts were documented to have various urinary tract abnormalities, including renal agenesis, hypoplasia, horse-shoe kidney and hydronephrosis [6,7]. Data from a previous study which analysed 32,589 consecutive fetuses over 10 years reported renal anomalies in 1.2% of the fetuses [8]. The study further suggested a strong association between external ear deformities and renal malformations, even after excluding patients with syndromic diagnoses.

Of greater interest is the value of chronic kidney disease (CKD) staging in predicting cochlear dysfunction among patients with progressive chronic renal failure. Govender *et al*. [9] investigated cochlear function in a spectrum of CKD patients using pure tone audiometric testing and Distortion Product Oto-acoustic Emissions (DPOAEs). Patients in CKD stages 1 and 2 presented with normal cochlear functioning defined by normal pure-tone thresholds and DPOAEs, while early cochlear dysfunction was identified by DPOAE testing in patients with advanced CKD, particularly patient with CKD stage 5.This was also shown in an earlier study in Nigeria by Lasisi *et al*. [10] who investigated pre- and post-haemodialysis hearing function in patients initiating maintenance haemodialysis. They found that hearing threshold was significantly reduced in patients with end stage renal disease (ESRD) following three sessions of haemodialysis. In combination with the profound fluid and electrolytes derangements seen in CKD patients, comorbidities such as high blood pressure [11] and ototoxic drugs including frusemide [9,12] play a role in the development of auditory dysfunction, which is very common in advanced CKD [13,14] .

Even though previous studies have postulated that infants with auricular pits or cup ears are among the highest-risk cohorts for renal malformations of any studied population with congenital birth defects, report from meta-analyses however showed a weak correlation between minor ear malformations and kidney anomalies [15].This is not surprising because kidneys and ears are formed from separate primordial cell lineages at different times, and grow at different rates. Metanephric mesenchyme and ureteric bud are derived from intermediate mesenchyme while external ear structures are derived from first branchial pouch, a derivative of surface ectoderm. Therefore, the intractable link between ear and kidney abnormalities could not be explained just by an isolated embryonic insult that may simultaneously affect both developing organs during morphogenesis. However, it is increasingly being recognized that various syndromes evidently link structural renal abnormalities to hearing impairment [16,17]. Moreover, molecular as well as the genetic basis for many of these syndromes have so far been elucidated, thus, providing an insight into the overlap between the renal and inner ear physiology. The objective of this review is to further explore the link between kidney and ear by systematically grouping human ear-kidney syndromes into two distinct pathologic mechanisms including; disorders of shared developmental control gene polymorphisms, and disorders involving dysfunction of shared transport or structural proteins. This review will also provide an overview of ear and kidney syndromes, while highlighting their molecular mechanisms and gene expression.

Materials and methods

This is a narrative review of ear and kidney syndrome. Pubmed Medline and Online Library search was conducted for literature/studies in English from their conception until September 2016 (without any date restrictions) using the following search words: ear-kidney syndromes, Oto-renal syndromes, hearing impairment, renal dysplasia, inheritable hearing disorders, nephrotoxicity, ototoxicity, Branchio-Oto-Renal syndrome, Townes-Brocks syndrome, Kallmann syndrome, Hypoparathyroidism, Deafness and Renal Dysplasia, HDR syndrome, Bartter syndrome, Distal Renal Tubular Acidosis with Deafness, dRTA, Alport syndrome.

Ear and kidney development: focus on molecular regulation

Embryology of ear

During human development, ear develops into three different structural parts; the inner ear, the middle

ear and the outer ear. The inner ear is formed by the third week of embryonic life.Otic placode develops on each side of the posterior aspect of the brain and subsequently grows to form otic vesicles. The saccule, cochlear duct and ductus reuniens are derived from the ventral part of each vesicle while the utricle, endolymphatic duct and semicircular canals are derivatives of the dorsal component. Approximately during the 6th week of embryonic life, saccule, a group of sensory cells that form epithelium of the inner ear, give rise to a tubular outgrowth representing primitive cochlear duct at its lower border and subsequently connect to cochlear duct through the ductus reuniens. The cochlear duct penetrate the surrounding mesenchyme up till the 8th week of embryonic life, following which, the cochlear duct's mesenchyme differentiate into a cartilage within which vacuolization later occur, leading to the formation of three cavities namely; the scala vestibule, the scala tympani and the scala media. Perilymphatic spaces (comprising both the scala vestibule and scala tympani) contain perilymph while the scala media contains endolymph. The cochlear duct, separated from scala vestibule by vestibular membrane (Reissners membrane) and from scala tympani by basilar membrane, is attached to the cartilage laterally by the spiral ligament. During the 6th week,statoacoustic ganglion is formed from otic vesicle, and then divides into cochlear and vestibular branch of cranial nerve VII to supply sensory cells in organ of Corti, saccule, utricle and semicircular canals [18].Following the development of otic vesicle, the transcriptional regulator EYA1, expressed in the otic ectoderm triggers a molecular signaling pathway involving SIX1, a transcription factor that regulates the growth and functions of all sensory cells in the inner ear [19].Moreover, PAX2 is expressed by the cells of otic vesicle, endolymphatic duct and cochlear hair cells while GATA3 is expressed mainly in the otic vesicle [20]. Available evidence showed that EYA1-deficient or SIX1-deficient mice undergo apoptosis of otic epithelium with the growth of the inner ear arrested at the stage of otic vesicle [21,22]. Furthermore, mice with homozygous PAX1 mutation lack endolymphatic duct and cochlear outgrowth [23] while heterozygous GATA3-deficient mice showed progressive loss of cochlear hair cells [20].

The middle ear is derived from the endoderm of first pharyngeal pouch, which gives rise to primitive tympanic cavity [18]. The distal portion of this primitive cavity form tubotympanic recess while the auditory tube develops from the proximal portion of the cavity [18]. The malleus and incus are derived from the first pharyngeal arch while the stapes is derived from the second arch. Even though, auditory ossicles are formed during the first half of the fetal life, they remain embedded in the surrounding ectoderm-derived mesenchymal tissue until 8th month when the tissues surrounding the ossicles undergo apoptosis, leading to the formation of tympanic cavity wall and eventual appearance of mastoid process [24,25].

External auditory meatus is formed from pharyngeal cleft during the 5th week of embryonic life and grows to its full length by the 18thweek [18,24,26]. Under no circumstances, did the pharyngeal cleft extend to its corresponding pouch, and as a result of this, the eardrum is a tridermal structure, originating from three different layers comprising; ectoderm, endoderm and connective tissue. The auricles are formed between 6th and 8th months, originating from the auricular hillocks, the 6 mesenchymal condensations of the first and second pharyngeal arches [18,24,26].

Embryology of the kidney

The permanent kidney originates from the metanephros, one of the three main structures initially derived from intermediate mesoderm [27]. The other two temporary kidney-like structures, the pronephros and the mesonephros, atrophy and disappear except in males where the mesonephric portion gives rise to male reproductive organs [27]. The cells of the intermediate mesoderm produce ODD1, a factor that functions to facilitate the formation of progenitor cells of metanephric blastema which expresses EYA1 and PAX2 in the developing kidney[28]. These regulating factors activate a cascade of transcription factors involving SIX1 and SALL1, leading to expression of Glial cell line-derived neutrophic factor (GDNF) gene, which induces budding of RET-containing nephric duct. The appearance of ureteric duct, an epithelial outgrowth of nephric duct, is positively regulated by PAX2/8, which regulates expression of GATA3(another transcriptional factor) and activation of RET gene which encode for a tyrosine kinase receptor that is localize to the cell surface[29,30]. Accordingly, homozygous mutations involving PAX2, GATA3 or RET gene have been shown to be associated with kidney defects in mice lacking tyrosine kinase receptor [31-33]. Similarly, humans with inactivating PAX2 mutation exhibit signs of renal-coloboma syndrome and renal hypoplasia [34]. The process of nephrogenesis is initiated when the ureteric bud penetrates the metanephric tissue thereby leading to induction of metanephric

mesenchyme and subsequent aggregation of mesenchymal cells around the tip of the ureteric bud, thus, triggering mesenchyme-epithelial transformation and formation of renal vesicles. As a result of the invasion of metanephric mesenchyme by the ureteric bud, there is repetitive branching of the bud leading to the formation of about 15 branch generations, with induction of new nephron by the interactions between corresponding newly formed ureteric branch tip and the adjacent metanephric tissue cap. Hence, the final nephron mass is a function of total number of resultant ureteric bud branches that arise during branching morphogenesis. Successive appearance of two clefts in the renal vesicles leads to the formation of S-shaped tubule, with the proximal cleft invaded by angioblasts and ultimately giving rise to glomeruli. The mature nephron is united to the collecting duct which in turn converges with other ducts in the medulla to form renal papilla. Approximately, by the 22nd and 34th week of gestation, the definitive cortex and medulla of the embryonic kidney are fully formed. In summary, ear and kidney develop from primordial cells that arise at different time and grow at dissimilar rate, and the development of both organs is synergistically regulated by PAX-SIX-EYA regulatory cascade.

Disorders of shared developmental control gene polymorphisms

Branchio-Oto-Renal Syndrome

Branchio-oto-renal Syndrome (BOR) syndrome, first described in 1975, is characterized by mixed conductive or sensorineural deafness, ear malformations, branchial cleft and renal abnormalities including renal hypoplasia, pelvic-ureteric junction obstruction and vesico-ureteral reflux [35].The prevalence was estimated at 1:40,000, with 2% of children with severe deafness affected [36,37].It is a heterogeneous genetic disorder caused by a variety of mutations affecting genes in the EYA/SIX pathway, with clinical expression extremely variable from one family to another, as minor anomalies have been documented in about 20% of BOR families [38]. Ear abnormalities include pre-auricular pits and appendages, atresia or stenosis of the external auditory meatus and auricular deformities, cervical fistulas and cysts as well as ossicular malformation relating to the developmental abnormalities arising from the first and the second brachial arches. Furthermore, the cochlea is underdeveloped; exhibiting fewer turns than normal, and occasionally there may be dilatation of the vestibular duct [17]. Renal hypoplasia is not pathognomonic, and when present only 5-10% of patients with BOR syndrome develop advanced chronic renal failure [16].The renal anomalies are characterized by decreased kidney size and volume with associated increased echogenicity and poor corticomedullary differentiation, and histological evidence of glomerular hyalinization, mesangial proliferation and splitting of glomerular basement membrane. Moreover, available evidence suggests that there are three differentiated phenotypes of BOR syndromes. In the first phenotype, the syndrome is associated with renal anomalies; while the second phenotype lacks renal abnormalities; the third phenotype however present with brachial and renal anomalies with no associated deafness.

In 1992, mutation involving EYA1 gene, the first BOR syndrome gene was identified and localized to the long arm of chromosome 8 [39,40] and subsequently several other mutations had since been reported in humans[41,42]. More than 80 different mutations involving EYA1 gene have been documented, with heterozygous mutation of EYA1 demonstrated in 30% of BOR syndrome patients. EYA1 gene, a homologous Drosophila developmental gene is expressed very early in human embryo around 4-6 weeks. More specifically, it is expressed in mesenchymal cells of the 1st branchial arch, from which the outer and inner ear structures are derived, thus explaining the outer ear deformities and conductive deafness that is observed in BOR syndrome patients. Similarly, EYA1 is also expressed in the otic placode and hair cells of the cochlea, thus implicating EYA1 in the differentiation and/or survival of the inner ear cell populations, thereby elucidating the sensorineural deafness in BOR syndromes [43]. Expression of EYA1 in the condensing mesenchyme of the kidney induces GDNF which is required for ureteric budding and branching, thus consistent with ureteric anomalies and renal hypoplasia in BOR syndrome. Furthermore, co-expression of EYA1 and PAX2 during ear and kidney development highlights the synergistic regulatory role of these two genes in controlling the pathway leading to mesenchymal-induced renal tubule formation. Also, EYA1 triggers a signaling cascade activating the member of SIX transcription family during ear and kidney development. This is in consistent with reports that demonstrated association between BOR syndrome and heterozygous mutations involving both SIX1 and SIX5 transcription factors [44,45].

Townes-Brocks Syndrome

Townes-Brocks syndrome (TBS) also known as renal ear anal radial syndromeis a rare autosomal dominant syndrome was first described in 1972 by Townes and Brocks [46,47]. It is a multisystem disorder with variable clinical manifestation, characterized by renal hypoplasia or dysplasia, sensorineural or conductive deafness associated with dysplastic ossicles and oval windows, external ear malformations (pre-auricular tags or pits, superior helix deformity), anorectal malformations including stenosis, anteriorly placed anus and imperforate anus, and hand deformities such as bifid thumb, preaxial polydactyly or triphalangeal thumb [17]. Diagnosis of TBS is suggested when two or more of these malformations are present in an individual [48].Townes-Brocks syndrome is caused by a mutation of the SALL1 gene, encoding a developmental regulatory factor that seems to play a crucial role in the embryonic development of the ear, limb, liver, brain, kidney as well as excretory system [17,49]. Townes-Brocks syndrome from dominant negative missense mutations of SALL1 has a more severe phenotype than that cause by SALL1 haploinsufficiency [50]. Renal dysplasia is thought to occur in TBS because of inactivating mutation involving the SALL1 gene which is expressed by metanephric mesenchymal tissues capping outgrowths of ureteric bud, thereby resulting in inadequate branching of the ureteric bud that ultimately induce formation of renal tubules [51]. Accordingly, study of murine model of SALL1 deficiency showed that mice lacking SALL1 failed to develop ureteric bud outgrowths and die of renal agenesis in perinatal period. Patients with heterozygous SALL1 gene mutations have been reported to develop renal agenesis that resulted in end stage renal disease, and ultimately requiring renal replacement therapy later in life [52]. Although, the role of SALL1 in developing ear is yet to be fully elucidated, report from available study suggested that patients with TBS exhibit mixed sensorineural and conductive deafness [17], thus suggesting that SALL1 may play a role in determining the fate of the first and second branchial arches as well as the differentiation of the otic vesicle.

Kallmann Syndrome

Kallmann syndrome is a congenital disorder characterized by hypogonadism secondary to deficiency of gonadotrophin-releasing hormone and anosmia caused by underdevelopment of olfactory bulb and/or tract. Three forms of Kallmann syndrome have been recognized based on mode of inheritance: an X-linked form resulting from mutation of Kal1 gene, encoding anosmin-1[53]; an autosomal dominant form arising from mutation of Kal2 gene, encoding FGFR1 protein [54]; and autosomal recessive forms, which is associated with mutations of the genes encoding prokineticin2 and its receptor [54].Anosmin-1, the protein encoded by Kal1 gene, is produced in the developing ear and kidney by the basal lamina cells of the outer hair cells of the cochlear and ureteric bud. Approximately a third of patients with X-linked Kallmann syndrome present with unilateral renal aplasia with associated bilateral sensorineural hearing loss but occasionally, they may also present with conductive deafness [55]. In addition, the absence of vas deferens (a derivative of mesonephric duct, which give rise to ureteric bud and expresses anosmin-1) on the same side to the missing kidney in a minority of patients, further suggests a role for anosmin-1 in the induction of mesenchymal blastemal by the ureteric branches. However, the variable penetrance of renal agenesis together with a functioning kidney in individuals with Kallmann syndrome [56,57] therefore raised a question regarding direct stimulating role of anosmin-1during branching morphogenesis and induction of nephrogenesis, while suggesting a possible compensating role for other proteins in individual with anosmin-1 deficiency. Available evidence suggest that anosmin-1 and FGFR1 (Kal2 gene product) co-localize and interact in the olfactory bulb during embryonic life, with anosmin-1 positively regulating FGFR1 signaling pathway. Taken together these findings, it was hypothesized that the higher prevalence of Kallmann syndrome in males may be explained by the gender difference in the expression of anosmin-1 [58].

Hypoparathyroidism, Deafness and Renal Dysplasia

Hypoparathyroidism, deafness and renal dysplasia (HDR) syndrome is transmitted as an autosomal dominant disorder involving mutation of GATA3 gene localized to the short arm of chromosome 10 [59]. It is characterized by undetectable parathyroid hormones levels associated with hypocalcemia, variable kidney malformations ranging from isolated vesicoureteral reflux with normal-sized kidney to renal agenesis, and moderate to severe sensorineural deafness [59]. GATA3, a developmental transcription factor is produced early in the parathyroid glands, cochlear hair cells and nephritic duct of the developing embryo. GATA3 seems to be essential for proper migration of nephric duct, with evidence from study of murine model showing failure of

induction of metanephric blastema as a result of abnormal migration of nephric duct [60]. Similarly, mice with heterozygote GATA3 mutation showed evidence of progressive perceptive hearing loss with associated outer hair cells apoptosis compared to mice with normal GATA3 gene, thus suggesting that GATA3 influence cochlear hair cell survival in the developing middle ear [60].

Disorders of shared transport and structural proteins

Bartter syndrome

Bartter syndrome is an inherited disorder of impaired salt transportation in thick ascending limb of Henle (TALH) characterized by hypokalemia, salt wasting, normal blood pressure and failure to thrive [61]. It is inherited as autosomal recessive and two types have been recognized namely; classic type and antenatal type otherwise known as Bartter syndrome with deafness (BSND) [62,63]. The classic type results from loss of function mutations affecting one of the three genes encoding sodium chloride transport proteins in the TALH. The commonest disorder is cause by mutation of the gene NKCC2, encoding sodium-potassium-chloride cotransporter on the apical membrane [64]. The second mutation affects KCNJI, encoding apical outwardly rectifying medullary potassium channel (ROMK) which recycle K^+ back to the tubular lumen in parallel to the function of sodium-potassium-chloride cotransporter [65]. A third mutation has been described in the CLCNKb gene, which encodes ClC-Kb, a voltage-gated chloride channel localized to basolateral membrane of TALH [66]. These three mutations are mild, associated only with classic Bartter syndrome, and are rarely associated with deafness [16]. Bartter syndrome with deafness has been reported in consanguineous families and is cause by mutation in BSND gene. This gene is localized to 1p31 and encodes Barttin which co-localizes with ClC-Kb channels and potassium secreting cells in the inner ear. Moreover, Barttin is co-expressed with both ClC-Ka and ClC-Kb throughout the renal tubules and the inner ear cells including; stria vascularis cells and vestibular apparatus [67-69]. Barttin seems to play a crucial role for the expression and regulation of function of the voltage-gated chloride channels because ClC-Kb is deficient when it is co-expressed with altered Barttin proteins [67]. Therefore, homozygous mutations of the BSND or heterozygous mutations in two chloride channels typically result in salt wasting and congenital sensorineural deafness [70,71].

Distal renal tubular acidosis with deafness

Classic distal renal tubular acidosis (dRTA), also known as type 1 RTA, is a disorder of distal renal tubular dysfunction characterized by the inability of α-intercalated cells to secrete hydrogen ion into the urine, thereby leading to defective urine acidification. Infants with dRTA typically present with inappropriately high urine pH, metabolic acidosis, osteomalacia, nephrocalcinosis and failure to thrive. Distal RTA is a genetically heterogeneous disorder with two patterns of inheritance identified; autosomal dominant form, which is caused by heterozygous mutation for the anion exchanger gene SLC4A1 [72] and autosomal recessive form caused by homozygous mutations of the ATP6N1B, which encodes the B1 subunit of hydrogen ion pump exclusively localized to the apical surface of α-intercalated cells of medullary collecting duct [73]. Moreover, two other autosomal recessive forms of distal renal tubular acidosis have been described in the setting of sensorineural deafness. The two responsible mutant genes encode the B1 (ATP6V1B1) and A4 (ATP6V0A4)subunits of the apical proton pump, which are co-expressed in the endolymphatic sac, cochlea as well as the kidney [74,75]. Therefore, mutations in the genes encoding these subunits of proton pump define two other categories of patients with distal renal tubular acidosis with deafness. These patients typically have inappropriately high urine pH as well as abnormal endolymph pH homeostasis, resulting in impaired auditory function. Individuals with homozygous mutations of B1 subunit gene develop dRTA and deafness at birth, with variable renal penetrance, as majority of these patients do not develop progressive renal failure in adulthood [76,77]. Compared to patients with ATP6V1B1 gene mutations, patients with ATP6V0A4 mutations are more common, have milder disease and become symptomatic later in life and is associated with variable hearing impairment [78].

Alport syndrome

Alport syndrome, a disorder of defective cross-linking of type IV collagen characterized by high frequency sensorineural deafness, ocular defects including anterior lenticonus, retinal flecks and corneal dystrophy, and progressive nephropathy. The incidence of Alport syndrome is 1:5000 and has been reported to cause end stage renal disease in 2% adults [79], usually in the 6th decade of life, although ESRD may occur earlier in young girls [80]. In approximately 85% of families, Alport syndrome is inherited as X-linked disease, which is due to

inactivation mutation of COL4A5 gene located at Xq22 and encoding α5 chain of type IV collagen. Autosomal recessive Alport syndrome involving homozygous or mixed heterozygous mutation of COL4A3 or COL4A4 genes located to chromosome 2 are responsible for the syndrome in about 15% of cases, while autosomal dominant missense mutations may be the cause in a few of kindreds [81]. Type IV collagen, comprising α3, α4, α5 chains is major constituents of basement membranes found in the kidney, ear and the eyes. The main defect in Alport syndrome usually affects the α5 chain of type IV collagen, invariably leading to faulty assembly of α3, α4, α5 collagen network of aural, ocular as well as glomerular basement membranes, thus leading to a collagen disease that usually affect the kidneys and the ears simultaneously. Affected individuals, usually males presented with persistent microscopic haematuria, which start at birth. Proteinuria is uncommon early in life, but progressively worsens with age and may occasionally result in nephrotic syndrome, indicating severe glomerulopathy as a result of damage to the podocytes. The risk of progression to ESRD is higher in affected males with X-linked Alport syndrome compared to females; greater than 90% of males progressed to ESRD by age 40, compared to 12% in females with X-linked Alport syndrome [80]. On light microscopy, histologic changes shows interstitial and tubular foam cells in young children, and as the disease progresses, there is patchy thickening of the glomerular basement membrane. In severe cases, the glomerular basement membrane may split into several layers interspersed by small clear areas, resembling a basket weave arrangement on electron microscopy. The degree of hearing loss varies, but majority may have developed hearing loss requiring hearing aids by 40 years of age.

Kidney and ear disorders caused by therapeutic agents: Gentamycin and Cisplatin

Gentamicin and Cisplatin are frequently associated with nephrotoxicity and ototoxicity in hospitalized patients. Even though the mechanism through which these agents cause injury in the kidney and ear is yet to be fully elucidated, co-localization of specialized transport proteins in the proximal tubular cells of the kidneys and cells of the stria vascularis in the middle ear, which takes up and concentrate drugs in this organs, seems to increase the vulnerability of these organs to drug toxicity [16]. The reported incidence of gentamicin induced kidney dysfunction ranges between 10-20%, characterized by a rise in serum creatinine and proximal tubular dysfunction. The degree of tubular dysfunction varies, as proximal tubulopathy, Fanconi syndrome or Bartter-like syndrome have previously been described in patients with gentamicin-induced nephrotoxicity [82]. As a result of their physicochemical properties, gentamicin binds to apical membrane via transient receptor potential cation channel (TRPV1) and subsequently concentrated by proximal renal tubular cells, cells of medullary striavascularis and cochlear hair cells [83,84]. Once gentamicin undergo endocytosis and build up inside lysosomes, ototoxicity and nephrotoxicity occurs following process involving stimulation of oxidative stress, mitochondrial dysfunction, eventually leading to interruption of functions of subcellular organelles [82]. Risk factors for nephrotoxicity includes, prolonged period of treatment usually greater 10 days, volume contraction, underlying chronic kidney disease, advanced age of patients, severe hypokalemia and co-administration with other nephrotoxins such as radiocontrast agent, cisplatin and amphotericin B. Host factor such as genetic defect may potentiate ototoxicity. The presence of a single nucleotide polymorphism in the mitochondrial DNA (A1555G) has been documented in patients who developed irreversible deafness after a single dose of gentamicin [85,86].

Cisplatin is associated with high incidence of nephrotoxicity and ototoxicity, even following prevention strategies involving volume repletion and maintenance of drugs within therapeutic range [87,88]. Although the mechanism of injury in both the kidney and ear is not very clear, nevertheless, oxidative stress, vascular injury and induction of intracellular injury pathway have been documented to play a role in the patho-mechanisms of the injury that eventually lead to apoptotic cell death [89]. Recently, OCT-2, a transport protein have been shown to contribute to the process of kidney injury [82], it remains to be seen whether OCT-2 is involved in the uptake of cisplatin in the ear.Renal manifestations of cisplatin-induced nephrotoxicity includenonoliguric AKI, Fanconi syndrome resulting from proximal tubulopathy and magnesium wasting caused by injury in the loop of Henle. Cisplatin caused hearing loss probably through induction of apoptotic process in cells of stria vascularis as well as cochlear hair cells [90].

Conclusion

The molecular regulation of development of the ear and the kidney and the presence of some shared developmental control gene polymorphisms and structural proteins are documented. The syndromes

discussed above are aimed to exemplify the overlapping physiology between ear and kidney. In addition, potential pathologies underlying human ear-kidney syndromes were grouped into two distinct groups; [1] disorders of shared developmental control gene polymorphisms; and [2] disorders of shared transport and structural proteins, including kidney and ear disorders that are caused by therapeutic agents. A careful clinical assessment of these mechanisms will facilitate better understanding and diagnosis of ear-kidney syndromes in affected patients. Furthermore, there is need for continued research especially among the Nigerian population as part of the global data.

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Congenital paediatric surgical cases in Ibadan: patterns and associated malformations

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Abstract

Background: There is paucity of data in the developing countries on the outcome of care of children with congenital anomalies managed in a general paediatric surgical setting. The aim of the study was to describe the pattern of congenital anomalies seen in a single tertiary hospital in Nigeria, highlight associated malformations and evaluate in-hospital outcome of care.

Methods: This was a retrospective review of patients who had congenital anomalies of general paediatric surgical nature and had surgery at the hospital over a five-year period. Information was retrieved on sociodemographic characteristics, types of anomalies, associated defects, and in-hospital outcome.

Results: Some 540 out of 1,539 patients, 419 (77.6%) males, operated during the period had congenital anomalies. Their ages ranged from 1 day to 23 years (median, 17 months); the majority (58.7%) presented after the first year of life. The most prevalent anomalies were anorectal malformations (51), exomphalos (27) and hypospadias (27). Patients with respiratory anomalies and anterior abdominal wall defects presented earlier compared to others ($p < 0.001$). Associated major lesions were mostly seen in patients with respiratory (63.6%), anterior abdominal wall (27.6%) and lower gastrointestinal (24.2%) anomalies. Nineteen patients died overall; in-hospital mortality was poorest in those with tracheoesophageal fistula.

Conclusion: Birth defects accounted for 35% of the operative workload of this general paediatric surgery unit. The major congenital anomalies seen were in the gastrointestinal and genitourinary systems; most patients presented late and outcome was worst among patients with tracheoesophageal fistula.

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Keywords: *Associated malformations; birth defects; congenital anomalies; general pediatric surgery; in-hospital outcome; developing country*

Résumé

Contexte: Dans les pays en voie de développement, il existe peu de données sur les résultats des soins prodigués aux enfants présentant avec des anomalies congénitales dans un cadre général de chirurgie pédiatrique. Le but de l'étude était de décrire le profil des anomalies congénitales observées dans un seul hôpital tertiaire au Nigeria, de mettre en évidence les malformations associées et d'évaluer les résultats hospitaliers des soins.

Méthodes: Il s'agissait d'un examen rétrospectif de patients présentant avec des anomalies congénitales de nature chirurgicale pédiatrique générale et opérés à l'hôpital, sur une période de cinq ans. L'information a été recueillie sur les caractéristiques sociodémographiques, les types d'anomalies, les défauts associés et les résultats hospitaliers.

Résultats: Quelque 540 sur 1 539 patients, 419 (77,6%) mâles, opérés au cours de la période avaient des anomalies congénitales. Leurs âges variaient de 1 jour à 23 ans (médiane, 17 mois); La majorité (58,7%) a présenté après la première année de vie. Les anomalies les plus fréquentes étaient les malformations ano-rectales (51), les exomphales (27) et les hypospadias (27). Les patients présentant avec des anomalies respiratoires et des anomalies de la paroi abdominale antérieure présentaient plus tôt que les autres ($p <0,001$). Les lésions majeures associées ont été surtout observées chez les patients souffrant d'anomaliesrespiratoires (63,6%), de murs abdominaux antérieurs (27,6%) et de gastro-intestinalesinférieures (24,2%). Dix-neuf patients sont morts dans l'ensemble; La mortalité intra-

hospitalière était la plus faible chez les patients ayant une fistule de trachée-œsophagienne.

Conclusion: Les anomalies congénitales représentaient 35% de la charge de travail de cette unité générale de chirurgie pédiatrique. Les principales anomalies congénitales observées étaient dans les systèmes gastro-intestinaux et génito-urinaires; La plupart des patients ont présenté tardivement et le résultat était le plus mauvais parmi les patients avec la fistule de trachée-œsophagienne.

Mots-clés: *Malformations associées; malformations congénitales; anomalies congénitales; Chirurgie pédiatrique générale; Résultats hospitaliers; Pays en voie dedéveloppement*

Introduction

Congenital anomalies represent a group of defects that are seen at birth or sometimes later in life. They can be major or minor depending on the severity of the functional and or cosmetic deficits in the organ-system involved. They affect the developing foetus usually at an early stage of embryogenesis, hence there could be involvement of more than one organ-system [1].

In some developing countries, birth defects account for about 2% of overall admissions to children's wards [2, 3] and 24% to 96% of paediatric surgical admissions or operations [4-7]. The most commonly treated major congenital anomalies in general paediatric surgical practice include gastrointestinal tract lesions such as anorectal malformations and Hirschsprung disease, anterior abdominal wall defects, genitourinary malformations and lymphatic or vascular malformations. Each of these has different propensity for syndromic or non-syndromic associated malformations. For instance, anorectal malformation, one of the most common major birth defects encountered in paediatric surgery, has other systemic associations in 28% to 60% [8-10].

Congenital anomalies are responsible for 8% of total neonatal deaths [11] and 24% of deaths in children [4]. The mortality from these birth defects reported from developing countries range from 15% to 52% [7, 9, 12] and as high as 73% in children with associated anomalies in other organ-systems [9]. The outcome, although improving in developed countries [13], remains poor in developing nations. This is due largely to such factors as poor awareness of congenital anomalies by women of reproductive age group [14]; absence/suboptimal uptake of formal preventive programmes such as periconceptional folate supplementation/fortification [15]; absence of perinatal screening for fetal congenital anomalies and sub-optimal access to maternal and child health care [4, 6, 8].

Although no known data-driven scientific report in this respect is available, high morbidity and mortality are the oft-reported outcome of care of these birth defects in developing nations. Most studies on this area of care have not provided information on the specific mortality rate in patients who had active intervention as well as a comparative outlook in each major group of anomalies following surgery. Furthermore, the lack of multi-disciplinary oriented studies has been a major limitation to obtaining accurate outcome of management considering that most major defects are handled by multiple groups of physicians. We have, recently, initiated a multidisciplinary birth defects group to address this challenge and improve the care of patients with congenital anomalies in our setting. The aim of this study, therefore, was to describe the pattern of such anomalies treated in our general paediatric surgical practice; document associated malformations, and evaluate the in-hospital outcome of treatment by a multidisciplinary team in a single tertiary hospital in Ibadan, Nigeria.

Materials and methods

This was a retrospective review of all cases of congenital anomalies of general paediatric surgical nature that were treated between January 2009 and December 2013 at the University College Hospital, Ibadan, Nigeria.

The University College Hospital is Nigeria's foremost tertiary university teaching hospital located in the Ibadan metropolis, arguably the largest city in sub-Saharan Africa. The hospital has 850 beds and runs specialist services in over 50 departments and units. Paediatric surgical admissions are accrued through four sources: the surgical outpatients, the accidents and emergency wards, neonataology wards and the children's emergency ward. The hospital is equipped with 12 modular theatre suites and has dedicated paediatric anaesthetists, hence offers surgery under general anesthesia to neonates and children of any age. Specialists in cardiovascular and thoracic surgery, neurosurgery, ophthalmology, oral and maxillofacial surgery, orthopaedics and trauma surgery, otorhinolaryngology, paediatric surgery, plastic and reconstructive surgery and urology perform surgical care for children in the hospital. This study focuses on only the patients operated in general paediatric surgery.

Information retrieved from the charts and operative records of patients admitted to the general paediatric surgical service of the hospital included sociodemographic details (age, gender, educational status and occupations of the parents), some obstetric

details, and family history of birth defects. The specific types of anomalies and other-system associations in each case were recorded. The type of surgery performed and in-hospital outcome of treatment were also retrieved. Patients who had minor anomalies that often do not require surgical treatment (like skin tags, small haemangiomas, isolated polydactyly etc) were not captured and were excluded from the study.

Results

During the study period 1,539 patients were operated in the division, of which 540 (35.1%) had congenital anomalies. These 540 patients also represented 47.1% of the patients in the larger multidisciplinary birth defects pool. The majority, 419 (77.6%), were males. The ages of the patients ranged from first day of life to 23 years with a median of 17.0 months (an outlier was a 23 year old female with anorectal malformation – the other patients age ranged from the first day of life to 15 years). The median ages at presentation were lowest in patients with respiratory anomalies (22 hours) and anterior abdominal wall defects (24 hours) and highest in those with hernias and hydroceles (3 years) and genitourinary anomalies (2 years), $p < 0.001$ (Table 1). A total of 223 (41.3%) patients presented within the first year of life. Twelve (2.2%) patients had twin brothers or sisters. The median age of the patients' mothers was 31.6 years, range (18 to 49 years). There was no record of consanguineous relationships.

Table 1: Types of malformations seen over the period grouped according to anatomical/embryological relationship

Group of malformation	Number (%) N = 568	% Male	Median age	Test statistic*	p value
Respiratory (Tracheoesophageal fistula)	11 (1.9)	57.1	22 hours	177.23	< 0.001
Upper GI (Pyloric stenosis, duodenal atresia, jejunoileal atresia, malrotation, biliary atresia)	32 (5.6)	63.0	2.6 months		
Lower GI (Anorectal malformation, Hirschsprung disease)	66 (11.6)	68.3	3 weeks		
Anterior abdominal wall (Omphalocoele, gastroschisis)	29 (5.1)	56.5	24 hours		
Hernia and hydroceles (Inguinal hernia, umbilical hernia, hydrocele)	276 (48.6)	88.0	3 years		
Genitourinary (Posterior urethral valve, hypospadias, undescended testis)	110 (19.4)	94.5	2 years		
Others (Thyroglossal cyst, DSD, sacrococcygeal teratoma, cystic hygroma)	44 (7.7)	54.5	4 months		

NB – Some patients had congenital malformations involving more than one major system
*DAMA – discharge against medical advice, GI – gastrointestinal, DSD – disorder of sexual differentiation. * - Kruskal Wallis Test*

Data were computed and analyzed using the IBM® SPSS version 21 (SPSS Inc, IBM Corp, Armonk-NY, USA). Descriptive variables were summarized using means and standard deviations (or median and range) for continuous data, and frequencies, ratios and proportions for categorical data. For the purposes of bivariate analysis, variables were dichotomized according to defined responses. In-hospital outcome was classified as alive, discharged against medical advice or dead during in-patient stay. Tests of association between variables were conducted using Chi-square statistics or likelihood ratio and medians were compared using the Kruskal Wallis test. The p-value for statistical significance was set at < 0.05.

The most common major congenital lesions documented in this retrospective database were: anorectal malformations in 51 (9.4%), exomphalos

Table 2: Associated major congenital malformations seen in the patients

Group of malformation	Number with major malformations in other systems (%)	Systems involved
Respiratory	7 (63.6)	Congenital Heart Disease (3), Upper GI (1), Lower GI (1), Genitourinary (2)
Upper GI	5 (15.6)	Respiratory (1), Genitourinary (3), Anterior abdominal wall defect (1)
Lower GI	16 (24.2)	Respiratory (1), Cleft lip/palate (2), Genitourinary (10), Limb malformations (3)
Anterior abdominal wall	8 (27.6)	Congenital Heart Disease (3), Cleft lip/palate (2), Upper GI (1), CNS (1), Limb malformations (1)
Hernia and hydroceles	29 (10.5)	Congenital Heart Disease (1), Upper GI (3), CNS (3), Genitourinary (18), Limb malformations (2), Anterior abdominal wall defect (2)
Genitourinary	26 (23.6)	Congenital Heart Disease (5), Respiratory (2), Upper GI (3), Lower GI (10), Cleft lip/palate (2), CNS (4)
Others	7 (15.9)	Congenital Heart Disease (4), CNS (3)

CNS = central nervous system; GI = gastrointestinal

Table 3: Outcome of treatment of patients with congenital malformations

Group of malformation	Died (%)	DAMA (%)	Alive (%)	Unknown (%)	Total (%) N = 568
Respiratory	7 (63.6)	1 (9.1)	3 (27.3)	0	11 (1.9)
Upper GI	4 (12.5)	1 (3.1)	25 (78.1)	2 (6.3)	32 (5.6)
Lower GI	2 (3.0)	0	62 (93.9)	2 (3.0)	66 (11.6)
Anterior abdominal wall	4 (13.8)	1 (3.4)	22 (75.9)	2 (6.9)	29 (5.1)
Hernia and hydroceles	1 (0.4)	1 (0.4)	268 (97.1)	6 (2.2)	276 (48.6)
Genitourinary	0	0	103 (93.6)	7 (6.4)	110 (19.4)
Others	1 (2.3)	2 (4.5)	37 (84.1)	4 (9.1)	44 (7.7)

DAMA – discharge against medical advice, GI – gastrointestinal, Unknown – implies missing data on survival status (Likelihood ratio statistic = 78.375, $p < 0.001$).

Table 4: Age at presentation vs. in-hospital outcome of treatment

Age at presentation	Alive (%)	Died (%)	DAMA (%)	Total (%) N = 518*	χ^2	p value
< 28 days	101 (83.5)	17 (14.0)	3 (2.5)	121 (100.0)	49.906	< 0.001
4 weeks – 1 year	112 (96.6)	1 (0.9)	3 (2.6)	116 (100.0)		
> 1 year	280 (99.6)	1 (0.4)	0 (0.0)	281 (100.0)		
Total	493 (95.2)	19 (3.7)	6 (1.1)	518 (100.0)		

*DAMA – Discharged against medical advice, * – 22 patients had incomplete records*

in 27 (5.0%), hypospadias in 27 (5.0%), Hirschsprung disease in 15 (2.8%), posterior urethral valve in 15 (2.8%) and tracheoesophageal fistula in 11 (2.0%) patients. Table 1 shows the distribution of the types of anomalies in each major grouping.

Associated major lesions were most prevalent amongst respiratory (63.6%), anterior abdominal wall (27.6%), lower gastrointestinal (24.2%) and genitourinary (23.6%) organ systems. Anomalies of the genitourinary system were seen to have occurred

in association with virtually all the other systemic groups of congenital defects respectively (Table 2).

A total of 19 (3.5%) patients died during their primary hospital admission, 6 (1.1%) were discharged against medical advice, 22 (4.1%) had incomplete records on survival status and 493 (91.3%) were alive as at the time of discharge or last follow up visit. Postoperative mortality was highest in patients with tracheoesophageal fistula and lowest in those with genitourinary anomalies, $p < 0.001$ (Table 3). The proportion of patients who died amongst those who presented within the first four weeks of life was higher than those who died after presentation at older ages, $p < 0.001$ (Table 4).

Discussion

Children with congenital anomalies accounted for one-third of all the patients operated in our division of paediatric surgery over the study period. This proportion is within the 24% to 96% reported in the literature [4, 5, 7]. Congenital anomalies account for a significant workload for general paediatric surgeons in both developed and developing countries since most patients present at or shortly after birth. This finding, therefore, perhaps corroborates the fact that birth defects may be as important as other considerations such as infectious diseases in the burden of neonatal health care in developing countries [16, 17].

The patients in this study presented to the hospital late at a median duration of 17 months, and nearly 60% presented outside the first year of life. Patients with more lethal anomalies such as tracheoesophageal fistulas and more grossly apparent defects such as omphalocoeles and gastroschisis presented significantly much earlier than those with other types of defects. In the same vein, patients with non-life threatening anomalies but are likely to have longer lasting physiologic alterations such as patients with genitourinary malformations presented to pediatric surgery quite late in this study. These findings are similar to those from the report of authors working in environments with comparable socioeconomic conditions. Bickler and Sanno-Duanda [4] reported that three quarters of the patients with congenital anomalies presented past infancy in Banjul, the Gambia. Delay in presentation is likely to be multifactorial. A contributory factor may be the cultural influence on the care of children with congenital malformations in the sub-region. This can range from pre-hospital intracommunal consultations to determine the cultural origins of any infantile dysmorphology, to initial attempts at self-help with alternative medicine, and to outright infanticide of children with gross structural birth defects [8, 12].

Nevertheless, delay in recognition both by those who took delivery of the baby as well as by the parents appear to play major roles since many of the malformations e.g. anorectal malformations should be apparent on thorough physical examination of the newborn. Yet as much as 86% of babies with anorectal malformations in Ile-Ife, a nearby town, also presented late to the hospital [8]. Compounding the problem is that 62% of births in Nigeria take place at home with rather little immediate postnatal check up by a registered health care worker [18].

Anorectal malformations, exomphalos and hypospadias were the most common major congenital anomalies treated in the division during the period covered by this study. In terms of the organ systems affected, the gastrointestinal tract accounted for 17% of the malformation in the present study. Kouame et al. [12] in a retrospective study conducted at three major teaching hospitals in Cote d'Ivoire over a period of 11 years reported that gastro intestinal anomalies accounted for 13% of the birth defects in their patients and anorectal malformation was the most prevalent in that group. Similarly, Bickler and Sanno-Duanda [4] reported that lower gastrointestinal malformations accounted for the highest proportion, 12%, of major congenital anomalies in the Gambia. Jangra et al. [5] on the other hand reported that 51% of the cases of birth defects in their study conducted in India were due to gastrointestinal malformations and one half of those patients had anorectal malformations. Gastro intestinal malformations are so relatively common likely because of the complex development of the foregut, midgut and hindgut derivatives, which involves interplay between various endodermal and mesodermal elements with different levels of molecular regulations that may ultimately fail [1].

The most critical phase for the development of congenital anomalies is in the first eight weeks of gestation and most of the anlage structures of the gastrointestinal, respiratory and genitourinary systems are formed, in major parts, between the third and eight weeks. Teratogenic insults at this period are likely to affect more than one organ system, thus giving rise to malformations in more than one system. In the present study, the patients had associated lesions in 10.5% to 63.6% of cases with the organ-systems most likely affected by multiple anomalies being the respiratory system, anterior abdominal wall, lower gastrointestinal tract and genitourinary system. These are regions whose embryological

developments are closely linked, hence are likely to suffer from similar interference with their formation.

In-hospital mortality was highest in patients with defects in the respiratory system, anterior abdominal wall and upper gastrointestinal tract. Patients with anomalies in these systems are prone to having multi-system involvement especially congenital heart diseases and other often-rapidly fatal defects. As much as 70% of mortality after surgery in patients with birth defects is attributable to the presence of multiple anomalies [9]. The odd exception in this category, patients with lower gastrointestinal malformations with mortality after surgery of 3%, is not unexpected because the majority of associated defects in patients with anorectal malformations in this study occurred in the genitourinary system. Genitourinary system anomalies were associated with the most favourable outcome in the present study.

A major limitation of this study is its retrospective nature with complete data not always available for the patients. It is a major drawback of a paper-based recording system and the survival status of some of the patients at the end of the study could not be accounted for. Furthermore, this study is tertiary university hospital based and there may be a referral bias in the type of cases that were treated. This calls for the establishment of prospective registry of birth defects in our unit, and ultimately possibly a surveillance system for studying this subject more comprehensively.

In conclusion, patients with birth defects accounted for 35% of the operative workload of this general paediatric surgery unit, and for 47% of all children with congenital anomalies in a multidisciplinary birth defect database in Ibadan, Nigeria. The major congenital anomalies seen were chiefly in the gastrointestinal and genitourinary systems; most patients presented late for surgery and outcome was worst among patients with tracheoesophageal fistula. In-hospital mortality was poorer in patients who had more grossly apparent or symptomatic anomalies and presented earlier.

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In vitro inhibition of glucose transport across the intestinal membrane of mice exposed to trivalent chromium.

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Abstract
Background: Trivalent chromium (Cr^{3+}) supplementation has been used in the management of type-2 diabetes mellitus and the small intestine plays significant role in glucose homeostasis. However, there is dearth of information on the glucose absorption ability of normal gut during Cr^{3+} exposure. In this study, we investigated the effect of Cr^{3+} exposure in the absorption of glucose in the normal gut.
Methodology: Thirty male slc:ddY mice (26.2 ± 1.1 g) were randomly and equally assigned to three groups: Group 1 (control) received drinking water while animals in groups 2 and 3 received 10 and 100 ppm Cr^{3+} respectively for 12 weeks through drinking water. Thereafter, they were sacrificed and their intestines excised, rinsed with ice-cold Ringer solution (RS) and nine everted-sacs were made, with addition of 200 µL RS. The sacs were incubated for 1 hour in 5 mL glucose-free RS and glucose concentrations were determined by spectrophotometry. Transmural potential change (PΔt) was assessed using the short-circuit currents. Data were analysed by one-way ANOVA and $p< 0.05$ was considered significant.
Results: A significant decrease in glucose concentration at the distal jejunum of the serosa in test groups compared with control was observed. The mucosa glucose concentration was elevated at the same region compared with control. The PΔt across the membrane reduced significantly at both the distal jejunum and ileum of Cr^{3+} exposed groups compared with control.
Conclusion: It may be concluded that Cr^{3+} exposure reduced intestinal glucose transport which might probably be a mechanism explored during management of diabetes.

Keywords: *Glucose transport, in vitro, trivalent chromium, transmural membrane, mice*

Résumé
Contexte: La supplémentation en chrome trivalent (Cr^{3+}) a été utilisée dans la prise en charge du diabète de type 2 et l'intestin grêle joue un rôle important dans l'homéostasie du glucose. Cependant, il ya une pénurie d'informations sur la capacité d'absorption du glucose de l'intestin normal pendant l'exposition au Cr^{3+}. Dans cette étude, nous avons étudié l'effet de l'exposition au Cr^{3+} dans l'absorption du glucose dans l'intestin normal.
Méthodologie : Trente rats mâle slc:ddY (26.2 ± 1.1 g) ont été aléatoirement et également assignésà trois groupes:Le groupe 1 (témoin) a reçu de l'eau potable tandis que les animaux des groupes 2 et 3 ont reçu respectivement 10 et 100 ppm de Cr^{3+} pendant 12 semaines par l'administration d'eau potable. Ensuite, ils ont été sacrifiés et leurs intestins excisés, rincés avec une solution de Ringer glacée (SR) et neuf sacs étirés ont été produits, avec addition de 200 µL de SR. Les sacs ont été incubés pendant 1 heure dans 5 ml de SR sans glucose et les concentrations en glucose ont été déterminées par spectrophotométrie. Le changement de potentiel trans-mural (PΔt) a été évalué à l'aide des courants de court-circuit. Les données ont été analysées par ANOVA à sens unique et $p <0,05$ a été considérée comme significative.
Résultats: Une diminution significative de la concentration en glucose au niveau dujéjunumdistal de la sérosa dans les groupes d'essai par rapport au témoin a été observée. La concentration en glucose des muqueuses était élevée dans la même région par rapport au témoin. Le PΔt à travers la membrane a diminué de façon significative à la fois au niveau du jéjunum distal et de l'iléon des groupes exposés au Cr^{3+} par rapport au témoin.
Conclusion: On peut conclure que l'exposition au Cr^{3+} a réduit le transport intestinal de glucose, qui pourrait probablement être un mécanisme exploré lors de la prise en charge du diabète.

Mots clés: *Transport du glucose, in vitro, chrome trivalent, membrane trans-murale, souris*

Introduction

The principal function of the small intestine is to absorb nutrients broken down through digestive processes. Most of these nutrients are absorbed in the jejunum and ileum [1]. Glucose is an important digestive product of carbohydrates and the main source of energy in eukaryotic organism. It plays

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significant role in cellular homeostasis and metabolism [2]. On the other hand, the small intestine play vital role during glucose uptake by the enterocytes of canine [3, 4] and rats [5], while glucose absorption is increased in the insulin-independent pathway especially in the jejunum [6].

It is well established that glucose, a product of digested carbohydrate, is absorbed in the small intestine by two steps format, the sodium dependent glucose transporter (SGLT-1) located on the apical end of the enterocyte which transport glucose into the intracellular space [7]. The second major pathway is through GLUT 2 located on the basement membrane of enterocytes and transport glucose into the interstitial space [8], while acting as a facilitative uniporter with a low affinity but high transport capacity [9]. Corroborating these mechanisms is the report from reverse transcription–polymerase chain reaction (RT-PCR), Northern blot analysis, and a highly specific Glc6Pase assay, suggesting the expression of Glc6Pase gene (mRNA) in human and rat small intestines [10], especially in diabetics or insulinopenia [11]. Thereby confirming that the small intestine has a gluconeogenic capacity apart from the established organs such as the kidneys and liver. Modification involving any of the two major steps stated above will affect intestinal glucose absorption.

Dietary modifications are important for glucose absorption from the jejunum and in the management of diabetes. This makes medical nutrition therapy essential in the regulation of blood glucose level and in the management of diabetes mellitus [12]. A delay in absorption of carbohydrate may be achieved by dietary fibers, α-amylase inhibitors, or α-glucosidase inhibitors [1]. Literature search shows a strong relationship between diabetes mellitus and trace elements in many research studies. Trace elements such as Cu, Fe, and Se play vital role in insulin action including activation of insulin receptor, serving as cofactor or components for enzyme systems involved in glucose metabolism [13]. Certain study also investigated the correlation of serum level of copper (Cu), zinc (Zn), selenium (Se), iron (Fe) in women with type 2 diabetes mellitus and their possible association with lipid profile [14]. In particular, diabetes mellitus has been shown to be associated with abnormalities in the metabolism of zinc, chromium and magnesium [15].

Chromium is a popular element in the earth's crust with bioavailability in several oxidation state, mostly as trivalent or hexavalent chromium. Trivalent chromium (Cr^{3+}) is present in several foods (e.g. cereals, spices, vegetables) and dietary supplements as essential compound. Hexavalent chromium is generated synthetically from industrial pollutions and from oxidation of trivalent chromium, and has been found to be highly toxic to some tissues of the body [16]. The relationship between chromium and glucose metabolism especially in diabetes has been long reported [17]. Its role in potentiating actions of insulin is traced to about six decades [17, 18], and its anti-hyperglycemic activities have been linked to a glucose tolerance factor (GTF) [17] which was responsible for the plasma glucose lowering ability observed in chromium treated diabetic mice [19]. Aside, there is increase in the daily consumption of Cr^{3+} as it has become a widely popular dietary supplement. In the US, there was evidence of an increase in sales of Cr^{3+} containing dietary supplements to customers and over 85 million dollars realized in 2002. This represented about 5.6% of the total dietary supplement market for the year [20]. The trend in consumption of dietary supplements is on the increase.

Previous reports on blood glucose concentration lowering effect of Cr^{3+} from some *in vivo* studies and its significance in the management of diabetes has been documented [21, 22]. However, the importance of trivalent chromium on intestinal glucose homeostasis in normoglycemic states has not been elucidated. This study sought to investigate the probable effect trivalent chromium exposure in mice might have on intestinal glucose absorption *in vitro.*

Materials and methods

Animals

Thirty, 5 weeks old male slc:ddY mice (26.2 ± 1.1 g) were obtained from Japan SLC Incorporation and housed under standard conditions. They were fed with standard mice pellets and had access to clean drinking water *ad libitum*. The animals were grouped into three, Control (water), test groups 10 ppm (Cr^{3+}) and 100 ppm (Cr^{3+}). Chromium was introduced to the test groups through their drinking water for 12 weeks and the control had only clean drinking water instead for the same period. These experiments were carried out in line with guidelines for animal experimentation in Maebashi Institute of Technology, Japan (No.: 15-009).

Chemicals

Trivalent chromium, potassium chloride, sodium chloride, calcium chloride, magnesium chloride, HEPES-Tris , sodium bicarbonates were purchased from Koshin Chemicals, Japan and Glucose kits (Glucose C2) for everted sac procedure was obtained from Wako, Japan.

Experimental procedures

Everted Sac method

Tissue preparation and mounting – Mice were anesthetized with 2.5% isoflurane and the intestines were isolated by cutting at 5 cm from the caecum distally and at the ligament of Treitz proximally. The mesentery was carefully removed and the excised intestine was quickly rinsed in ice-cold Ringer solution (glucose free) (mM)- 140 NaC1, 5 KC1, 3 $CaC1_2$, 1 $MgCl_2$, 20 $NaHCO_3$; 10 HEPES-Tris, distilled water, pH 7.4). The entire length was divided into 9 equal segments (a-i segments) of about 3 cm each after the intestine's length had been measured. They were subsequently everted into sacs with a glass rod from where each piece was slipped over the tip of a glass rod 3 mm in diameter and about 20 cm long. The sleeve of tissue was ligated on one end and 200µL of Ringer solution (Glucose-free) was gently released into the serosa end of the sac and again ligated from the opened end. This was then introduced into a test tube containing 5 mL Ringer solution (with 10 mM Glucose), and appropriately gassed with 5% CO_2, 95%, O_2 and incubated at 37ºC for 1 hour. During this preparatory phase, mounted and un-mounted tissues were kept in ice-cold Ringer gassed with 5% CO_2, and 95% O_2. On expiration of the incubated period of 1 hour, 20 µL each of fluid in the serosa and that in the test tube (representing mucosa fluid) were added to 3 mL reagent from Glucose-C kit (Wako®, Japan). These were incubated in separate test-tubes for another 5 minutes. The glucose concentration from each test tube was then determined by spectrophotometry after incubation. Weight of each segments post experiment was taken with a digital weighing scale and recorded. The glucose concentrations were used to determine various serosa and mucosa glucose absorptions from the isolated 9 segments which were everted into sacs.

Glucose Concentration (mg/dL) = (Sample Absorbance/Standard Absorbance)* k (200)/ weight of tissue.

Glucose-evoked transmural potential change method

The intestine was isolated and excised as earlier described above, the excised intestine was quickly rinsed in cold Ringer solution (glucose-free) (mM) - 140 NaC1, 5 KC1, 3 $CaC1_2$, 1 $MgCl_2$, 20 $NaHCO_3$; 10 HEPES-Tris, distilled water, pH 7.4). The intestine was separated into segments of about 3 cm each. The segments were everted and made into sacs with a glass rod and each piece was slipped over the tip of a glass rod 3 mm in diameter and about 20cm long. The sleeve of tissue was ligated on one end and the other opening mounted on a 20 mL graduated syringe. The serosa end was filled with Ringer solution (Glucose-free) and gently lowered into a 20 mL Magnus tube filled with Ringer solution for incubation and aeration with carbogen (95% O_2 and 5% CO_2)

Transmural potential, a potential difference between the electrodes inserted in the serosa fluid and mucosa fluid was determined by attaching the electrodes to the positive and negative ends of the short-circuit current. The potential change following the addition of different concentrations of glucose (1 M, 2 M, 5 M and 10 M respectively), to the mucosa fluid was recorded. The electrodes were linked by means of a salt bridge (a polyethylene tube filled with 3M-KCl / 3% agar) using a modified method of Tasaki et al., [23]. The transmural potential differences were recorded on Sekonic(R) recorder.

Statistical analysis

Results were expressed as Mean ± SEM and one-way ANOVA with Newman-Keuls comparison *hoc* Hoc test was adopted using GraphPad Prism version 5.0 for Windows (GraphPad software Inc., San Diego, CA), $p<0.05$ was considered significant.

Results

Fasting blood glucose concentration before and after exposure to chromium.

There was no significant difference in the blood glucose levels of all the groups prior to and after the period of exposure to chromium (Table 1).

Table 1: Effect of oral chromium exposure for 12 weeks on fasting blood glucose (n=5)

Fasting Blood Glucose (mg/dL)	Control	10ppm	100ppm
Glucose Concentration (Onset)	74.0±4.6	76.0±5.2 ^{ns}	71.8 ± 4.9^{ns}
Glucose Concentration (Final)	81.2±7.1	77.3±4.3 ^{ns}	78.8±7.4 ^{ns}

ns- No significant difference compared with the control

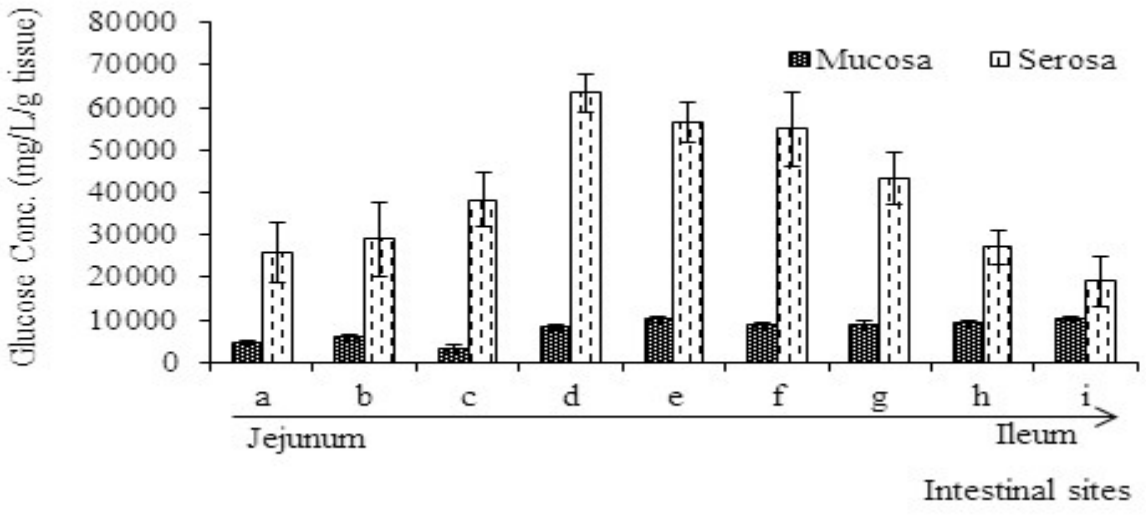

Fig. 1: Glucose concentration at different intestinal sites (a – i) of mucosa and serosa from upper jejunum down to lower ileum in control group using the everted sac method after 12 weeks of exposure to chromium.

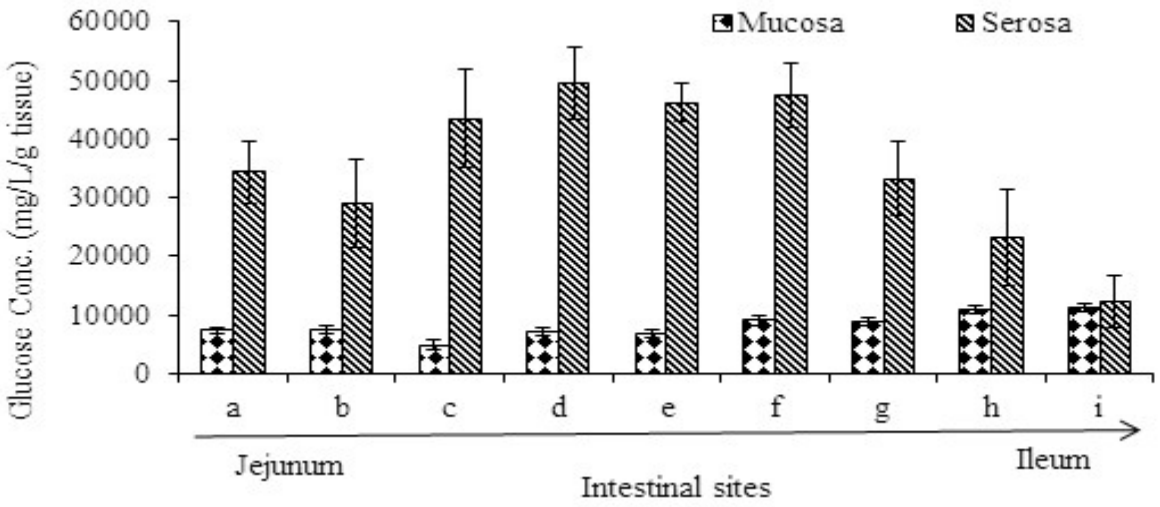

Fig. 2: Glucose concentration at different intestinal sites (a - i) of mucosa and serosa from upper jejunum down to lower ileum in 10 ppm group using the everted sac method after 12 weeks of exposure to chromium

Effect of exposure to chromium on intestinal glucose uptake using the everted sac method

Glucose uptake by the serosa end reduced significantly at the *d* and *e* sites (which constitutes the distal jejunum) for 10 ppm [(49.5 ± 6.2) x 10^3 mg/L/g tissue)], [(46.2 ± 3.1) x 10^3 mg/L/g tissue)] and 100 ppm [(44.5 ± 4.2) x 10^3 mg/L/g tissue), [(45.2 ± 3.8) x10^3 mg/L/g tissue)] compared with control [(63.5 ± 4.4) x 10^3 mg/L/g tissue)], [(56.4 ± 4.7) x 10^3 mg/L/g tissue)], respectively (Figs. 1 to 4). On the other hand, the mucosa glucose concentration increased significantly at three major sites d, e and f (constituting the distal jejunum) of the chromium exposed groups, 10 ppm [(6.1 ± 0.70) x10^3 mg/L/g tissue, (6.9 ± 0.7) x 10^3 mg/L/g tissue and (7.1 ± 8.2) x 10^3 mg/L/g tissue)] and 100 ppm [(6.3 ± 0.6) x 10^3 mg/L/g tissue , (7.5 ± 0.7) x 10^3 mg/L/g tissue and (9.0 ± 0.8) x 10^3 mg/L/g tissue)] compared with control [(3.2 ± 0.90 x 10^3 mg/L/g tissue, (5.2 ± 0.4) x 10^3 mg/L/g tissue and (6.7 ± 0.7) x 10^3 mg/L/g tissue)] respectively, (Figs. 1, 2, 3 and 5).

Effect of 12 weeks exposure to chromium on glucose absorption using the glucose-evoked transmural potential change method

Results for the proximal jejunum were not significant when test groups were compared with control (Plate 1 and Figure 6). However, there was significant

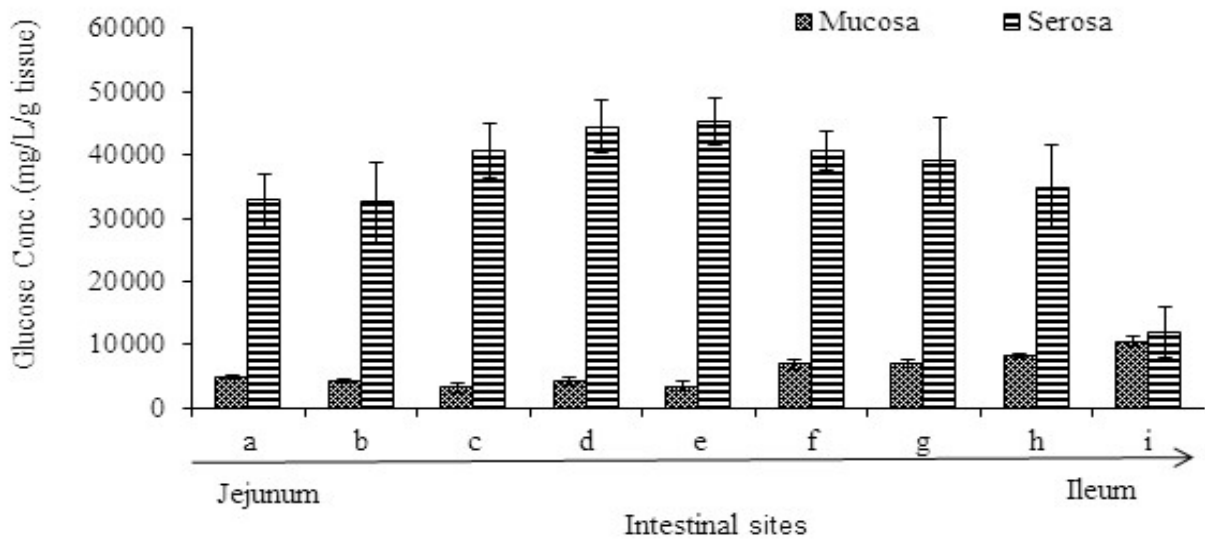

Fig. 3: Glucose concentration at different intestinal sites (a – i) of mucosa and serosa from upper jejunum down to lower ileum in 100ppm group using the everted sac method after 12 weeks of exposure to chromium.

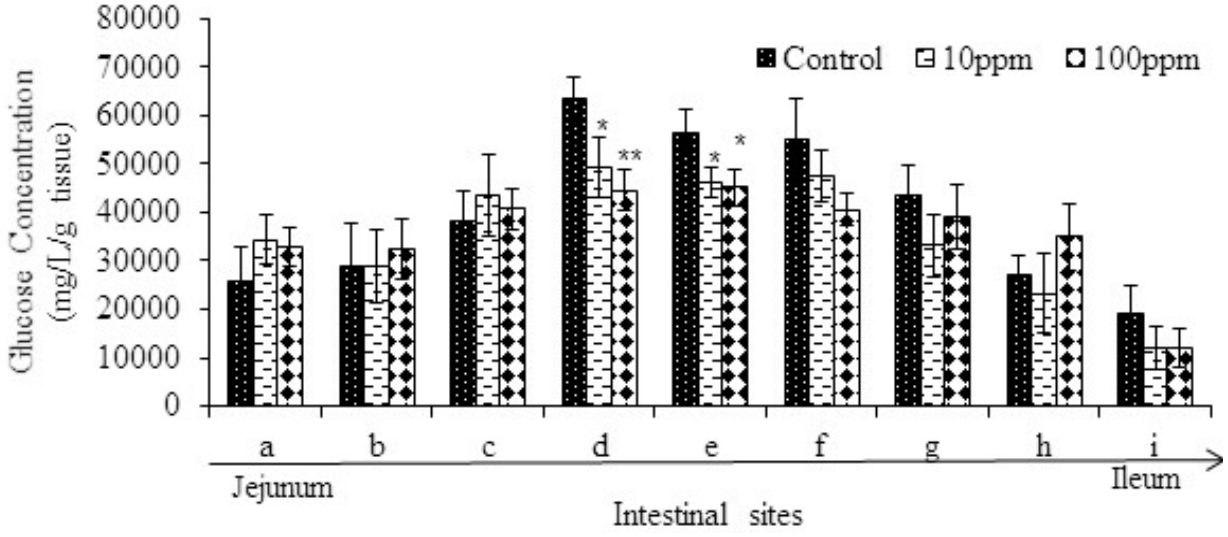

Fig. 4: Serosa Glucose uptake at different intestinal sites from upper jejunum down to lower ileum in the entire group using the everted sac method after 12 weeks of exposure to chromium.
**-significant at p<0.05 compared with the control, **-significant at p<0.01 compared with the control.*

decrease in potential change at the distal jejunum in all the glucose concentration adopted for the study when test groups were compared with control. A significantly decreased potential change was observed on applications of 1 mM, 2 mM, 5 mM and 10 mM glucose concentration to the mucosa end of the distal jejunum sites in 10 ppm (1.06 ± 0.11mV, 2.0 ± 0.34 mV, 3.38 ± 0.45 mV and 3.88 ± 0.52 mV) and 100 ppm (0.40 ± 0.24 mV, 0.75 ± 0.42 mV, 1.27 ± 0.44 mV and 1.45 ± 0.67 mV) compared with control (2.0 ± 0.22 mV, 3.35 ± 0.54 mV, 5.1 ± 0.82 mV and 5.7 ± 0.88 mV), respectively (Plates 2 and Figure 7).

The ileum part shows significant decrease in the potential change at glucose doses of 1 mM and 2 mM in the 100 ppm (0.38 ± 0.22 mV and 0.95 ± 0.27 mV) compared with control (1.15 ± 0.23 mV and 1.9 ± 0.27 mV), respectively (Plates 3 and Figure 8).

Discussion

The fasting glucose levels pre- and post- exposure to chromium were not significantly different from the control and were within the normal range for rodents [24]. A lot has been said about the role of chromium in glucose metabolism in diabetics. But

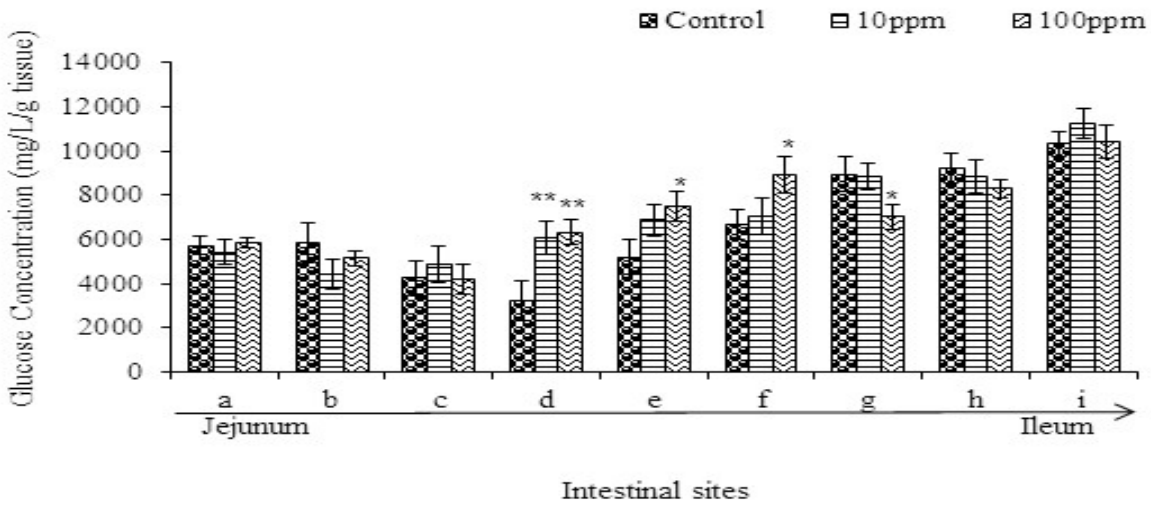

Fig. 5: Mucosa Glucose uptake at different intestinal sites from upper jejunum down to lower ileum in the entire group using the everted sac method after 12 weeks of exposure to chromium.
**-significant at p<0.05 compared with the control, **-significant at p<0.01 compared with the control*

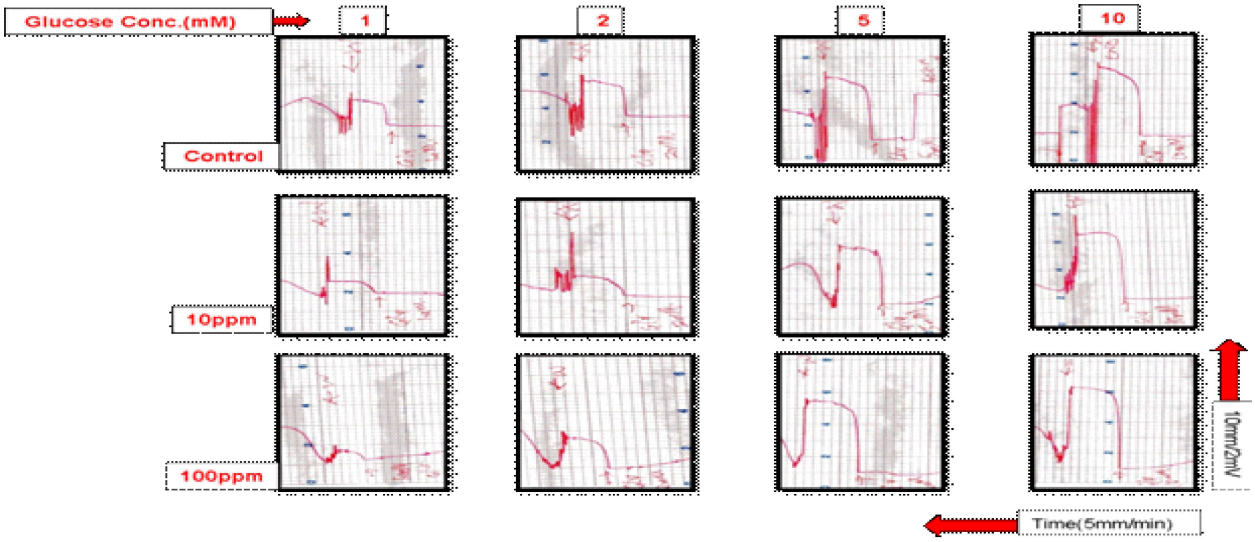

Plate 1: Glucose-evoked potential changes in the proximal jejunum after 12 weeks of exposure to chromium.

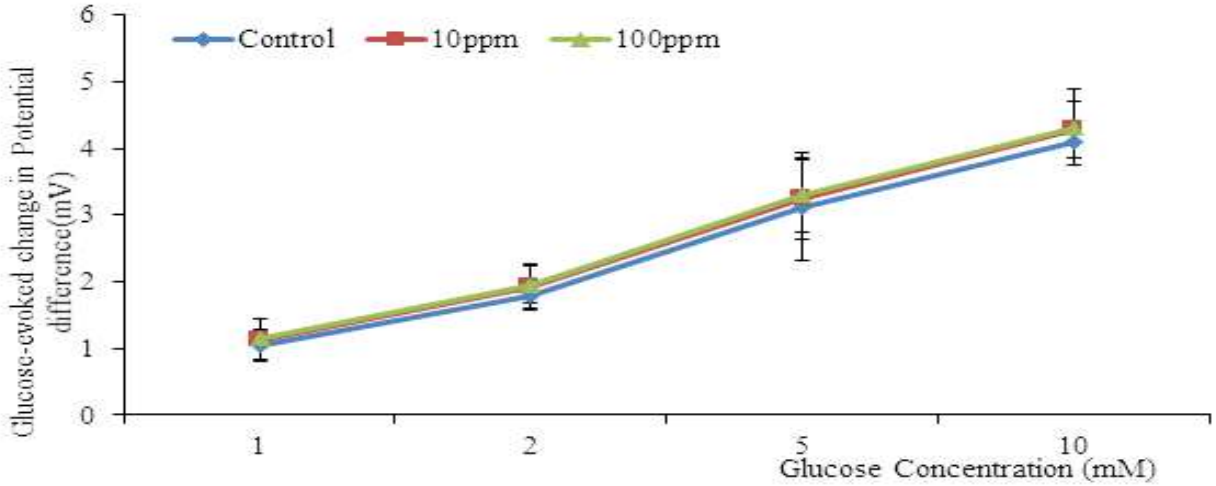

Fig. 6: Influence of 12 weeks exposure to chromium on glucose evoked potential change on proximal jejunum. *No significant difference noted at any point of evaluation.*

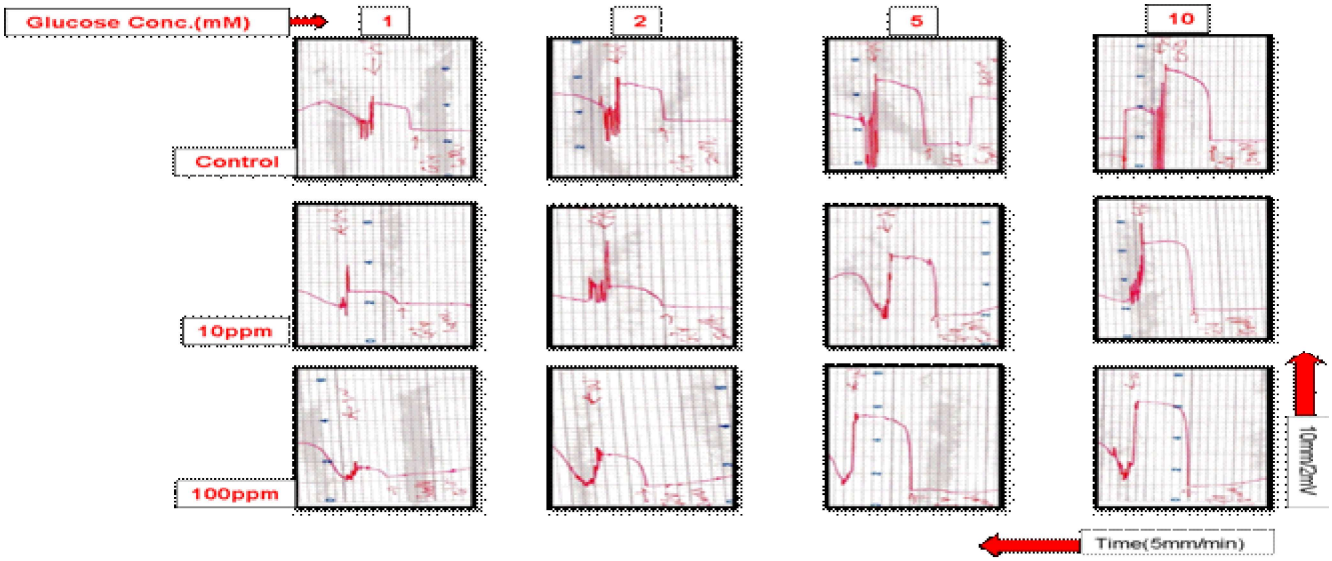

Plate 2: Glucose evoked potential changes in the distal jejunum after 12 weeks of exposure to chromium.

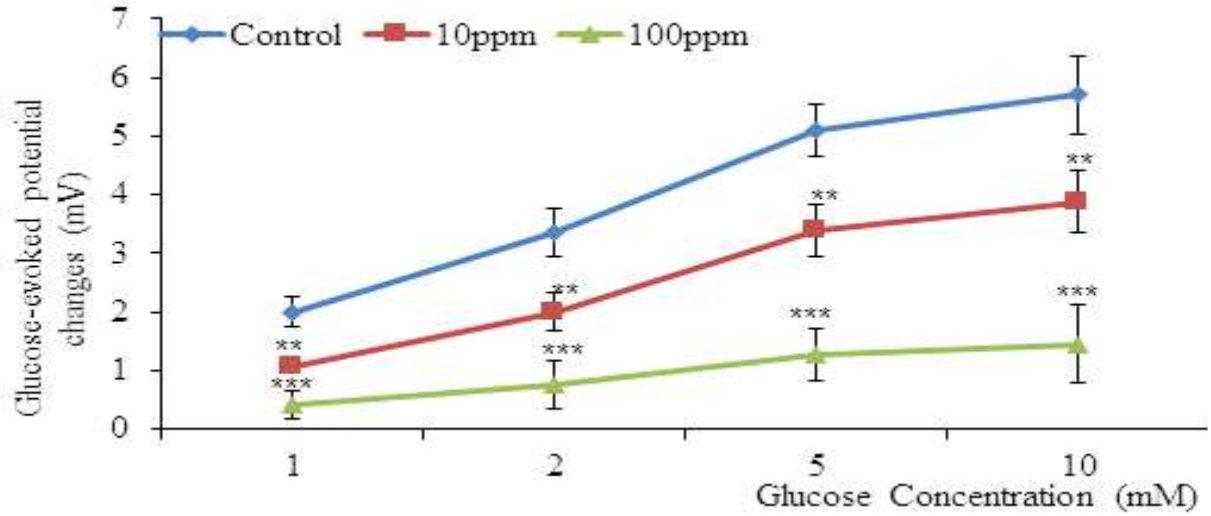

Fig. 7: Influence of 12 weeks exposure to chromium on glucose evoked potential change on distal jejunum.
***significant at P<0.01, ***significant at P<0.001 compared with the control.*

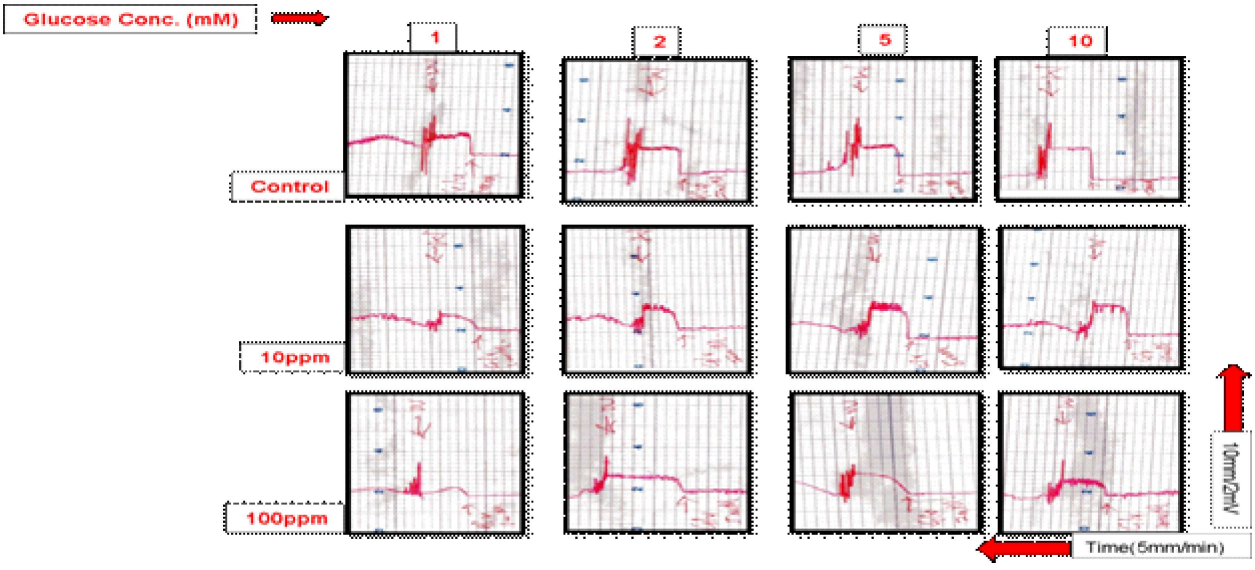

Plate 3: Glucose-evoked potential changes in the ileum after 12 weeks of exposure to chromium.

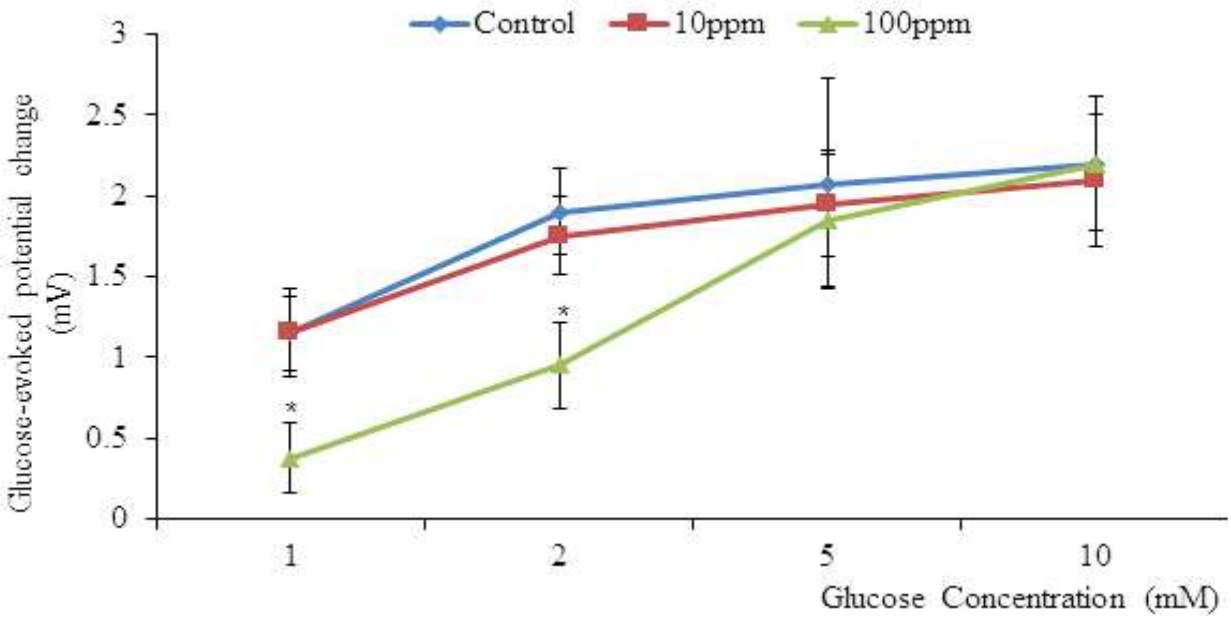

Fig. 8: Influence of 12 weeks exposure to chromium on glucose evoked potential change on Ileum.
**significant at P<0.05 compared with the control.*

there is no report on its normoglycemic state and its effect on intestinal regulation of glucose uptake. A number of studies on human [25, 26], pigs [27] and rats [28] have reported the possibility of chromium influencing glucose tolerance and insulin resistance after supplementation. Everted sac and transmural potential change findings from this current study, mirror each other with similar inhibition of glucose uptake at the distal jejunum compared with control. Thus, buttressing the importance of jejunum in glucose uptake and its' possible use in providing treatment interventions in deranged glucose states.

Previous works on effect of chromium supplementation on fasting blood glucose showed no significant change in diabetic patients [29, 30]. In our study using normal mice, similar results were obtained. It is believed that reducing glucose uptake would reduce its availability in blood which is classical means some anti-diabetic medications such as α-glucosidase inhibitors [31] were designed among many other mechanisms [32]. It is possible that trivalent chromium might be reducing glucose transport in diabetics, hence its use in managing the disease. In the management of diabetes, a reduced transport of glucose suggested by trivalent chromium exposure in this study might be of importance.

The ileum plays an important compensatory role in increasing glucose uptake following clinical resection of the jejunum [33, 34] and some researchers have suggested up-regulation of intestinal hexoses transporters as a major mechanism of ileum improved sugar uptake following resection [35, 36]. What is not certain at this point is the clinical relevance these findings of chromium inhibiting glucose transport especially in the jejunum could suggest in cases requiring re-sectioning of the small intestine. In which case, the compensatory effort of ileum in increasing glucose uptake for instance, during short bowel syndrome [37] might be compromised in persistent chromium supplementation. This may impair or derange the adaptive processes to glucose uptake by ileum, especially when different modulatory mechanisms are in place suggesting the compensatory effect of ileum in glucose absorption following major intestinal resection [33, 34, 38, 39], might be affected.

In conclusion, it is unclear at this point how chromium suppresses intestinal glucose uptake and is unlikely to be due to physical inhibition or presence of dietary fibers. Chromium may inhibit glucose absorption by either reducing or suppressing cellular proliferation (hypoplasia) or acting on SGLT-1 gene by down regulating its expression which was not determined in this present study. This might be a mechanism to be verified.

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Reliability and application of Pont's index in a Nigerian population

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Abstract

Objective: To determine the reliability and applicability of Pont index in Nigerian subjects.

Methods: One hundred and thirty two subjects with normal occlusion (well aligned arches) and who had not previously received any form of orthodontic treatment were recruited from the dental diagnosis clinic and general out-patient clinic of the University College Hospital, Ibadan. Ethical approval was sought and gotten from the University of Ibadan/ University College Hospital, Ibadan Ethics Committee. All selected subjects had their maxillary impression made in alginate impression material and was poured immediately in dental stone. Digital calipers was used in measuring the maxillary incisal teeth sizes and arch width and all the data were entered into a spread sheet and analyzed with SPSS version19 computer software. The level of confidence was set at $p < 0.05$.

Results: The mean age was 22.24 ± 1.74 years and the sample comprise of 66 males and 66 females. Mean maxillary inter – premolar and inter – molar arch widths were 41.87 ± 2.70mm and 51.47 ± 2.69mm respectively. Comparison of measured and predicted (Pont) arch widths revealed a statistically significant differences of 2.32 ± 3.20mm ($p = 0.000$) and 2.03 ± 3.83mm ($p = 0.000$) for inter-premolar and inter-molar arch widths respectively for the entire studied population

Conclusion: Pont's index underestimated the maxillary inter-premolar and inter-molar arch width in our study. Clinical applicability of Pont index in our environment is questionable.

Keywords: *Pont's index, Arch width, inter-premolar and inter-molar.*

Résumé

Objectif: Pour déterminer la fiabilité et l'applicabilité de l'indice du Pont chez des sujets Nigérians.

Méthodes: Cent trente-deux sujets ayant une occlusion normale (arcs bien alignés) et qui n'avaient jamais reçu de traitement orthodontique ont été recrutés dans la clinique de diagnostic dentaire et dans la clinique générale du Collège Hospitalier Universitaire d'Ibadan. L'approbation éthique a été demandée et obtenue duComité Ethique de l'Université d'Ibadan / Collège Hospitalier Universitaire, Ibadan. Tous les sujets sélectionnés avaient leur impression maxillaire réalisée en matériau d'empreinte d'alginate et ont été versés immédiatement dans la pierre dentaire. Des calibres numériques ont été utilisées pour mesurer la taille des dents incisales maxillaires et la largeur de l'arc et toutes les données ont été saisies dans une feuille de calcul et analysées avec le logiciel SPSS version19. Le niveau de confiance était fixé à $p < 0,05$.

Résultats: L'âge moyen était de 22,24 ± 1,74 ans et l'échantillon comprenait 66 hommes et 66 femmes. Les écartements moyens desarcs inter - prémolaires et inter - molaires maxillaires ont été 41,87 ± 2,70 mm et 51,47 ± 2,69 mm respectivement. La comparaison des écartements d'arc(Pont) mesurées et prédites a révélé des différences statistiquement significatives de 2,32 ± 3,20 mm ($p = 0,000$) et de 2,03 ± 3,83 mm ($p = 0,000$) pour les écartements inter-prémolaires et inter-molaires respectivement pour l'ensemble de la populationétudié.

Conclusion: L'indice de Pont a sous-estimé l'écartement inter-prémolaire et inter-molaire maxillaire de l'arc dans notre étude. L'applicabilité clinique de l'indice de Pont dans notre environnement est discutable.

Mots-clés: *Indice de Pont, Ecartement d'arc, inter-prémolaires et inter-molaires.*

Introduction

The analysis of the tooth bone ratio of the arches is an important aspect of clinical orthodontics. A precise or accurate assessment and analysis of the arches especially in the mixed dentition stages is required for appropriate treatment planning and alignment of the teeth. In a situation of crowded arches, interdental stripping, expansion of the arches [1] and or extractions of teeth are procedures by which space is created on the arch to align the teeth.

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Though, non-extraction therapy in orthodontics is currently being emphasized [2] and this has resulted in a reduction in the number of teeth extracted for orthodontic reasons [3]. Arch expansion has been documented to have been used to treat Angle's class I malocclusion subjects satisfactorily, though, this is dependent on the level of severity of crowding [1]. The level of arch width expansion required to achieve any desirable and stable result post treatment has being an issue of controversy [4] and this has led to the introduction of various indices to guide the clinician in predicting the ideal arch width required to produce a stable arch [5]. Some of these indices were proposed by Bonwill, Hawley, Pont, Schwarz, Korkhaus and McNamara [5]. Pont described a method which predetermines the maxillary arch width in the premolar and molar region using the maxillary incisors. This method of predetermining the maxillary arch with is today known as the "Pont's index'. He assumed a constant relationship between the sum of maxillary incisor widths and the widths of the dental arch in an ideal uncrowded dentition using an undisclosed sample of French population [6]. The Pont method of predetermining arch width has been found to be reliable in some societies and or races while in others, it is said to be unreliable [5-9]. Though, this is not surprising as he had already stressed that ethnicity and race [9] are likely to affect the reliability of his index hence he advised that it should be tested in other ethnic and racial groups for reliability. Also, he felt that arch width determination during orthodontic treatment planning was not based on teeth measurement alone. Other factors to consider include facial profile, Angle's classification, relationship of the arches and the midline [6].

Therefore, this study aimed to evaluate the reliability of the Pont's index in a sample of Nigerian population with normal occlusion

Materials and methods

The study was cross sectional and descriptive in design. It was conducted among 132 consenting consecutive individuals of age 18years and 25years who fulfilled the selection criteria and who were attending the dental and general out-patient clinics of the University College Hospital, Ibadan. Ethical approval was sought and obtained from the University of Ibadan/University College Hospital Ethics Committee.

The following criteria were used to select the studied population;

- Subjects of Yoruba decent in Nigeria (at least of two generation)
- Subjects aged 18years – 25years old.
- Subjects with full complement of the permanent dentition.
- Subjects with normal skeletal and dental anteroposterior and vertical relationships.
- Subjects with normal tooth-bone ratio.
- Normal maxillary first premolar and molar inclination shape and sizes.
- No missing teeth and no presence of supernumerary teeth.
- No history of previous orthodontic treatment
- No history of major jaw surgeries
- No history of sickle cell disease and cleft palate
- Absence of obvious transverse jaw discrepancy
- No history of sucking habits
- Subjects with no peg shaped lateral incisors.
- No dental caries or teeth fracture related to the maxillary incisors, first premolars and first permanent molars.
- No dental restoration related to the maxillary incisors, first premolars and first permanent molars.

The sample size was calculated as 132 subjects based on a significance level of 0.05 and a power of 95% confidence using the equation;

$$n = \frac{z^2\ SD^2}{d^2}$$ (Betty and Kirkwood[10])

n= the desired sample size

z= the standard normal deviation (1.96) corresponds to a 2-sided level of significance of 5%

SD= the standard deviation of arch width measured in a pilot population (30 randomly selected Individuals) = 1.41mm

d = Precision (assume 18% of standard deviation, assumption of not more than 20% suggested for accuracy) = 0.252

All selected eligible subjects had their maxillary arches impression made with alginate impression material (elastic cromo, spofadental) and disinfection with cidex (2% glutaraldehyde) for five minutes. The impressions were poured immediately in dental stone (Kerr orthodontic model mix stone type). The set cast model was then carefully retrieved from the impression to avoid breakage or crack of any of its parts especially the dental structures (teeth). Each model was then serialized and kept in a safe place.

The landmarks for measurements of the arch width as demonstrated by Pont were located manually and the measurements were done using

electronic caliper with sharpened beaks (CB Mitutoyo corp. Tokyo Japan, accuracy of 0.01mm).

- Mesio-distal width of the maxillary incisors (MWMI) – mesio-distal width of the maxillary central incisors and the lateral incisors were measured from one anatomical contact point (mesial) to the other (distal) at a level of the widest portion of the tooth [6].
- Maxillary Inter-premolar Width (MIPW) – measured from the distal pit of the maxillary right first premolar to the distal pit of the maxillary left first premolar [6].
- Maxillary Inter-molar Width (MIMW) – measured from the depth of the central fossa of the maxillary right first molar to the central fossa on the maxillary left first molar [6].

In cases of mild attrition, the landmark for the measurement was determined using the middle of the wear facet on the tooth [6].

To determine intra-observer reliability associated with measurements, 20 cast models of the sample ***subjects*** were randomly selected and they were measured and re-measured at 2 weeks interval by the same observer. The mean differences between the first and repeated measurements were not significantly different from zero. The error margin using Dahlberg's equation [11] ranges from 0.06mm to 0.27mm for tooth size width measurements and 0.08mm to 0.32mm for arch width dimensions. These values were found not to be statistically significant.

Arch width were also predicted using Pont's formula as stated below and predicted values were also entered into the spreadsheet;

Prediction of arch width by Pont;

Inter-premolar arch width = SI × 100/80

Inter-molar arch width = SI × 100/64

Where SI is the sum of the mesio-distal widths of the maxillary incisors [6]

Statistical analyses were performed using the Statistical Package for Social Sciences software (Windows version 19; SPSS Inc., Chicago, IL, USA). Level of significance was set at 5%. Independent t-test was used to compare means of measure inter-premolar and inter-molar arch widths between males and females subjects and dependent t-test was used to compare measured and predicted means of arch widths (inter-premolar and inter-molar) among the total sample, males and females.

Results

The gender distribution of the sample was 66 males and 66 females with a mean age of 21.62 ± 1.67 years and 22.86 ± 1.60 years respectively. The mean age of all the subjects is 22.24 ± 1.74 years. Mean maxillary arch widths observed for the studied population were 41.87 ± 2.70mm and 51.47 ± 2.69mm for inter-premolar width and inter-molar width respectively. In relation to gender, the mean maxillary widths observed for males were 42.48± 2.62mm and 52.14 ± 2.27mm for inter-premolar width and inter-molar width respectively. While that for females were 41.26 ± 2.67mm and 50.79

Table 1: Mean arch widths and comparison of gender arch widths

Arch width	Mean maxillary Arch widths Total sample(mm)	Male mean maxillary arch width (mm)	female mean maxillary arch width (mm)	Mean difference (male and female) (mm)	P value
Inter-Premolar	41.87 ± 2.70	42.48 ± 2.62	41.26 ± 2.67	1.22 ± 0.46	0.009*
Inter-molar	51.47 ± 2.69	52.14 ± 2.27	50.79 ± 2.93	1.35 ± 0.46	0.004*

**P < 0.05 statistically significant*

Table 2: Comparison of measured and predicted (Pont) arch widths in the studied sample (Reliability)

Arch width	Measured arch widths (mm)	Predicted (Pont) arch width (mm)	Mean difference (mm)	P value
Inter-Premolar	41.78 ± 2.70	39.55 ± 2.58	2.32 ± 3.20	0.000*
Inter-molar	51.47 ± 2.69	49.44 ± 3.22	2.03 ± 3.83	0.000*

**P < 0.05 statistically significant*

±2.93mm for inter-premolar width and inter-molar width respectively. (Table1).

Comparison of measured and predicted (Pont) arch widths revealed a difference of 2.32 ± 3.20mm and 2.03 ± 3.83mm for inter-premolar and inter-molar arch widths respectively for the studied population (Table 2). In relation to gender, the comparison of measured and predicted (Pont) arch widths revealed a difference of 2.56 ± 3.25mm and 2.26 ± 3.69mm for inter-premolar and inter-molar arch widths for males subjects and 2.09 ± 3.16mm and 1.81 ± 3.99mm for inter-premolar and inter-molar for females respectively (Table 3).

for inter-premolar and inter-molar arch widths respectively for males subjects and 2.09 ± 3.16mm (p = 0.000) and 1.81 ± 3.99mm (p = 0.000) for inter-premolar and inter-molar respectively for females (Table 3). The reliability was also found to be greater with the inter-molar width than width the inter-premolar width with statistically significant differences of 1.22 ± 0.46mm (p = 0.009) and 1.35 ± 0.46mm (p = 0.004) observed for inter-premolar and inter-molar widths respectively between males and females subjects (Table 1).

Comparing our study with other global studies we found similar Pont's index value underestimation in [6,12-15]. Contrary to our findings, overestimation

Table 2: Comparison of measured and predicted (Pont) arch widths in male and female subjects (Reliability)

Arch width	Male				Female			
	Measured arch widths widths (mm)	Predicted (Pont) arch width (mm)	Mean difference (mm)	P value	Measured arch widths (mm)	Predicted (Pont) arch width (mm)	Mean difference (mm)	P value
Inter-Pm	42.40±2.66	39.84±2.56	2.56±3.25	0.000*	41.34±2.66	39.25±2.58	2.09±3.16	0.000*
InterMolar	52.06±2.37	49.81±3.20	2.26±3.69	0.000*	50.87±2.88	49.06±3.23	1.81±3.99	0.000*

**P < 0.05 statistically significant*

Discussion

The Pont's index is a simple tool which provides considerable guidance on arch width in clinical orthodontic practice. It has been evaluated by different authors in literature and its clinical application has been questioned by some authors whose observations in their various studies do not agree with that of Pont [5-9] therefore; its clinical applicability is controversial.

In this study, Pont's index was found to have underestimated the arch width for Nigerians (p = 0.000). Comparison of measured and predicted (Pont) arch widths revealed a statistically significant differences of 2.32 ± 3.20mm (p = 0.000) and 2.03 ± 3.83mm (p = 0.000) for inter-premolar and inter-molar arch widths respectively for the entire studied population (Table 2). There was scarcity of literature regarding the applicability of this index in our environment as none was found in literature therefore, we could not compare our result with other local study. Though, Pont underestimation of the studied population made its applicability in clinical practice unacceptable in our environment, the index was found to be more reliable in predicting maxillary arch width in females than in males. The comparison of measured and predicted (Pont) arch widths revealed a statistically significant differences of 2.56 ± 3.25mm (p = 0.000) and 2.26 ± 3.69mm (p = 0.000) was observed in other ethnicities and races [7-9,16-18]. The findings from our study further confirms documented evidence in literature of variations in Pont estimation of maxillary arch widths [19,20] and Pont [9] reservations concerning his study when he said his observations is likely to be affected by ethnic and racial variations hence the index should be tested in other populations.

The maxillary arch width observed in this study 41.87mm and 51.47mm for both inter-premolar and inter-molar respectively was different from that observed in a similar Nigerian study in Lagos by Aluko *et al* [19]. The difference was attributed to protocol in arch landmarks. While our study strictly observed Pont [6] protocol in arch landmarks, Aluko et al relied on the buccal cusp tip of premolars and mesio-buccal cusp tips of the molars as the landmarks for their study resulting in a value difference of 4.0mm and 5.0mm for the premolar and molar measurements in both studies respectively.

Male subjects were found to have wider arch widths than females and this confirms other documented evidence in literature about gender dimorphism in arch width [19,20].

Conclusion

Pont's index underestimated the maxillary inter-premolar and inter-molar arch width in our study.

Its clinical applicability especially when orthodontic arch expansion is needed and it cannot solely be relied upon in our environment.

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Diet and the metabolic syndrome

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Abstract
Background: The metabolic syndrome constitutes a complex health problem for populations worldwide. Apart from associated healthcare and management costs, it is also implicated in increased predisposition to cardiovascular disorders with their attendant morbidities and mortality. The complications arising from this syndrome are diverse, with microvascular dysfunction being a key element. Diet is one of the key factors that lead to obesity; the precursor to metabolic syndrome.
Design: We carried out a comprehensive search of academic databases (up to 2015), with specific emphasis on PubMed-cited articles, for studies on metabolic syndrome, obesity and induced inflammation, type II diabetes mellitus, body fat and the role of diet in obesity. All results obtained across studies were pooled using a random-effects meta-analysis.
Purpose and findings: This review examines current literature on this disorder, its complications and management. It also explores current concepts and perceptions on genetic influences on this syndrome, while emphasising the influence of diet on both its development and management. It also endeavours to explore these linkages in order to identify new avenues for research into this syndrome.

Keywords: *Diet, metabolic syndrome, epigenetics*

Résumé
Contexte: Le syndrome métabolique constitue un problème de santé complexe pour les populations du monde entier. Outre les coûts de santé et de gestion associés, il est également impliqué dans la prédisposition accrue aux troubles cardiovasculaires avec leurs morbidités associées et mortalité. Les complications liées à ce syndrome sont diverses, avec le dysfonctionnement micro-vasculaire étant un élément clé. L'alimentation est l'un des facteurs clés qui conduisent à l'obésité; le précurseur du syndrome métabolique.
But : Nous avons effectué une recherche exhaustive des bases de données académiques (jusqu'en 2015), en mettant l'accent sur les articles cités dans Pub-Med, pour les études sur le syndrome métabolique, l'obésité et l'inflammation induite, le diabète de mellite de type II, la graisse corporelle et le rôle du régime alimentaire dansl'obésité. Tous les résultats obtenus au cours des études ont été regroupés au moyen d'une méta-analyse à effets aléatoires.
Objectif et résultats: Cet examen examine la littérature actuelle sur ce trouble, ses complications et sa prise en charge. Il explore également les concepts actuels et les perceptions sur les influences génétiques sur ce syndrome, tout en soulignant l'influence du régime sur son développement et sa gestion. Il s'efforce également d'explorer ces liens afin d'identifier de nouvelles pistes de recherche sur ce syndrome.

Mots-clés*: Régime alimentaire, syndrome métabolique, épi-génétique*

Introduction

Diet comprises different nutrients, and non-nutrients, in varying proportions consumed by an individual. At the cellular level, these nutrients are absorbed and utilised for energy in the body through the body's metabolic processes [1]. Nutritionally-poor diets have been linked to several chronic diseases including many metabolic syndrome components [2].

Metabolic syndrome (MetS) is a group of disorders that has become a problem of epidemic proportions, not only in the developed countries, but increasingly so in the developing societies. It also comes with a high social and economic cost as management costs run into billions of dollars yearly [3]. Overall, metabolic syndrome is believed to be a major health problem and it often presents a confounding therapeutic challenge [4]. Lifestyle modifications, including low caloric 'healthy' diets, regular exercise and in some cases, pharmacological interventions are the main therapies utilised in combating this syndrome

Along with the high prevalence of MetS, an increasing incidence is being recorded yearly in many countries. The prevalence rates in adults

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around the world have been reported to be about 15.5%; in the U.S. 23.7%, Russia 17.6%, and in Finland 13.7% [5]. In Africa, the prevalence of MetS has risen significantly, and unlike the days when such conditions were considered rare, MetS is now a relatively common occurrence [6-8]. Following the official publication of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) MetS diagnostic criteria [9], studies have shown that more than one in five adults in the United States population meet the conditions for MetS [10]. However, prevalence rates in African countries are now comparable to those from the developed world. This was described as 30.3%, 17.9%, 27.1%, and 34% in Seychelles [11], Ethiopia [12], Congo [13], and Botswana [14]. In Enugu, Nigeria this was reported to be 15.9% [15], while two studies in Lagos, Nigeria reported rates greater than 50% of the population [16,7].

Metabolic syndrome is characterised by an aggregation of interconnected factors that increase predisposition to coronary heart disease and other forms of cardiovascular disorders, as well as Type II diabetes mellitus. The components of this syndrome include elevated triglycerides and apoprotein B–containing lipoproteins, reduced High Density Lipoprotein (HDL), arterial blood pressure elevation, insulin resistance with or without imbalances in glucose homeostasis and proinflammatory and prothrombotic states. The main manifestations of MetS however are insulin resistance and abdominal obesity [17].

Table 1: The International Diabetes Federation (IDF) Definition [19]

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have: **Central obesity** (defined as waist circumference* with ethnicity specific values) **plus** any two of the following four factors:

Raised Triglycerides	≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in femalesor specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes mellitus If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

** If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.*

Metabolic syndrome

Many definitions have been proposed over time for MetS [18]. In 2005, the International Diabetes Federation (IDF) proposed a wide definition for MetS. This is a modification to the previous World Health Organisation (WHO) definition and Adult Treatment Panel III (ATP III) criteria which was directed at international relevance utilisation in clinical settings. IDF defined MetS as central obesity with at least two of the other 4 parameters as shown in Table 1 [19]. Nowadays, the two most widely-accepted definitions for MetS are those of the National Cholesterol Education Program: Adult Treatment Panel (NCEP: ATP III) and the IDF focusing specifically on waist circumference, which is a surrogate measure of central obesity [17].

Obesity, the main predisposing factor to MetS, continues to be one of the leading causes of overall morbidity and mortality in Western societies and its prevalence continues to increase worldwide [20]. It is estimated that by 2030, the number of overweight and obese adults will be at least 1.35 billion and 573 million respectively [21]. Other abnormalities have been added to the above-stated factors, including; non-alcoholic fatty liver disease, sleep apnea, as well as prothrombotic and proinflammatory conditions. Obesity is a main cause of insulin resistance, a result of impairment in the insulin signalling cascade, and molecular mechanisms like oxidative stress, Endoplasmic Reticulum stress, disruption of lipid and free fatty acid homeostasis, hypoxia, as well as mitochondrial dysfunction have been implicated in its pathophysiology [22].

On release from the pancreas, insulin binds its receptor on insulin-responsive cells like hepatocytes, resulting in autophosphorylation of the

insulin receptor at its Tyrosine residues, and subsequent activation of tyrosine kinase [23,24]. This triggers a sequence of events, eventually inducing translocation of GLUT4 and consequent glycogen synthesis [25]. It is this pathway that is disrupted by obesity through obesity-induced inflammation, causing insulin resistance. The adipose tissue, in obesity, expresses extremely high amounts of inflammatory mediators, especially adipose tissue macrophages, dendritic cells, neutrophils, eosinophils, mast cells, T and B lymphocytes, which are involved in the development of obesity-induced inflammation [25]. Excess abdominal adiposity enhances insulin resistance by the release of large amounts of non-esterified fatty acids which overloads the liver and muscle or by increasing lipolysis of lipoproteins [26].

Insulin resistance leads to an inability of the body to maintain glucose homeostasis, thus resulting in hyperglycaemia [26]. Endothelium damage, a main consequence of this hyperglycaemia, is caused by excess production of superoxide by the electron transport chain in the mitochondria which brings about decreased Nitric oxide levels, decreased prostacyclin production and endothelial dysfunction. The hyperglycaemia-induced reactive oxygen species formation promotes increased vascular permeability which is responsible for increased manifestation of endothelial mitogen vascular endothelial growth factor, a factor implicated in diabetic microangiopathy [27]. Reactive oxygen species can also elevate prostanoid and endothelin formation, thereby promoting atherosclerotic plaque formation [27].

Hypertension in MetS is caused by the individual and collective influences of all components of MetS, however, obesity seems to be the most important as it influences the onset and progression of all other components [28]. Excess body weight, especially central abdominal deposition of fat, has been indicated as responsible for most cases of essential hypertension [28]. The extent of obesity has been shown to have a direct relationship with the renin-angiotensin system and Angiotensin II influences blood flow to, growth of, and metabolism of adipose tissue, essentially playing a large role in development of insulin resistance and hypertension [29]. Overall, increased activity of the renin-angiotensin system and the sympathetic nervous system, as well as insulin resistance and hyperinsulinaemia cause increased sodium retention in obese individuals which results in increased extracellular fluid volume and rise in blood pressure [28].

Fibrinolytic and thrombic markers show strong correlations with all components of MetS [30]. High concentrations of Plasminogen plasminogen activator inhibitor 1 in plasma, fibrinogen, and tissue-type plasminogen activator have been reported in MetS, suggesting of defective fibrinolytic mechanisms [31,18]. Also, in MetS, haemostatic factors VII, X, as well as the anticoagulant Protein C and Protein S show significantly elevated concentrations [30].

Complications of metabolic syndrome

According to the IDF, people with MetS have a five times greater risk of developing Type 2 diabetes mellitus, one of the most common chronic diseases and the fifth leading cause of mortality in the developed world [32]. Components of MetS also represent some of the most predisposing risk factors for cardiac arrest [33]. In individual comparison of different definitions of MetS with fatal and non-fatal cardiovascular disease (CVD), the ATP III definition was associated with twice the age-adjusted risk for fatal CVD in men and non-fatal CVD in women, while other definitions showed a slightly lower ratio [34]. Metabolic syndrome and insulin resistance have also been described as mutually independent predictors of risk of cardiovascular events in angiographed patients [35]. Metabolic syndrome has also been related to ischemic heart disease [36], aortic valve calcification [37], echocardiographic left ventricular mass [38], coronary heart disease [39], and overall mortality [40].

Constituents of the metabolic syndrome like insulin resistance, dyslipidemia, arterial hypertension, and abdominal obesity, have been reported to independently influence microvascular function [41]. In obesity, pathological adipose tissue deposition is associated with microvascular dysfunction, while perivascular adipose tissue in particular has been established as a crucial modulator of vascular function [42-44]. Metabolic syndrome has been associated with an increased risk of such cardiovascular disorders such as myocardial infarction, stroke [45], and coronary microvascular dysfunction linked to a microvascular form of angina pectoris [46]. Microvascular dysfunction has also been described as being in association with poor cardiovascular outcomes, including left ventricular remodelling [45,47,48].

In the Warfarin Aspirin Symptomatic Intracranial Disease Trial [49], half of individuals with symptomatic intracranial atherosclerotic disease had MetS. After a 1.8-year follow-up, results showed that individuals with MetS had a shorter period

before their first ischemic stroke, myocardial infarction, or vascular death. Metabolic syndrome also increases the rate and risk of loss of cognitive functions, especially in older people with high levels of inflammation [50]. It also increases the risk of dementia in the middle to latter years of life [51].

MetS is strongly associated with the prevalence of many dysfunctions that affect organs in the body. Insulin resistance is one of the most common factors involved in the aetiology of non-alcoholic steatohepatitis [52], and high levels of liver diagnostic markers have been reported to increase the risk of MetS [53].Abdominal obesity is also known to increase predisposition to non-alcoholic fatty liver diseases like non-alcoholic steatohepatitis [52]. Renal injury is also attributed to MetS due to dysfunctional pressure natruiresis, increased excretory loads on the kidneys, chronic inflammation and prothomobosis, impaired endothelial function etc. [54]. These are reported to decrease glomerular filtration, and eventually result in chronic kidney disease and microalbuminuria [55]. In addition, self-reported cancer cases are more likely in individuals with MetS, with it showing a higher prevalence in individuals with breast cancer [56]. Metabolic syndrome also has strong associations with both hypogonadism and/or low testosterone levels in males [57,58], while in women, MetS is associated with the prevalence of Polycystic Ovary Syndrome [59,60], and since both conditions have insulin resistance as a common characteristic, Polycystic Ovary Syndrome has been theorised to be a female-specific manifestation of MetS [61].

Influences of diet on the metabolic syndrome

Diets with high concentrations of saturated fatty acids (SFA) reportedly increase the development of MetS and insulin resistance as well as Type 2 Diabetes mellitus. This occurs through alterations in the factors that affect inflammation, adiposity and insulin sensitivity [62], whereas diets rich in monounsaturated fatty acids (MUFA) are linked with significant enhancements of insulin sensitivity in healthy individuals [63]. MUFA-rich diets have also been reported to have beneficial influence on both glucose and insulin concentrations while showing associations with decreases in body fat regain [64]. Studies in cells and animals have shown evidences of beneficial effects of long chain *n*-3 polyunsaturated fatty acids (LC *n*-3 PUFA) on both inflammation and insulin sensitivity [65].

The amount and type of carbohydrate consumption is a major factor linked with insulin resistance in individuals who are genetically at risk of Mets. Refined carbohydrates, especially, result in high insulin concentrations which might result in or be a result of insulin resistance. Maegewa *et al*., [66] reported high insulin concentrations in animals fed a high-sucrose (73% by weight) diet, and when compared with a high-fat (60% by weight) diet, the high-fat diet also had elevated insulin concentrations but this was highest in the high-sucrose fed animals. Many other animal studies have corroborated this finding of a relationship between refined carbohydrates and insulin resistance [67-73].

Increasingly, scientific evidence suggests that high dairy and/or calcium consumption is beneficially related to weight management [74]. Earlier studies had suggested that calcium promotes lipolysis while inhibiting lipogenesis, due to increased production of parathyroid hormones and/or 1,25-$(OH)_2$ vitamin D_3 [75]. Subsequent studies, both animal and human, confirmed that calcium is involved in the modulation of energy metabolism and exerts an "anti-obesity" effect [76,77]. In relation to this, the Third National Health and Nutrition Examination Survey (NHANES III) study showed an inverse relationship between obesity and calcium intake [78]. Other studies reflecting this correlation in different countries include, the Coronary Artery Risk Devel-opment in Young Adults (CARDIA) study, the Heritage study, and the National Nutrition and Health Survey (EN-NyS, Argentina) [79-81].

Many other nutrients have been reported to have effects on metabolic syndrome. High Magnesium consumption in diet was inversely correlated with the incidence of MetS by He and coworkers [82]. After adjusting for variables like lifestyle, diet and baseline status of each element in MetS, they concluded that increased Magnesium intake was associated with a decline in risk of MetS. High levels of serum Ferritin have however been strongly associated with increased predisposition to MetS [83]. Insulin resistance also increased with increase in ferritin, even after they adjusted for age, race/ethnicity, C reactive protein, smoking, alcohol intake and Body-mass Index. Another nutrient of interest in MetS is Vitamin D. The deficiency of this vitamin has been described as a risk factor for MetS [84] (, with individuals having low levels showing a higher prevalence of the components of the syndrome [85].

A major component of metabolic syndrome is believed to be augmented oxidative stress [86], and oxidative stress was reported to be increased in healthy but obese subjects with metabolic syndrome when compared with BMI-matched obese individuals without the syndrome [87]. Recently, a

study confirmed that induction of decrease in weight by dietary caloric restriction reduces oxidative stress which is concurrent with an improvement in the clinical components of metabolic syndrome [88]. Their results suggested that obese individuals with the syndrome were hyperglycaemic and manifested chronic low-grade inflammation which resulted in increased production of Reactive Oxygen Species (ROS) and consequently increased oxidative stress. They therefore concluded that Very Low Calorie Diet- (VLCD-) induced weight loss brings about an improvement in glucose metabolism and may decrease inflammation as a result of decreased adiposity and adipokine/cytokine secretion. All these will reduce oxidative stress in these individuals [88]. These and other findings suggest that this syndrome will cause an increase in generation of ROS which will eventually lead to oxidative stress.

Influence of genes on metabolic syndrome

Management of MetS has focused to a large extent on the nutritional approach which is traditionally directed at factors that influence energy balance, such as reduced energy intake or increased energy expenditure. Different diets have been described by investigators as having therapeutic effects on components of MetS, especially obesity. The main focus of these interventions has been on diets that can stimulate an increase in metabolism and energy expenditure.

Evidence has been accumulating that the familial clustering attributed with obesity might not only be due to shared environmental factors. Reports from studies in twins, adoptees and families show that close to 80% of the variances observed in Body-Mass index (BMI) are results of genetic factors. It is noteworthy that adoptees' weights are more similar to that of their birth parents than the adopted ones [89]. On the other hand, when monozygotic twins were compared to dizygotic twins, the results showed high relative risk ratios as well as concordance rates in favour of obesity in monozygotic twins [90]. The concordance rates for monozygotic twins, at 60-90%, are significantly greater than that in dizygotic twins. Metabolic syndrome has been described as having heritability rates of between 10-30% [91,92], while that of BMI has been estimated at between 25-40%. These figures indicate that these conditions are to an extent heritable. Results of family studies on first-degree relatives of Type 2 Diabetes mellitus (T2DM) individuals show that they have an approximately threefold increase in likelihood of developing the disease than people without a prior family history [93].

Research is increasingly focused on the role played by genetic influences in the incidence of MetS [94-96]. Failure in function of key regulatory genes and enzymes has been extensively reported as being the root cause of metabolic syndrome [97]. Genome-wide association studies have demonstrated numerous genes and regions, which are susceptible to individual MetS risk factors such as hypertension, obesity, and diabetes mellitus [96-100]. However, studies have not been able to locate any genetic loci that mediate clustering of metabolic syndrome components [94,101]. MiR-33 mediated regulation has been reported in metabolic pathways such as lipid metabolism (cholesterol homeostasis, HDL biogenesis, and fatty acid, phospholipids, and triglyceride, and bile acid metabolism), inflammatory response, insulin signalling, and glucose homeostasis [102]. MiR-33 is an intronic microRNA located within the sterol regulatory element-binding protein (SREBP) genes and it is one of the main regulators of cholesterol and fatty acid metabolism.

Bowden *et al*., [103] traced evidence of coincident linkage of MetS, type II diabetes mellitus and CVD into four loci on chromosomes, and when all the traits were mapped into a super phenotype, there was a linkage on chromosome 3p. Circulating ICAM-1 is associated with MetS phenotypes and is inheritable [104]. It shows positive genetic correlations with factors such as insulin resistance, BMI, waist circumference and BMI. Furthermore, *Pst*1 polymorphism in the gene for insulin has an association with high hypertriglyceridemia in MetS, while the *Mae*III polymorphism has been shown to be related to high fasting insulin concentration [105]. The location of a susceptibility locus on chromosome 1q21-q25 was also reported by Ng *et al*., [106] to be involved in the pathogenesis of multiple metabolic abnormalities.

There is a growing evidence of knowledge which suggests that an individual's phenotype is the result of a complex interaction between both genetic and environmental factors over the course of their life (epigenetics). Nutrition amounts to one of the most fundamental environmental factors involved in the pathogenesis and progression of most common polygenic, diet-related metabolic conditions and in relation therefore, the concept of gene-diet interaction describes dietary modulation of the effect of genotype on particular phenotypes and/or modulation of the effect of a dietary factor on a particular phenotype by a genetic variant [107]. This and other concepts are backed by findings that in certain ethnic groups such as the Pima Indians, Pacific Islanders, Afro-Americans and Hispanic

Americans, obesity and T2DM climbs to epidemic proportions [108]. However, the much lower prevalence of metabolic disease in Pima Indians located in Mexico in comparison with their counterparts in America reflects that even in genetically-predisposed groups, their development is still largely determined by environmental conditions [109,110]. Dietary fat is an important environmental nutritional factor, especially as affects obesity, and current evidence substantiating the nutrigenetics concept with respect to obesity, the MetS and T2DM is based to a large extent on data relating to dietary fat [111,112], although carbohydrates and fibre could also play a role.

Conclusion

Metabolic syndrome is a worldwide problem of significant import. Possible genetic influences in this syndrome have been reported in individual components but a specific loci for the metabolic syndrome is still subject to future research. Results from different studies have shown significant effects of diet as a mode of management of the syndrome, with the lipolytic activity of calcium being a key factor of note. It is therefore pertinent for research in this area to explore the interesting possibilities of diet having an influence on genes implicated in the metabolic syndrome disorders.

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Absence of the head of the humerus in an adult Nigerian- a case report

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Abstract
The spherical head of the humerus forms the ball of the ball-and-socket of the shoulder joint, with the glenoid cavity of the scapular acting as the socket. The rounded shape of the head of the humerus allows the humerus to move in a complete circle (circumduction) and rotate around its axis at the shoulder joint. In absence of the head of the humerus, the above functions of the shoulder joint will be lost resulting in rotator cuff injury, frequent dislocation of the shoulder which is extremely painful and may require surgical repair or even cause permanent damage. The humerus described in this case report showed absence of the head with normal greater tubercle, lesser tubercle and intertubercular sulcus, intact shaft and distal extremity. Absence of the head of the humerus has been generally considered to be a rare condition and has not been previously described in a Nigerian. This defect recorded may be recognized as a group of deformities (Congenital or fractured) of the shoulder joint.

Keywords: *Absence, head, humerus,circumduction*

Résumé
La tête sphérique de l'humérus forme la boule de l'articulation de l'épaule, avec la cavité glénoïde du scapulaire agissant comme la douille. La forme arrondie de la tête de l'humérus permet à l'humérus de se déplacer dans un cercle complet (circumduction) et de tourner autour de son axe au niveau de l'articulation de l'épaule. En l'absence de la tête de l'humérus, les fonctions ci-dessus de l'articulation de l'épaule seront perdues résultant dans la blessure de la coiffe du rotateur, luxation fréquente de l'épaule qui est extrêmement douloureux et peut nécessiter une réparation chirurgicale ou même causer des dommages permanents. L'humérus décrit dans le présent rapport de cas a montré l'absence de la tête avecnormalplus grand tubercule, tubercule inférieur et sulcus inter-tuberculaire, fût intact et l'extrémité distale.

L'absence de la tête de l'humérus a été généralement considérée comme une maladie rare et n'a pas été précédemment décrit chez un Nigérian. Ce défaut enregistré peut être reconnu comme un groupe de déformations (congénitales ou fracturées) de l'articulation de l'épaule.

Mots clés: *Absence, tête, humérus, circumduction*

Introduction

Previous literature search indicated that this rare condition has been described in less than ten cases and none of these cases has been described in a Nigerian. This congenital absence of the head of the humerus and some anatomical variations in the proximal part of the humerus may be a contributory factor in congenital malformations involving the shoulder joint [1]. Congenital absence of the head of the humerus has also been described clinically by [2-4] in which they reported that in all three cases, in addition to absence of the head of humerus, the patients had other congenital bone and joint malformations. Congenital absence of the head of the humerus has not been previously described in a Nigerian, hence the description of this case report.

Case Report

In the course of distribution of bones from our bone library (Department of Anatomy, College of Medicine, University of Ibadan, Ibadan, Nigeria) to the second year Medical and Dental students, we observed a left humerus of an unknown age, sex and ethnicity without a head, but had normal greater and lesser tuberosities, as well as the intertubercular sulcus or bicipital groove (Figures 1-3).

The humerus had a length of 28.0 cm (from the tip of the greater tubercle to the trochlea, using a calibrated ruler) (Fig 4), thickness of 15.9 mm (middle of the shaft, using a digital vernier caliper) (Fig 5) and a total dry weight of 81.6 g, using an electronic weighing balance [5, 6].

Discussion

Andreasen (1948) [1] described two rare cases of absence of the humeral head and concluded that

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Fig 1: Posterior view of the proximal part of the left humerus with absence of the head of the humerus

Fig 2: Lateral view of the proximal part of the left humerus with absence of the head of the humerus

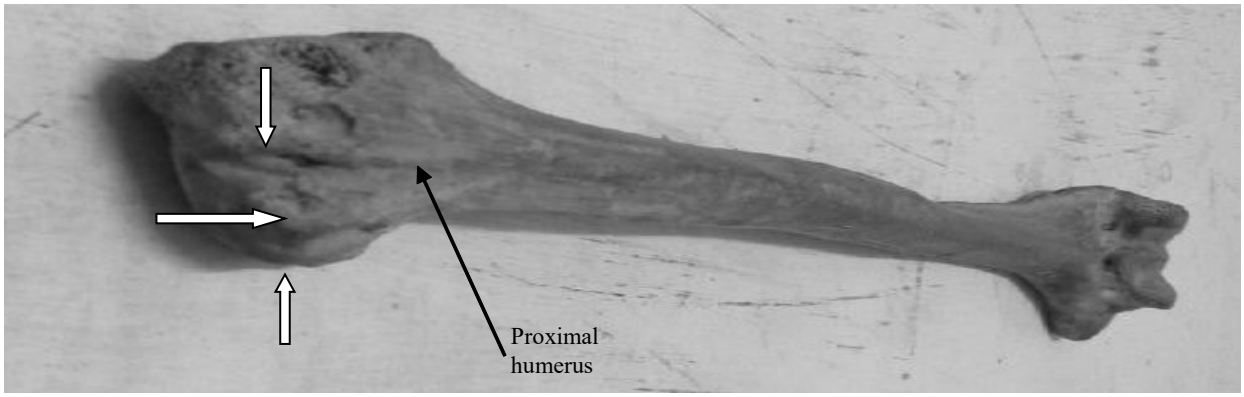

Fig 3: Anterior view of the proximal part of the left humerus with absence of the head of the humerus, but with normal greater and lesser tuberosities, and intertubercular sulcus (white arrows).

Fig 4: Measurement of the length (cm) of the humerus from the tip of the proximal humerus to the tip of the trochlea in the distal part, using a calibrated ruler

the condition is probably congenital, and represented varying degrees of a typical but hitherto unrecognized deformity of the shoulder joint. Congenital absence of the head of the humerus occurs at a very early stage of embryonic life. This may be due to failure of development of the tissue

Fig 5: Measurement of the thickness (mm) of the humerus, midway in the shaft between the proximal and distal ends of the humerus, using a digital vernier caliper

in which the capital epiphysis should form [1] and may be completed by the non-appearance of the ossification centre for the head of humerus in the fourth and sixth months of development [7]. At a very early stage of development when the primitive joint begins to form, an accident may occur which may alter the process of separation in the mesenchyme to form the articular ends of joints [1]. In this case report, it was likely the brunt of force of the accident (caused either by genetic or environmental factor) fell upon the head of the humerus.

Absence of the head of the humerus may also occur in complex fracture with multiple fragments where interruption to the blood supply is more likely and in fracture of the surgical neck resulting in avascular necrosis of the humeral head. This leads to flattening of the head of the humerus with the resultant pain and stiffness in the shoulder, malunion of the shoulder joint, associated glenohumeral dislocation and associated rotator cuff injury [8].

The shoulder joint is vulnerable to dislocations from sudden jerks of the arm especially in children before strong muscles have developed. The spherical head of the humerus forms the ball of the ball-and-socket shoulder joint, with the glenoid cavity of the scapular acting as the socket. The rounded shape of the head of the humerus allows the humerus to move in a complete circle (circumduction) and rotate around its axis at the shoulder joint. These functions will be lost in absence of the head of the humerus and may result in frequent dislocation of the shoulder which is extremely painful and may require surgical repair or even cause permanent damage. Deformities of the shoulder resulting from congenital absence of the head of the humerus may be prominent in lesions of the rotator cuff muscles [9]. The rotator cuff muscles are four short (supraspinatus, infraspinatus, teres minor and subscapularis muscles) which help prevent nipping of the synovial fluid and stabilizes the head of the humerus at the level of the shoulder joint [10].

In spite of the loss of some movements (circumduction and rotation) of the shoulder joint as a result of absence of the head of humerus, this study was not able to ascertain if the absence of the head of the humerus was congenital or as a result of fracture because of lack of proper records of documentation.

The case report described above has not only added to the existing literature of absence of the head of the humerus, but can also occur in a Nigeria, sub-Saharan African. However, the frequency of occurrence and sex distribution of the absence of the head of the humerus should be further determined.

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Chemotherapy-associated renal insufficiency in cancer patients.

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Abstract
Background: Malignancy or its treatment can produce a variety of renal diseasesand renal insufficiency frequently complicates malignancy and its treatment. The aim of this study is to assess the effect of different chemotherapeutic agents on the renal function of patients receiving treatment in a tertiary institution in Nigeria.
Methodology: This is a retrospective study of Glomerular filtration rate assessment among patients who received chemotherapy in Lagos University Teaching Hospital, Lagos, Nigeria from December, 2012 to November, 2013.
Results: 473cases were studied. The mean age was 50± 15.5 years. The peak age range was 4th decade 123(26%). Commom cancers treated were breast cancer (159 cases), cervical cancer (103 cases) and prostate (35 cases). Stages recorded were stage III, 193(40.8%), stage II, 150 (31.7%), stage IV, 115 (24.3%), stage I, 15(3.2%). Treatment modalities revealed that 115(24.2%) had a combination of surgery and chemotherapy, 106 (22.4%) had chemotherapy alone, while 103 (21.8%) had a combination of surgery, chemotherapy and radiation therapy. There was a marked decrease in average GFR from 106.92 at beginning of treatment to 70.49 after completion of chemotherapy. The use of cisplatin showed the highest reduction in the GFR(43 %)after completion of chemotherapy.
Conclusion: Renal Insufficiency is common in cancer patients and drug dosage adjustments might be necessary. Renal function should be evaluated in all cancer patients in a bid to identify patients with a high risk for drug toxicity.

Keywords: *Renal, Insufficiency, Cancer*

Résumé
Contexte: La malignité ou son traitement peut produire une variété de maladies rénales et l'insuffisance rénale complique fréquemment la malignité et son traitement. Le but de cette étude est d'évaluer l'effet de différents agents chimio-thérapeutiques sur la fonction rénale des patients recevant un traitement dans un établissement tertiaire au Nigeria.
Méthodologie: Ceci est une étude rétrospective de l'évaluation du taux de filtration glomérulaire parmi les patients qui ont reçu une chimiothérapie à l'Hôpital d'Enseignement Universitaire deLagos, Lagos, au Nigeria de décembre 2012 à novembre 2013.
Résultats: 473 cas ont été étudiés. L'âge moyen était de 50±15,5 ans. La tranche d'âge maximale était la 4eme décennie 123 (26%). Les cancers communs traités étaient le cancer du sein (159 cas), le cancer du col de l'utérus (103 cas) et la prostate (35 cas). Les phasesenregistrées étaient laphase III, 193 (40,8%), phase II, 150 (31,7%), phase IV, 115 (24,3%), phase I, 15 (3,2%). Les modalités de traitement ont révélé que 115 (24,2%) avaientune combinaison de chirurgieet de chimiothérapie, 106 (22,4%) avaientuniquement la chimiothérapie, tandis que 103 (21,8%) avaient une combinaison de chirurgie, de chimiothérapie et de radiothérapie. Il y avait une diminution marquée du TFG moyen de 106,92 au début du traitement à 70,49 après l'achèvement de la chimiothérapie. L'utilisation du cisplatin a montré la plus forte réduction du TFG (43%) après achèvement de la chimiothérapie.
Conclusion: L'insuffisance rénale est fréquente chez les patients atteints du cancer et des ajustements posologiques peuvent être nécessaires. La fonction rénale doit être évaluée chez tous les patients atteints du cancer dans le but d'identifier les patients présentant un risque élevé de toxicité médicamenteuse.

Mots-clés: *Rénale,Insuffisance, Cancer*

Introduction

Malignancy or its treatment can produce a variety of renal diseases. Renal insufficiency frequently complicates malignancy and its treatment. These complications are often preventable or reversible with prompt diagnosis and treatments[1]. Renal insufficiency is a medical condition in which the kidneys fail to adequately filter waste products from

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the blood. Because the mechanisms of renal insufficiency vary significantly in patients with different types of cancer, detection of the disorder is possible only through a careful assessment of the pathophysiologic abnormalities, symptoms and antineoplastic therapy involved in each case [2]. Several antineoplastic agents are potentially nephrotoxic; previous renal impairment as well as combinations with other nephrotoxic drugs may increase the risk of nephrotoxicity during administration of chemotherapy. A few antineoplastic drugs with clearly established nephrotoxicity include: methotrexate which most frequently occurs with high-dose therapy and can be avoided by forced alkaline diuresis and administration of folic acid, streptozotocin but toxicity is prevented by drug discontinuance. Mitomycin-associated renal failure and cisplatin nephrotoxicity is clearly dose-related and used to be considered dose limiting. Renal insufficiency can be prevented by hydration and forced diuresis and thus circumvent the dose-limiting effect of cisplatin-induced renal toxicity [3-7]. A number of methods for evaluating renal function have been proposed, although they have not been specifically evaluated in patients with cancer. The serum creatinine concentration is an unreliable measure in the evaluation of renal function, owing to the influence of a number of non-renal factors[8]. The determination of 24-hour urine creatinine clearance (Clcr) provides a more accurate estimation of the glomerular filtration rate (GFR) than does the serum creatinine concentration alone, but this test is often inconvenient for patients and can be inaccurate in those who do not have cancer. The Cockcroft-Gault formula [9], which estimates the GFR from serum creatinine concentration, is used to detect the onset of renal insufficiency and has been shown to correlate with the 24-hour urine Clcr test. A commonly used surrogate marker for estimatingcreatinine clearance is the Cockcroft-Gault (CG) formula, which in turn estimates GFR in ml/min.It is named after the scientists who first published the formula [9] and this formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the United State of America. The resulting value is multiplied by a constant, 0.85, if the patient is female.

AIM

The aim of this study is to assess the effect of different chemotherapeutic agents on the renal function of patients receiving treatment at the Department of Radiation Oncology.

Materials and methods

The study was carried out in the Department of Radiation Oncology, Lagos University Teaching Hospital, Idi-araba, Lagos, Nigeria. A retrospective cross-sectional study which reviewed case notes of patients who received chemotherapyin the department over a period of 12 months from the 1st of December 2012 to 30th of November 2013. A total of 473 case notes of cancer patients were reviewed.

The following data were collected for eachpatient using a data extraction form: sex, age, GFR before commencement of chemotherapy and after completion, tumour site, stage of cancer presentation andante cancer drugs prescribed. All patients received six courses of prescribed chemotherapy drugs. Estimations of renal function were made by calculating the Glomerular Filtration Rate (GFR) using the Cockcroft-Gault formula. GFRindicatesglomerular filtration rate, and Serum Creatinine is measured in mg/dL. The formula, as originally published, the equation should be as this:

$$Cr = \frac{(140 - Age)mass(kg)x0.85(iffemale)}{72xSerumCreatinine(mg/dL)}$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the USA. The resulting value is multiplied by a constant, 0.85 if the patient is female. Patients who presented with acute renal failure were excluded. Patients with GFR less than 60ml/min/1.73m2 were also excluded in the study.Data was analyzed using the SPSS version 17.Frequency tables were generated to present results and a $p< 0.05$ at 95% confidence interval was considered as statistically significant. Ethical approval was obtained from Lagos University Teaching Hospital, Lagos,Nigeria.

Results

Four hundred and seventy three cases where studied. The mean age was50 ±15.5 years and the peak age range was 4th decade 123(26%). These are presented in Table 1.

Most (363) patients were females accounting for 76.7% of cases, while110 (23.3 %) cases were males as presented in Table 2.

The commonest type of cancer was Breast cancer with 159 cases, followed by cervical cancer with 103 cases and Squamous cell Carcinoma with 30 cases as presented in Table 3.

Most (193) cancer cases were presented in stage 3 of the disease and this accounted for 40.8% of the case. This is followed by 150 cases of stage 2

(31.7%) and 115 cases of stage 4 (24.3%). These are presented in Table 4.

Table 1: Age distribution

Age group(Years)	Frequency	Percentage
<10	6	1.3
11 – 20	2	0.4
21 – 30	37	7.8
31 – 40	87	18.4
41 – 50	123	26.0
51 – 60	97	20.5
61 – 70	70	14.8
71 – 80	43	9.1
81 – 90	8	1.7
Total	473	100.0

Table 2: Sex distribution

Sex	Frequency	Percentage
Male	110	23.3
Female	363	76.7
Total	473	100.0

Treatment modalities include surgery, chemotherapy and radiotherapy. The combination of surgery and chemotherapy was the commonest treatment modality which accounted for 115 cases (24.2%) followed by Chemotherapy alone, 106 cases (22.4%) and combination of three modalities in 103 cases (21.8%) and as presented in Table 5. One hundred and fifty four (154) patients (32.6%) received combination of Cyclophosphamide/ Adriamycin/5-flurouracil, 80(16.9%) received Cisplatin, 68(14.4%) received Oxaliplatin while 60(12.6%) received Capecitabine and the remaining patients 23.5% received other chemotherapeutic agents as presented in Table 6

Overall effect of chemotherapeutic agents on GFR showed statistical significance. There was a markeddecreaseof 34% from an average GFR of 106.92 to 70.49 after completion of Chemotherapy and a p-value of 0.001. The use of cisplatin showed a marked reduction of 43%in the GFR after completion of chemotherapy followed by the use of a combination of Cyclophosphamide/ Adriamycin/Fluorouracil(37%)and Taxanes (31%).Age and gender did not show any significant relationship with GFR and chemotherapeutic agents as P value were > 0.05. (Table 7)

Table 3: Histologic subtypes

Histologic subtypes	Frequency	Percentage
Brain and spinal cord	4	0.8%
Gliomas	2	
Medulloblastoma	1	
Meningioma	1	
Head and Neck	28	6%
Retinoblastoma	3	
Nasopharyngeal carcinoma	12	
Maxillary antrum carcinoma	5	
Thyroid cancer	4	
Mandibular cancer	1	
Carcinoma of the tongue	3	
Chest region	164	34.7%
Breast	159	
Lungs	5	
Gastrointestinal	26	5.5%
Rectal cancer	5	
Colonic cancer	17	
Carcinoid	1	
Hepatocellular carcinoma	4	
Urinary system	14	3%
Bladder cancer	4	
Renal Cancer	8	
Wilms tumor	2	
Gynecologic cancer	137	29%
Endometrid cancer	13	
Cervical cancer	103	
Ovarian cancer	15	
Vulvar cancer	5	
Leiomyosarcoma	1	
Male genitals	35	7.4%
Prostate	35	
Skin cancers	38	8.0
Baso squamous cancer	1	
Dermatofibrosarcoma	2	
Liposarcoma	2	
Melanoma	3	
Squamous cell carcinoma	30	
Bone tumours	3	0.6%
Osteosarcoma	3	
Blood and lymphatic system	23	5.0%
Lymphomas	14	
Plasmacytoma	1	
Multiple myeloma	2	
Kaposi sarcoma	6	
Total	473	100

Table 4: Stages of cancer diseases

Stage	Frequency	Percentage
1	15	3.2
2	150	31.7
3	193	40.8
4	115	24.3
Total	473	100

Table 5: Cancer Treatment Modalities

Treatment modality	Frequency	Percentage
Chemotherapy	106	22.4
Radiotherapy	50	10.6
Chemotherapy and Radiotherapy	58	12.3
Surgery/Chemotherapy	115	24.2
Surgery/Chemotherapy/ Radiotherapy	103	21.8
Surgery/Radiotherapy	41	8.7
Total	473	100.0

Table 6: Type of administered chemotherapy

Drug name	Frequency	Percentage
Adriamycin	6	1.3
Carboplatin	25	5.3
Cyclophosphamide/Adriamycin/ 5- Fluorouracil	154	32.6
Cisplatin	80	16.9
Cyclophosphamide	14	3.0
Darcabazine	6	1.3
Taxanes(Docetaxel, Paclitaxel)	38	8.0
Gemcitabine	10	2.1
Oxaliplatin	68	14.4
Vincristine/Epirubicin/ Cyclophosphamide	12	2.5
Capecitabine	60	12.6
Total	473	100.0

Discussion

This study was conducted to review the incidence of renal insufficiency in cancer patients who received a variety of chemotherapeutic agents whether as single agents or in combination for their treatment. The Cockcroft gault formula[9]was used to estimate the glomerular filtration rate from serum creatinine. This is a much more convenient way of measuring GFR when compared to the 24-hour urinary creatinine clearance estimation which entailed collection of urine over a 24-hour period [10]

Most of the patients enrolled in this study were female,this could be due to the fact that breast cancer accounted for the highest number of cases, it also correlates with other studies done in Nigeria[11], which showed a higher incidence of malignancies among women. However most previous studies done internationally showed a high preponderance of cancers among male [12-13].

A mean age of 50years was noted in this study and this is in agreement with local studies done in this region on cancer incidence [11] as most cancers present in the mid-40s' but contrasts with most studies done internationally [14].The commonest histopathology seen was breast cancer, this is in line with most studies which showed that breast cancer is the commonest malignancy amongst women [11,15].Most of them presented in the late stages of the disease, previous studies done on pattern of presentation of cancer patients in sub-Saharan Africa showed that most presentation are in late stages [16-17]. Also late presentation may be due to poverty, ignorance, wrong diagnosis and alternative treatment which includes native herbal concoction and visit to prayer houses. This late presentation thereby affects prognosis of diagnosis.Most of the chemotherapeutic agents prescribed caused some degree of renal insufficiency in patients but the most reduction was seen in patients who received cisplatin, this is in agreement with most studies done worldwide [4,6]. Cisplatin is a platinum compound, effective therapy for many carcinomas. Its major adverse effect is nephrotoxicity associated with renal insufficiency, although ototoxicity also occurs[18,19]. Cisplatin injures multiple renal compartments. Nephrotoxicity is generally reversible, but it can be permanent. Cisplatin's mechanism of nephrotoxicity is related to its drug characteristics, its renal handling and the kidney response to the cisplatin molecule. Pre-hydration with intravenous normal saline or hypertonic saline was found to be effective in counteracting the toxic effect. Also the addition of mannitol to induce a forced diuresis was also found useful [20]. The use of chemotherapeutic drugs in combination was also found to be associated with nephrotoxicity in this study. There is therefore need for chemotherapy dose adjustments, whether as single agent or in combination, for patients undergoing cancer management

Conclusion

This study has demonstrated the need for assessment of the renal function prior to administration of chemotherapy drugs in order to prevent nephrotoxicity in patients on chemotherapy. The use of antineoplastic agents like cisplatin is associated with severe renal impairment and precautionary measures should be taken prior to administration and dose adjustments made where necessary.

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Brain atrophy in African stroke survivors: The CogFAST Nigeria study

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Abstract

*Introduction***:** Cerebral atrophy is a common accompaniment of ageing and several neurological conditions. Magnetic Resonance Imaging (MRI) was used to compare brain volumes of stroke survivors with stroke-free controls in this first report from sub-Saharan Africa.

*Methods***:** Participants comprised 45 stroke patients and 54 stroke–free controls. Structural brain MR images were acquired from participants and volumes of grey, white matters and CSF extracted.

Results: The % of white matter in Intracranial Volume (ICV)(stroke:0.45±0.03, control: 0.47±0.03, p=0.02) and the % of total brain volume in ICV (stroke:0.85±0.03, control: 0.87±0.02, p=0.002) were significantly greater in the controls than stroke patients.The % of CSF in ICV (stroke:0.15±0.03, control:0.13±0.03, p=0.002) was significantly smaller in the controls than the stroke patients. The controls (68.9±10.0 years, p<0.001) were significantly older than the stroke (59.8±11.0 years) subjects. When adjusted for age, the % of white matter in ICV (male:0.44±0.03, female:0.46±0.04, p=0.043) was significantly less in male than female in the stroke group.

*Conclusions***:** Our results showed that stroke patients develop greater brain atrophy compared to controls. We also found that male stroke patients had greater white matter atrophy than their female counterparts. These findings may have implications for cognitive functions in stroke patients.

Keywords: *Africa, Brain atrophy, MRI, Stroke*

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Résumé

Contexte: L'atrophie cérébrale est un accompagnement fréquent du vieillissement et de nombreuses
conditions neurologiques. L'imagerie par résonance magnétique (IRM) a été utilisée pour comparer les volumes cérébraux de survivants d'attaque paralytique avec des témoins sans d'attaque paralytique dans ce premier rapport de l'Afrique subsaharienne.

Méthodes: Les participants comprenaient 45 patients avec attaque paralytique et 54 témoins sans attaque paralytique. Des imagesstructurelles parRM du cerveau ont été acquises provenant des participants et les volumes de matières grises, blanches et de CSF ont été extraits.

Résultats: Le pourcentage de substance blanche dans le volume intracrânien (VIC) (attaque paralytique: 0,45 ± 0,03, témoin: 0,47 ± 0,03, p = 0,02) et lepourcentagedu volume cérébral total dans VIC (attaque paralytique: 0,85 ± 0,03, témoin: 0,87 ± 0,02, p = 0,002) étaient significativement plus grands chez les témoins que chez les patients ayant subi uneattaque paralytique. Le pourcentage de CSF dans le VIC (attaque paralytique: 0,15 ± 0,03, témoin: 0,13 ± 0,03, p = 0,002) était significativement plus faible chez les témoins que chez les patients ayant subi uneattaque paralytique. Les témoins (68,9 ± 10,0 ans, p <0,001) étaient significativement plus âgés que les sujets ayant subi uneattaque paralytique (59,8 ± 11,0 ans). Une fois ajusté pour l'âge, le pourcentage de substance blanche dans le VIC (homme: 0,44 ± 0,03, femme: 0,46 ± 0,04, p = 0,043) était significativement moins élevé chez les hommes que chez les femmes dans le groupe ayant subi uneattaque paralytique.

Conclusions: Nos résultats ont montré que les patients ayant subi uneattaque paralytique développent une atrophie cérébrale plus importante

que les témoins. Nous avons également constaté que les hommesayant subi uneattaque paralytiqueavaient une atrophie de la substance blanche plus importante que leurs homologues féminins. Ces résultats peuvent avoir des implications pour les fonctions cognitives chez les patients ayant subi uneattaque paralytique.

Mots-clés: *Afrique, Atrophie cérébrale, IRM, attaque paralytique*

Introduction

Stroke is the second leading cause of death worldwide, with increasing incidence in developing countries [1-4]. It has been estimated that one in three persons worldwide will develop a stroke, dementia or both in a lifetime [5, 6]. The growing burden of stroke parallels increasing population ageing, lifestyle changes and growing prevalence of vascular risk factors [3]. Stroke and related non – communicable diseases are gaining increased attention in public health systems [7, 8].Whereas stroke has received much research attention in the developed countries, such efforts have been limited in Africa due to limited manpower, lack of funding and facilities as well as poor stroke literacy[9, 10].

Magnetic Resonance Imaging (MRI) makes possible the objective quantification of structural and functional brain changes (e.g. atrophy) and their correlates. Brain atrophy manifests as a decrease in the total brain tissue volume, decrease in the volume of other specific tissue classes like grey or white matter volumes, increased ventricular volumes and/or enlargement of the superficial sulci [11, 12] and may be normal in ageing individuals or result from specific neurological diseases such as degenerative disorders and dementias. [13, 14].

There is some evidence that brain atrophy is also associated with stroke[3, 15, 16], but some studies have reported no association [17], hence more studies are needed to understand the relationship between stroke and brain atrophy.

Currently, there is little information on the relationship between brain atrophy and stroke in populations of African ancestry. We used MRI imaging to compare brain volumes in Nigerian African stroke survivors with those of stroke – free controls participating in the Cognitive Function After Stroke (CogFAST) Study[18]. We hypothesized that brain atrophy would be significantly greater in stroke survivors compared to the control group. We present findings from the first study of its kind in Africa that used volumetric analysis of brain MRI for evaluating brain atrophy in stroke patients.

Methods

Stroke patients

Detailed description of stroke subjects has been presented elsewhere [18]. In brief, stroke patients (N=45) were recruited from two specialist hospitals (Federal Medical Centre Abeokuta and University College Hospital Ibadan, South Western Nigeria) and diagnosed by senior physician/attending neurologists between July 2010 and June 2012. Subjects and their family/caregivers were approached regarding participation in the study at discharge from hospital or during the initial outpatient visit. Stroke survivors were screened for eligibility to participate in the CogFAST Study three months after the ictus to allow for the resolution of post – stroke delirium. Exclusion criteria were: [i] age less than 45 years, [ii] subarachnoid hemorrhage, [iii] significant physical illness and motor impairment that precluded paper and computer-based neuropsychological evaluation(e.g. visual impairment, moderate-severe aphasia, hemiparesis affecting the dexterous hand, MRC power grade < 3), [iv] any co-morbid psychiatric or neurologic illness (background dementia, schizophrenia, major depression, manic-depressive disorder and Parkinson's disease), [v] any systemic disease that could impair cognition e.g. chronic liver disease, chronic kidney disease, and [vi] failure to give consent.

Control Subjects

The control group (N=54) comprised healthy volunteers who were free from any clinically-evident stroke or neuropsychological conditions. They were recruited from among community-dwelling adults participating in a community health literacy program. Written informed consent was obtained from all participants under protocols approved by the local health research and ethics committees for the study (Federal Medical Centre Abeokuta and Oyo State Ministry of Health Research Ethics Committee).

Brain MRI Acquisition

Brain MRI was performed on stroke survivors three months after the ictus and on stroke – free control subjects using low-field MR scanners (0.2-0.35T) MAGNETOM Concerto (Siemens Medical) and Mindray Magsense 360 (Mindray China). T_1-weighted(T1W) whole brain images were acquired from all participants, Echo Time (TE) 15 milliseconds, Repetition Time (TR) 570.4 milliseconds, Voxel dimension 0.98 by 0.98, 6 mm resolution, matrix dimension 256 by 256 and 21 slices. Figure 1 (a and e) shows representative for the control images and stroke subjects.

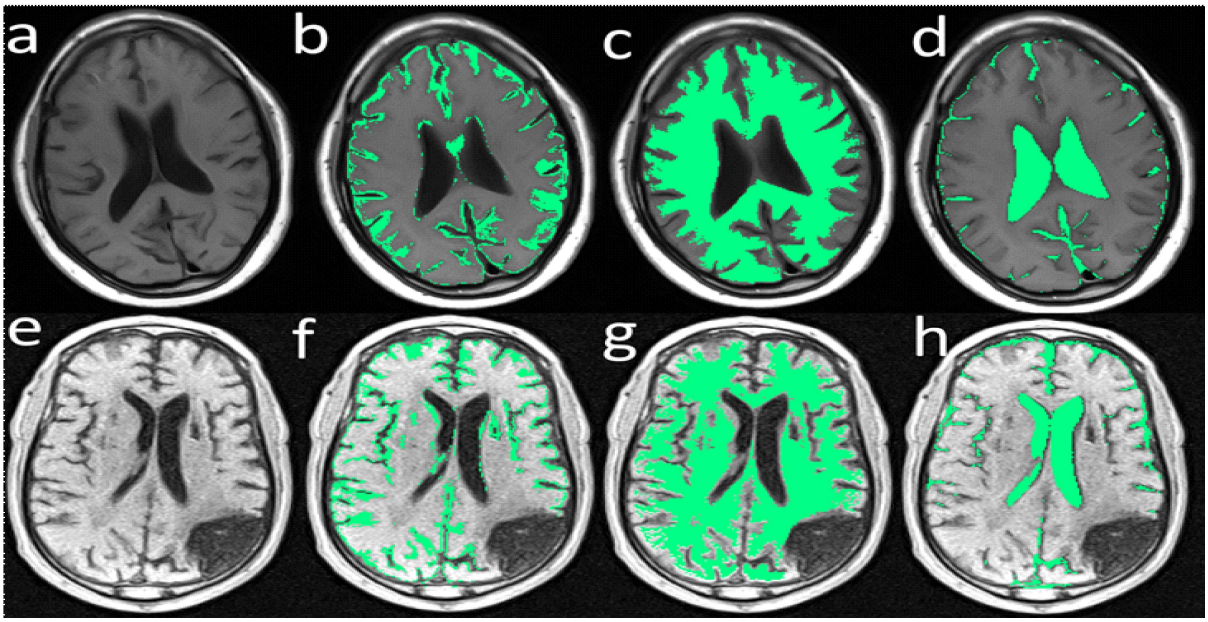

Fig.1: Axial slice of a representative images showing the T1W images of control (top) and stroke (bottom) subjects with the tissue class overlays – grey matter (b and f), white matter (c and g) and CSF (d and h)

Brain Tissue Volume Measurements

All analyses were performed blind to all cognitive and clinical data. The DICOM files were converted into Analyze 7.5 format [19] before image processing. Prior to image segmentation, the T1W images were extracted using the brain Extraction Tool (BET) from the FSL software (www.fmrib.ox.ac.uk/fsl/). Each subject's anatomical scan was segmented into grey matter (Figure 1), white matter and cerebrospinal fluid (CSF) using Gaussian mixture model implemented in Statistical Parametric Mapping (SPM12, www.fil.ion.ucl.ac.uk/spm). The total brain tissue volume was calculated as the sum of grey and white matter tissues while the intracranial volume was calculated as the sum of the total brain tissue volume and CSF. All volumetric measurements were expressed as percentage of Intracranial Volume (ICV) and the percentage tissue in ICV was hence used as a measure of atrophy.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 21 (IBM SPSS Corporation, New York, USA), with all statistical tests being two-tailed, and p values < 0.05 considered to be statistically significant. Brain volumetric measurements were normally distributed and hence group and gender comparisons used independent t-test. Age was corrected for because the mean ages of stroke survivors and stroke - free control subjects were significantly different ($p<0.01$). Correction for age used analysis of covariance implemented in SPSS.

Results

Of the 45 stroke patients, 24 (53%) were male while 36 (67%) of the 54 stroke – free control participants were male. The control subjects (68.9 ±10.0 years, $p<0.001$, Table 1) were significantly older than the stroke (59.8 ± 11.0 yrs) patients but there was no significant age - related difference between the male and female participants within each of the two groups.

We found that the volumes of grey (stroke: 328.97±68.52 ml, control: 395.60±60.30, $p<0.0001$, Table 1), white (stroke: 370.50±61.89, control: 457.60±62.84, $p<0.0001$), total brain tissue volume (stroke: 699.47±124.10, control: 853.20±117.60, $p=0.001$) and ICV (stroke: 823.09±136.98, control: 984.50±136.70, $p<0.0001$) were significantly higher in the control group than the stroke group, but these differences were annulled when grey was corrected for ICV. However, the differences remained significant in white matter (stroke: 0.45±0.03, control: 0.47±0.03, $p=0.02$, Figure 2) and total brain tissue (stroke: 0.85±0.03, control: 0.87±0.02, $p=0.002$) after correcting for ICV. There was no significant difference between volumes of CSF in the stroke and the control groups, but the % of CSF in ICV (stroke: 0.15±0.03, control: 0.13±0.03, $p=0.002$) was significantly higher in the stroke group than in the controls. All the significant differences

Table 1: Volumetric measurements of tissue classes of the stroke (N=45) and control (N=54) subjects, and the t-test comparisons of the two groups.

	Mean (STD)	
	Stroke	Control
Grey matter volume in ml	328.97(68.52)	395.60(60.30)**
White matter volume in ml	370.50(61.89)	457.60(62.84)**
CSF volume in ml	123.62(29.61)	131.30(28.40)
ICV in ml	823.09(136.98)	984.50(136.70)**
Total brain volume in ml	699.47(124.10)	853.20(117.60)**
Grey matter in ICV	0.40(0.03)	0.40(0.02)
White matter in ICV	0.45(0.03)	0.47(0.03)*+
CSF in ICV	0.15(0.03)	0.13(0.02)*
Total brain volume in ICV	0.85(0.03)	0.87(0.02)*
Age in years	59.80 (11.00)	68.90 (10.00)**

* Stroke significantly different from control ($p<0.05$).
** Stroke significantly different from control ($p<0.001$).
+ Significance disappeared after correcting for age.
Abbreviations: ICV, intracranial volume; STD, standard deviation

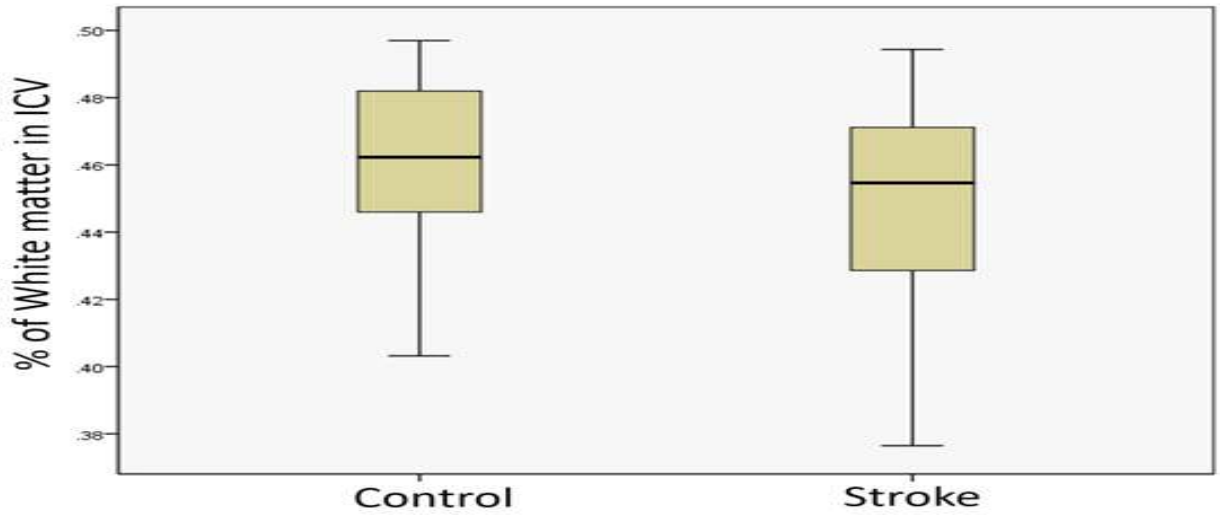

Fig. 2: Boxplot showing that the percentage of white matter in ICV of the stroke survivors is significantly smaller than those of the control group

remained even after correction for age, with the exception of % of white matter in ICV.

In the controls, the volumes of white matter (male: 471.22 ± 68.64 ml, female: 430.37 ± 37.85 ml, p=0.007, Table 2) and total brain tissue (male: 874.90 ± 128.43, female: 809.79 ± 78.51, p=0.026) were significantly higher in male than female but these were negated when volumes were corrected for ICV. However, in the stroke group, the volumes of grey (male: 353.59 ± 69.40, female: 300.84 ± 56.85, p=0.008), CSF (male: 134.62 ± 29.70, female: 111.05 ± 24.58, p=0.006) and total brain tissues (male: 738.20 ± 126.35, female: 655.21 ± 108.00, p=0.02) were significantly greater in males than in females. These differences disappeared when volumes were corrected for ICV. ICV was significantly greater in males than in females in both groups and the % of white matter in ICV (male: 0.44±0.03, female: 0.46±0.04, p=0.043) was significantly less in male than in female stroke survivors. This indicated that in the study group, the males had more atrophy of white matter compared to the females among stroke patients.

Discussion

This study was the first in Africa to use volumetric analysis of brain MRI images to evaluate brain atrophy in stroke survivors. We found significantly longer brain atrophy in stroke patients compared to older stroke– free controls. This volumetric analysis of brain MRIs of a modest sized cohort of Nigerian Africans exhibited not only greater loss of total brain tissue but also white matter volume was affected, particularly in male stroke survivors. The global brain tissue loss was compensated for by increases in the percentage of CSF in ICV, which was higher in the stroke patients than the controls. Additionally, we found that the male stroke patients had higher intracranial volumes than their female counterparts. Our finding of global brain atrophy in stroke patients is supported by results from some studies in Caucasian stroke subjects with cognitive impairment and dementia [5-8], and cerebral small vessel disease arising from vascular risk factors such as hypertension, type 2 diabetes mellitus and dyslipidaemia[2, 20, 21]. The finding of male stroke patients having larger brain volume than their female counterparts is in tandem with previous studies showing gender differences in ICV of normal ageing population [22, 23].

Our finding that male stroke patients exhibited worse white matter atrophy than the female counterparts is in agreement with other studies in normal ageing population[24-26] and in those with Wilson's disease [27]. The finding of men with higher ICV also having larger brain atrophy agrees with the notion of brain reserve, suggesting that people with larger head volumes and possibly higher brain reserve need to lose greater volume of brain tissue in order to lose their resilience to structural brain disorders[24, 25].

Although cerebral atrophy has often been interpreted as a signature of neurodegenerative diseases such as Alzheimer's, there is growing evidence in favour of a possible vascular basis for neurode generation and brain atrophy[5]. Qui et al [28] reported a significant association between aggregated vascular risk factors and reduced hippocampal volume in older men, while hippocampal neuronal atrophy was found to correlate with post – stroke dementia in another cohort with insignificant degenerative pathology[15, 17].

Table 2: Volumetric measurements of tissue classes of the stroke (N: Male = 24, Female = 21) and control (N: Male = 36, Female = 18) subjects, and the t-test comparisons of male and female groups

		Mean (STD), mm3	
		Stroke	Control
Grey matter volume in ml	Male	353.59(69.40)**	403.69(64.78)
	Female	300.84(56.85)	379.42(47.76)
White matter volume in ml	Male	384.61(62.36)	471.22(68.64)**
	Female	354.36(58.67)	430.37(37.85)
CSF volume in ml	Male	134.62(29.70)**	131.70(30.42)
	Female	111.05(24.58)	130.50(24.64)
Total brain volume in ml	Male	738.20(126.35)*	874.90(128.42)*
	Female	655.21(108.00)	809.79(78.51)
ICV in ml	Male	872.82(140.03)**	1006.60(149.61)
	Female	766.25(111.23)	940.29(95.19)
Grey matter in ICV	Male	0.40(0.03)	0.40(0.02)
	Female	0.39(0.03)	0.40(0.02)
White matter in ICV	Male	0.44(0.03)*	0.47(0.03)
	Female	0.46(0.04)	0.46(0.02)
CSF in ICV	Male	0.15(0.03)	0.13(0.02)
	Female	0.15(0.04)	0.14(0.02)
Total brain volume in ICV	Male	0.85(0.03)	0.87(0.02)
	Female	0.85(0.04)	0.86(0.02)
Age in years	Male	58.8 (8.7)	68.5(9.6)
	Female	61.1(13.4)	69.7(9.8)

* Male significantly different from female ($p<0.05$).
** Male significantly different from female ($p<0.01$).

Other recent findings have shown a direct relationship between microstructural abnormalities in white matter hyper intensities (due to small vessel disease) and reduced cortical thickness [29, 30]. The impact of atrophy on cortical neuronal network, particularly in subcortico –frontal circuits, further accentuates cognitive impairment apart from the independent impact of vascular brain disorders.

A major strength of this study is its uniqueness in being performed in African stroke patients who underwent MRI. We used volumetric analysis based on current standards and well validated image analysis tools, such as FSL and SPM. The study has limitations, nonetheless. The sample size is relatively modest because of limited availability and high cost of MRI in Africa. Clearly, a larger sample size is needed but we do not anticipate that findings will be vastly different from those reported here although the longitudinal trend of atrophy over time would be valuable to report. Hence, the cross-sectional nature of the study also limits the study. Another limitation is the investigation of global atrophy, a regional or voxel wise analysis could provide useful information on region specific atrophy e.g. cortical thickness. Our focus in the current study was on global atrophy, future studies will consider regional atrophy. Another limitation of this study is the fact that stroke lesions were not quantified or excluded from the tissue classes. It is possible that some lesions were included in CSF during tissue segmentation. This could reduce the tissue affected by stroke and increase CSF volume. Stroke lesions were not segmented because we have not validated any lesion segmentation tool on our data, and lack of manpower makes it impossible to do manual lesion segmentation. In order to reduce the effect of this, we did brain extraction of T1W images before tissue segmentation. This process removed some of the lesions and reduced the chance of misclassification. Additionally, we compared the left and right hemisphere of the stroke survivors lesions and found no significant difference.

Finally, the mean age of the control group was significantly higher than that of the stroke group. Inclusion of this, in fact, strengthened our study because it confirms that the greater atrophy in stroke patients is not due to an effect of ageing per se. Age is a well known risk factor for brain atrophy with the older adults having more atrophy than the younger ones [13, 14], but we found that the stroke patients who were actually younger than the controls had larger brain atrophy. Notwithstanding, we corrected for age in our analysis. This confirms that the differences in atrophy level observed in this study either result from the stroke injury itself or other predisposing factors prior to stroke.

In summary, our results show that Nigerian African stroke survivors exhibit higher brain atrophy compared to stroke – free controls and African males with stroke injury have more atrophy of total brain white matter than females of the same age group. Further studies on the association between brain atrophy and cognitive variables could further reveal the impact of brain atrophy on cognitive functioning after stroke in people of African ancestry.

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Titles should be short, specific and clear. Omit phrase such as "The use of, "observations on". Authors should provide a short running title and six keywords. Manuscripts must include a structured abstract not exceeding 250 words in a separate page. The abstract will be translated into French by the journal office at a cost to the author. Currently, the fee for translation is N2,500.00 ($50.00) non-refundable, which shall be paid when article is found acceptable for publication. The numbers of photographs and illustrations should be kept to a minimum. The legends for figures and tables should be numbered in Arabic numerals and should appear on a separate page.

The author(s) must pay for publication of coloured figures at the time of acceptance. All details on charts and graphs must be legible when reduced to the size used in this journal.

The onus of preparing a paper in a suitable form for publication rests with the author(s). The need for editorial revision for badly prepared typescripts or diagrams may lead either to rejection of the article or delay in publication.

Authors should indicate by a statement in the body of their paper that they complied with the standard requirements of the Ethics Committee of the institution in which the work was done. A Letter of Ethics Committee approval must also accompany the manuscripts at the time of submission. Where an Ethics Committee is not readily available, the Helsinki Declaration principles as revised should be followed strictly.

Workshop and conference reports should not exceed 3 to 10 double-spaced A4-sized pages. Viewpoints which could be papers expressing personal or group opinion on political, socio-economic and other matters as they relate to the practice of medicine should be limited to 10 A4-sized typed pages. Letters to the Editor may be comments on papers published in the Journal or clinical observations, replies to comments, or other matters of importance and relevance to medicine and related professions. It should not exceed 500 words with a few references and one or two tables and figures.

This Journal has agreed to accept manuscripts prepared in accordance with the Vancouver style and the Editor will consider only papers conforming to this style.

References should be numbered in the order in which they are cited in the text. At the end of the article, the references should be listed as numbered in the text. Each reference should give the names and initials of all authors (unless there are more than six, when only the first three should be given, followed by *et al.*). The authors' names should be followed by the title of the article, the journal title (abbreviated according to the style of *Index Medicus)*, the year of publication, the volume number and the first and last page numbers. Titles of books should be followed by the publisher, place of publication, and year. Examples of format for references are as follows:

Edington GM, Osunkoya BO and Smith JA.
Immunopathology of Burkitt's lymphoma. West Afr Med J 1986; 85: 76 – 87.

Brown A. Primary Health Care and the Medical Curriculum Edinburgh: Universities Press. 1977.

Lewis A. Primary liver cell carcinoma. In: Ajose A. Odeku EL, Eds. Priorities in Health Planning. Ibadan: University Press, 1983; 110 - 117

Reference to tables should be in Arabic numerals, e.g. Table 3, and tables should include titles, which make therein without reference to text. Tables should be typed separately from the text. Referencing within the body of the article should be in block form, i.e [1,2].

Proof corrections are expensive and correction of proofs other than printers' errors should be kept to a minimum. Authors must return proof corrections within 3 days of receipt. Failure to do this will result in the paper being published with the Editor's corrections only. Papers accepted for publication remain the copyright of the Journal.

Offprint which will be available in the Editorial office of the Journal must be paid for at the time of final acceptance of the paper. Four journal pages will be printed at four hundred and fifty naira (N450.00). Extra pages will attract page-printing charges at the rate of N700.00 (£5, $7) per page. (approximately 5 quarto-size pages of manuscript).